PREPARATION AND EVALUATION OF DIRECTLY
COMPRESSIBLE STARCH FROM MANIHOT UTILISSIMA (POHL)


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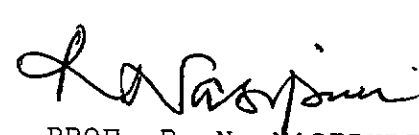

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## CERTIFICATION

This is to certify that the Thesis titled:
THE PREPARATION AND EVALUATION OF DIRECTLY
COMPRESSIBLE STARCH FROM <u>MANIHOT UTILISSIMA</u>, (POHL)
submitted to the School of Postgraduate Studies,
University of Lagos for the award of the degree
of Ph.D in Pharmaceutics and Pharmaceutical Technology
is a record of original research carried out by
Mrs. M. O. Odusote in the Department of Pharmaceutics
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## PREPARATION AND EVALUATION OF DIRECTLY COM-PRESSIBLE STARCH FROM MANIHOT UTILISSIMA (POHL)

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Ph.D) in the Department of Pharmaceutics and Pharmaceutical Technology, School of Pharmacy, College of Medicine of the University of Lagos, Lagos, Nigeria.

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## ACKNOWLEDGEMENT (Contd.)

## DEDICATION

This book is dedicated to my children;
Tosin, Ade, Yinka, Bola, Dolapo and Olufunmilayo
to serve as an example to them that trusting
in God and endurance in life can lift mountains.

Remember what the great man Dada J.P Vaswani
once said:

"The key to the success of most heroes lies
in the simple fact that they - Never, Never, Give
up -".

# ABSTRACT

This study has been on the preparation of starch
powder from local sources with the aim of purifying
the starch to the B.p .specifications. Results
show that an acceptable directly compressible starch.
(termed  modified starch) has been prepared.

The starches were prepared by extraction and
purified by thorough washing with water. Variation
of processing techniques such as binder volume,
binder temperature and massing time as well as
determination of reworking potentials were employed
in choosing cassava starch as the most  suitably
utilized source of directly compressible diluent.
Cassava starch was then pregelatinised at two
temperature ranges; $68°$ - $70°C$ and $98°$ - $100°C$.
Three different size fractions of the pregelatinised
starch; 120ums,  180ums,  and 250ums  were used in
different proportions to mix with the plain cassava
starch of particle size., $<180\mu$ms. Granules and
tablets produced from these mixtures were evaluated
and compared with other universally acceptable
directly compressible diluents.  The results show
that crushing strength of the tablets increased with

## ABSTRACT (Contd.)

increasing concentration of pregelatinised starch up to about a concentration of 60 - 80% W/W pregelatinised starch after which the crushing strength decreased.

Pregelatinization temperature of 98° - 100°C produced harder compacts which however had a faster disintegration. This has been explained with respect to swellability and water absorption capacity of the mixtures at the two pregelatinization temperatures.

Heckel's theory has been used to explain the compressional behaviour of the blends. When the modified cassava starch was compared with official directly compressible diluents, Avicel$^{(R)}$ pH 102 and spray dried lactose as a carrier for paracetamol, compacts made from the modified cassava starch exhibited a faster release of the medicament than the Avicel$^{(R)}$ pH 102 and the spray dried lactose.

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## SCOPE OF THE THESIS

Direct compression of tablet making is the compression of tablets from powder blends of active ingredients and suitable excipients which flow uniformly into a die cavity and compress into a firm compact without need for a granulation step. Direct compression offers a number of advantages, particularly in regard to ease and economy of manufacture and increased product stability and dissolution rate. Since the majority of drugs lack sufficient bulk, satisfactory compression characteristics, or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation (1) and direct compression process of tablet making requires the incorporation of direct compression diluents to impart such properties to the drug to be compressed.

Few chemicals possess the flow, cohesion and lubricating properties under pressure to make firm compacts. Direct Compression excipients particularly filler-binders, are specialty excipients. In most cases, they are common materials which have been

modified to impart to them greater fluidity and compressibility. The first of such vehicle was spray-dried lactose, which, although was subsequently shown to have short-comings in terms of compressibility and colour stability initiated the direct compression revolution because of the advantages of the method over other methods of producing tablets.

Starches from local sources, though have been found useful as diluents, binders, disintegrants and lubricants in tablet formulation do not possess good flow property or compressibility. A survey of the published reports also show that little or no efforts have been made to convert these starches to directly compressible vehicles suitable for direct compression tabletting.

It was therefore thought appropriate to extract starch from this cheap easily obtainable and bulk produced commodity like cassava, yam, potato and maize, and to investigate their efficacy in the preparation of directly compressible filler-binders. In doing so, attention has been paid to convert particularly the cassava starch in such a way that it will have the ideal properties of direct compression filler-binder, as much as possible, which

include high flow rate, increased compressibility,
and capability of being reworked without loss
of flow or compressibility.

This work will therefore be an attempt to
prepare  pure cassava starch from the tubers,
modify it and evaluate its usefulness as a directly
compressible diluent.

INTRODUCTION


CHAPTER I

## PREPARATION AND EVALUATION OF DIRECTLY COMPRESSIBLE STARCH FROM MANIHOT UTILISSIMA

1.1                    PREAMBLE

The successful application of direct compression as a tabletting procedure is dependent upon the development of suitable materials which in themselves are both highly fluid and cohesive. Direct compression offers a number of advantages, particularly in regard to ease, economy of manufacture and increased product stability. Since the majority of drugs lack either sufficient bulk, satisfactory compression characteristics or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation. However, the number of filler-binders reported to be useful for direct compression is quite limited.

A natural, innocuous substance is desirable as a filler or additive, and a naturally occurring polymer such as starch is a good candidate.

Manihot utilissima (Cassava) grows abundantly in Nigeria. The caryopsis of these plants are used as diet. The starch obtained from it is white in colour and seems promising as directly compressible tablet diluent.

Cassava starch is in mass production in Nigeria. Yet it has not yet achieved a wide spread pharmacopoeal acceptance compared to maize, rice and wheat starches. Hence its application in the pharmaceutical industry is still limited. Some of the directly compressible diluents in the market today are microcrystalline cellulose prepared from alpha-wood cellulose, spray-dried lactose, anhydrous lactose, dicalcium phosphate dihydrate and modified corn starch (Sta-Rx 1500). These materials are not manufactured in our country. The technology is not even known, therefore they have to be imported. It was therefore considered of interest to prepare and evaluate some directly compressible tablet diluents from cassava.

The starch was processed from the caryopsis and purified using a published method. The standard starch was modified by wet granulation using many variables to acquire expected granular properties.

Formulation variables like the effect of pregelatinised component, and pregelatinization temperature on compact properties particularly the hardness were evaluated using the Heckel plots.

The most promising formulation was compared with two market samples as carriers for paracetamol.

As expected, Cassava starch compacts released the medicament faster than Microcrystalline cellulose and spray-dried lactose.

The hardness of the modified Cassava starch was much better than that obtained for spray-dried lactose, being well above 7.0kg.

## 1.2 DIRECT COMPRESSION PROCESSES OF TABLET MAKING; ITS ADVANTAGES AND DISADVANTAGES

Direct compression of tablet making is the compression of tablets from powder blends of active ingredients and suitable excipients which flow uniformly into a die cavity and compress into a firm compact without need for a granulation step. Direct compression offers a number of advantages, particularly in regard to ease and economy of manufacture and increased product stability. Since the majority of drugs lack sufficient bulk, satisfactory compression characteristics, or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation (1) and direct compression process of tablet making requires direct compression diluents to impart such properties to the drug to be compressed.

The advantages of direct compression, include less number of processing stages and hence less cost of procedure as well as high disintegration rate (2).

The disadvantages include more critical physical properties for raw materials (like particle size, particle size distribution, flowability, density, moisture content and surface type). Consequently the excipients are specialty items, available only from a single supplier (2).

1.3     DIRECT COMPRESSION FILLER-BINDERS

Until the late 1950's the vast majority of tablets produced were manufactured by a process requiring granulation of the powdered constituents prior to tabletting (2). The primary purpose of the granulation step was to produce a free-flowing and compressible mixture of active ingredients and excipients. The availability of new excipients or new forms of old excipients particularly fillers and binders, and the invention of new (or the modification of old) tablet machinery have allowed compression of tablet by the much simpler procedure of direct compression.

Few chemicals possess the flow, cohesion and lubricating properties under pressure to make firm compacts. Direct compression excipients particularly filler-binders, are specialty excipients. In most cases, they are common materials which have been modified to impart to them greater fluidity and compressibility.

The first of such vehicle was spray-dried lactose (3,4) which, although it was subsequently shown to have short-comings in terms of compressibility and colour stability, initiated the direct compression revolution.

## 1.3.1 <u>CLASSIFICATION</u>

Compression filler-binders may be classified into two groups:

(a) organic

(b) inorganic

The organic ones in turn can be sub-classified into carbohydrate based materials and non-carbohydrate. The following table shows the examples of the various classes, the trade names and the suppliers.

(A)                              <u>ORGANIC</u>

| Trade Name | Description | Company |
|---|---|---|
| Ac-Di-Sol | Internally Cross-linked form of sodium carboxy-methyl cellulose | FMC Corp: Philadelphia, PA 19103 |
| Anhydrous Lactose | Lactose Anhydrous | Sheffield Chemical Union, NJ 07083 |
| Avicel 101, 102 | Microcrystalline Cellulose | FMC Corp. Philadelphia, PA 19103 |
| Cel-O-Cal | Co-processed Microcrystalline Cellulose and Calcium Sulphate | FMC Corp Philadelphia, PA 19103 |
| Destab Sugar | Compressible Sugar | Desmo Chemical Corp. Elmsford, NY 10523. |
| Di-pac | Direct Compression Sucrose Compressible Sugar | American Sugar Co. New Yor, NY 10020 |
| Elcema | Compressible Microfine Cellulose (powdered Cellulose). | Degussa D-6000 Frackfort (Main)1, Germany. |
| Emdex | Direct Compression Dextrose (Dextrates) | Edward Mendell Co. Carmel, NY 10512 |
| Explotab | Sodium Starch Gluconate | Edward Mendell Co. Carmel, NY 10512. |
| Fast Flo | Direct Compression Lactose, Hydrous | Formost Foods Corp. Crocker Plaza Sar Francisco, CA 94104. |
| Krafen | Sweet Whey | Kraft, Inc. Menphis, TN 38101 |

| Trade Name | Description | Company |
|---|---|---|
| Neosorb-60 | Direct Compression Sorbitol | Roquette Corp. 645 5th Ave. NY, Ny 10022 |
| Nymcel | Sodium Carboxy Methyl Cellulose | Nyma Nigmegen, Holland. |
| Nu-Tab | Direct Compression Sucrose (Compressible Sugar) | Ingredient Technology Inc. Pennsauker, W.J. 08110 |
| Polyplas-done XL | Crospovidone, (Cross Linked polyvinyl pyrrolidone) | GAF Corp. New York, NY 10020 |
| Primogel | Sodium Starch Glucolate (Carboxymethyl Starch) | Generichem Corp. Little Falls, NJ 07424 |
| Solka-Floc | Cellulose floc | Edward Mendell Co. Carmel, NY 10512 |
| Sta-RX 1500 (Starch 1500) | A carbohydrate | Color Con, Inc. West Point P.A. 19486 |
| Sorbitol 1162 834 | Sorbitol, (Crystalline) | I C I United States Wilmington, DE 19897 |
| Sugar-Tab | Direct Compression Sucrose | Edward Mendell Co. Carmel, Ny, 10512 |
| Spray-Dried Lactose | Direct Compression Lactose | Foremost-Mckesson San Francisco, CA 94104 DMV Corp, Veghel, Holland. |
| Tablettose | Hydrous Lactose | Fallek Chemical Co. New York, NY 10022. |

(B)                    <u>INORGANIC</u>

| Trade Name | Description | Company |
|---|---|---|
| Tri Tab | Tricalcium phosphate Anhydrous | Stauffer Chemical Co. West Port, CT. 06880 |
| Di Tab | Dibasic Calcium phosphate (Unmilled) | Stauffer Chemical Co. CT 06880 |
| En Compress | Special size Fraction of Dibasic Calcium phosphate | Edward Mendell Co. Carmel, NY, 10512 |

Spray-dried lactose is the first tablet filler designated for direct compression (4,5). Spray-dried lactose has a high degree of fluidity. Compressibility is reported not good enough and variability existed from batch to batch. The product is said to be impure and brown on ageing due to the contaminants in the mother liquor, mainly due to 5-hydroxyfurfural.

In the production of spray-dried lactose, lactose is first placed in an aqueous solution and chemically treated to remove impurities. Partial crystallization is then allowed to occur before spray-drying the slurry. As a result, the final product contains a mixture of large crystals of lactose mono-hydrate and spherical aggregates of smaller crystals held together by glass or amorphous material.

Spray-dried lactose contains 5% moisture as water of hydration. The free surface moisture is less than 0.5% and does not cause significant formulation problems. It is relatively nonhygroscopic. It has a high bulk density meaning that die fill weight is excellent. Anhydrous lactose on the other hand contains no water of crystallization. It is available in a white crystalline form which has good

flow properties and is directly compressible.  It

can be reworked or milled with less loss of

compressibility (6).  Because of the high percent

of fines (15 to 50% pass through a 200 mesh screen),

fluidity is less than optimal.

Extra-fine crystalline lactose has been suggested

as a direct compression filler due to its superior

fluidity when compared to regular crystalline

lactose U.S.P.  However, the material contains no

agglomerates or glass form, and is not as compressible

as spray-dried lactose.

The discovery of microcrystalline cellulose forms

a turning point in direct compression, not only

because it is highly compressible but  increases the

compressibility of other excipients when added in small

quantities (7,8).

The properties of microcrystalline cellulose

include:

(a)    Excellent compressibility at low

       compression pressures.

(b)    Effective dry binder in low

       concentrations.

(c)    Sufficient fluidity to be directly

       compressed.

(d)    Anti-adherent.

(e)    Disintegrant properties.

Microcrystalline cellulose is derived from a special
grade of purified wood cellulose by severe acid
hydrolysis to remove the amorphous cellulose portions,
yielding particles consisting of bundles of needle-
like microcrystals. It comes in two grades: pH 101
which is the original product and pH 102, which is a
partially agglomerated product, with a larger particle
size distribution and slightly better fluidity but
with no significant decrease in compressibility than
Avicel pH 101. Avicel pH 102 is the most compressible
of all the direct compression fillers and has the
highest dilution potential. The microcrystalline
particles are held together by hydrogen bonds. The
hydrogen bonds between hydrogen groups on adjacent
cellulose molecules account almost exclusively for
the strength and cohesiveness. Under compaction
forces, the microcrystalline cellulose particles are
deformed plastically due to the presence of slip
planes and dislocations, and the deformation of the
spray-dried agglomerates. A strong compact is formed
due to the extremely large number of clear surfaces
brought in contact during the plastic deformation.
It has a low bulk density and a broad range of
particle sizes and therefore exhibits a high dilution
potential on a weight basis and provides optimum
packing density.

Microcrystalline cellulose has an extremely low coefficient of friction (both static and dynamic) and therefore has no lubricant requirements itself.

Because of cost and density considerations, Microcrystalline cellulose is generally not used as the only filler in a direct compression tablet. Although it is not as effective a disintegrant as starch in equivalent concentrations, it can be used as the only disintegrant at levels of 20% or higher. Hard compacts of Microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydrogen bonds.

The disadvantages of Microcrystalline cellulose include:

(i) Poor fluidity.

(ii) Low bulk density - which may lead to poor mixing when extremely low dose drugs are tabletted.

(iii) High moisture sorption profile and high moisture content at working temperature and humidity, is a great disadvantage to very moisture sensitive drugs (9).

Modified Microcrystalline Cellulose prepared by microencapsulation with polyglycerol stearate phthalate and granulated with sodium carboxy methyl cellulose proved to be very promising as a directly compressible diluent (10).

Another approach of preparing Microcrystalline cellulose (MCC) was also reported by Baichwal et al (11). This method is by treating absorbent cotton with 4N hydrochloric acid at 80°C for 4 hours.

Baker and Anderson (12) have suggested microencapsulation as a method for preparing free flowing powders.

Unmilled dicalcium phosphate dihydrate is an inorganic direct compression filler. It is available under the name of Emcompress$^R$ or Ditab$^R$. This substance is relatively inexpensive and possesses a high degree of physical and chemical stability. It is non-hygroscopic at a relative humidity of up to 80%. In its directly compressible form, it exists as a dihydrate. The fluidity of dicalcium phosphate dihydrate is good, and glidants are generally not necessary. It deforms by brittle fracture when compressed, forming clean bonding surfaces. It is slightly alkaline with a pH of 7.0 to 7.3, which precludes its use with active ingredients that are sensitive to even minimal amounts of alkalinity.

Sucrose has been extensively used in tablets as a filler, in the form of a solution (syrup) as a binder in wet granulations. Attempts to directly compress sucrose crystals have never been successful, but various modified sucroses have been introduced into the direct compression market place. One of the first such products is Dipac$^R$, which is a co-crystallization of 97% sucrose and 3% highly modified dextrins. Dipac$^R$ has good flow properties and needs a glidant only when atmospheric moisture is high (greater than 50% relative humidity).

NuTab$^R$ is also a directly compressible sugar consisting of processed sucrose, 4% invert sugar and 0.11 to 0.2% each of corn starch and magnesium stearate. NuTab$^R$ has a relatively large particle size distribution which makes for good fluidity.

Emdex$^R$ is directly compressible dextrose. This product is spray crystallized and consists of 90 to 92% dextrose, 3 to 5% maltose, and the remainder higher glucose saccharides. It is available as both anhydrous and a hydrous product (9% moisture). Reports indicate that the anhydrous form is slightly more compressible than the monohydrate, but the compressibility of both is excellent (2). The commercially available product is the monohydrate and, as water of hydration does not appear to affect drug stability, it is the most widely used form.

Cellutab is a white, sweet tasting, free flowing dry compound composed of spherical, porous granules, which are aggregates of dextrose microcrystals intermixed and cohered with a small proportion of higher molecular weight sugars (16). The tabletting properties were studied by Bergman et al 1971 (17).

Crystalline Sorbitol - Sorbitol is one of the most complex of all direct compression fillers. It exists in at least two polymorphic crystalline forms as well as an amorphous form. The less stable polymorphic forms of sorbitol will convert to the more stable form. More recently more stable products such as sorbitol[R] 834, and Neosorb[R], as -sorbitol, are being manufactured which seem to overcome some of the problems (18).

Starch is one of the most widely used tablet excipients but does not, in its natural state, possess the two properties necessary for making good compacts; compressibility and fluidity. Starch B.P has been modified to improve its binding and flow properties. The only modification which has received acceptance in direct compression is Sta-Rx-1500 starch (15).

It is a partially hydrolysed starch which is relatively free-flowing (compared to starch U.S.P) and

which compress into a compact and still maintains
its disintegrant properties. It consists of intact
starch grains and ruptured starch grains which have
been partially hydrolyzed and subsequently agglo-
merated. It has an extremely high moisture content
(12 to 13%), but there is little indication that
this moisture is readily available to accelerate
the decomposition of moisture - sensitive drugs (15).

Although this substance will readily compact
by itself, it does not form hard compacts. Its
dilution potential is minimal, and it is not generally
used as the filler binder in direct compression, but
as a direct compression filler disintegrant(15). The
major advantage is that it retains the disintegrant
properties of starch without decreasing the fluidity
and compressibility of the total formulation, as is
the case+ with plain starch. Because Sta-Rx-1500
starch, like all starches deforms elastically when
a compression force is applied, it imparts little
strength to compacts. As few clear surfaces are
formed during compaction, lubricants particularly the
alkaline stearate lubricants, tend to dramatically
soften tablets containing high concentrations of
starch 1500, and they should be avoided whenever
possible in formulating tablets.

An attempt was made to modify yam and cassava starches
by wet granulation process.

The fluidity and compressibility of the granules

obtained were comparable with spray-dried lactose

and microcrystalline cellulose (19).

Cavalli et. al. (U.S. Pat. No. 3,584,114)

describe combining "poor flowing" powders (e.g. corn

starch) with melted waxylike edible materials such

as stearic acid, carbowax, glyceryl monostearate

and the like.  These patentees confirmed what others

have already pointed out that is, that a typical

corn starch is a poor flowing powder and requires

improvement in its flowability to be useful in

direct compression tabletting.  The method disclosed

by these patentees is complex, and requires

additional ingredients (19b).

## 1.4  IDEAL PROPERTIES OF DIRECTLY COMPRESSIBLE DILUENTS

The requirements of direct compression filler

binder (otherwise known as direct compression diluent)

are many that only/a few substances find their way into

commercial production.  Their ideal properties were

enumerated by Kanig (20).  They include high flow

rate, increased compressibility, physiological

inertness, high dilution capacity, compatibility, no physico-

chemical changes on ageing, stability to moisture,

heat and air, should be cheap, tasteless and colour-

less.  It must also have particle size range

equivalent to most active ingredients and be capable
of being reworked without loss of flow or compres-
sibility.

Avicel appears to be quite effective as directly
compressible diluent (DCD) or filler binder, since
it can add significant hardness to compacts when
it is present at a weight concentration of as low
as 3% or as high as 65% for poorly compressible
drugs. However, like compressible starch, Avicel
has poor flow characteristics. Poor flow can be
eliminated by use of suitable glidants or by
blending onto compressible excipients with different
flow properties (21).

Nyquist (22) and Nicklasson studied the effect
of water sorption on the physical properties of
tablets containing Avicel. They found that water
sorption from the atmosphere into plain Avicel tablets
is a very rapid first order rate process that brings
about substantial change in the physical properties
of tablets. The changes in crushing strength, thick-
ness and disintegration time were also found to be
irreversible as shown by disorption experiments.
The fast penetration of moisture into Avicel tablets
was found to occur even at low tablet porosities (23).
This behaviour was explained to be due to breaking of

hydrogen bonds between Microcrystalline particles and subsequent widening of pores in the tablet core (24). When the moisture content of microcrystalline cellulose was reduced, it was found that this led to reduced compressibility (25). The crystalline structure of most of these substances is known to be one of the factors responsible for their compressibility. Other factors that determine the compaction behaviour of substances include particle size distribution, crystal shape, bulk density, moisture content and the shape of punches used for compression (26).

The disintegrating behaviour of formulation containing Avicel has been studied by Khan and Rhodes (27). Comparative evaluation of direct compression excipients has also been made. Some of the evaluation parameters employed include moisture - uptake, tablet hardness, change in volume of tablet and disintegration time (26).

Optimum tabletting characteristics of direct compression vehicles can be made by blending materials. Armstrong and Lowndes (28) investigated the mixtures of spray-dried lactose (SDL) and microcrystalline cellulose (MC) in order to combine the good flow property and bulk density of the lactose with high compressibility profile and hardness of MC. Their results showed that an increase in the proportion of

spray-dried lactose in the mixture decreased the tablet strength. However, the ability of the tablet to withstand reworking was increased.

Microcrystalline cellulose has good reworkability and this is attributed to its fibrous structure which undergoes plastic deformation on compression (29). Compressible starch exhibits a fairly high degree of cohesiveness and maintains satisfactory compressibility upon addition of several commonly used active ingredients. By itself, it is self-lubricating and self-disintegrating (15).

Compressible starch can be compressed into tablets with a relatively wide range of hardness.

An increase in tablet hardness usually occurs in plain tablets during the first week of storage at elevated temperatures, and is accompanied by a loss of weight due to a loss of moisture. If the compressibility of starch can be partially attributed to hydrogen bonding, this bonding would be strenthened as drying occurs.

1.5    Physico-chemical and Physico-technical
              Properties of Powders

For many years, the properties of bulk solids used in the manufacture of pharmaceutical products were defined by chemical analytical means and little attention was paid onto the physico-technical

properties. This resulted in materials varying in physico-technical properties from batch to batch, such that the processes involved in manufacture - especially in tabletting required empirical , experienced, judgement decisions in order that they resulted in a satisfactory product.

The quality of tablets, once formulated, is as a general rule primarily dictated by the physico-chemical properties of the granulation from which the tablets are made and in case of direct compression tabletting, on the physico-chemical and physico-technical properties of the direct compression filler-binders.

Recently, Pharmaceutical Scientists have turned their attention to the characterisation of bulk particulate material such that it is now possible more accurately to define the variability that may occur in any particular ingredient (30).

The derived properties of directly compressible filler-binders include: Packing characteristics like the bulk density, bed porosity, changes under imposed stress, bed permeability, caking tendencies, Flow characteristics and reworking potentials.

Particle size and size distribution plays an important role in many of the fundamental properties of pharmaceutical solids e.g. appearance, solubility

rate, wettability, packing characteristics, caking
tendencies, flow properties and compression
characteristics.

Heywood (31) described three different types
of particle densities:  True density, Apparent
particle density and Effective particle density.
True density is the mass of a particle(s) divided by
the volume of the particle(s).  Apparent particle
density is the mass of a particle(s) divided by the
volume of the particles(s), excluding open pores but
including closed pores.  Effective particle density
is the mass of a particle(s), divided by the volume
of the particles, including open and closed pores.

The mercury displacement method of determining
granule density is described by Strickland et.al.(32).
Their method gives a value of Pg that approximates
the effective particle density.  This method is based
on the fact that in a sample of granules, intra
particule  pores are sufficiently smaller than inter
particle pores, which permits differential determina-
tion of granular volume without including open pores
between particles.  Other authors  have  used the
pycnometer method, employing an organic solvent
in which the granules are not soluble (33,34).

At every stage of the handling and manipulation
of pharmaceutical bulk solids, changes in their

packing characteristics occur e.g., during transport, hopper transfer and compression. It should be recognized that the state of packing of a bulk solid is an important variable in determining the degree of penetration of liquids into the mass, its compression properties and its flowability.

Since materials vary in particle size and shape distribution, the particular packing in which they occur will vary significantly from lot to lot during the process of manufacture. The overall packing characteristics can be described by a number of quantitative parameters such as $P_B$ bulk density =

$$\frac{Mass}{Volume}$$

$$\frac{1}{P_B} = \text{bulkiness} = \frac{1}{\text{bulk density}}$$

$$\text{bed porosity} = 100 \left(1 - \frac{\text{bulk density } PB}{\text{particle density } Pg}\right)$$

Some studies involving granule porosity have been reported in the literature (35,36). When a poured bed of bulk solid is subjected to variation or tapping motion, the particles rearrange and pack down to a close array. A useful empirical guide to flowability can be obtained by measuring the difference between the initial poured, loose density and the final tap density. A suitable parameter is the carr compressibility index which measures the volume reduction as

a percentage term following tapping and can be related
to flowability (37).  Percentage compressibility
between 5 - 15 was said to have excellent fluidity
18 - 21 just fair, while between 23 - 40 were
described as being bad.

## 1.6    Compaction behaviour, and factors determining their compaction behaviour

The compaction of powdered materials is carried
out primarily to increase the density of the material.
The ultimate goal of the over-all process is the
attainment of minimun porosity.  Compaction is
responsible for most of the densification.  The
general terms "compactability" and "compressibility"
have been used to rank powders qualitatively
according to their compaction characteristics. To
restore a quantitative nature to the subject and to
prevent confusion, it was proposed that compactibi-
lity be defined as the minimum pressure needed to
produce a given green strength, while compressibility
should be used to indicate the extent to which the
density of a powder is increased by a given pres-
sure (30).  Probably the most widely used of the
compaction parameters is the "compression ratio",
which is generally defined as the ratio of the compact
density obtained by pressing at a given pressure to
the apparent density of the loose powder (30).

When powders are compressed in dies, strong
inter particulate forces develop which assist in
holding the powders together in the form of compacts
or tablets (38). It has been suggested (39) that
because of the high pressures which develop during
tabletting at the microscopic asperities of pouts
of contact between the particles, melting of the
asperities may occur. Results of recent work (40)
Jayasinghe, Pilpel & Harwood, 1969, Jayasinghe, 1970;
York & Pilpel, 1972, appear to confirm the validity
of this suggestion. In particular, it has been found
that the tensile stress and shear properties of
powders are markedly dependent on the temperature
at which the experiments are made.

Formation of solid bonds might contribute to the
strength and hardness of pharmaceutical tablets (41).

The existence of several stages of consolidation
during the compaction of powders has been reported
by many authors (42 - 46).

These stages may be enumerated as follows:

(i)     inter-particulate slippage leading to
        closed packing;

(ii)    formation of temporary struts, columns
        and vaults, which protect small voids
        and support the imposed  load;

(iii)   failure of the particles by plastic or
        elastic deformation;

(iv)    cold working, with or without fragmenta-
        tion;

(v)     development of a structure that supports
        the applied load, so that any further
        reduction in volume involves the normal
        compressibility of the solid material.

The attempts that have been made to quantify
the consolidation of particulate matter as compres-
sion proceeds have been adequately reviewed by
Kawakita and Tsutsuni (47). Most of the theoretical
treatments contain constants with obscure physical
significance and consider only the two main mechanisms
of consolidation, i.e. particle slippage and defor-
mation (47).

Hersey and Rees (48), considered two theoretical
treatments to study the consolidation behaviour of
different particle size fractions of sodium chloride
and of lactose powder. One of these methods makes
it possible to readily determine whether particle
size has any effect upon consolidation, and also to
calculate the yield strength of the powder and to
obtain considerable information on the mechanism of
consolidation for an individual powder (48).

The knowledge of the behaviour of a powder
during compression is an advantage in tablet

formulation, especially when using directly compressible materials. Higuchi and Rao also observed the 3 stages of compaction; rearrangement and close packing of individual particles; elastic or plastic deformation; and finally bond formation in the compact with or without fragmentation (49).

Particle rearrangement are said to occur mostly at low compression pressures and plastic deformation occurs at high pressures. All these events lead to a greater area of true inter-particle contact with high compression pressure, resulting in extensive areas of true particle contact. At these true areas of contact, Van der Waals forces act to provide strong bonds that maintain the integrity of the compact. Increasing compressive load brings about a failure of the temporary structures of the granules. The true area of particle contact begins to increase, and bonding occurs at these points. Studies have shown that the surface area of the compact goes through a maximal value as the compression force is increased (49).

Rubinstein (50) has studied granule consolidation during compaction by measuring the deformation of small cylindrical aggregates of di-basic calcium phosphate. It was obtained that at low pressures of

up to 200 MNm$^{-2}$, there was an increase in aggregate diameter accompanied by a corresponding reduction in thickness. There was only a relatively small reduction in aggregate value. This phase may be attributable to inter particulate slippage, which leads to a closer packed rearrangement. The increase in diameter is the result of granules being squeezed outward by the descending upper punch. At about 200 MNm$^{-2}$, the aggregate diameter no longer increase because solid bridges are formed between the particles making up the granules and the die walls, preventing any further squeezing out of the granules. From 200 to 420 MNm$^{-2}$, failure of the granular material occurs by plastic deformation and a consolidation occurs by a reduction in aggregate thickness only. Finally, from 420 to 800 MNm$^{-2}$, a structure is formed that can support the applied load without further consolidation (50).

Hiestand et al. (42) stated that during compaction particles undergo sufficient plastic deformation to produce die wall pressures greater than can be relieved by elastic recovery when the punch pressure is removed. This die wall pressure causes enough internal stress in some materials to cause a crack to propagate and initiate fracture of the compact in the die.

During the formation of a strong compact, individual particles or granules are converted from a relatively free flowing bulk mass into a strong compact. Several stages during this process can be identified. These can be demonstrated by reference to the changes in bed volume (or compact overall density) that occur following the application of an axial stress (42).

Some indication of the differences in the strength of materials that can be encountered in tabletting can be obtained from the work of Markova and Balabudkin (51). This study showed that the ratio of drug excipient in tablet formulations will have profound effects on the overall deformation properties of the compact and that the failure properties of any particle substance or combination of substances will be dependent upon the particular compression stress imposed during compaction.

The term "hardness" used to express compact strength, has been used for many years to describe the force which will break a tablet when subjected to a diametral load, often in an uncontrolled manner. Hardness has a definite meaning in the field of material science and it is preferable to use the term "breaking force" or "breaking strength" (30). The

relationship between breaking force and compression pressure is a good indication of the differences between materials used for pharmaceutical tablets. It can be used to provide an index of comparison of formulations and direct compression materials.

The volume of a powder placed in a tablet die is usually reduced when pressure is applied to the press. Even before any pressure is applied, as powder flows into the die, a reduction in volume of the quantity already settled in the die takes place. This reduction in volume is due to closer packing of particles and the void space or porosity decreases. Packing of particles is increased by vibration which causes them to move relative to one another. The initial packing of particles depends on the physical properties of the powder and the geometry of the die. Packing of powders has been discussed by several authors (52).

When pressure is applied to a powder bed, the individual particles fracture to create fresh clean surfaces which enhance inter particulate bonding. The mechanical strength of a compact depends not only on the particle size of the powder, the porosity, density or specific surface but also on the quantity

of the bonding forces and the area over which they act.

For direct compression materials, the liquid surface film theory (2) which attributes bonding to presence of liquid films at powder inter faces proposes that the liquid film produced during compression is due to fusion or solution at the surface of the particles. Increase in bond strength may also occur as a result of mechanical interlocking of the particles which, however, makes a minor contribution to the compact strength. The bonding mechanisms during compact formation has been reviewed by Rumpf (53). The mechanisms include the existence of interfacial, adhesive, cohesive intermolecular and electrostatic forces, also the formation of solid bridges and mechanical inter locking.

Techniques used for the determination of mechanical strength of compacts include crushing strength (54, 55) bonding strength (54), fracture resistance (55) and tensile strength (54, 55).

The mode of action of dry binders in increasing tablet strength could be, to increase the number of bonds or to produce a number of stronger bonds that can withstand stress relaxation and the elastic

recovery of the compressed particles.

The method of consolidation of a number of powders has been reported. These include aspirin which undergoes predominantly plastic deformation, mannitol and di-calcium-phosphate-dihydrate which show brittle behaviour. Plastic flow is reported to be important in the particle - particle bonding of micro crystalline cellulose (2).

Wells and Langridge (56) obtained good tablets from micro-crystalline dicalcium-phosphate-dihydrate mixtures. The tensile strength of the compacts increased with increasing proportions of micro-crystalline cellulose up to a maximum at all compaction pressure used. Strongest tablets were obtained from compacts containing 90% W/W MC and 10% dcd. It was surprising that tablets containing 100% MC was found to cap and were weaker than compacts containing 90% W/W MC and 10% dcd (56).

The mechanism by which the binary blend of excipients formed good tablets was explained by their different modes of deformation. MC undergoes plastic deformation and the mechanical strength of its compacts is largely controlled by hydrogen bonding (56). The number and area of the contact points increases with increase in compaction pressure and this leads to an increase in tensile strength.

On the other hand, dcd increased the tensile strength of the compacts by improving flow and the initial filling of the die. Thus, during the compression of the mixture, dcd fills the void spaces as a result of extensive fragmentation (56). This fragmentation interferes with boundary lubrication of lubricants such as magnesium stearate and this affects bonding and strength of compacts (56). When the mixture was reworked, flow was not impaired but the tensile strength and friability were adversely affected. The decrease in tensile strength was attributed to work-hardening (56). Simple inorganic materials like NaCl, and sta- RX show evidence of work-hardening. Larger molecules such as sucrose, lactose, avicel and Emdex seem not to work harden. Work hardening is due to high · dislocation densities per unit load and it prevents increased plastic flow of materials.

Changes in the overall time of compression will have profound effects on the compaction behaviour of many particulate bulk solids. This is particularly relevant to starting materials indirect compression. It has been suggested that materials which exhibit extensive plastic deformation are more likely to form compacts than materials showing low plasticity (2).

Thus, as the time during which the material is subjected to compression increases, it may be expected that the degree of bonding and hence tablet strength will increase for those materials which possess time dependent plastic deformation.

Thus, the amount of plastic deformation that occurs during compression (and hence tablet strength) can depend upon the overall time of compression, or contact time, the rate of applied compressive force and time during which the material is subjected to a maximum force i.e. dwell time. This time dependent effect has been demonstrated by a number of authors (30,2).

The effect of temperature on the flow and tensile strengths of powders was studied by some workers (57). Under compression the asperities on the surfaces of a variety of powders deform plastically and may melt to form welded bonds. The activation energy of bonding for different materials studied was between 8 and 12 KJ mole$^{-1}$. Certain polymers and thermo-setting resins soften on heating but harden subsequently due to cross-linking and other chemical reactions. The softening is usually accompanied by an increase in the tensile strength of any bed or compact into which the powder may have been formed,

irrespective of whether the tensile strength is measured at the elevated temperature or after the specimen has been allowed to cool (57). The process of sintering and compaction of powders at elevated temperatures have been extensively investigated (57, 58).

The effect of moisture content on the compression of bulk solids has been studied (59 - 62). The presence of moisture in bulk solids can seriously impair the flow properties of materials and thus cause non-uniform dosage in preparations or loss of efficiency in processing. It may, however, be used to advantage in granulation. More recently, measurements of the strength of moist agglomerates and compressed beds of bulk solids have shown that significant changes in tensile strength can occur according to the physical location of moisture within the specimen (61, 62).

The tensile strength of bulk solids at different humidities depends, among other variables, on the rate of moisture uptake and loss by the powder bed. This, in turn, may be expected to vary with the state of packing and dept of the beds.

It has been shown that free moisture exists in beds of bulk solids in at least two states; a

'pendular' state where liquid bridges occur between individual particles and a 'capillary state' where all the pores of the bed are filled with liquid which forms concave menisci at the pore ends. A 'transition' region between these two states is also suggested (63).

For the thin beds of sodium chloride, potassium chloride and sucrose, the increase in moisture content, is accompanied by changes from the 'pendular' state through to the 'capillary' state. The significant changes in tensile strengths obtained for these materials may be explained by the changes in the number and magnitude of the surface tension forces during the transition from various states of moisture location.

At low total moisture contents, there is an uneven distribution of the water but as the moisture content increases uniform distribution occurs, a higher moisture content being necessary in the thick beds for this state to be reached. This even distribution of moisture remains until the "Capillary" state is reached when subsequent moisture uptake produces a supernatant layer.

For potato starch, the equilibrium moisture content obtained at 85% relative humidity agrees

with the results obtained by Shotton and Harb
1965 (61). However, the tensile strengths
obtained by Shotton and Harb (61) at similar
equilibrium moisture contents are lower than the
values obtained by Eaves and Jones (55). This is
probably due to the use of a different packing
density. This emphasizes the importance of packing
density as a variable in tensile strength deter-
minations. A small change in the contact distance
or coordination number of the particles in a bed of
bulk solid will produce a significant change in the
nature of inter-particulate bonding. The moisture
present in lactose at equilibrium with high relative
humidities is likely to approach the pendular state
only; the tensile strength are not significantly
different.

A study of the effect of temperature on the
tensile strength of lactose coated with fatty acid
was made by Malamataris and Pilpel (63). The
strengths at a fixed packing fraction of 0.86
depend on the temperature at which they are measured.
They decrease with the amount of acid employed,
initially increase as the temperature during
compression is increased, then pass through minima.
They also depend on the storage conditions and on
the melting points of the fatty acids concerned.

The results conform to the Arrhenius equation and are explained in terms of the masking of Vander wall forces between lactose particles and the formation of welded bonds by the coating (63).

The results published by York and Pilpel(58) postulated that under the influence of pressure, melting can occur at the points of contact between particles at temperatures below their conventional melting points.

Pilpel and Britten (57) observed that under compression, the asperitieson the surfaces of particles deform plastically and may melt, if the temperature is raised above about 0.9 of the conventional melting point in ok, to form welded bonds.

1.7                    HECKEL ANALYSIS

The compaction behaviour of pharmaceutical powders can be investigated by studying their pressure - density relationships.  The Heckel equation can be successfully used to interpret compaction behaviour (64).  Heckel considered the consolidation behaviour of a powder mass to be analogous to a first order chemical reaction. The rate of change of density (D) of the compaction

with applied pressure (P) was related to the void fraction. The graph of $\ln \left(\frac{1}{1 - D}\right)$ vs P in equation

$$\ln \left(\frac{1}{1 - D}\right) = kp + \ln \left(\frac{1}{1 - Do}\right) \text{ would be expected}$$

to give a straight line with slope K and intercept $\ln \left(\frac{1}{1 - Do}\right)$.

The value of K is a measure of the compaction characteristics of the material and is used to evaluate the properties of the compact (64). A linear relation is obtained when the material undergoes plastic deformation without fragmentation. If fregmentation occurs during compression, a plot of the Heckel equation is not linear (65).

Thus the information concerning the bonding mechanisms taking place during the compression of powders in dies can be obtained by investigating the relationships between the applied pressure and the densities of the resulting tablets (64, 65). Several different mechanisms appear to be involved. These can be operated simultaneously or sequentially depending upon the properties of the material and the consolidating conditions employed (64, 65).

In the recent past most of the pressure density equation proposed, related to single chemical

substances covering a relatively narrow range of particle sizes (64, 65). Many of the equations contain terms whose physical significance is not clear. Relatively little work was done on the pressure density relationships of mixtures of the type employed in pharmaceutical tablets (64, 65).

Kurup and Pilpel (65) investigated the compression characteristics of binary, ternary and quaternary mixtures of the ingredients of a typical griseofulvin tablet formulation. The results were analysed in terms of the compression equations of Heckel, and of Cooper and Eaton and in terms of Cheng's equation for tensile strength. Both have been used to try and distinguish the different stages that occur in the compaction process. The first linear portion of the Cooper and Eaton plot and the curved region of the Heckel plot for type B- materials both correspond to densification occurring by particle rearrangement. The lower linear portion of the Cooper and Eaton plot and the linear portion of the Heckel plot relate to densification by plastic and elastic deformation and fragmentation of the particles. In general, the Heckel equation appears to be more sensitive for

distinguishing between the various stages of
the compaction process (65).

Heckel classified materials into two cate-
gories according to their compression character-
istics, Type A and Type B (64). B - behaviour
is characterized by an initial curved section up
to a certain compressive force, followed (presuma-
bly) by a linear section. In the curved section
the powders are apparently behaving as collections
of discrete individual particles whose packing
arrangement is altering under load to produce
increase in packing fraction. In the linear
section, densification is believed to be occur-
ring by plastic deformation of particles and cold
working of their surfaces with or without
fragmentation.

In type A, the plots do not exhibit an initial
curved section and the whole plot is linear. This
indicates the absence of any particle rearrangement
and is characteristic of type A materials (64).

The term K obtained in the Heckel equation is
a material constant and has been shown to be
the reciprocal of its mean yield pressure (66).
Soft ductile powders have higher K values than
hard powders (64). "A" represents the densification

due to particle rearrangement and is primarily a function of the size and shape of the particles (66). However, the packing arrangement of particles will also be influenced by their hardness, and hard powders tend to have high values of A. The formulations having high proportions of starch and polyvinyl-pyrrolidone had lower values of A than those with low concentrations of these ingredients, indicating that they were generally softer and more readily compressible (64). York and Pilpel (62) reported a similar result for other relatively soft powders like lauric, palmitic and stearic acids.

## 1.8    NIGERIAN STARCHES AS TABLETTING ADDITIVES

Nigerian starches have been commercial products in this country because of the following basic properties. They have been prized as staple foods as they are readily digested, metabolised and have a high calorific value. They have been used in the textile Industries for textile printing, finishing and sizing (67, 68). Some have entered the Nigerian Pharmaceutical Industries as tabletting excipients, binders, disintegrants and glidants (69 - 75).

Cold water starch was prepared from cassava starch for textile printing and finishing (67). The processed cassava starch was examined physically and chemically and the properties were found comparable with commercial starches. The performance of the modified cassava starch as a thickening agent in printing pastes was found suitable for textile finishing purpose.

Other workers (68) in the same Institute modified cassava starch for textile sizing in 1984. This modification was by Torrefaction and acid hydrolysis. Laboratory tests indicated that the starches would be suitable for use in textile sizing. Industrial evaluation indicated that the hydrolysed starches can be substituted for imported starches in the sizing of yarns and light finishing of fabrics without significant changes in weaving efficiency and quality of finished products.

Nigerian starches like all other starches are inert, abundant, and cheap. Because of these qualities, interest has of late been stimulated pharmaceutically, to research into the usefulness of those starches of local origin, such as cassava, yam, and cocoyam starches. A survey of published reports show that whereas considerable work has

been done on the four starches in the British pharma-copeia, namely potato, maize, wheat and rice, very little work is reported on yam and cassava starches which are most abundant and cheap locally.

Yams (several species of the genus Dioscorea) are important food crops in many tropical countries particularly Nigeria. The greatest yam growing area of the world, the eastern part of West Africa produces about two-thirds of all the yams grown in the world while Nigeria alone produces almost half the global figure. Three species of yam are usually cultivated, the water yam (D. alata), the yellow yam (D. Cayenesis) and the white yam (D. rotundata). The white yam is the most popular and most widely grown species.

The disintegrating property of yam starch has been reported in the formulation of tablets, containing lactose, sodium hydrogen carbonate and calcium carbonate. The usefulness of yam starch both as a binder as well as disintegrant in the formulation of tablets containing organic medicinal substances was investigated (73). The physical properties of the produced tablets were

compared with those prepared using acacia as a binder and potato starch as binder and disintegrant. Results showed that tablets prepared with starch paste as binding agent gave comparatively lower disintegration time than those prepared with acacia mucilage as the binding agent.

A study has been made on the influence of aging at various storage conditions on the physical stability of sulphadimidine and promethazine hydrochloride tablets with differing formulation containing yam starch paste, gum acacia solution or potato starch paste as binder and dried yam or potato starch as disintegrant. The tablets were evaluated relative to changes in hardness, friability, disintegration time and dissolution rate. Yam starch was found to be a better binding agent than gum acacia because hardness and disintegration time of tablets prepared with acacia were increased on storage at various storage conditions. Yam and potato starch gave almost comparative values as tablet binder and disintegrant (73).

Previously Nasipuri (70) evaluated the physical properties of sulphathiazole and promethazine hydrochloride tablets prepared with cassava starch

as binder and disintegrant after storage for eight months at room temperature. He reported that although the hardness of the tablets decreased to some extent, increase in the friability values were negligible. There was also slight increase in the disintegration times of both types of tablets but that was well below the permitted limit of 15 minutes.

Physical stability of sulphadimidine, chlorphemiramine maleate, sodium bicarbonate and calcium carbonate tablets prepared with cocoyam starch as binder and disintegrant were investigated by Nasipuri (74) after 12 months of shelf - storage at a temperature between 22 - 35°C. It was observed that hardness and disintegration of sodium bicarbonate tablets increased after the storage but there was little effect on the tablets of other drugs. He also studied the effects of various storage conditions on the physical properties (including dissolution rate) of sulphadimidine and chlorphemiramine tablets formulated with cocoyam starch as binder and disintegrant (75). The influence of aging for a period of 8 months on these tablets were compared with similar tablets

prepared with gum acacia and potato starch as binders and potato starch as disintegrant. The starches were found to be better binders than acacia because the values of hardness and disintegration time of tablets prepared with acacia as binder were increased with aging. Potato and cocoyam starches gave almost comparative results as binder and disintegrant. The result of the effect of aging at various storage condition on the hardness, friability, disintegration time and dissolution rate of sulphadimidine and promethazine hydrochloride tablets prepared with yam starch as binder and disintegrant were comparable with similar tablets prepared with gum acacia and potato starch as binders and potato starch as disintegrant.

Recently Jaiyeoba and Opakunle (71) investigated the usefulness of both yam and cassava starches as directly compressible diluents. The cassava and yam starches were granulated using the appropriate starch mucilages as binders. The granulations were found to have excellent flow properties. The placebo tablets prepared with these modified starches (MYS and MCS) were excellent in terms of physical properties such as tablet weight variation, hardness,

friability and disintegration time. Formulations of promethazine Hcl containing MYS and MCS a diluents gave excellent tablets and the two excipients were found superior to MCC as diluent in terms of physical properties of tablets formed. They were also superior to spray dried lactose with respect to disintegration and dissolution characteristics (71).

Also the effects of various granule size fractions of the modified starches (MYS, MCS) on the physical properties of the prepared tablets were investigated by Nasipuri and Kuforiji (76). All the granule size fractions used gave tablets of suitable physical properties. Although yam starch granules produced tablets of slightly greater mean weight with relatively smaller limits of error than cassava starch granules, there were no significant variation in the weight of tablets prepared with different sized granules. There was found to be no definable relationship between crushing strength of tablets and granule size of starch and a decrease in granule size generally produced tablets that showed a decrease in dissolution rate (76).

Odusote and Nasipuri (77) found a correlation between the physical properties of some locally

available starches and their tabletting
characteristics.  Locally available starches fell
in line with the imported starches.

With all the above findings, cassava starch
has not yet achieved a wide spread pharmacopoeal
acceptance compared to maize, rice and wheat starch
and hence its application in the pharmaceutical
Industry is still so limited.  Elmarakby and
Abdullahi(78)  extracted starch from cassava flour
and  used it in the preparation of Acetyl salicylic
acid (Aspirin) tablets, testing its disintegration
capacity, as well as its effects on the other
physical properties of the tablets.  Maize starch
was used for comparison.  Effect of using
different concentrations of cassava starch as a
disintegrant on the physical parameters of aspirin
tablets was also considered.  Effect of Aspirin
granules fineness on the efficiency of cassava as
compared to maize starch was evaluated.   From the
results obtained, cassava starch can be used as a
disintegrant and lubricant in the production of
Aspirin tablet and emphasis should be laid on
using pure starch, right percentage concentration
and suitable compression force to ensure that the

tablets produced pass all the necessary tests.

Cassava is a two species plant of spurge family (Euphorbiaceae) namely the bitter cassava (Manihot esculenta and sweet cassava (Manihot Dulcis). In the preparation of cassava flour, the poison contained in the juice of the bitter cassava (Cyanogenitic glycoside) is rendered harmless by pressing out the juice and exposing the cassava pulp to the sun heat which renders the poison harmless by converting it to prussic acid which escapes. Cassava starch was found to have swelling property which complied with the European pharma-copeia requirements. The rate determining step of the disintegration was the water penetration into the tablet porous structure. Cassava starch was able to develop the capillary structure in Aspirin tablets (78).

It is to be noted that it is only the Brazilian and Portugese pharmacopoeias which included cassava starch in addition to the European phar- macopoea varieties. The pharmaceutical Industries may be using those starches in preference to the . cassava starch in the European countries due to inavailability of cassava in temperate regions. As it is not the case in West Africa, particularly

in Nigeria, it was thought appropriate to extract
starch from this cheap, easily obtainable and
bulk produced commodity and to investigate its
efficacy in the preparation of directly compressible
filler-binders.

1.9          GELATINISATION OF STARCH

The composition of the starch granule accounts
for some of its physical properties like solubility,
viscosity and gelatinisation temperature.  The
granule is composed of linear and branched molecules,
amylose, amylopectin respectively which are
associated by hydrogen bonding either directly or
through water hydrate bridges to form radially
oriented micelles or crystalline areas of various
degrees of order.  The overall strength of the
micellar network, which in itself is dependent on
the degree of association and the molecular
arrangement, controls the behaviour of the starch
in water.

Unmodified starch granules in water exhibit
a limited capacity for absorbing cold water and
swelling reversibly.  Thus intermicellar network
must possess a limited degree of elasticity.  The
subjection of an aqueous suspension of unmodified

starch to the influence of heat or appropriate chemicals weakens the micellar network within the granules by disrupting hydrogen bonds. This permits further hydration and irreversible granule swelling - a process termed <u>gelatinisation.</u>

The gelatinisation of starch in various media is attributed to the chemical affinity of the starch molecules (particularly the hydroxyl groups) for the solvent. When starch is gelatinised in an aqueous medium, the individual granules undergo a series of physical changes of which the most important is swelling. Gelatinisation of unmodified starch can be achieved either by thermal or chemical treatment.

Thermal gelatinisation occurs when an aqueous suspension of unmodified starch is heated. The granules do not change in appearance until a certain critical temperature, the gelatinisation temperature is reached. At this point, some of the granules become highly hydrated and swell to many times their original volumes. Continued heating, particularly in the presence of shear, produces cooked pastes which are mixtures of swollen granules, granule fragments and molecularly dispersed starch molecules leached from the granules (79)..

Microscopical evidence revealed that swelling originates at the periphery of the granules. A loss of birefringence and characteristic polarisation crosses also result.

Gelatinisation is believed to begin in the more accessible and amorphous intermicellar areas of the granules where the bonding is weakest. The degree of association in these amorphous regions differs in individual granules of each starch species, and consequently, the granules gelatinise over a temperature range.

Granule swelling and disintegration during the cooking process are accompanied by significant changes in the viscosity and other rheological properties of the paste (80). Microscopic observation indicated that gelatinisation was directly correlated with granule swelling.

The swelling and gelatinisation behaviour of natural starches varies considerably according to the source and previous history of the samples. However, most starches follow the same general pattern of behaviour. In cold water, most starches are insoluble and swell only to a limited extent (81). On heating, little further swelling occurs until the temperature reaches about 60°C when the

granules start to swell very rapidly with increasing temperature.

The temperature at which swelling starts is called the initial gelatinisation temperature. Apart from swelling, a number of other changes occur. The granules begin to lose their birefringence, the solubility of starch increases due to the loss of low - molecular weight amylose from the granules and the solution becomes viscous and sticky. If the solution of gelatinised starch is sufficiently concentrated it will set to a rigid gel on cooling to room temperature.

The extent of cold-water swelling is governed by the granule structure. The crystallite regions hold the granules together and limit the amount of distortion which a granule can undergo on swelling. The extent of gelatinisation on heating also depends to a large extent on the granule structure.

The various X-ray diffraction patterns elucidated by Katz (82) the A, B, and C patterns indicate that the crystallites themselves differ in structure. Moreover the U pattern found in certain algae starches showed a lower crystalline - amorphous ratio.

Working with wheat starch, katz found two stages of gelatinisation corresponding to two changes in crystallinity. The first stage, which occurs at about 60°C, approximately coincides with the initial gelatinization temperature, when the x-ray pattern changes from the A to the less crystalline U pattern.

The second stage occurs when the starch is heated to about 100°C with a large excess of water. At this stage, the x-ray pattern changes to an amorphous pattern, suggesting a complete break down of granule structure. Although cold water swelling is exothermic, gelatinization is endothermic, since energy is required to break down the crystallites. The complete break down of granular structure coincides with the leaching of ·amylose from the swollen granules.

Different varieties of starch show different swelling characteristics. Granules of potato starch in general tend to disintegrate at lower temperatures than wheat starch granules.

In addition to swelling other changes occur during gelatinisation. The gelatinized granules are able to absorb certain staining materials. The granules lose their birefringence. Among staining

materials, congo red and iodine have been used.
Damaged granules absorb congo red in the cold
(83). Normal undamaged granules will not absorb
congo red unless gelatinised.

Heintz (84) used iodine staining as a
means of following gelatinization. This depends
on the formation of blue complex between dissol-
ved amylose and iodine. Heintz kept starch sus-
pensions at different temperatures and then
filtered. He considered the starch had commenced
to gelatinize when the filtrate gave a blue colour
with iodine. On this basis, he found that rice
starch commenced to gelatinise at 55°C and that
the process was completed at 75°C.

Leach, McCowen, and Schoch (85) investigated
the behaviour of different varieties of starch by
measuring the sediment-weight. With potato starch,
swelling increases very rapidly with increasing
temperature above the gelatinization temperature.
They suggested that potato starch granules contain
weak bonding forces of approximately uniform
strength.

The curve for tapioca starch commences to rise
at almost the same temperature as that of potato

starch, but rises at a slower rate. It was suggested that the bonding forces within the tapioca granule represent a wider range of bond strength than those in potato starch.

Harris and Jespersen (86) heated a known weight of dried starch with a large excess of water in a thermostat for five minutes. The swollen granules were centrifuged off. They found that the amount of sediment produced from a given weight of starch depended on the variety of starch. The sediment weight is considered to be a direct measure of the extent of swelling.

There is much evidence in the literature of interaction between starch and surfactants (78, 87 88, 89, 90). It was suggested that an absorbed layer of surfactant on the granules reduces the tendency of the granules to flocculate, so that although the size of the particles is increased they can infact pack into a smaller volume. Gray and Schoch (89) have studied the effects of a series of fatty acids and surfactants on both the solubility and sedimentation weight. They found that fatty acids reduce both the solubility and the amount of sediment, but no exact correlation was found between the two sets of results.

In general, tuber starches are more easily dispersed than cereal starches and it has been suggested that cereal starches have a more compact structure and a different crystallinity (90). Infact, most cereal starches give an A type X-ray diffraction pattern, whereas tuber starches give a B - pattern.

There is evidence that the ratio of amylose to amylopectin influences swelling. For example, Schoch and Maywald (91) found that waxy starches which contain almost 100% of amylopectin have similar initial gelatinization temperature to their normal blue staining conterpacts but that the waxy granules swell more rapidly at higher temperatures and are more fragile.

The nature and extent of non-carbohydrate materials is also important. for example, Sauec (92) has suggested that the presence of phosphate in the form of a phosphate ester is partially responsible for the viscometric behaviour of starch. It is known that the presence of traces of protein (93), fats, and electrolyte also affect swelling.

The swelling characteristics may also be modified by intense drying. It has been mentioned that drying of potato starch results in a lowering of the degree of crystallinity. With corn starch, Whistler and his associates (94) have shown that air drying reduces the swelling tendency. They showed that drying produces cavities in the granule. This alone would increase swelling, but they consider that the main effect is a 'Case hardening' of the granule shell.

Thin - boiling starches may be produced by depolymerization which can be brought about by a number of methods, including alkali and acid hydrolysis, enzyme action, and irradiation. Warm dilute acid weakens the polymer network (95) so that when soaked in hot water the granules fall apart to give a paste of greatly reduced viscosity. It was found that wheat - starch granules when treated with 0.2 molar hydrochloric acid at 45° C are degraded to a lesser extent than potato starch treated similarly.

In addition to chemical cross - linking and depolymerization, the properties of starch may be modified by esterifying some of the hydroxyl

groups (96). Ethylation of corn starch increases the paste transparency due to a reduction in the tendency for molecular association by hydrogen bonding between hydroxyl groups.

## 1.10   EVALUATION OF PROPERTIES OF DIRECT COMPRESSION FILLER BINDERS

All the parameters enumerated in section 1.5 have been used to evaluate the properties of direct compression filler binders. These parameters include, granule size, hardness, friability, granule desities, flow characteristics and reworking potentials.

Chalmers and Elworthy (97) noted that the addition of micro crystalline cellulose decreased bulk density and increased bed porosity for oxy tetracycline granulated with water.

Eaves and Jones (98) described the effect of increasing moisture content on the packing properties of various particulate materials. These authors found that the inherent cohesiveness of the bulk solid plays an important role in determining the effect of moisture on packing variation in compression properties of Elcema 9250 (98).

Many different types of angular properties
have been employed to assess flowability (99,100).
Other methods of determining the repose angle are
given by Pathrirana and Gupta (101). The angle of
repose is best suited for particles > 150 um (95).
In this size range, cohesive effects will be
minimal and the coefficient of friction will be
largely dependent upon the normal component of
the weights of the test specimens. Values for
angle of repose < 30° generally indicate a free -
flowing material, and angel < 40° suggest a
poorly flowing material (102). Nelson found that
as the percentage of fines (100 mesh) was
increased, the repose angle increased. Gold et al
report on the effect of small concentrations of
talc, magnesium stearate, silicon dioxide, and
starch on the repose angle of aspirin, and spray -
dried lactose particles. Other reports of
interest are those of Wash et al (103). The
effect of moisture on repose angle has been noted
by some researchers (103, 104, 105, 106).

Particle shape has been found to have an effect
upon the angle of repose. Ridgway and Rupp found
that as the shape coefficient of sand particles

increased (particles becoming more irregular), repose angle increased (107).

Another parameter of interest in predicting flow properties of a material is a quantity known as the materials flow factor (100, 101). The flow factor measurements from shear cell testing has been used for assessing the effect of glidants on the flowability of cohesive pharmaceutical powders (102 - 106).

Generally the granulation properties of directly compressible filler binders may affect quality features of the tablets made from them. Such properties like compressibility, unit dose accuracy, porosity, hardness, friability, capping tendencies, disintegration, and dissolution rate are readily influenced. A single granulation property can influence many different tablet properties. Therefore for successful direct compression of tablets, the characteristics of the binder - fillers must be accurately defined, since they primarily dictate the quality of the final tablets.

## 1.11    PROPERTIES OF COMPACTS OF DIRECT COMPRESSION MATERIALS

Pharmaceutical tablets or compacts are evaluated for their chemical, physical and biological properties.

Until recent decades, only the chemical stability of solid dosage forms was recognised as an important stability consideration. Pharmaceutical scientists now understand that various physical properties of tablets can undergo change under environmental or stress conditions, and that physical stability, through its effect on bio-availability in particular, can be of more significance and concern in some tablet systems than chemical stability. In evaluating a particular formation or establishing an expiration date for a product, the stability of all three classes of properties must be considered. These include, the physical properties, chemical properties and the bioavailability.

These properties are generally size, shape, colour, unique identification markings, hardness, weight uniformity, friability, general appearance, disintegration, weight variation, potency and

content uniformity, dissolution, porosity, and physical stability.

The control of the size and shape of the tablet is essential to consumer acceptance, tablet - to - tablet uniformity and trouble - free manufacturing (114).  In 1971, the Academy of pharmaceutical sciences published its IPT standard specifications of Tabletting Tools (114). In this publication, the IPT approved dimensional and tolerance specifications for tableting tools and made recommendations for the inspection and control of tools.  With standardized tooling, the length and width dimensions (or diameter) and the shape become constant values for the tablet, leaving the thickness of the tablet as the only variable (114).

A tablet requires a certain amount-of-strength, or hardness to withstand mechanical shocks of handling in its manufacture, packaging and shipping. Historically, the strength of a tablet was determined by breaking a tablet between the second and third fingers with the thumb acting as a fulcrum. If there was a "sharp" snap, the tablet was deemed to have acceptable strength (108).  More recently,

however, tablet hardness has been defined as the force required to break a tablet in a diametrical compression test. To perform this test, a tablet is placed between two anvils, pressure is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed "tablet crushing strength". Several devices operating in this manner have and continue to be used, to test tablet hardness: the Monsanto tester (109), the strong - Cobb test (110), the Pfizer tester (111), the Erweka tester (112), and the Heberlein tester (113). Unfortunately, the several testers do not produce the same results for essentially the same tablet. Literature review showed that operator variation, lack of calibration, spring fatigue, and manufacturer variation contribute a great deal to the lack of uniformity (114). Even more sophisticated testers designed to eliminate operator variability have been found to vary (114).

Lubricants can affect tablet hardness when used in too high a concentration or mixed for too long a period. The lubricants will coat the granulation particles and interfere with tablet bonding (115, 116).

A hardness of about 5.0 kg is probably minimal
for uncoated tablets (117) there should be a
balance between a minimally acceptable tablet
hardness to produce an adequate friability value
and a maximally accepted tablet hardness to achieve
adequate tablet dissolution.

Another measure of a tablet strength is its
friability.  Friability is related to a tablet's
ability to withstand both shock and abrasion
without crumbling during the handling of manufac-
turing, packaging, shipment, and consumer use.
A laboratory friabilator tester known as the Roche
Friabilator has been developed (118).  This device
subjects a number of tablets to the combined
effects of abrasion and shock by utilizing a
plastic chamber which revolves at 25 rpm, dropping
the  tablets a distance of 6 in with each revolution.

Tensile strength is preferred to tablet
crushing strength.  The crushing strength of a
tablet greatly depends on its dimensions (119).
The mode of fracture of a tablet under load would
depend on its strength and dimensions.  Different
modes of tablet fracture may account for the
variation in crushing strength when different

hardness testers are used (120). The diametral fracture test has been extensively used in evaluating the strength of compacts (119). Providing the compact under tension fractures diametrally, the tensile strength S, of flat compact can be calculated from the equation:

$$S = \frac{2\ P}{\Pi D T}$$

where P is the breaking load, D & T are the diameter and thickness respectively.

In most cases, the tensile strength of a compact increases as the compaction pressure is increased (119, 121, 122). It has been reported that the tensile strength of Aspirin - Encompress compacts increased as the proportion of Emcompress increased in the mixture (122).

The ability of a powdered solid to undergo reworking can be evaluated by compressing it at varying pressures. The variation of tensile strength with compaction load is determined after which the compact is milled to the original particle size and recompressed at the initial compaction load. The variation of tensile strength with the load is reassessed. The variation is presented on a graph and the areas under the curves are measured.

The reworking potential (RP) can be obtained from the equation R. P. $= \frac{A1}{A2}$ x 100 where A1 is the area under recompression curve and A2 is the area under the first compression. RP affords a method of comparing the strength of tablets made from different powder mixture under a similar range of pressures.

Direct compression property of materials is often attributed to their possession of a characteristic structure which may be lost on compression. This, may be particularly so, if like lactose, the materials consolidate by fragmentation (123). It would be a source of financial loss in production if defective tablets cannot be reworked by communition and recompression. It was noted with micro crystalline cellulose – dicalcium phosphate blends that tablet strength and friability were both reduced by the extent of precompression. A higher level of reduction in tablet strength was reported at higher pressures (123). Similar results were reported for Avicel pH 101, spray dried Lactose mixtures (123).

After ingestion, the first important step for most tablets is the breakdown of the tablets into

smaller particles or granules. This process is known as disintegration. The time that it takes a tablet to disintegrate is measured in a device described in the United States pharma-copeia . (124) Wagner (125). It has been established that one should not expect a correlation between dis- integration and dissolution (125). However, since the dissolution of a drug from the fragmented tablet appears to partially or completely control the appearance of the drug in the blood, disinteg- ration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as an in - process control test to ensure lot - to - lot uniformity (125).

The measurement of the disintegration of a tablet has been attempted in several ways other than by the official test. Rubinstein and Wells (127) followed the disintegration of phenylbuta- zone tablets by the measurements of the surface area of the generated particles in a coulter counter model TA. Thermal analysis has been used by Wakai et al (128), not only to measure the disintegration of sugar - coated tablets but to follow the dissolution of the sugar components, the

inhibitive action of the barrier coat, the
release of the vitamins from the core, the reaction
of the calcium carbonate with the acid media, and
the reaction of the ascorbic acid with the metal
ions in solution.

The United States Pharmacopoeia(124) has long
had a device to test disintegration. To be in
compliance with USP standards, the tablets must
disintegrate and all particles pass through the
10 - mesh screen in the time specified. The
operator should be aware that the media used, the
temperature of the media and the operator recording
the results can have a significant effect on
disintegration times (126). In addition, many
factors involved with a tablet's formula and method
of manufacture can affect the disintegration. The
nature of the drug, the diluent used (127), the
binder, the amount of binder, and the method of
incorporation can have an influence in tablet
disintegration (128 - 130). The type and amount
of disintegrating agent can also have a profound
effect on disintegration times (130, 131). The
presence of excess amounts of lubricants or
overly mixed lubricated mixes can cause an increase

in disintegration times. The compaction pressure used to make the tablets also influences the disintegration. In general, disintegration times increase with an increase in pressure (131).

Madan (126) lists several design deficiencies of the USP apparatus that do not allow the disintegration test to correlate better with in vivo conditions.

A tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. To check that a tablet contains the proper amount of drug, the weight of the tablet being made is routinely measured. To help alleviate this problem, the United States pharmacopeia (124) provides limits for the permissible variations in the weights of individual tablets as a percent of the average weight of the sample. The weight variation test is not sufficient to assure uniform potency of tablets of moderate to low - dose drugs, in which excipients make up the bulk of the tablet weight (131).

The causes of weight variation can be separated into granulation problems and mechanical problems. If everything is working well

mechanically, the weight can be caused to vary by a poorly flowing granulation, which causes a spasmodic filling of the dies. If the granulation particle size is too great for the die size, the dies will not be uniformly filled, causing weight variation (131). Ridgway and Williams (132) found for a uniform size granulation that as the particle shape became more angular, the weight variation increased.

In addition to the potency and content uniformity of solid pharmaceutical dosage forms, a new concept of potency is not the amount of drug that is in the product and determinable by assay, but the effective drug content which is the amount of drug in the product that is present in an absorbable or bioavailable form. Many controlled studies in humans (125) indicate that the effective drug content of solid dosage forms is frequently not 100% of the assayable drug content of the product but may be as low as 50% or less the labelled and assayed drug content.

The utility of using in vitro results for dissolution has been presented in many literature for 15 - 20 years (125). Many different

dissolution test apparatus have been reported
on in the literature (124). Significant
differences in dissolution rate profile have
been reported.

CHAPTER   2

CHARACTERIZATION OF MATERIALS

AND

EXPERIMENTAL METHOD

## 2.1                  MATERIALS

Starches were processed from natural sources and obtained locally. The following were used to prepare the starches: Cassava (Manihot utilissima polh) from the rhizomes uprooted fresh from Agege farm; Tubers of Yam (Dioscorea Rotundata); Tubers of Potato (Solanum tuberosum), the caryopsis of maize (Zea mays); all obtained from Mile 12 Market, Lagos.

Spray - dried lactose was obtained from British Drug Houses Chemical Limited, Poole, England through Nigerian Hoechst Ltd. Ancel pH 102 (Asabi chemical Industry Co., Ltd.) was obtained through Roche (Nigeria) Ltd.

- Polyvinylpyrrolidone (PVP, K29 - 32) and Acacia powder B.P. were supplied by Courtin and Warner Ltd, Lewes, Sussex, England.
- Gelatin B.P. was obtained from Evans Medical Ltd. Speke, Liverpool.
- Paracetamol (Marsing & Co. Ltd.) was obtained through the Manufacturing Laboratory, Yaba (Federal Ministry of Health).

## 2.2            EQUIPMENT

### 2.2.1           EQUIPMENT FOR PROCESSING

The mixer was Kenwood Chef Mixer (Thorn - EMT Domestic Appliances, Great Britain).

Hammer Mill (Peppink Deveeter Hammer Mill, Heemaf, Starlet, England).

Hydraulic Press (Schimadzn Corp., England). Oscillating Granulator (Jackson and Crockatt No. 6, Jackson and Crockatt Manufacturing Co. Ltd., Glasgow, Scotland).

Equipment for Testing include: Endecott Test Sieves, an Endecott Test Sieve shaker, a Rotap machine (made by Pascall Engineering Company Limited, Crawley, England).

A Model of Manesty Disintegration Time Testing Unit an Erweka Disintegration Time Testing Unit, 1980.

A Roche friabilator, and an Ohaus Moisture Determination Balance.

Dissolution rate Apparatus (Paddle Dissolution Apparatus Distec Inc. Model 2000), and an Ultra-Violet Spectrophotometer by Philips (Pu 8620 LV/VIS/NIR).

Micrometer screw Gauge by Moore and

Wright, Neil Tools Limited, Napier Street,

Scheffield S11 8HB,England.

## 2.3   PREPARATION AND EVALUATION OF PURE STARCH.; THE GRANULATIONS AND THE COMPACTS

### 2.3.1   PREPARATION OF PURE STARCHES FROM THE NATURAL SOURCES

Tubers of Manihot utilissima were dug up and immediately (within two hours of uprooting) peeled, washed and milled using a thoroughly washed local commercial cassava mill in the Iju Agege area of Lagos State.

The milled cassava was dispersed in copious amounts of potable water.  The dispersion was passed through sieves of mesh size 44 and 60, successively, twice, to remove the fibres of cassava root (otherwise known as the shaft). The milky starch suspension obtained was then filtered through a fine Muslin bag before being allowed to settle.

On settling, the supernatant fluid was decanted and discarded.  The cassava starch was resuspended in potable tap water and allowed to settle before decanting.  This process was

repeated twice with distilled water.

The final dispersion was tested for Hydrocyanic acid using sodium picrate paper and pH paper respectively. The sodium picrate paper did not react and the pH was found to be approximately neutral (i.e. pH = 6.8). After the final decantation, the starch was dried (within 24 hours after extraction) in the oven (Jovan type) at a temperature of 60°C for 3 days. The moisture content was determined and was found to be 6.0% W/W. The starch was passed through a sieve mesh 85 and stored in non-reactive, tightly closed plastic containers.

In like manner, starches were extracted from yam, potato tubers and maize caryopsis.

## 2.3.2    DETERMINATION OF STARCH PROPERTIES

## 2.3.2.1    DETERMINATION OF GRANULE SIZE AND GRANULE SHAPE

A little starch was mounted on a microscope slide using lactophenol. The slide was viewed under the microscope at a magnification of x 10, x 40 and the slide preparation was adequately adjusted to allow good dispersion of granules prior to measurement. The hilum and transverse striations were also brought into sharp focus.

The eyepiece micrometer used in the measurement of the granule size was pre-calibrated using a 1 mm stage micrometer (Graticules Ltd., Kent, England) at x 10 (low-power) and x 40 (high power) objective magnifications. The calibrations are as stated below:

Low Power (x10) Calibration:

(a)  85 eyepiece divisions (e.p.d) = 1000 µm

$$1 \text{ e.p.d.} = \frac{1000}{85} \text{ µm}$$

$$= 11.76 \text{µm (a)}$$

(b)   43 e.p.d.                         $= 505\ \mu$

       1 e.p.d.                         $= \dfrac{505}{43}\ \mu$

                                        $= 11.74\ \mu$  (b)

(c)   20 e.p.d.                         $= 235\ \mu$

 !   1 e.p.d.                         $= \dfrac{235}{70}\ \mu$

                                        $= 11.75\ \mu$  (c)

Average value for 1 e.p.d.     $= \dfrac{a + b + c}{3}$

                                        $= 11.75\ \mu$

The stage micrometer was replaced by the prepared slide and twenty granules were carefully measured using a biased selection of larger, medium - and small-sized granules from different view fields. All the granule sizes were then converted to microns and the range was calculated.

## 2.3.2.2    DETERMINATION OF SULPHATED ASH

Sulphated ash of the starches was determined following the B.P. 1980 method as follows: A silica crucible was heated to redness for 10 minutes, and

allowed to cool in a desiccator and weighed. IG
of the starch was accurately weighed in the cruci-
ble. 2 ml of M/1 sulphuric acid was added, heated
on a water bath and then over a flame to about
600°C. The heating was continued until all black
particles have disappeared and was then allowed
to cool. A few drops of M/1 sulphuric acid was
added, heated to ignition as before and allowed
to cool. A few drops of 2M ammonium carbonate
was added, evaporated to dryness and cautiously
ignited. It was then cooled, weighed, again
ignited for 15 minutes. The whole procedure was
repeated until two successive weighings did not
differ by more than 0.5mg.

### 2.3.2.3. DETERMINATION OF AMYLOSE CONTENT

Two methods were used, and the results
compared. The first method utilizes the principle
of aqueous leaching while the second method
utilizes the aqueous dispersion technique.

## METHOD I     (Ref. 29)

1 Gm. starch was accurately weighed into a round - bottomed flask. 1000 ml distilled water was added and boiled for 1 hour. Liquefied phenol (B.P.) was freshly made and 2 ml (2.12g) was added. The flask was cooled down in a running tap water until cold.

On cooling slowly, the amylose combines with the fractioning agent (liquefied phenol) to form a crystalline complex, which separated out. The separation was allowed to take place overnight, and then the supernatant liquid was separated by filtration. The crystals were washed with water and the washing was added to the filtrate. The crystals on the tarred filter paper was allowed to dry in an oven at 50°C for 4 hours and then cooled, and reweighed. The weight of the dry crystals (amylose complex) was obtained by subtracting the weight of the filter paper.

The weight of the phenol left in the filtrate was determined quantitatively (B.P. '73), and the weight of the phenol used to crystallize the complex was calculated.

Using the equations:

$$Y = A - X$$

$$M = B - Y$$

where  M  =  weight of Amylose

B  =  weight of complex

A  =  Total phenol used

X  =  Phenol in filtrate

Y  =  Phenol in Amylose Complex

The experiment was repeated and the average of M was taken to be the weight of Amylose in IG starch.

## DETERMINATION OF AMYLOSE CONTENT
## METHOD II (GATIN-GRUZEWSKA  METHOD)

1G    starch was placed in a round bottomed flask and 100 ml 1% NaoH solution was added.  The mixture was kept aside until a smooth and clear mucilage was formed.  Using phenol phthalein as the indicator, the mixture was neutralized with glacial acetic acid, drop wise until the pink colour turned colourless.   The precipitate (A) that formed concurrently is said to be amylopectin, while the filtrate (B) is said to contain amylose

amylopectin was filtered through a weighed filter paper, and was washed to remove traces of acid or alkali, discarding all washings. The amylopectin was dried in an oven to a constant weight at 70°C.

A small amount of alcohol (10 ml) was added to the filtrate (B) to crystallize the amylose. Again the amylose crystals was filtered using a tarred filter paper, dried and reweighed, to get the actual weight of amylose in 1 Gm. of the starch.

## 2.3.3   PREPARATION OF GRANULES BY WET GRANULATION

200 Gm. batch of starch powder was premixed for 2 minutes in the Kenwood Chef Mixer. Pure distilled water was used as the binder. Addition was made in four aliquots at an interval of 5 minutes. The total massing time was 20 minutes.

The wet mass was forced through a mesh 16 screen on an oscillating granulator. The wet granules were then dried in a tray dryer at a drying temperature of 50°C for $3\frac{1}{2}$ hours to a moisture content of about 12.0%. After drying,

the granules were rescreened though 1 mm mesh
screen. The resulting granules obtained were
stored in well closed jars.

Variables studied include volume of binder,
temperature of binder, binder concentration and
binder type.

### 2.3.3.1        EFFECT OF BINDER VOLUME

To determine the effect of binder volume,
water was used as the binder.  For the same amount
of starch powder, various quantities of water expressed as
(20 - 60% W/W) at room temperature were used to
prepare the granules in the same way as described
above.

### 2.3.3:2          EFFECT OF TEMPERATURE

To study the effect of temperature of the binder on
granular properties, same volume of water at
various temperatures were used as the binder to
prepare the pure starch granulations.

### 2.3.3.3      EFFECT OF BINDER CONCENTRATION

To determine the effect of binder concent-
ration on granular properties, starch mucilages
of various concentrations, 2% W/W, 5% W/W,
10% W/W, 20% W/W were used as binders to prepare
starch granulations.

Mucilages were made by suspending the required
weight of starch in an equal weight of cold water
aading boiling water with stirring to make-up the
required weight to form the transparent mucilages.

The binding solution was added in four
aliquots. The total massing time was 20 minutes,
massing for 5 minutes after each addition.

### 2.3.3.4      EFFECT OF MOISTURE CONTENT

To determine the effect of moisture content
on granular properties, same volume of water
at room temperature was used as binder to prepare
the starch granulations. The drying time was
varied and samples taken and stored after $\frac{1}{2}$hr, 1hr, 1$\frac{1}{2}$hrs,
2hrs, 2$\frac{1}{2}$ hrs, 3.0 hrs, 3$\frac{1}{2}$ hrs. Moisture content of
samples were then determined using the moisture
balance.

2.3.4    PREPARATION OF PREGELATINISED STARCH

200 Gm.,      pure starch was suspended
in 500 ml water at room temperature.  The sus-
pension was heated to 68 - 70°C for about  15
minutes with continuous stirring until the
starch gelatinised.  Another batch was prepared
at a higher temperature of  98 - 100°.

The pastes obtained were thinnly spread to a
thickness of about 0.05 inches on stainless steel
trays and dried in a hot air oven at 60°C for 5 days
until the moisture content was 2.0% W/W.

The flakes obtained were milled  to fine
powder using the hammer-mill.  The pregelatinised
starch thus obtained was fractionated into various
particle sizes using assorted sieves.  Particle
sizes of 120 $\mu$m, 180 $\mu$m, 250 $\mu$m and 360 $\mu$m were
chosen for further experiments.

All the starches studied were treated in the
same way.

2.3.5    CHARACTERIZATION OF PREGELATINISED STARCH

The pregelatinised starch obtained from
cassava, yam, potato and maize were compared with

their pure untreated counter-parts using the
following.

### 2.3.5.1  MACROSCOPIC DESCRIPTION

The colour, odour, presence of specks were
observed for the pregelatinised starch made. The
dispersability in cold water was also studied.

### 2.3.5.2  MICROSCOPICAL DESCRIPTION

A pin - head size of pregelatinised starch
was mounted with lactophenol on the microscope
slide, and examined under polarized and non-
polarized light both at low and high magnifications.
(x10, x40).

### 2.3.5.3  REACTION TO DYES

The microscopic sample on the slide was
stained separately with a drop of iodine, and
congo-red, and again mounted using lacto-phenol.
Samples were examined under polarized and unpolari-
zed light x 10, and x 40 magnifications. The
observations were compared with those obtained
with the original starch.

## 2.3.6 THE EFFECT OF PREGELATINISED STARCH COMPONENT ON THE PHYSICAL PROPERTIES OF STARCH BLEND

Pure starch was passed through mesh size 85. The corresponding pregelatinised starch was also passed through mesh size 85 and was admixed with pure starch at various concentrations; 20% W/W, 40% W/W 50% W/W, 60% W/W 80% W/W and 100% W/W. Using 200 G batch size, the blend was mixed in the Kenwood Chef mixer for 2 minutes in the dry form. 80 ml distilled water at the room temperature of 28°C was added in 4 aliquots and was massed for 5 minutes after each addition, the total massing time being 20 minutes. The moist mass was force-screened through mesh 16 and dried in an air oven at 50°C for $3\frac{1}{2}$ hours. The moisture content of the various granulations ranged between 12.0 to 14.0%. The samples were subjected to various tests and the results obtained are seen in Tables 3.3.2.1 - 3.3.2.6.

### 2.3.7 THE EFFECT OF PREGELATINISED STARCH PARTICLE SIZE ON THE PHYSICAL PROPERTIES OF STARCH BLEND

The various particle sizes of starch pregelatinised at 68 - 70°C were blended with pure starch at various concentrations. The same procedure was done for starch pregelatinised at 98 - 100°C. All the batches were granulated as described in section 2.3.6. The granulations were subjected to various tests and the results are presented in Figs.3.3.2.1 - 3.3.2.9.

### 2.3.8 THE EFFECT OF PREGELATINIZATION TEMPERATURE ON THE PHYSICAL PROPERTIES OF STARCH BLEND

180 μm sized starch pregelatinised at 68 - 70°C and 98° - 100°C were used to study the effect of pregelatinization temperature on the physical properties of starch blend.

Same portion of the 2 batches were blended with various concentrations of (180 μm) pure starch. The blending was achieved using the Kenwood Chef Mixer as described previously. All the batches were granulated as described in section 2.3.6.

The granulations were subjected to various tests and the results are presented in Figs. 3.3.2.1 - 3.3.2.9.

## 2.3.9    EVALUATION OF GRANULAR PROPERTIES

The granulations obtained from the different experiments were evaluated to determine the following:

1.    The average granule size.

2.    The flowability of granules.

3.    The packing densities.

4.    Granule strength and granule friability.

## 2.3.9.1    GRANULE SIZE ANALYSIS

Size analysis of the granules was performed by the sieve method.  Endecott Test Sieves with aperture sizes ranging from 75 um to 1,500 um were weighed and stacked on one another with aperture size decreasing from top to bottom.  The stack was placed on a previously weighed receiving container and all were firmly secured onto an Endecott test sieve shaker after placing 100 G of granule sample in the top - most sieve and

covering tightly to avoid spillage of the material.
The shaker was made to vibrate for 10 minutes,
after which the weight of granules retained on each
sieve was determined by substracting the weight of
sieve when empty from the weight of sieve plus
granule fraction retained on it.

From these values, the cumulative percentage
weight oversize was obtained for each size fraction.
The size distribution curve was plotted and the
average granule size was determined by taking the
granule size at which 50 percent by weight of the
granules were oversize.

### 2.3.9.2    DETERMINATION OF DENSITIES

Loose and Bulk Density determinations were
performed simultaneously for all granule samples
using the following method.

### 2.3.9.2.1    LOOSE DENSITY

A known weight of the sample was slowly poured
into a measuring cylinder with an internal diameter
of 55 mm. The latter was inclined at about 45° when
the sample was poured into it.

It was later positioned vertically on a
horizontal plane and lightly tapped manually for
two times through a distance of 2 inches. The
volume of the sample was recorded and the Loose
Density was calculated from the following formula:

Loose Density $= \dfrac{\text{Sample weight (g)}}{\text{Sample volume (ml)}}$

The mean of five determinations was taken as the
Loose Density of the material.

### 2.3.9.2.2      BULK DENSITY

The Bulk Density was determined immediately
after the Loose Density using the same sample. The
measuring cylinder was tapped about 300 times
(until a constant volume is obtained), through a
distance of 2 inches in the apparatus designed
during the course of this project. (Fig. 2.3.1.)

Care was taken to pad the measuring cylinder
with cotton wool both at the middle closest to the
barrier and at the bottom. The pads were necessary
to absorb some of the shock from the hefty taps of
the apparatus. The volume of the sample was recorded.

Bulk Density was calculated from the following formula:

Bulk Density $\quad = \quad \dfrac{\text{Sample weight (g)}}{\text{Sample volume (ml)}}$

after tapping 300 times

The mean of five values was recorded.

2.3.9.2.2 (a)     DESCRIPTION OF THE DESIGNED
                  APPARATUS FOR BULK DENSITY

This consists of a wooden cubic box of 14
inches wide, the inside of which contains a parti-
tion, 2 inches high from the bottom (containing 2"
wooden block as seen in Fig. 2.3.1).  The box is
opened on one side to permit removal of the piece
of wood when the box is in use.  Right in the centre
of this box is carved a cylindrical hole 2" diameter
to hold a 500 ml measuring cylinder.  When in use,
200g of granules is placed inside and tapped as
described under loose and bulk densities.  The inner
surface of the barrier and the inner surface of the
lower part of the box were lined with pads to
absorb some of the shock from the hefty taps of the
apparatus. (Fig. 2.3.1)

2.3.9.2.3     APPARENT DENSITY

The apparent Density (Pg) of the granules was
determined by granule displacement of benzene in
a specific gravity bottle.

The granules were de-aerated by subjection of
the bottle to a vacuum for 10 minutes after placing

Fig. 2.3.1.    Bulk Density Apparatus
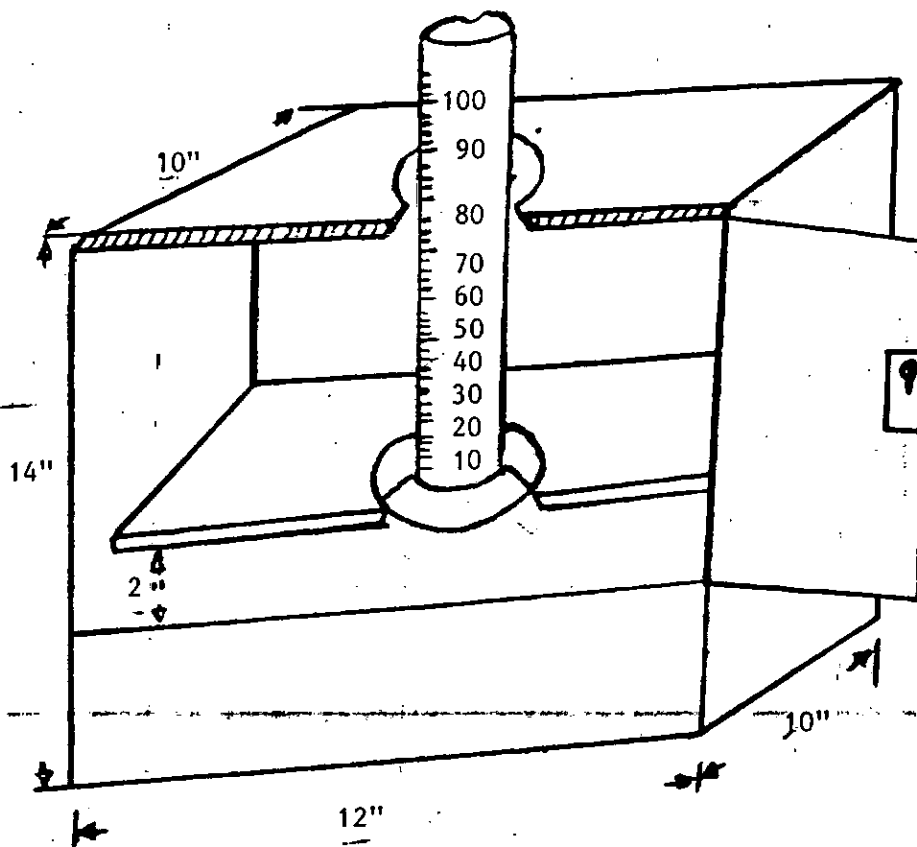
a known weight of granules and enough benzene to submerge it in the bottle. The determinations were carried out at the room temperature. The following measurements were taken:

(i)   Weight of specific gravity bottle   (Wo)

The bottle was washed clean inside and outside with water, alcohol (90 percent) and lastly benzene. It was allowed to dry and weighed on an analytical balance (Sauter - balance) with a sensitivity of about $10^{-5}$ G. The weight was tarred to zero reading.

(ii)  The weight of water filling the bottle was recorded ($W_1$).

(iii) The bottle was dried and the weight of benzene filling the bottle was also recorded ($W_2$). The specific gravity (sb) of benzene was calculated from these values as follows:

$$\text{Specific Gravity of benzene (sb)} = \frac{\text{Weight of benzene } (W_2)}{\text{Weight of water } (W_1)}$$

(iv)  Weight of granules used in the test ($W_3$).

(v)   Weight of granules plus benzene after

de-aeration and making up to volume with
benzene $(W_4)$.

The Apparent Density of the granules was
.calculated from the following relationship:

$$Pg = \frac{W_3}{W_1 - \frac{(W_4 - W_3)}{(W_2/W_1)}}$$

### 2.3.9.3       HAUSNER QUOTIENT

This is the ratio of the Bulk Density and the
Loose Density.

### 2.3.9.4       GRANULE FRIABILITY

Some quantity of the granules were passed
through mesh size 85. Twenty grammes of the granules
retained by mesh size 85 were subjected to rotate in
a Roche friabilator at 25-r.p.m. for 4 minutes.
The granules were taken out and passed again through
sieve of mesh size 85. The loss in weight was

calculated and the percent friability was determined by using this formula:

$$\text{Friability} = \frac{\text{Loss in wt.}}{\text{Original wt.}} \times 100\%$$

### 2.3.9.5       GRANULE HARDNESS

Granule hardness was tested using an apparatus (Fig. 2.3.2) which simulate the Beam balance designed by Pilpel and Harwood (133).

The modified beam balance comprises of 2 horizontal plates on both sides.

The experimental 'granule' was carefully placed in the middle of the left plate. A glass pan was gently placed on top of the granule with the concave side on the surface. Lead shots were gradually placed one by one on the glass pan, until the granule broke (seen through a thimble).

All along, the other side of the beam balance was counter - loaded with some lead shots.

The total weight on top of the granule was taken to be the granule strength.

Fig. 2.3.2.          Granule Strength Determination Apparatus
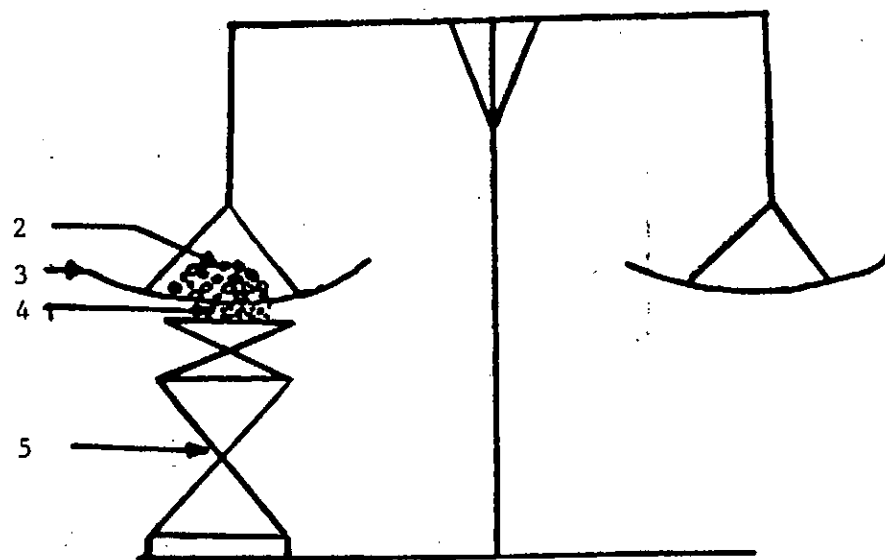


Harwood and Pilpel
Apparatus (1968)
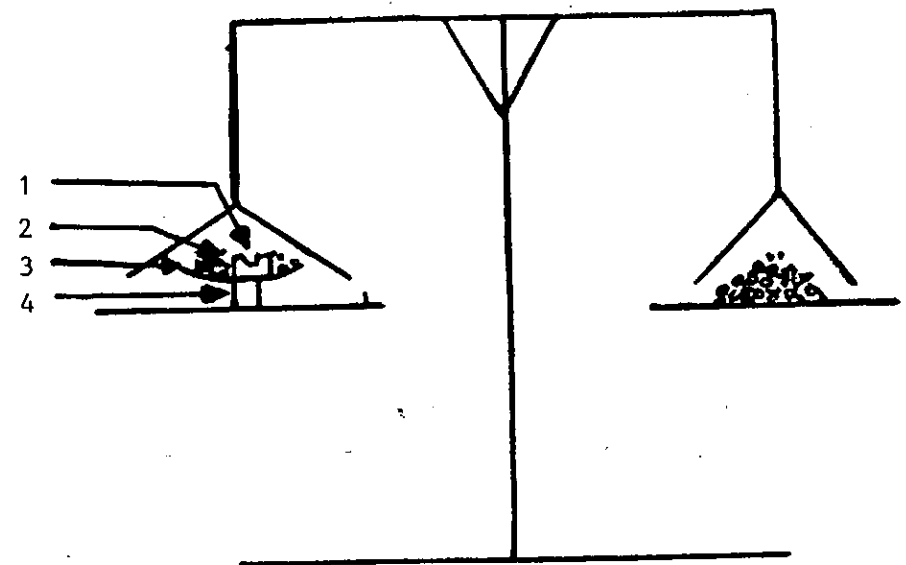
Modified Beam Balance

1. Thimble    2. Lead-shots    3. Petri-dish,    4. Experimental granule    5. Lab-Jack

### 2.3.10    PREPARATION OF STARCH COMPACTS

500 mg. of granule portions were compressed at various pressures to produce flat 13 mm diameter compacts using  hydraulic press (Schimadzn Corp., England) at a controlled relative humidity and temperature of the room.  The compacts were kept in air-tight jars at room temperature for 4 hours to allow for elastic recovery and then evaluated as follows:

### 2.3.11    EVALUATION OF COMPACT PROPERTIES

The physical properties of the compacts include crushing strength, friability, bulk density, disintegration time.

These tests were performed on the compacts of all batches of the granulations as well as on the compacts of the direct compressible diluents.

### 2.3.11.1    CRUSHING STRENGTH

The crushing strength of a tablet is its resistance to a diametrically applied pressure (Force/Unit area).  This is a measure of the mechanical strength of compacts.

The crushing strength of the compacts in this

study was determined using the schleuniger
electronised Tablet Hardness Tester.   The mean of
five readings was taken as the crushing strength
of that batch of compacts.

### 2.3.11.2                     FRIABILITY

The friability of a tablet is the resistance to
abrasion due to falling or rolling in contact with
similar tablets.   This property, like hardness or
crushing strength is also a measure of mechanical
strength of tablets as well as a measure of inter-
particulate cohesiveness. (121)

Friability was measured by subjecting five
compacts of known weight to a controlled series of
falling shocks in a Roche friabilator, the drum of
which was made to rotate at 25 revolutions per
minute for four minutes.   The compacts were then
taken out, brushed lightly to make them free from
powdered particles and reweighed.   The loss in
weight as a percentage of the original weight of
the compacts provides the numerical value,

$$\text{Friability} = \frac{\text{weight loss}}{\text{original weight}} \times 100\%$$

### 2.3.11.3       THE BULK DENSITY

The Bulk Density was determined by weighing
a tablet or compact and measuring its thickness
and diameter using Micrometer screw gauge. This
was possible because the compacts were compressed
with flat - faced non - bevelled punches.

Apparent Volume     $= \Pi r^2 t$

Where  $\Pi$         $= 3.142$ (a constant)

         $r$     $=$ radius of the compact in

                    centimetres

         $t$     $=$ thickness of the compact in

                    centimetres

$$\text{Bulk Density/Apparent Density} = \frac{\text{Tablet weight} \quad (Gm)}{\text{Apparent Tablet volume} \ (ml)}$$

### 2.3.11.4       DISINTEGRATION TIME

The compacts were tested for disintegration
time according to B.P 73 specifications. Five
compacts were put in a basket of the Manesty
Disintegration time testing unit and tested for
disintegration using distilled water at 37°C ± 1°
as the medium.

### 2.3.11.5     REWORKING POTENTIALS

50 (500 mg) compacts were evaluated by measuring the crushing strength, friability, disintegration Time, thickness and Diameter. Similar compacts from the same batch were crushed and forced screened through mesh 85 (the original granule size before first compression). The fine granules thus obtained were again compressed for 2 minutes using the same compressional pressure of 1,000 kg. The 500 mg compacts obtained were again evaluated for crushing strength, friability, disintegration time, thickness and diameter. The results obtained are shown in table 3.3.4.

### 2.3.12     PREPARATION OF TABLETS

Tablets of paracetamol were made to contain 50 mg paracetamol in 500 mg of the compact by direct compression, using cassava starch blend containing 0%, 60%, 80% and 100% W/W starch pregelatinised at 98 - 100°C (180 μ particle size) as diluent.

Similar tablets containing 50 mg paracetamol were also made using Avicel pH 102 and spray dried lactose as diluents. The tablets were made using the

hydraulic press without a lubricant at 1000 kg $Cm^{-2}$ pressure.

### 2.3.13    EVALUATION OF TABLET PROPERTIES

All the properties as mentioned under sub-section 2.3.10 were evaluated for the tablets as well. Similar methods were used as described earlier. Besides these, dissolution rate of the tablets was also determined by the following method.

### 2.3.13.1    DISSOLUTION RATE

The paddle Dissolution Apparatus (Distek Inc. Model 2000) was used at 50 revolutions per minute, to obtain the dissolution rate of the active drug, paracetamol in the compact of the modified starch and the commercial directly compressible diluents Avicel pH 102 and spray dried lactose.

900 ml of 0.1 N hydrochloric acid maintained at 37 ± 0.5°C was used as the dissolution medium. One compact was placed through a specific aperture into the dissolution medium. The bulk of the medium was stirred at 50 revolutions per minute. 20 ml samples of the medium were withdrawn using paraly-

tical pipettes with inbuilt filters at intervals of one minute.

20.0 ml of 0.1 N Hcl was used to replace every sample taken from the bulk of the dissolution medium.

The samples were diluted to 100ml ± 0.1ml with 0.1 N Hcl in volumetric flasks and the concentration of paracetamol in each sample was determined spectrophotometrically using a pye - unicam SP8 - 100 U V spectrophotometer by measuring the absorbance at 243 nm

A standard paracetamol solution containing 50 mg in 900 ml (55.6 mg/1000 ml) was prepared, various dilutions were made to prepare a calibration curve. Using this curve, the percentage of paracetamol dissolved in the dissolution media was plotted against time from the average of two runs.

T 50% values were obtained from these plots as seen in Table 3.4.5.2.

CHAPTER  3

RESULTS  AND  DISCUSSION

### 3.0                    INTRODUCTION

In this study various starches (Cassava, potato, yam and maize) were prepared from locally available sources, as described in page 77. The cassava, potato, and maize starches were purified to agree with the B. P. specifications (Tables 3.1.1, 3.1.2 & 3.1.4) The same procedure was followed for yam starch purification and the results obtained are seen on Table 3.1.3.

The effect of formulation and process variables mentioned in section 2 on the physical properties of cassava starch were studied. Granulations were made by varying binder volume and concentration, binder type and binding temperature.

Starches obtained from the various sources were separately gelatinised at 68 - 70°C and 98 - 100°C. The photomicrographs of the denatured granules were shown on Figs. 3.3.1.1-3.3.1.4. The pregelatinised starch obtained were blended with their plain starch counterpart in various proportions and granulated. The influence of the pregelatinised starch on the compact properties of the various starches was determined.

Cassava starch was chosen for its cheapness and high reworking potentials. Further work was carried out on this starch by studying the effect of particle size of the pregelatinised starch and pregelatinization temperature on both the granulations and compacts.

When directly compressible diluents are used to make tablets with small-dose drugs, the properties of the tablets will largely depend on those of the diluents. Studies have shown that granule properties are influenced by a variety of process and formulation variables (32 - 35). In other words, the tablet obtained using a directly compressible diluent will be influenced by the way in which the diluents are processed and manufactured. Therefore, to ascertain the usefulness of the newly formulated cassava starch diluent made from the pregelatinised starch blend, comparison was made with some established direct compression diluents, e.g. Avicel pH102, and spray dried lactose.

The results obtained from the above variations and comparison are discussed in this section.

### 3.1     CHARACTERIZATION OF STARCHES

A number of starches are recognized for pharmaceutical use. These include maize (_Zea mays_ L.), rice (_Oryza sativa_ L.), wheat (_Triticum aestivum_ L) and potato (_Solanum tuberosum_ L.). Maize, wheat and potato starches are official in the USP. Tapioca or cassava starch (Manihot utilissima) may be used in place of the above in tropical and subtropical countries.

The B. P. 1980 described specifications for pharmaceutical grade starches. With these qualities in mind, the various starches were processed to obtain pharmaceutical grade as described in section 2. The results obtained are described below. Tables 3.1.1 - 3.1.4 give the description of the various starches studied.

### 3.1.1     MACROSCOPICAL CHARACTERS

All the starches occur in irregular, angular masses or as white powders. They are insoluble in cold water but form colloidal solutions on boiling with about fifteen times their weight of

water, the solutions forming translucent jellies
on cooling. The starch mucilages are coloured
deep blue with solution of iodine, the colour
disappearing on heating to about 93°C but
reappearing on cooling. When the aqueous
suspensions of various starches were progressively
heated, their viscosities gradually increased and
they became thicker and sticky as they became
gelatinised due to the swelling of the granules.
The temperatures at which these changes commence
and  end  ⁻ vary with different starches (82).

### 3.1.2  MICROSCOPICAL CHARACTERS

The starches were identified under the low
power (x10) and high power (x40) of the microscope
as described in section 2.

Results show that the size, shape and structure
of the starch granules vary within definite limits,
so that it was possible to distinguish between the
starches derived from the different sources.
Starch granules were either single or compound
(Tables 3.1.1 - 3.1.4)

The hilum of a starch grain marks the
starting point of formation of the granule. The
hilum was observed to be central or accentric,
depending on the source, and were usually longer
than broad under polarised light. Polar crosses
were seen to originate from the hilum, when
viewed under polarised light. Depending on the
source of the starch grain, the hilum takes the
form of a rounded dot or of a simple, curved or
multiple cleft (Tables 3.1.1 - 3.1.4, Figs. 3.3.1 -
3.3.4).

TABLE 3. 1. 1

DESCRIPTION OF CASSAVA STARCH

| Description | Observation<br>Processed Starch | B.P. 1980<br>Specifications |
|---|---|---|
| Granule Shape | Simple granules, sub-spherical, or rounded polyhedral | Simple granules or rounded polyhedral |
| Granule size | Smaller - 9.4 μm<br>Larger - 35.2 μms<br>Mean of<br>40 - 22.9 μm | 5 - 10 μm<br>20 - 35 μms |
| Hilum | Central, punctuate, Linear or tri-radiate | Central, punctuate, Linear or tri-radiate |
| Striations | Faint, Concentric | Faint, Concentric, |
| Aggregation of granules | Compound granules few | Compound granules, few of 2 or 3 unequal components |
| Loss on drying at 105°C | 6.5% W/W | Not more than 15.0% W/W |
| Sulphated ash | 0.1% W/W | Not more than 0.6% |

## TABLE 3. 1. 2

### DESCRIPTION OF POTATO STARCH

| Description | Observation<br>Processed Starch | B.P.<br>Specifications |
|---|---|---|
| Granule Shape | Mainly ovoid,<br>Some rounded | Irregular,<br>ovoid, rounded. |
| Granule size | Smaller – 20.0µm<br>Larger –102.8µm<br>Mean of<br>40 – 44.8µm | 10 – 35 µm<br>30 – 100 µm |
| Hilum | Eccentric | Eccentric |
| Striations | Clearly visible<br>concen tric | Clearly visible<br>concentric |
| Aggregation of granules | Compound granules rare. | Compound granules rare, consisting of two or four elements |
| Loss on drying at 105°C | 8.5% W/W | 20% W/W |
| Sulphated ash | 0.18% W/W | Not more than 0.6% W/W |

TABLE 3. 1. 3

DESCRIPTION OF YAM STARCH

| Description | Observation<br>Processed Starch | B. P.<br>Specifications |
|---|---|---|
| Granule shape | Irregular, slightly ovoid or rounded | – |
| Granule size | Smaller – 15.6 µm<br>Larger – 70.5 µm<br>Mean of<br>40 – 35.0 µm | –<br>–<br>– |
| Hilum | Eccentric | – |
| Striations | Clearly visible concentric | |
| Aggregation of granules | Mostly single granules | – |
| Loss on drying at 105°C | 7.2% W/W | – |
| Sulphated ash | 0.15% W/W | – |

TABLE 3. 1. 4

## DESCRIPTION OF MAIZE STARCH

| Description | Observation<br>Processed Starch | B. P.<br>Specifications |
|---|---|---|
| Granule Shape | Polyhedral granules, sub-spherical or rounded | Angular polyhedral granules, rounded |
| Granule size | Smaller – 6μms<br>Larger – 35μms<br>Mean of $\frac{}{40}$ – 25 μms | 2 – 23 μms<br>25 – 32 μms |
| Hilum | Central with 2 – to 5 – rayed cleft | distinct cavity or 2- to 5- rayed cleft |
| Striations | No concentric striations | No concentric striations |
| Aggregation of granules | Mainly singles | – |
| Loss on drying at 105°C | 6.5% W/W | Not more than 15.0% W/W |

The starch granule is built up by the deposition
of successive layers around the hilum, and these
layers are seen as concentric rings or striations
which are clearly visible microscopically in the photo-
micrographs. The position and form of the
hilum and the presence or absence of well-defined
striations are of importance in the characteriza-
tion of starches. Maize granule hilum was central,
triangular with 3 to 5 stellate cleft. There were
no striations. The granules were mostly single.
The size ranged from 6 $\mu$.ms to 35 $\mu$.ms but mostly
between 15 - 25 $\mu$ms. Potato starch - hilum
appeared as points. The concentric striations
were well-marked. Some rings were however, more
distinct than others. They were mostly simple-
wedge shaped granules. A few compound granules of
2 or 3 components were firmly fused together. The
size ranged between 20 - 110 $\mu$ms with an average
range of between 44 - 60 $\mu$ms.

Cassava starch granules were mostly single, sub-
spherical, muller-shaped or round polyhedral. The
hilum was punctuate or cleft and the striations
were concentric. The sizes ranged between

5 to 10 μms for the small ones, and 20 - 35 μms
for the larger ones.

Yam starch granules resembled those of potato
starch granules. The hilum appeared as points.
The concentric striations were well marked. They
were mostly simple wedge - shaped but smaller than
those of potato starch granules. The size ranged
between 15 - 80 μms with an average range of
between 25 μms - 60 μms.

A few compound granules of 2 or 3 components
were firmly fused together. The compound granule
may however be formed by the aggregation of a
large number of simple granules (82).

### 3. 1. 3 Chemical Composition of Starch

Chemically, starches are polymers of anhydro-
glucose units linked through alpha glucosidic
bonds. Most contain two types of polymers,
amylopectin (α - amylose) and amylose (β - amylose).
Amylopectin constitutes over 80 percent of most
starches and the balance amylose (184). Fraction-
ation of the two components can be achieved by
selective precipitation involving the formation

of an insoluble complex of amylose with such polar
organic substances as butanol or thymol. $\beta$-amylose
consists of linear chains, whereas amylopectin has
a branched structure; these differences give the
two substances different properties and it is
their variation in proportion that contributes
towards the distinctive characteristics of a starch
from a particular biological source (79, 80).

Amylose is mainly responsible for the deep
blue colouration given by starch and iodine. The
strong affinity of amylose for iodine means that
it will take up to 19 percent of its weight of
iodine (82) but it would actually depend on the
fraction of amylose in the starch. On the other hand,
solutions of amylopectin gives purple colouration
with iodine, and the iodine - binding is low.

The amylose content of the starches was deter-
mined using two methods as described in section 2,
results of which show that Method I appears to give
a better result than Method II.

Amylose in cassava starch was found to be 15.00%.
The amylose in maize, potato and yam was 20% W/W,

18% W/W and 22% W/W respectively. Some of these values were slightly lower than the ones reported in some literature ( 79 , 80 ) where maize starch amylose ranged between 21 - 24.0% W/W, potato 18 - 23% W/W, tapioca 16.7% - 19% W/W. This may be due to variation in the soil or in the sub-species.

### 3.1.4    Sulphated ash Content and Water content

Most of the starches were found to contain between 0.1 - 0.3% sulphated ash content, although the B. P. 1980 specifies the range between 0.1 - 0.6%. The loss on drying of the various samples of starches determined on the moisture balance at 105°C ranged between 6.5 - 8% W/W. This is within the B. P. specification of not more than 15% of its weight when dried to constant weight at 105°C.

3:2    Having met all the B. P. specifications, cassava starch in powdered form, was subjected to formulation and processing variables, to find its effect on granulation characteristic  measurements.

### 3.2.0    The Effect of Processing and Formulation Variables on the Granular Properties of Cassava Starch Granulations

The variables considered were the binder volume, binder temperature, binder type and binder concentration.

### 3.2.1    The Effect of Binder

Water was used as binder in the concentration of 20% W/W, 30% W/W, 40% W/W, 50% W/W, 60% W/W, for 200g batch at room temperature. Table 3.2.1 showed that as the binder volume increased, the average granule size of the granulations increased. This is in line with the work done by Hunter and Ganderton (36). They studied the properties of lactose granules prepared by massing and force screening using different volumes of water as binder. Although lactose is soluble in water and starch is practically insoluble in water at room temperature, because of the solvent action of water in certain materials like lactose and starch, it changes the powdered material to granules, and the residual moisture retained enables the material to adhere together when compressed (36 ).

Generally, as the volume of the binder solution increased, the mean granule size increased.

Bulk densities decreased as the granule size increased. The smaller granules were able to form a closer and more intimate packing than were the larger granules. Bed porosity is often referred to as percent voids or extragranular porosity ($\epsilon$ b) and it is defined as $\epsilon b = 1 - \dfrac{P_b}{P_g} \times 100$

where $\epsilon b$ = bed porosity

    $P_b$ =     -- bulk density

    $P_g$ = Apparent density

As with granule density, and granule porosity, the tapped density and bed porosity may be used as granule character measurements for quality control specifications, or raw material evaluations.

Hunter and Ganderton (36) found that as the amount of water used to granulate lactose powder increased, bed porosity went through a maximum value. In an ideal system consisting of microsized particles that are spherical, bed porosity can range from 26% to 48%, 26%, if it is rhombohedral packing and 48% if it is cubical packing. But granules for tabletting are neither monosized nor spherical. It is a heterogenous

. system and in such systems, packing arrangement can become quite complicated. Smaller particles can fill interstices between large particles, thus reducing void space. On the other hand, this reduction in void space may be nullified by the fact that fine particles tend to form arches and bridges or chain formation that results in increase in void space e.g. very fine particles of carbon black may have a voidage as high as 96 to 98% (52).

However table 3.2.1. showed bed porosities of between 45% and 70.38%. The region of poor packing was found with binder volume of between 50 - 55% W/W where the bed porosities were 69%, and 70.38% respectively.

Nyquist and Nicklasson (22) used the Hausner Quotient which is the ratio of the bulk and loose densities of a material to characterise some direct compression excipients such as Fast - Flo Lactose and other grades of direct compression lactose. The ratio depends on the fluff or poured density Do and the bulk density at equilibrium D. The quotient is simply given as $Q = \dfrac{D}{Do}$

Q is a measure of interparticulate friction and could

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be used to predict powder flow property.

Table 3.2.1 shows Hausner Quotient range
of    1.16 - 1.45.  It has been postulated that
powders that have low interparticulate friction such
as spheres have ratios of approximately 1.2.  High
ratios may be due to high interparticulate cohesion
associated with low particle size (99).  Results
showed that as the binder volume increased, the
Hausner Quotient reduced from 1.45 to 1.16, showing
that the latter granulations experienced low inter-
particulate friction since they become larger and
more spherical.  On the other hand, low binder
volumes formed high interparticulate cohesion as the
particles were much smaller in size.

The values of Do and D were also used to calculate
the percent compressibility of the powder according
to the equation proposed by Carr (37).

$$\% \text{ compressibility} = \frac{D - Do}{D} \times 100$$

The percent compressibility of a powder is a  useful
method of measuring the flow properties.  According
to Carr, materials that have compressibility of
5 - 15% would probably show excellent flow behaviour.

Those powders that have % compressibility of 12 - 16, 18 - 21 and 23 - 25% would show very good, fair and poor flow properties respectively.

Staniforth (26) reported that % compressibility is a direct measure of the potential powder arch or bridge strength, and stability. Powdered solids with 38% - 40% compressibility are very cohesive and show poor flow characteristics. Table 3.2.1 showed values of between 30.88% to 14.00 meaning that the granulations became more flowable as the binder volume increased. The granulations showed excellent flow behaviour of % compressibility 14.0% when the binder volume was 70% W/W.

The average granule strength was found to increase and the granule friability decreased, as the binder volume increased (33, 34). Davies and Gloor showed that increasing the amount of water used to granulate lactose caused densification by rapidly eliminating larger pores, reducing mean pore diameter, and increasing granule strength.

### 3.2.2 Effect of the Temperature of Water Binder on Granulation Properties of Cassava Starch

To study the effect of temperature on granular properties, same volume of water at various temperatures were used as the binder to prepare the pure starch granulations. Since the equipment was not maintained at the test temperature, the results obtained in Table 3.2.2 could only be accepted as comparative values and not the real values that would obtain in a thermostatically controlled environment. When water at higher temperature (70° or 80°C) was added to the starch powder, some form of gelatinization at the immediate vicinity may have taken place, which at any rate was dispersed as massing continued. The granulations obtained showed larger average granule size and granule strength with water added at elevated temperatures. The higher the temperature, the larger the granules.

The bulk densities decreased as the temperature increased. Granulation obtained at room temperature had the least flow rate of 0.104 grammes per second, that of 80°C was 0.125 grammes per second. This is because

the larger granules formed at higher binder temperature were probably more spherical and were able to flow more evenly than the smaller cohesive granules formed at lower binder temperature.

Previous workers have shown the influence of temperature on the viscosity of cassava starch (76). The viscosity of cassava starch paste increases above thegelatinization temperature of 59.3°C and then becomes thinner above 70°C (76). When the water binder was added to the starch powder during granulation, the water added above the gelatinization temperature of the cassava starch gelatinises the starch in the immediate vicinity and the paste was later dispersed as granulation continued. Higher viscosity has been found to be a result of increase in binder concentration. A simultaneous increase in the strength of liquid bridges may as well result in a larger granule size. In like manner the average granule strength was found to increase as the temperature of the binder increased. The viscous liquid bridges formed at elevated temperatures between the starch granules later dried up to form hardened bridges and stronger granules.

The bulk densities decreased slightly as the temperature increased. This is obvious since the average granule size was found to increase as the temperature increased. In short, the average granule size of a granulation has been described as the key objective of a formulator. The smaller granules obtained at the lower temperatures packed into a closer packing, resulting into enhanced bulk densities and reduction of granule porosity. Particle density affects the rheological properties of powder through its influence on the relative contributions of gravity and surface forces. If the particle density is higher it will favour free flow. So particles with a high density and low internal porosity tend to possess free flowing properties but this can be offset by surface roughness which leads to poor flow characteristics due to friction and cohesiveness (1). In general, the distribution of pores is related to initial particle size. Ganderton and Hunter (35) and Hunter and Ganderton (36).

Bulk density and bed porosity are measures used to describe a packing of granules. To date, however, it

has not been possible to relate these measures of packing's to other superficial features of the particles themselves.

### 3.2.3 Effect of Binder Type and Concentration on Granular Properties

Various concentrations of cassava starch mucilages and gelatin solutions were prepared. 5% W/W of each was used to granulate 200g batch size of pure cassava starch.

Results showed decreased mean granule size as the binder changed from pure water to starch mucilage. This is in line with the work done by Chalmers and Elworthy (97) when they studied the effects of various formulation and processing variables on the granule size of oxytetra cycline tablet granulations. When changing from pure water to the same volume containing 1.25% polyvinyl pyrrolidone (PVP), as the granulating solution increased, average granule size decreased (360 µms versus 210 µm).

This decreases in granule size may be attributed to a decrease in the penetration and wetting capabilities by the starch solution which was brought about by the

lowering of the surface tension of the pure water.
Preliminary studies have shown that while the surface
tension of pure water has been given as 72 $MNm^{-1}$,
2 - 5% cassava starch mucilage gave a surface
tension of 66 $MNm^{-1}$.

Although the surface tension of starch mucilage
and gelatin solution further decrease with increase
in the concentration (provided a mono-layer is main-
tained) their viscosities also rise. This
increase of the viscosity of the liquid binder
with increase in the concentration of the binder,
counteracts the previous effect, by forming
increased granule size.

The corresponding bulk densities decreased
as the granule size increased (Table 3.2.3.1). The
apparent granule densities increased. As described
previously, smaller granules were able to pack more
closely than larger granules. Since granules
have open or closed pores, Heywood (31) described
three different types of particle densities.

Apparent particle density is the mass of a
particle(s) divided by the volume of the particle(s)

excluding open pores but including closed pores.

Effective Particle Density is the mass of a
particle(s) divided by the volume of the particle(s),
including open and closed pores. True Density
is the mass of particle(s) divided by the volume
of the particle(s) excluding open and closed pores.
When one speaks of granule density Pg, one is
generally referring to apparent particle density
or effective particle density. Taking the bulk
density as the true density, the bed porosity
of the granulation $(\varepsilon = 1 - \frac{P_b}{P_g}) \times 100$

where Pb is the bulk density

. Pg is the apparent density.

Results showed that the bed porosity decreased as
the granule friability of the granulation
increased and as the binder concentration increased.
Since the granules crumbled easily to form fines,
the smaller granules obtained were able to form
closer packings and reduction in void spaces.

Generally, the degree of granule friability
was found to be inversely proportional to the
granule size as obtained in (Tables 3.2.1 - 3.2.2).
These results were verified by numerous readings.

With cassava starch mucilage as binder, as the size of the granules became bigger, there was found increased average granule strength, and a rather unusual increased friability. This weight loss due to material detaching from the granule surface has been obtained because of the weakness of the bond formed by cassava starch mucilage.

Gelatin solution appeared to be a better binder for cassava starch powder than cassava starch mucilage. Table 3.2.3.2 showed that as the gelatin binder concentration increased, the average granule size of the granulation increased and the bed porosity went through a maximum value.

The packing densities; tapped densities and Apparent densities increased as the binder concentration increased and as the granule size increased. The larger granules are probably more spherical with low internal porosity. In like manner particles with a high density tend to possess free flowing properties. This excellent flowability is also reflected in the volumetric flow rate.

The Hausner Quotient ranged between 1.22 and 1.26 showing that the powders have low interparticulate friction. They are spherical and they

possess excellent flowability.

The percent compressibility confirmed the
above findings since 2% W/W and 5% W/W gelatin
concentration gave values below 20%. Carr (37)
described materials having percent compressibility
of 20% and below as being very flowable. 10% W/W
gelatin solution, however gave 21.9% indicating
that at the higher concentration of 10%, the
granules became more cohesive.

In line with the above, the volumetric
flow rate described a flow rate of 0.056g/sec for
2% W/W gelatin binder and 0.052 gramme/sec for
10.0% W/W gelatin binder.

The average granule strength in grammes was
found to increase as the granule size increased.
The corresponding friability in percent decreased
as the concentration of gelatin binder increased.
A possible explanation could be due to the particle –
particle bonding mechanism involved in adhesion
and cohesion of particles brought about by Van der
waals forces and the surface tension of the liquid
added. The resulting particle – liquid – particle
bonding became stronger as the concentration of

the gelatin solution increased. This is as a result of the increase in the viscosities of the liquid bridges holding particles together during the granulation phase, and the hardened bond that forms after drying becomes thicker and stronger forming less friable granules.

RESULT

### 3.2.1 EFFECT OF BINDER VOLUME ON THE PHYSICO-TECHNICAL PROPERTIES OF PURE CASSAVA

STARCH GRANULATION:

BINDER: WATER AT $28^0$C

| Binder Volume % V/W | Average Granule Size in /ums | Bulk Denisity G/ml | Apparent Granule Density in G/ML | Hausner Quotient | Percentage Compressibi- bility in % W/W | Volumetric Flow Rate In GM/Sec | Average Granule Strength In Grammes | Granule Friabili- ty in Percentage | Granule Bed- porosity in Percentage |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 200 | 0.49 | 1.45 | 1.45 | 30.88 | 0.04 | 10.94 | 43.5 | 45.0 |
| 40 | 300 | 0.49 | 1.45 | 1.35 | 24.02 | 0.12 | 13.05 | 17.3 | 67.0 |
| 50 | 340 | 0.46 | 1.55 | 1.27 | 20.08 | 0.10 | 12.04 | 12.0 | 69.0 |
| 55 | 330 | 0.46 | 1.55 | 1.26 | 20.73 | 0.10 | 12.10 | 9.3 | 70.38 |
| 60 | 360 | 0.46 | 1.56 | 1.25 | 20.00 | 0.11 | 13.77 | 4.5 | 68.45 |
| 70 | 430 | 0.40 | 1.65 | 1.16 | 14.00 | 0.14 | 12.46 | 1.7 | 68.47 |

## 3.2.2  EFFECT OF TEMPERATURE OF BINDER FLUID ON PHYSICO-TECHNICAL PROPERTIES

### OF STARCH GRANULATION

### BINDER : WATER

(BINDER VOLUME: 40% OF THE POWDER.)

| Binder Temp. in $^0$C | Average Granule Size in /um | Bulk Density in G/mL | Apparent Granule Density in G/mL | Hausner Quotient | percentage Compressib- ility | Volumetric Flow Rate in Gm/Sec | Average Granule Strength in /um | Granule Friabi- lity in Percentage | Granule Bed- porosity in Percentage |
|---|---|---|---|---|---|---|---|---|---|
| 28 | 300 | 0.49 | 1.58 | 1.35 | 24.02 | 0.10 | 13.05 | 17.5 | 50.80 |
| 40 | 360 | 0.49 | 1.61 | 1.35 | 24.91 | 0.11 | 15.45 | 17.7 | 67.65 |
| 50 | 360 | 0.49 | 1.62 | 1.32 | 22.49 | 0.11 | 16.85 | 14.0 | 68.09 |
| 60 | 380 | 0.48 | 1.61 | 1.31 | 22.91 | 0.11 | 17.95 | 12.0 | 77.60 |
| 70 | 380 | 0.45 | 1.64 | 1.30 | 21.00 | 0.12 | 18.08 | 3.3 | 78.56 |
| 80 | 385 | 0.45 | 1.66 | 1.21 | 17.49 | 0.12 | 22.51 | 1.2 | 78.09 |

FIG. 3.3.1.1
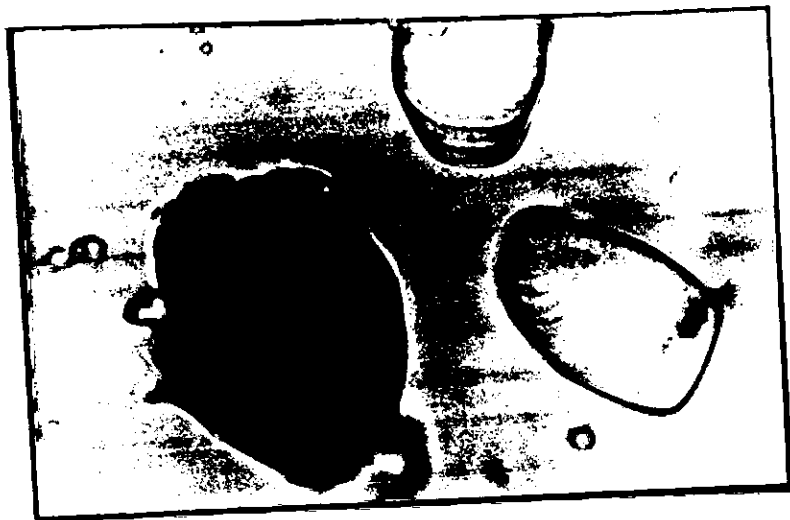


(1) YAM STARCH GRAINS (UNPOLARISED X400)



(2) YAM STARCH GRAINS (UNDER POLARISED LIGHT X400)



(3) YAM STARCH GRAINS
(PARTIALLY PRE–GELATINISED AT 68°C–70°C X400)



(4) YAM STARCH GRAINS
(COMPLETELY PRE–GELATINISED AT 98°C–100°C X400)

### 3.2.3 EFFECT OF BINDER TYPE AND CONCENTRATION ON THE PHYSICO-TECHNICAL PROPERTIES OF

### PURE CASSAVA STARCH GRANULATION USING CASSAVA STARCH MUCILAGE AS BINDER

| Starch Mucilage Concentration % W/W | Average granule Size in μm | Bulk Density in G/ml | Apparent Granule Density | Hausner Quotient | Percentage Compressibility | Volumetric Flow Rate | Average Granule Strength | Granule Friability in Percentage | Granule Bed-porosity in Percentage |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 340 | 0.46 | 1.55 | 1.27 | 20.08 | 0.10 | 12.04 | 12.00 | 69.00 |
| 2 | 240 | 0.53 | 1.54 | 1.46 | 28.50 | 0.06 | 32.22 | 5.17 | 57.3 |
| 5 | 240 | 0.53 | 1.55 | 1.41 | 27.33 | 0.05 | 56.51 | 5.67 | 65.25 |
| 10 | 260 | 0.52 | 1.56 | 1.40 | 28.02 | 0.03 | 60.76 | 2.93 | 62.90 |
| 20 | 340 | 0.52 | 1.59 | 1.40 | 25.71 | 0.01 | 94.41 | 2.17 | 65.2 |

### 3.2.3.2 USING GELATIN SOLUTION AS BINDER

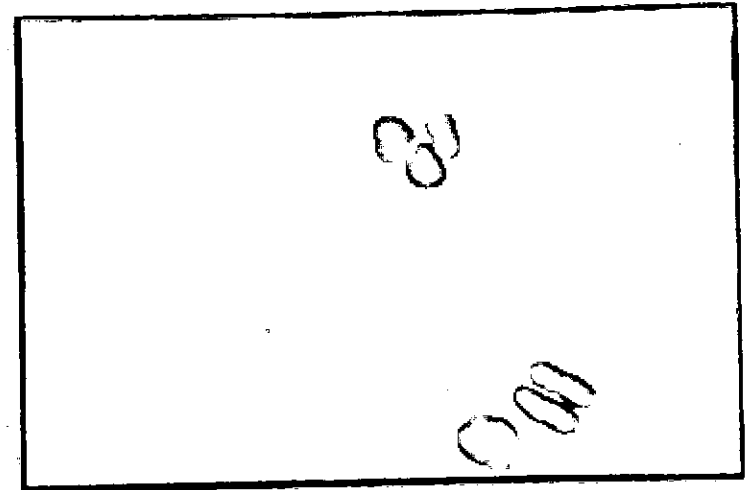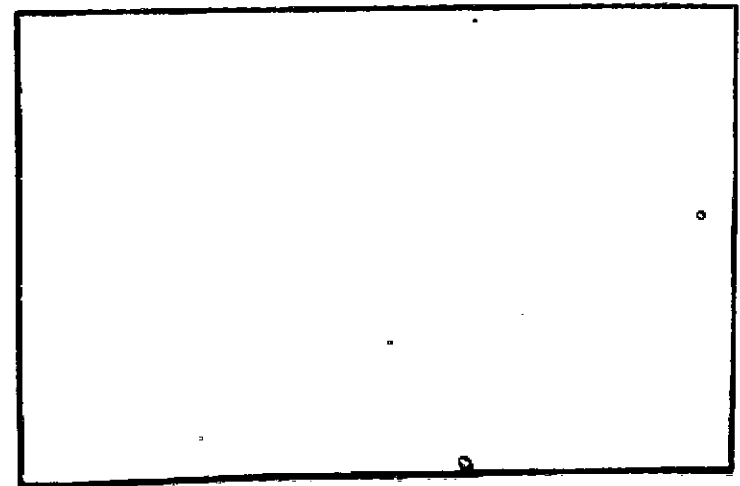| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 340 | 0.46 | 1.55 | 1.27 | 20.08 | 0.10 | 12.04 | 12.00 | 69.00 |
| 2 | 275 | 0.33 | 1.67 | 1.22 | 18.18 | 0.05 | 12.26 | 4.00 | 67.48 |
| 5 | 280 | 0.33 | 1.67 | 1.21 | 18.18 | 0.05 | 13.37 | 0.60 | 67.54 |
| 10 | 280 | 0.31 | 1.67 | 1.20 | 11.95 | 0.05 | 73.56 | 5.50 | 73.90 |

FIG. 3.3.1.2
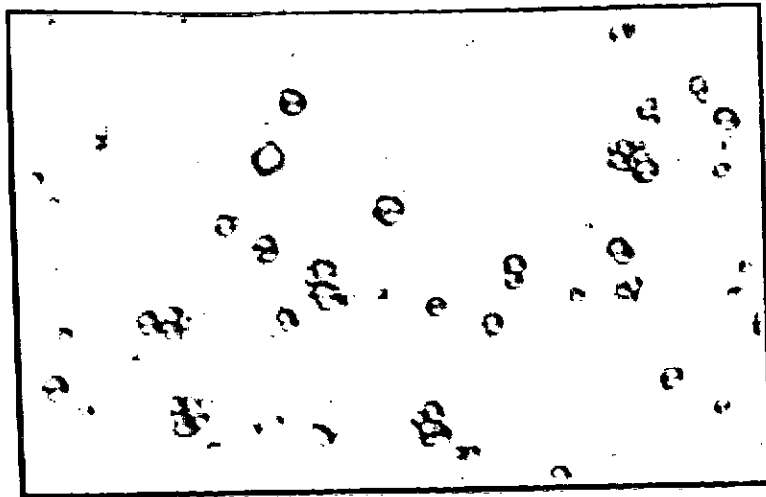


(1)  MAIZE STARCH GRAINS (UNPOLARISED X100)
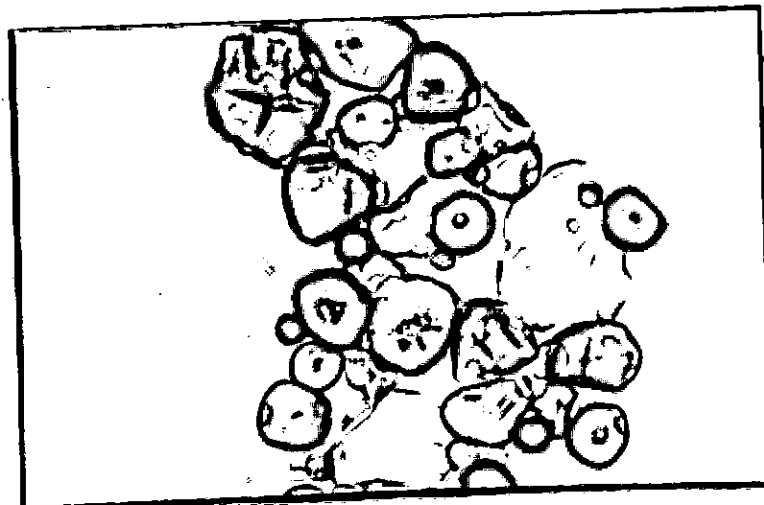


(2)  MAIZE STARCH GRAINS (UNPOLARISED X400)



(3)  MAIZE STARCH GRAINS
     (PARTIALLY PRE–GELATINISED AT $68^0C-70^0C$.
     UNDER POLARISED LIGHT X400)



(4)  MAIZE STARCH GRAINS
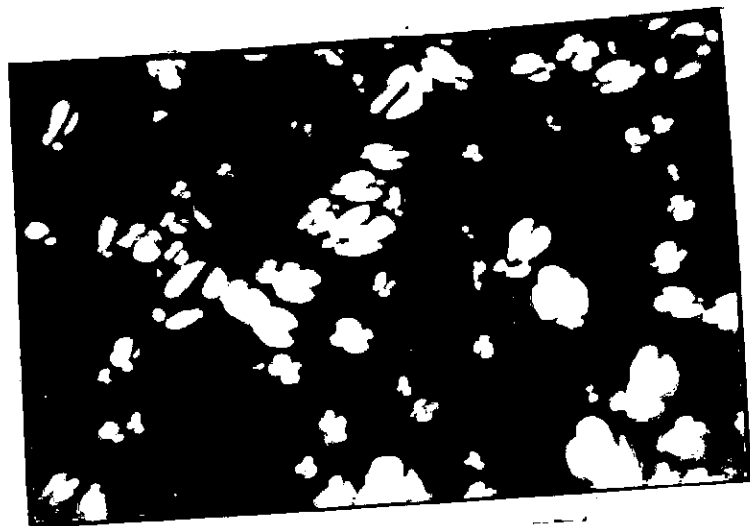     (COMPLETELY PRE–GELATINISED AT $98^0C - 100^0C$ X400)

### 3.3.1    The Effect of Pregelatinization on
### starch grain characteristics

Starches obtained from cassava, maize, potato and yam were gelatinised at 68° - 70°C and 98 - 100°C as described in section 2. Photomicrographs of the various starches before and after gelatinization were taken under plain light and polarized light at both low and high powers and were compared. The effect of pregelatinization temperature on the structure of the starch grains was vividly shown (Figs. 3.3.1.1 - 3.3.1.4)

Normal starch grains showed concentric striations, and hilum. Polar crosses were observed under polarised light for normal starch grains. The starch pregelatinised at 68° - 70°C showed some denatured structures while some grains still kept their usual characteristics. The starch pregelatinised at 98° - 100°C lost their identity and formed a completely denatured mass with no striations.

In 1719, Leeuwenhoek studied starch granules microscopically and made accurate observations on the swelling phenomena shown by starch when heated in water. He suggested that the swelling

FIG. 3.3.1.3



(1) POTATO STARCH GRAINS (POLARISED X100)
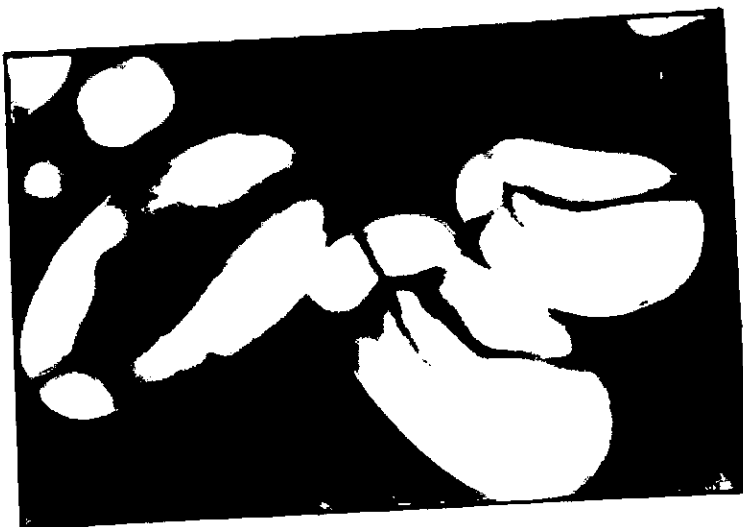
(3) POTATO STARCH GRAINS
(PARTIALLY PRE–GELATINISED AT 68°C – 70°C X400)



(2) POTATO STARCH GRAINS (POLARISED X400)

(4) POTATO STARCH GRAINS
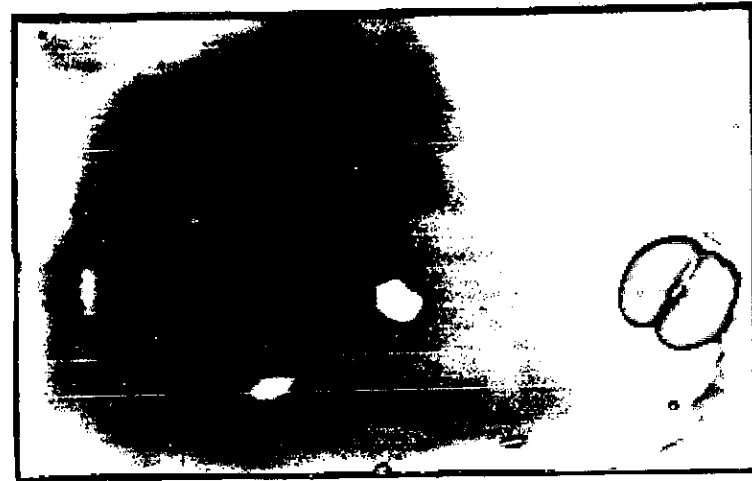(COMPLETELY PRE–GELATINISED AT 98°C – 100°C X400)

starch grains contained a soluble substance
which escaped from the fissures  he observed
in the outer insoluble sac.

In cold water, most starches are insoluble
and swell only to a limited extent.  On heating,
little  further swelling occurs until the
temperature reaches the initial gelation
temperature when the granules start to swell
very rapidly with increasing temperature.
Apart from   swelling, a number of other
changes occur.  The granules begin to lose
their birefringence, the solubility of starch
increases due to the loss of low - molecular
weight amylose from the granules and the solution
becomes viscous and sticky.  If the solution of
gelatinised starch is sufficiently concentrated
it will set to a rigid gel on cooling to room
temperature.

FIG. 3.3.1.4

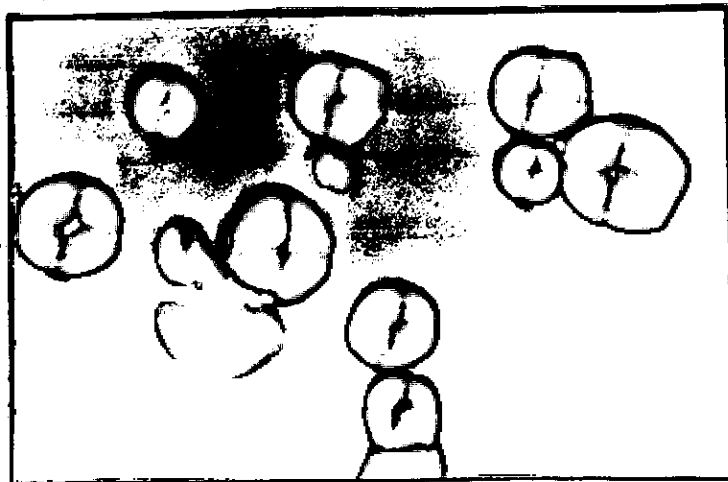(1) CASSAVA STARCH GRAINS (UNPOLARISED X400)

(2) CASSAVA STARCH GRAINS (UNDER POLARISED LIGHT X400)

(3) CASSAVA STARCH GRAINS
(PARTIALLY PRE–GELATINISED AT 68°C – 70°C X400)

(4) CASSAVA STARCH GRAINS
(COMPLETELY PRE–GELATINISED AT 98°C –100°C X400)

### 3.3.2      The Effect of pregelatinised starch component on the properties of starch granulations

In this study, cassava starch was blended with various portions of pregelatinised component, 20% W/W, 40% W/W, 50% W/W, 60% W/W, 80% W/W, and 100% W/W. The various blends were granulated using only water as binder.

The greatest effect, the concentration of this substance has on plain cassava starch granulation appears to be its effect on granule hardness and strength. The higher the binder level, the stronger and larger the granules obtained.

Carr's percent compressibility and Hausner Quotient decreased as the concentration of the pregelatinised starch component increased, meaning that the granules become more spherical and flowable as the concentration of pregelatinised starch increased.

In fig 3.3.2.1 is seen that increasing the concentration of pregelatinised starch in the blend leads to an increase in granule size. Sharp increase was obtained when the concentration of the pregelatinised component was above 80% W/W.

Pregelatinised starch is reported to be a
dry tablet binder (124). The binding in the dry
state is probably due to forces of adhesion and
cohesion in bonds with restricted movement.
However, these molecular forces, though an
important binding mechanism in dry granulation
are very weak forces, particularly Van der Waals
forces where particles are less than $10mm^{-8}$
($100A°$) apart.

When the granules from pure cassava starch
are prepared using a liquid binder, granules are
probably formed by pendular bonds. But when the
pure starch is mixed with higher concentrations
of its pregelatinised component, both pendular
bonds (liquid bridges) and molecular forces may
be operating. The quantity of water used as the
liquid binder probably dissolves only a part of
the soluble fraction of the pregelatinised starch
forming the binder solution, while molecular forces
may operate in the unwetted portions of the starch.

The growth of the granules initiated by
pendular bridges and molecular forces continue
by a secondary process in which small granules
are crushed by larger ones (52). The fragments
then join the larger granules by coalescence.

In the case of plain cassava starch, the limit of growth is quickly reached due to the lone pendular bonds operating in the absence of the molecular forces generated by the pregelatinised component. Thus the granule size at which crushing occurs is never reached. In the dry state, the strength of the granule of the plain cassava starch is due to cohesive forces only and to both cohesive and molecular forces in the blends containing pregelatinised starch. Preliminary studies showed that pregelatinised starch is a plastic material and the large strength variation is consistent with the Heckel theory (64).

The strength of the granules would also be expected to vary due to irregularities in their shape and the presence of localized plain cassava starch powder, or voids. It may be pertinent to say that as the concentration of the pregelatinised starch increased, the adhesion forces increased and the diameter of granules also increased.

The greatest effect the concentration of this substance has on the granule appears to be

its effect on granule hardness and strength. .
The higher the binder level, the stronger the
granules obtained (fig. 3.3.2.2 ).
It has also been shown that the larger granules
possess more strength than the smaller ones and
that the smaller granules are more  poorly
formed and thus less robust than are their
larger counterparts ( 52).

Percent compressibility is a  useful method
of measuring the flow properties of powders or
granules.  According to Carr (37), materials
that have compressibility of 5 - 15% would
probably show excellent flow behaviour. The
powders that have percent compressibility of
12 - 16, 18 - 21 and 23 - 25% could show very
good, fair and poor flow properties respectively.
Fig. 3.3.2.5 indicated that Carr's percent
compressibility decreased as the concentration
of the pregelatinised starch component increased,
meaning that the granules became more flowable
as the concentration of pregelatinised starch
increased.

The Hausner Quotient similarly, is a measure
of interparticulate friction and could also be

used to predict powder flow property. Powders
that have low interparticulate friction are
spherical : Fig. 3.3.2.4 , indicated that
Hausner Quotient reduced as the concentration
of pregelatinised starch increased and therefore
the granules obtained could be described as
being more spherical and more flowable.

Often, it is of interest to know bed
porosity or percent of void space in a packing.
Bed porosity (- b percent, is determined by
equation

$$(-b = (1 - \frac{Pb}{Pg}) \ 100 \quad (\ 52)$$

where    (- b  =  bed porosity,

   Pb   =  Bulk : density

   Pg ·  =  Apparent density.

Particle  density and bed porosity also affect
the rheological properties of powder through
their relative contributions of gravity and
surface forces. Results showed that blends
containing high concentration of pregelatinised
starch formed highly porous beds, the granules
being probably more spherical than the blends
containing lower concentration of pregelatinised
starch (Fig. 3.3.2.6). Ideal systems consisting

of monosized spherical particles should have low
bed porosities of between 26% - 48%.  Very fine
particles may, however, have a very large voidage,
because of the formation of arches and bridges, Examples
are the very fine particles of carbon black, which
have a voidage as high as 96 to 98% (52).

However, tablet granulations are heterogeneous
systems where smaller particles can fill inter-
stices between large particles, thus reducing
void space.  The bed porosities of all the cassava
starch granulations were found to range from
57 - 66% (Fig. 3.3.2.6).  At 40% W/W pregelatinised
concentration,  the bed porosity of all the blends
were least  and highest at 100% W/W pregelatinised
concentration,  meaning that the granules were
able to pack into closest volumes at 40% W/W
pregelatinised concentration.

3.3.2.1     EFFECT OF PREGELATINISED STARCH CONCENTRATION ON GRANULAR PROERTIES OF

CASSAVA STARCH BLEND (120 um)

(Pregelatinization Temperature 68 - 70°C)

| Granular Properties | Concentration of Pregelatinised component in % W/W | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
| Moisture content in % W/W | 12.90 | 13.10 | 13.1 | 13.00 | 13.1 | 12.5 | 10.50 |
| Loose Density in GM/ML | 0.49 | 0.49 | 0.501 | 0.50 | 0.44 | 0.41 | 0.45 |
| Bulk Density in GM/ML | 0.57 | 0.60 | 0.618 | 0.61 | 0.53 | 0.52 | 0.50 |
| Percent compressionability in & W/W | 20.9 | 18.17 | 18.93 | 18.03 | 17.11 | 16.73 | 11.24 |
| Hausner Quotient | 1.26 | 1.22 | 1.23 | 1.22 | 1.21 | 1.20 | 1.13 |
| Flow Rate in g/sec. | 0.34 | - 0.10 | 0.10 | 0.9 | 0.12 | 0.14 | 0.15 |
| Average Granule size in Microns | 158.5 | 235.00 | 288.50 | 296.20 | 325.00 | 738.00 | 500.00 |
| Apparent Density in GM/ML | 1.45 | 1.50 | 1.520 | 1.53 | 1.52 | 1.519 | 1.151 |
| Bed Porosity in % W/W | 61.00 | 60.00 | 59.00 | 60.00 | 65.00 | 66.00 | 67.00 |
| Granule Strength in GMS | 13.05 | 14.00 | 14.3294 | 16.15 | 17.67 | 18.4297 | 19.8372 |
| Granule Friability in % W/W | 17.70 | 11.00 | 4.20 | 3.00 | 2.00 | 1.50 | 1.10 |

**TABLE 3.3.2.2**     EFFECT OF PREGELATINISED STARCH CONCENTRATION ON
GRANULAR PROPERTIES OF CASSAVA STARCH BLEND (180μ)

(Pregelatinization Temperatur  68 – 70°C)

| Concentration of Pregelatinised component in %W/W | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|---|
| Moisture Content in % W/W | 12.90 | 13.00 | 13.50 | 13.30 | 13.00 | 12.50 | 11.20 |
| Loose Density in Gm/Ml. | 0.49 | 0.52 | 0.51 | 0.51 | 0.51 | 0.48 | 0.46 |
| Bulk Density in Gm/ml | 0.57 | 0.60 | 0.62 | 0.62 | 0.60 | 0.55 | 0.51 |
| Percent Compressibility in % W/W | 20.90 | 21.75 | 18.93 | 16.88 | 15.00 | 11.88 | 9.11 |
| Hausner Quotient | 1.26 | 1.27 | 1.20 | 1.20 | 1.17 | 1.13 | 1.10 |
| Flow Rate in Gm/Sec | 0.34 | 0.38 | 0.41 | 0.44 | 0.60 | 0.66 | 0.77 |
| Average Granule size in μm | 200.50 | 237.00 | 250.00 | 267.00 | 267.00 | 668.40 | 595.20 |
| Granule Strength in grammes | 12.81 | 13.24 | 13.87 | 15.84 | 16.91 | 17.67 | 17.67 |
| Apparent Density in Gm/ml. | 1.45 | 1.49 | 1.56 | 1.45 | 1.44 | 1.43 | 1.42 |
| Bed Porosity in % W/W | 60.00 | 59.00 | 60.00 | 57.00 | 58.00 | 62.00 | 64.00 |
| Granule Friability in % W/W | 17.70 | 11.50 | 4.50 | 3.20 | 2.50 | 2.00 | 2.00 |

**TABLE 3.3.2.3**  **EFFECT OF PREGELATINISED STARCH CONCENTRATION ON GRANULAR PROPERTIES OF CASSAVA STARCH BLEND (250µ)**

**(Pregelatinization Temperature 68 – 70°C)**

| Granule Properties | Concentration of pregelatinised Component in % W/W | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
| Moisture Content in % W/W | 12.90 | 12.40 | 12.50 | 14.40 | 13.50 | 12.90 | 11.50 |
| Loose Density in GM/Ml. | 0.49 | 0.53 | 0.56 | 0.58 | 0.58 | 0.56 | 0.52 |
| Bulk Density in GM/ML | 0.57 | 0.65 | 0.68 | 0.65 | 0.64 | 0.62 | 0.56 |
| Percent Compressibility in % W/W | 20.90 | 18.00 | 16.47 | 10.84 | 10.49 | 9.90 | 7.77 |
| Hausner Quotient | 1.26 | 1.22 | 1.20 | 1.12 | 1.12 | 1.11 | 1.08 |
| Flow Rate in grammes per sec. | 0.41 | 0.53 | 0.61 | 0.66 | 0.68 | 0.71 | 0.83 |
| Average Granule size in Microns | 158.50 | 237.20 | 266.10 | 290.00 | 299.00 | 316.30 | 708.10 |
| Apparent Density in GM/ML | 1.45 | 1.42 | 1.42 | 1.43 | 1.44 | 1.43 | 1.42 |
| Bed Porosity in % W/W | 61.00 | 54.00 | 52.00 | 54.00 | 55.00 | 56.00 | 60.00 |
| Granule friability % W/W | 17.70 | 11.20 | 5.50 | 3.60 | 2.95 | 2.00 | 2.00 |
| Granule Strength in GMs | | 3.69 | 12.35 | 15.24 | 16.30 | 17.67 | 17.67 |

TABLE 3.3.2.4    EFFECT OF PREGELATINISED STARCH CONCENTRATION ON GRANULAR PROPERTIES OF CASSAVA STARCH BLEND (120µ)

(Pregelatinization Temperature 98 - 100°C)

| Granule Properties | Concentration of pregelatinised Component in % W/W | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
| Moisture Content in % W/W | 12.90 | 11.20 | 13.40 | 13.00 | 12.00 | 12.70 | 9.60 |
| Loose Density | 0.49 | 0.50 | 0.53 | 0.52 | 0.50 | 0.48 | 0.45 |
| Tapped Density | 0.57 | 0.62 | 0.64 | 0.62 | 0.60 | 0.56 | 0.50 |
| Percent Compressibility | 20.90 | 18.70 | 17.24 | 16.21 | 15.33 | 15.49 | 11.24 |
| Hausner Quotient | 1.26 | 1.23 | 1.21 | 1.19 | 1.18 | 1.18 | 1.13 |
| Flow Rate in Gms per second. | 0.34 | 0.50 | 0.33 | 0.27 | 0.33 | 0.33 | 0.41 |
| Average Granule size in Microns | 158.50 | 0.30 | -296.10 | -290.00 | 350.10 | 794.30 | 592.30 |
| Granule friabil- ility % W/W | 17.70 | 4.50 | 4.00 | 3.80 | 2.60 | 1.50 | 0.80 |
| Apparent Density in GM/ML | 1.61 | 1.44 | 1.46 | 1.47 | 1.46 | 1.47 | 1.48 |
| Bed Porpsity in % W/W | 61.00 | 57.00 | 56.00 | 58.00 | 59.00 | 62.00 | 66.00 |
| Granule Strength in GMs | 13.05 | 13.87 | 14.63 | 14.93 | 16.75 | 18.42 | 19.49 |

TABLE 3.3.2.5    EFFECT OF PREGELATINISED STARCH CONCENTRATION ON GRANULAR PROPERTIES OF CASSAVA STARCH BLEND (180µ)

(Pregelatinization Temperature 98 - 100°C)

| Granular Properties | Concentration of pregelatinised component in % W/W | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
| Moisture Content in % W/W | 12.90 | 12.80 | 13.50 | 13.20 | 12.80 | 12.20 | 11.00 |
| Loose Density | 0.49 | 0.53 | 0.54 | 0.54 | 0.53 | 0.43 | 0.45 |
| Tapped Density | 0.57 | 0.64 | 0.64 | 0.64 | 0.62 | 0.49 | 0.49 |
| Percent Compressibility | 20.90 | 17.60 | 16.20 | 16.25 | 14.99 | 11.69 | 9.10 |
| Hausner Quotient | 1.26 | 1.21 | 1.19 | 1.19 | 1.18 | 1.13 | 1.10 |
| Flow Rate in Gms per second. | 0.34 | 0.31 | 0.38 | 0.45 | 0.35 | 0.38 | 0.71 |
| Average Granule size in Microns | 200.50 | 235.00 | 250.00 | 248.90 | 266.50 | 610.00 | 512.00 |
| Granule friability % W/W | 17.70 | 5.00 | 4.50 | 3.90 | 2.60 | 1.10 | 1.10 |
| Apparent Density in GM/ML | 1.61 | 1.47 | 1.51 | 1.51 | 1.47 | 1.49 | 1.47 |
| Bed Porpsity in % W/W | 61.00 | 57.00 | 57.00 | 57.50 | 57.50 | 62.00 | 66.00 |
| Granule Strength in GMs | 13.05 | 13.11 | 13.87 | 14.78 | 16.75 | 19.03 | 19.18 |

TABLE 3.3.2.6    EFFECT OF PREGELATINISED STARCH CONCENTRATION ON
GRANULAR PROPERTIES OF CASSAVA STARCH BLEND (250µ)

(Pregelatinization Temperature 98 – 100°C)

| Granular Properties | Concentration of pregelatinised component in % W/W | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 20 | 40 | 50 | 60 | 80 | 100 |
| Moisture Content in % W/W | 12.90 | 12.00 | 12.90 | 12.10 | 11.50 | 11.20 | 10.80 |
| Loose Density in GM/ML | 0.49 | 0.54 | 0.60 | 0.59 | 0.59 | 0.58 | 0.58 |
| Bulk Density in GM/ML | 0.57 | 0.66 | 0.69 | 0.66 | 0.66 | 0.65 | 0.59 |
| Percent Compressibility in % W/W | 20.90 | 18.54 | 13.79 | 11.24 | 10.44 | 10.14 | 2.00 |
| Hausner Quotient | 1.26 | 1.23 | 1.16 | 1.13 | 1.12 | 1.11 | 1.02 |
| Flow Rate in Gms per second. | 0.34 | 0.33 | 0.50 | 0.50 | 0.68 | 0.71 | 0.86 |
| Average Granule size in Microns | 158.50 | 240.90 | 266.10 | 292.00 | 350.00 | 388.90 | 750.00 |
| Granule friability % W/W | 17.70 | 8.30 | 6.20 | 5.50 | 4.00 | 1.20 | 1.10 |
| Apparent Density in GMs/ML | 1.61 | 1.50 | 1.50 | 1.51 | 1.50 | 1.50 | 1.48 |
| Bed Porpsity in % W/W | 61.00 | 56.00 | 54.00 | 56.50 | 56.50 | 57.00 | 60.00 |
| Granule Strength in GMs | 13.05 | 8.10 | 11.29 | 12.35 | 14.63 | 18.88 | 19.30 |

Fig 3.3.2.1 — Effect of pregelatinised starch concentration on the Average granule size of cassava starch granulations
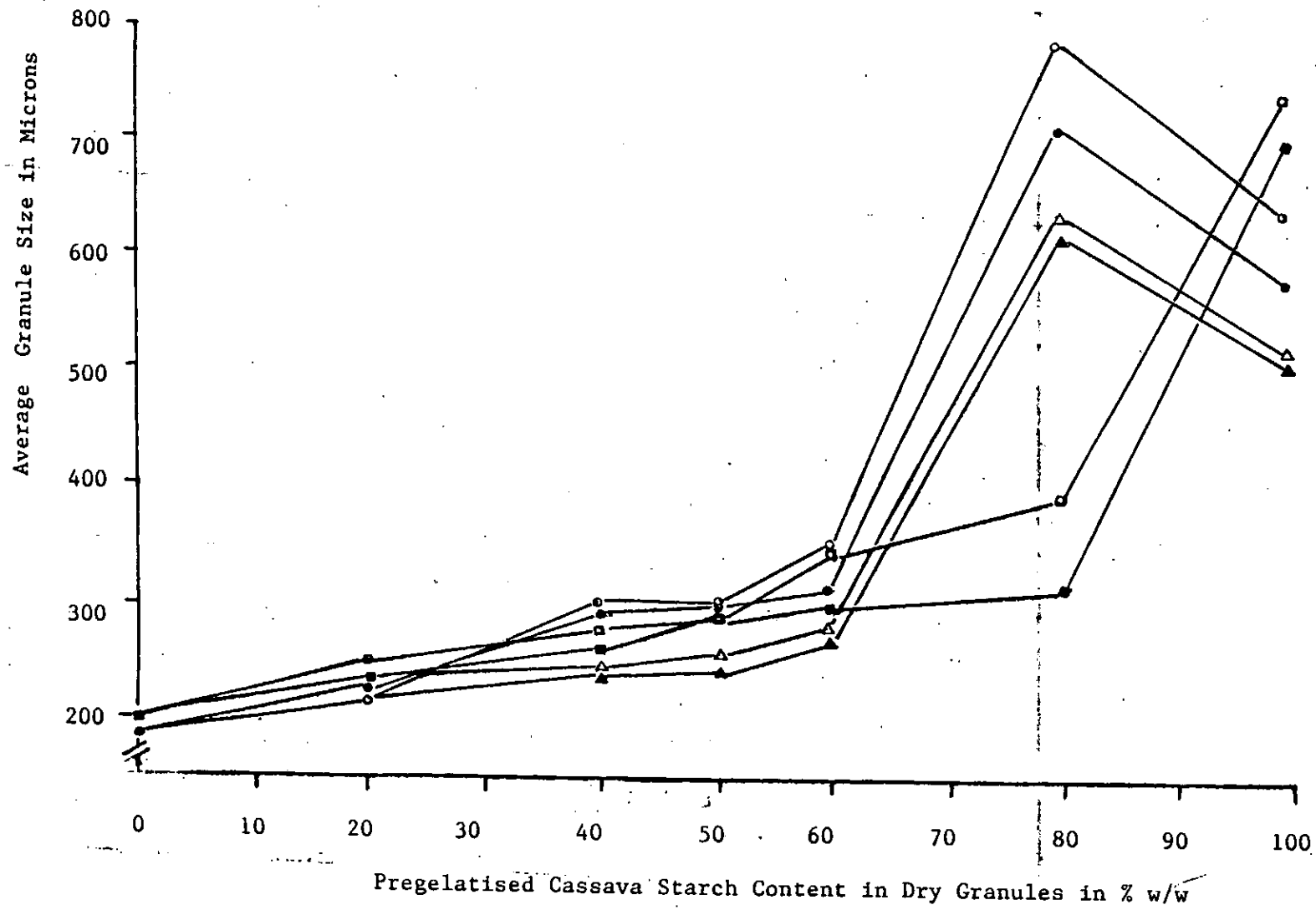
Key for Fig. Nos. 3.3.2.1 To, 3.3.2.9

    o    120μms at 68 - 70°C

    •    120μms at 98 - 100°C

    △  180μms at 68 - 70°C

   ▲  180μms at 98 - 100°C

  o   250μms at 68 - 70°C

  ■  250μms at 98 - 100°C

Fig 3.3.2.2 - Effect of pregelatinised starch concentration on the granular
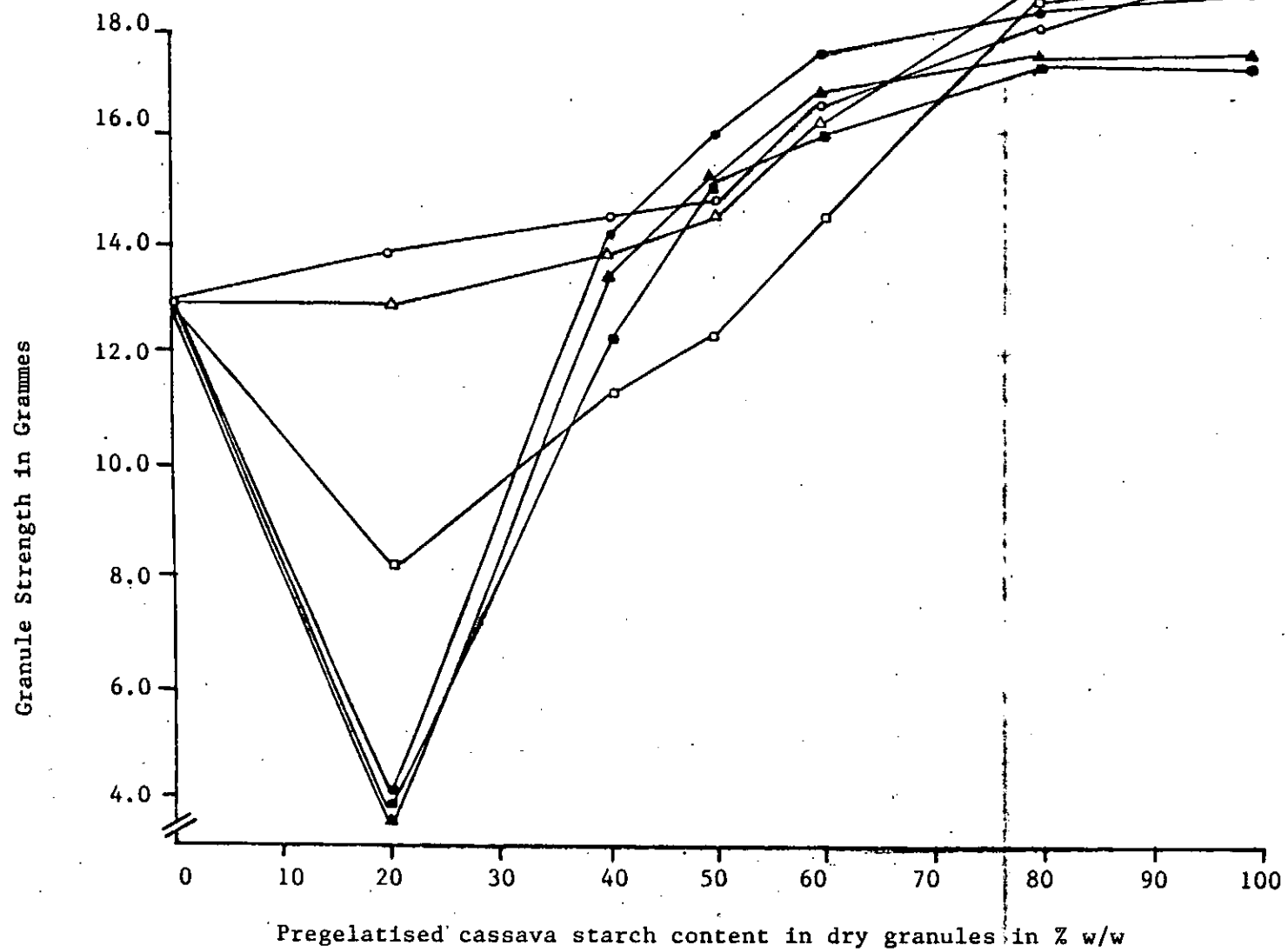Strength of cassava granulations

Fig 3.3.2.3 - Effect of Pregelatinised starch concentration on the
Flow Rate of cassava starch granulations



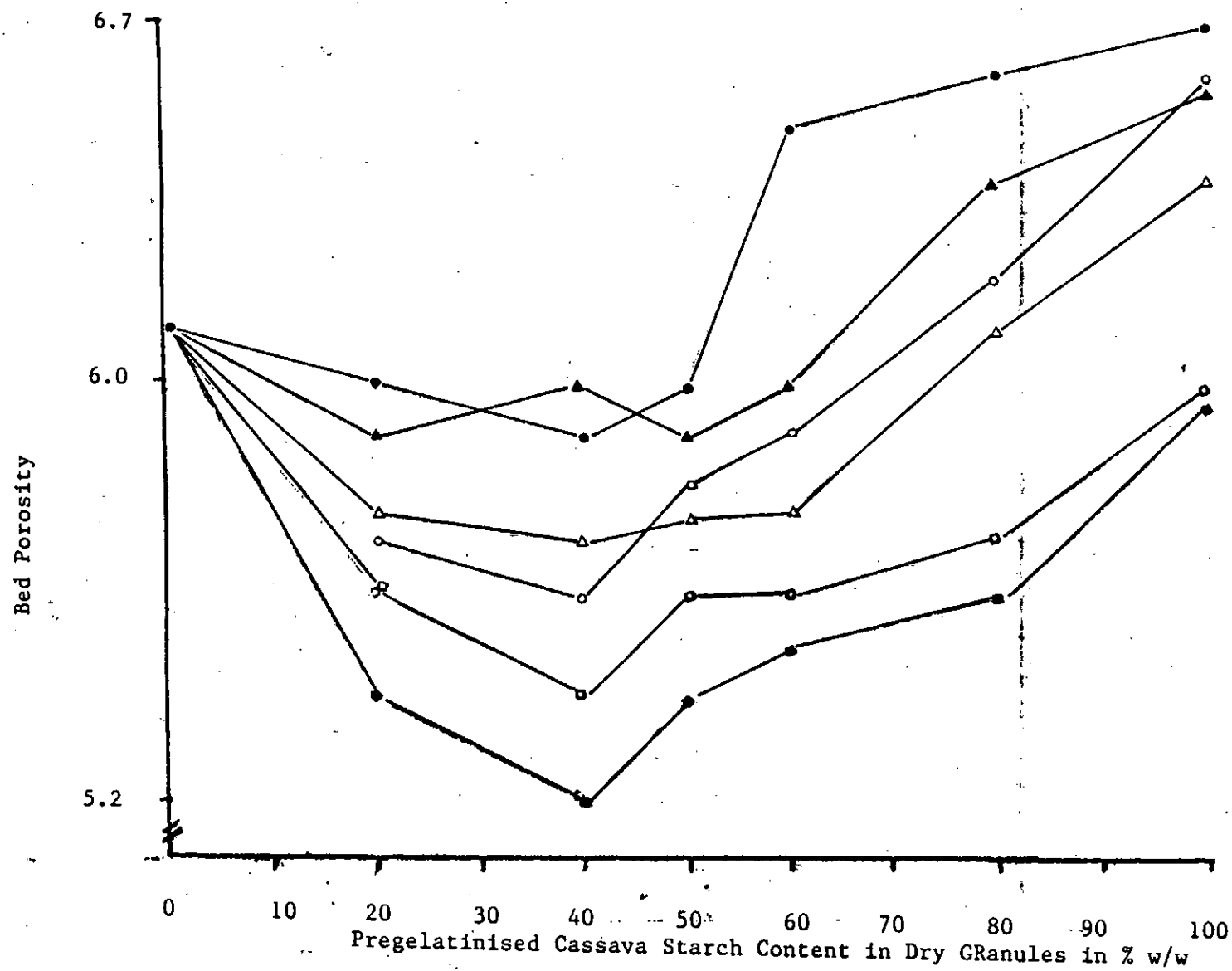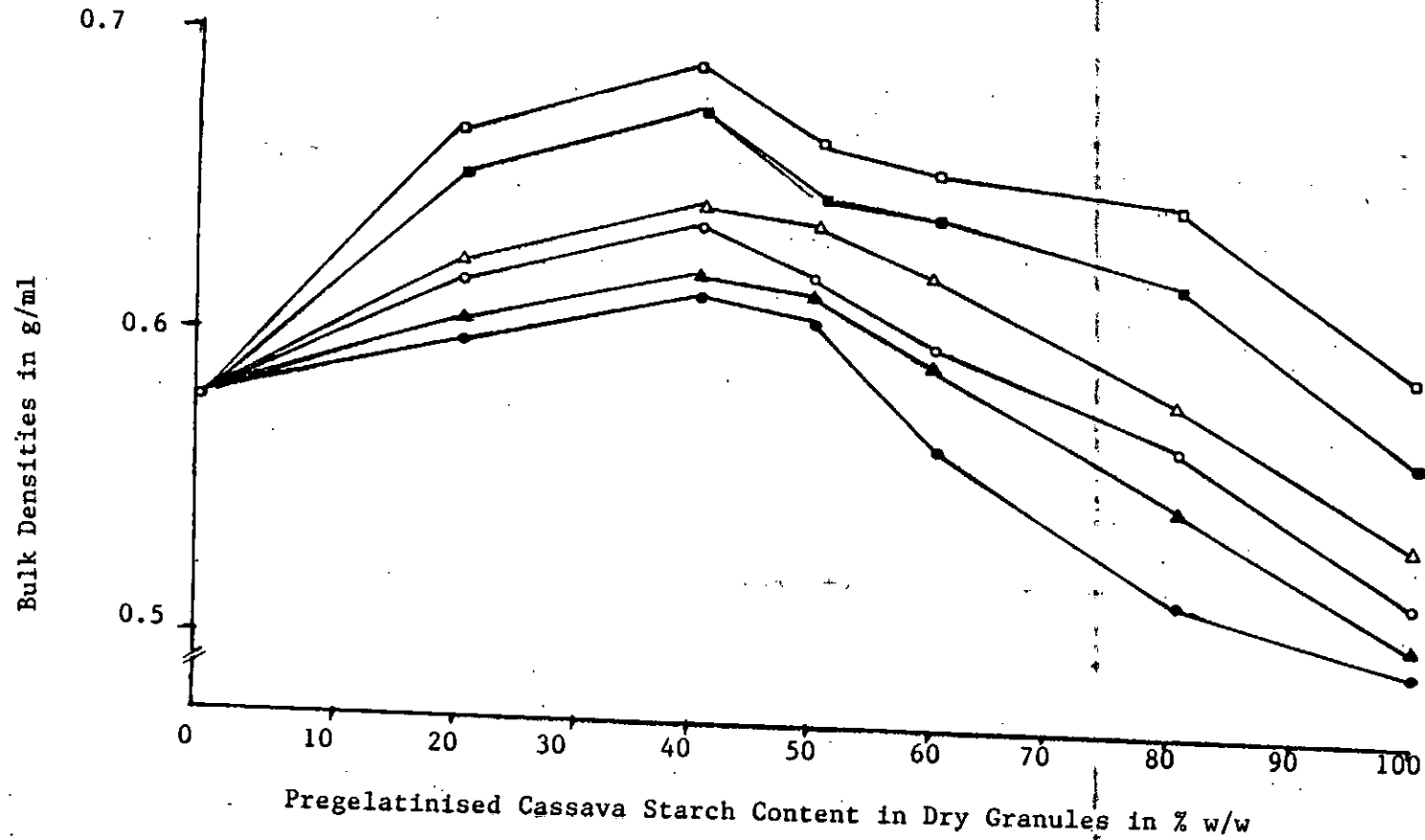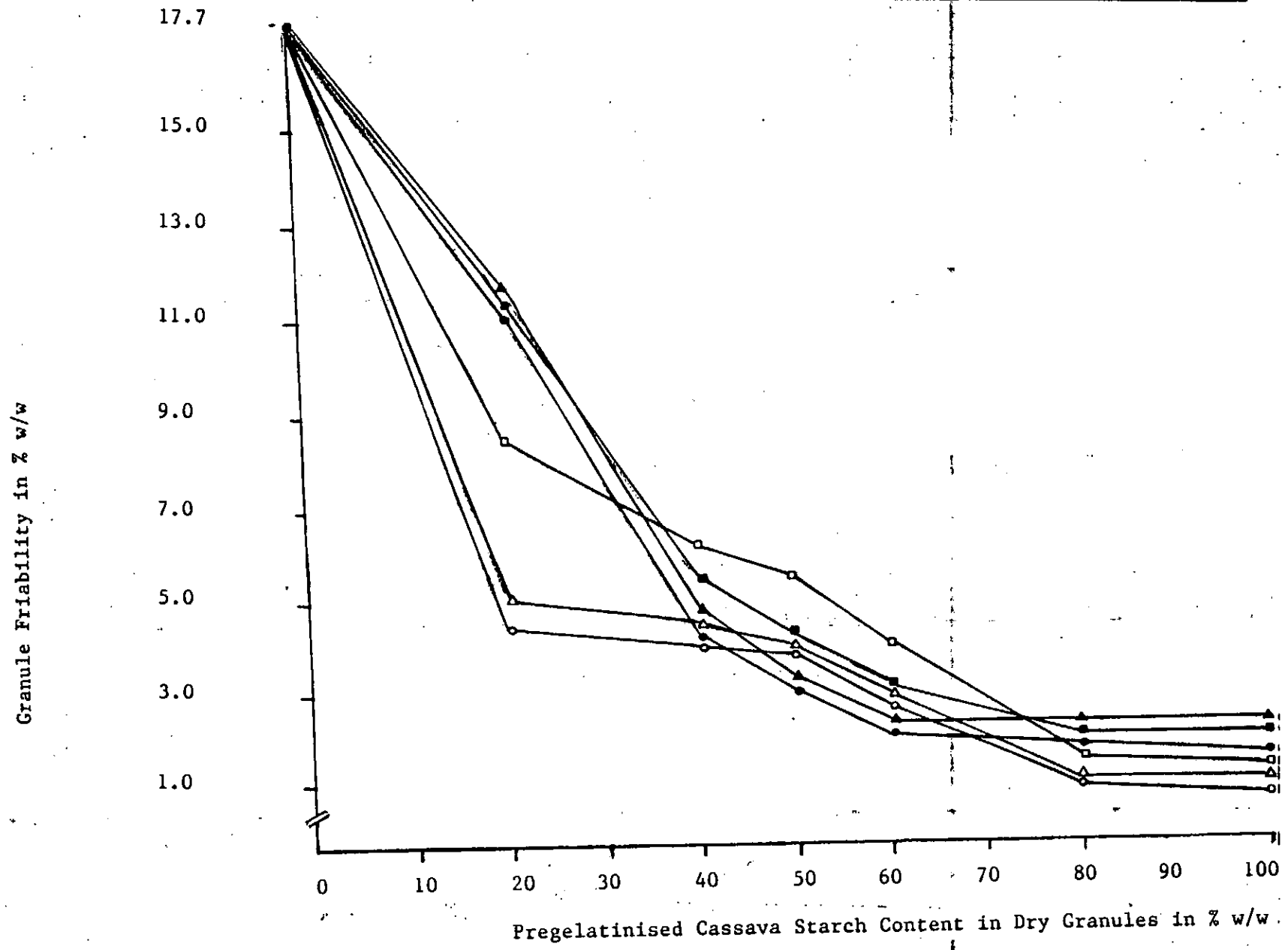Pregelatinised Cassava Starch Content in dry granules in % w/w
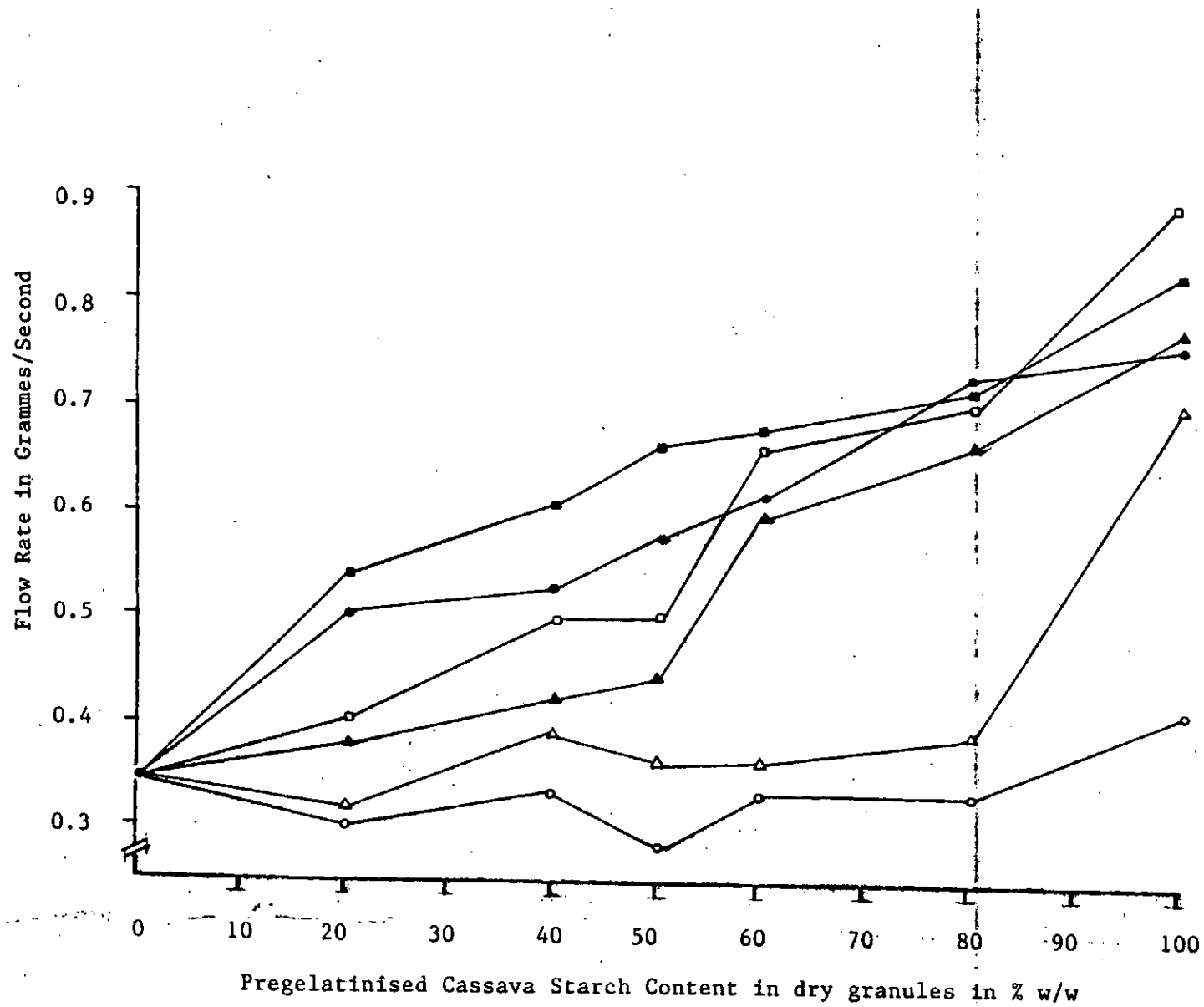
Fig 3.3.2.4 - Effect of pregelatinised starch concentration on the Hausner Quotient of cassava starch granulations
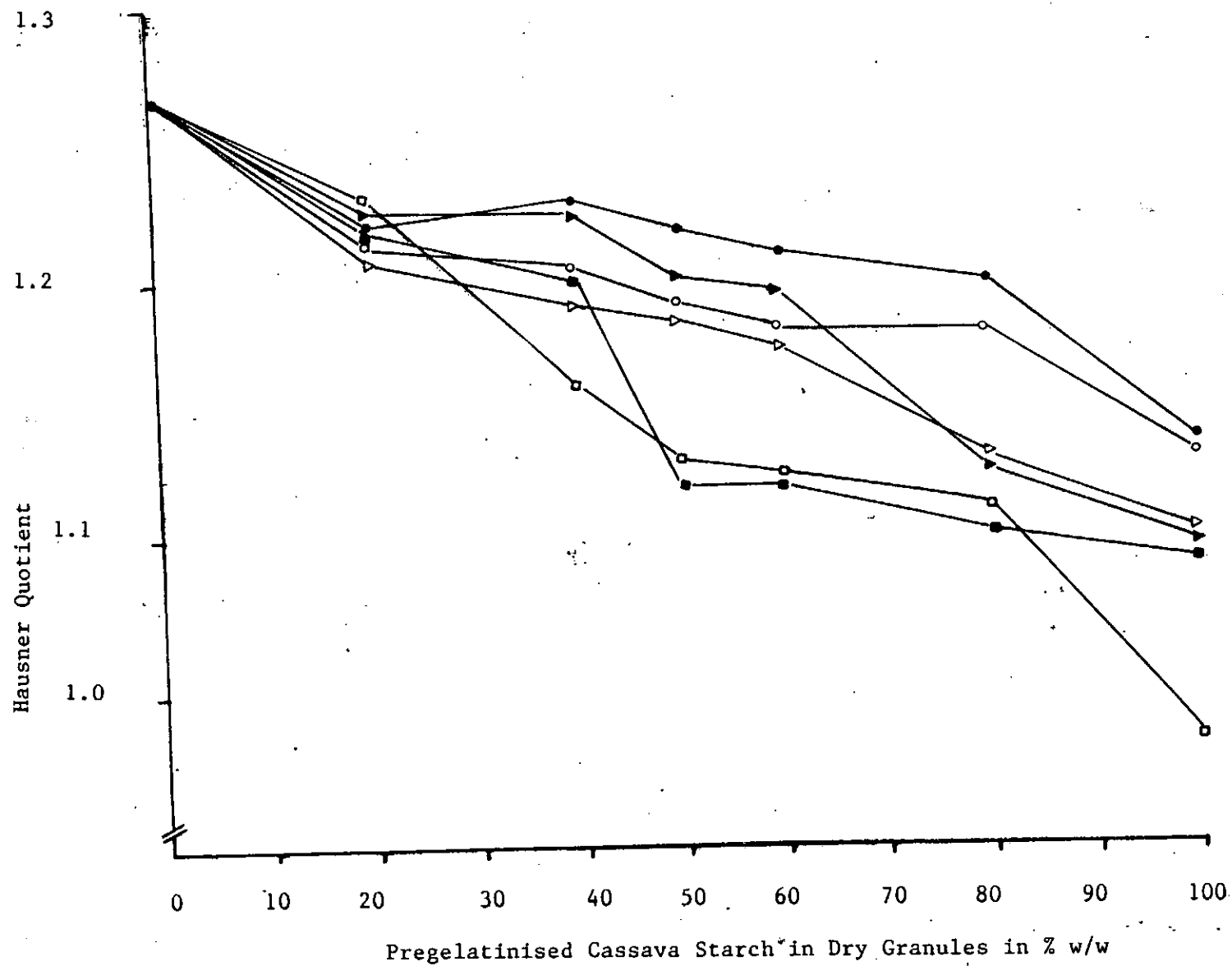
Fig 3.3.2.5 - Effect of pregelatinised starch concentration on the
Carr's percent compressibility of cassava starch
granulations



Carr's Percent Compressibility

Pregelatinised Cassava Starch Content in Dry Granules in % w/w
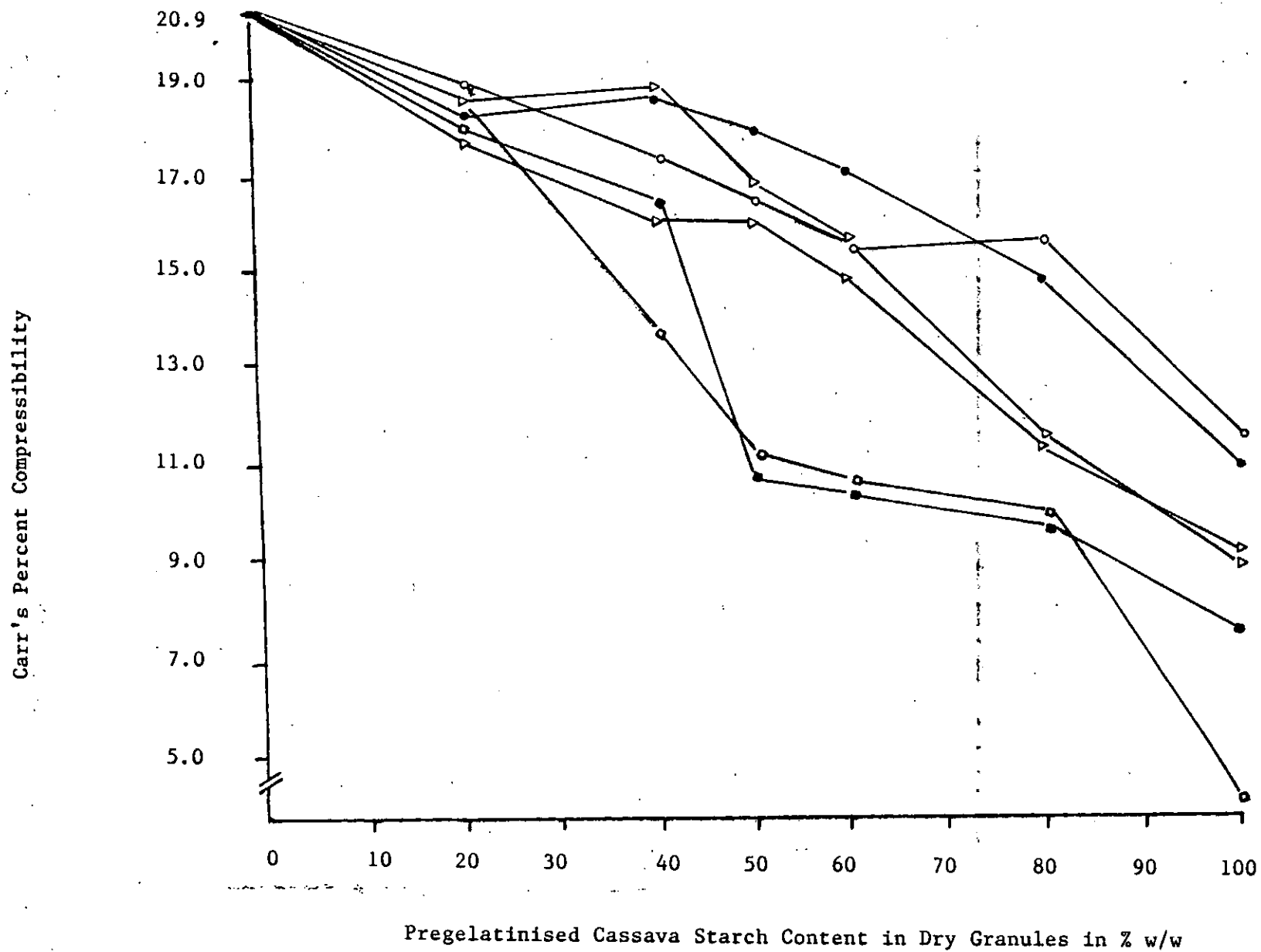
Fig 3.3.2.6 – Effect of pregelatinised starch concentration on the Bed porosity of cassava starch granulations

Fig 3.3.2.7 - Effect of pregelatinised starch concentration on bulk
densities of cassava starch granulations

Fig 3.3.2.8 - Effect of Pregelatinised starch concentration on
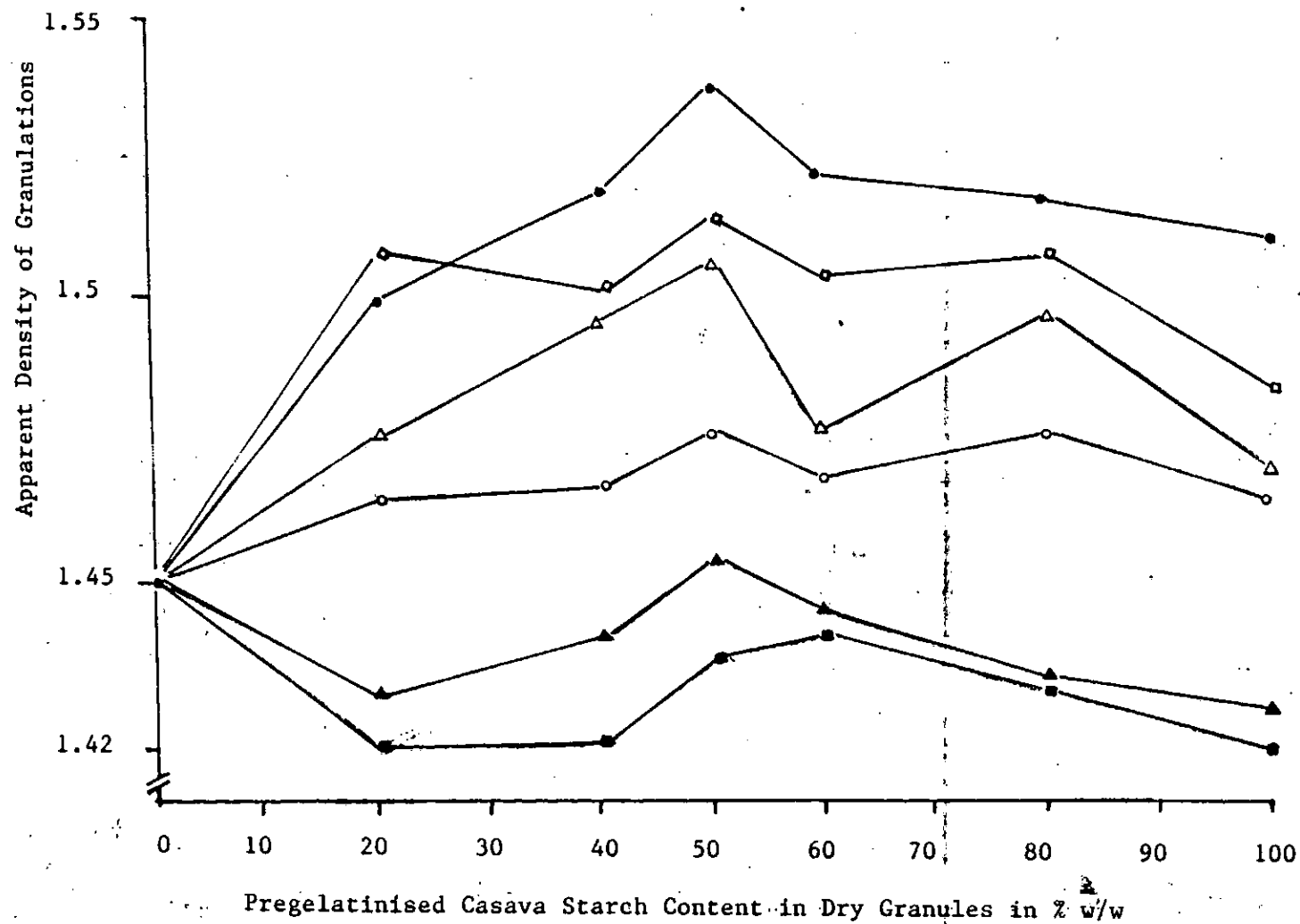the granule friability of cassava starch granulations

Fig 3.3.2.9 - Effect of pregelatinised starch concentration on

the Apparent density of cassava starch granulations

## 3.3.3

### The effect of pregelatinised starch particle size on the granular properties of cassava starch

Results on the effects of various particle sizes; 120 μms, 180 μms , and 250 μms of starch pregelatinised at 68 - 70°C;and 120 μms, 180 μms and 250 μms of starch pregelatinised at 98 - 100°C are shown in Tables 3.3.2.1 - 3.3.2.6

Pregelatinised starch is a dry tablet binder (124). In the presence of the granulating fluid, during the wet granulation phase, part of the pregelatinised starch dissolve in the water binder to form surface film, while a vast majority presumably blends with the plain cassava starch as a diluent.

In the study of the effect of particle size of pregelatinised cassava starch on the granulation properties, these two possibilities are considered.

As part of the diluent blend, the particle size of the pregelatinised starch contributes its quota on the granule growth which comprises three stages; nucleation, transition and ball growth regions (.2.). At the start of the nucleation region, nuclei of two or more primary particles are formed, held together by liquid bridges which

primarily are pendular.  In the nucleation region,
further growth occurs, the remaining primary
particles being bound to nuclei by pendular bindings.
It is easier to bind a primary or smaller particle
to another one than to bind two nuclei or larger
particles, because the tensile strength of liquid
bridges is inversely proportioned to the diameter
of the particles ( 2 ).  An increase in the particle
size of the starting material therefore gives a
lower growth rate.  The explanation could be that
tensile strength increases from the pendular to the
capillary state.          Larger droplets thus being
able to bind larger particles together due to
formation of funicular, or capillary bindings.
The number of bindings of these types, and thus
granule growth rate in the nucleation region,
increase simultaneously with a rise in the amount
of water on the surface of the particles which may
be caused by increasing the surface area of the
pregelatinised starch.  Thus the smaller particle
sizes formed larger average granule size than the
larger ones (fig. 3.3.2.1).  After addition of
water in a certain quantity, most of the primary
particles including the plain cassava starch particles

and the pregelatinised starch particles are agglo-
merated. Previous workers have shown that a
definite relationship exists between granule
strength and granule size (i.e. surface area) and
that within limits the relation; granule strength
= K  x surface area is applicable ( 2 ).

Fig. 3.3.2.8 showed that granules obtained
with 120 ums particle sizes of the pregelatinised
starch showed the least granule friability
(fig. 3.3.2.8) and largest granule strength
(fig. 3.3.2.2). Granule strength and friability
are important, as they affect changes in particle
size distribution of granulations and consequently
compressibility into cohesive tablets. Generally,
it was observed from results that the smaller the
particle size of the pregelatinised starch, the
larger the average granule strength (fig. 3.3.2.2)
at both the two pregelatinization temperatures
studied, and the lower the granule friability.

A granule is an aggregation of component parti-
cles held together by the presence of bonds of
finite strength. The strength is the outcome
of the initial surface tension and viscosity of the
liquid binders holding the particles together in

liquid bridges during the wet granulation phase,
drying of which resulted in the formation of
fusion or re-crystallization of particles and
curing of the adhesive binder. Van der Waals
forces have some contributions on the granule strength.
The resultant strength of the granule is dependent
upon the base material particularly the particle
size and      kind and amount of the granulating agent
used.          Granules produced with 120 ums particle
sized pregelatinised starch were much stronger,
owing to the larger number of bonds formed per
unit volume. Essentially, the number of bonds
formed with the fine grades of pregelatinised
starch is a function of particle size. Thus, with
the finer grades of pregelatinised starch, more
bonds were formed during granulation and granule
strength was therefore greater for these granules
than for those produced from the coarse grades of
pregelatinised starch.

Another line of thought is due to the enhanced
surface area  of the finer particle sizes of the
pregelatinised starch, which is exposed to the
solvent action. More of the finer particles of the
pregelatinised starch dissolved in the water binder

than the coarser grade, causing enhanced viscosity
and enhanced granule size.

In like manner, the bed porosity increased as
the particle size of the pregelatinised starch
decreased, because the granules of the finer grades
tended to be more spherical than the coarser grades.
With the smaller particles, the number of points
at which liquid bonds form increases, resulting in
more porous bed and greater strength of granules
upon drying.

The bulk and Apparent densities (Figs. 3.3.2.7
and 3.3.2. 9) indicated that as the particle size
of the pregelatinised starch decreased from 250ums
to 180ums, to 120ums, the densities decreased and
the bed porosities increased.

An important measure that can be obtained
from bulk density determinations is the percent
compressibility C, which is defined as:

$$C = \frac{D - Do}{D} \times 100$$

where $Do$ = Loose density

$D$ = Bulk density

In theory, the more compressible a bed of particu-
lates is, the less flowable the granulation will

be (37). Fig. 3.3.2.5 shows that the pregelatinised cassava starch with particle size of 120 µms had the highest Carr's percent compressibility followed by particle sizes of 180 µms and 250 µms at both pregelatinization temperatures studied; meaning that granulations obtained with the coarse particle sizes of the pregelatinised starch formed more flowable granulations. Fig. 3.3.2.4 showed the Hausner Quotient of all the granulations containing various particle sizes of the pregelatinised cassava starch. Generally, the lower the Hausner Quotient, the more flowable the granulation.

### 3.3.4  The effect of pregelatinization temperature on the granular  properties of cassava starch

Using the various particle sizes, 120µms, 180µms and 250µms in section 3.3.2, the effect of pregelatinization temperatures (68° - 70°C), and (98° - 100°C), on the binding effect of pregelatinised starch on plain cassava starch powder was studied. Results are shown in figs. 3.3.2.1 - 3.3.2.9.

It is necessary to distinquish between the temperature ranges referred to, in this text.  T  is the range of the pregelatinization temperature of the starting material.  The temperature of the granulating fluid was kept constant at the room temperature of 28°C.

Results have shown that the pregelatinization temperature  T, influences the soluble fraction of pregelatinised starch.  The one pregelatinised at the lower temperature of 68°- 70°C is less soluble than that pregelatinised at 98°- 100°C.

As explained earlier, pregelatinised starch with more soluble fraction will increase the viscosity of the liquid bridges between the particles which on drying will give harder and stronger  bonds.

This probably explained why the granule strength was foun

to be greater using the starch pregelatinised

at 98 - 100°C.

Although gelatinization of cassava starch

started at 59.3°C (134), this study has shown

that the gelatinization was incomplete even at

68 - 70°C (Fig. 3.3.1). However completion was

obtained at 98° - 100°C.

As gelatinization temperature increased there

was a rise in viscosity. The mass gelatinised

at 98° - 100°C became very viscous, tough, elastic

and more rigid than the counterpact made at the

lower temperature ranges. Even after drying,

powdering and granulating with the water binder, the

granules obtained became stronger, and bigger due

to the strong mechanical bonds inherited from the

starting material, made at the higher pregelatini-

zation temperature.

Generally, it was found from results that the

higher pregelatinization temperature of 98° - 100°C

formed the larger average granule size, granule

strength and least friability for all the particle

sizes studied.

The bed porosity increased as the pregelatini-
zation temperature increased because the granules
of the fully gelatinised starch tended to be
more          than the partially gelatinised
starch. (Fig. 3.3.2.6)

The Bulk and Apparent densities (figs 3.3.2.7
and 3.3.2.9) indicated that starch pregelatinised
at 98° - 100°C formed increased densities meaning
that the die - fill is excellent.

The Carr's percent compressibility is obtained
from the equation

$$C = \frac{(D - Do)}{D} \times 100$$

where  $Do$ = loose density

          $D$ = tapped (bulk) density

Results (fig. 3.3.2.5) show that at the lower
concentrations of the pregelatinised starch
(20 - 60% W/W), the granulations made with the
starch pregelatinised at 68 - 70°C appeared to
have higher Carr's percent compressibility than
the counterpacts made at 98° - 70°C, meaning that
the granulations made using the starch pregelatinised
at 98° - 70°C were more flowable and probably more
spherical.

Fig. 3.3.2.4 showed the Hausner Quotient obtained for all the granulations. Generally, the lower the Hausner Quotient the more flowable the granulation. This figure shows that the starch pregelatinised at 68 - 70°C had the higher Hausner Quotient for most of the granulations studied, while 98° - 100°C had the least. This again has confirmed the earlier probability that the granulations made with starch pregelatinised at 98° - 100°C exhibited better fluidity.

### 3.4.0 The effect of starch type of the reworking potentials of starch compact

Reworking potential is the ability for compacts to undergo reworking without losing its compressional characteristics. In this study, 500 mg compacts were prepared from granulations containing various concentrations of pregelatinised starches of cassava, yam, maize and potato. The compacts were evaluated for hardness, friability and disintegration time.

Similar compacts were then remilled to the original particle size by passing through mesh 85 and recompressed into 500 mg compacts as before using the same compaction pressure. These new compacts were again evaluated as described in section 2.3.11.

The results obtained are seen in Table 3.4.0, Figs. 3.4.0.1 and 3.4.0.2. The compacts made from maize starch had the best disintegration and hardness properties before reworking. The hardness for maize starch containing 80% W/W pregelatinised starch was found to be 7.5 kg, while those for cassava, potato and yam were 5.8 kg, 5.8kg and 6.5 kg respectively. While working with starch-lactose compacts, Eriksson (117) reported 5.0 kg as being an acceptable hardness value for tablets. This study also showed the

corresponding disintegration times as 55 seconds
for maize, 360 seconds, 240 seconds and 240 seconds
for cassava, potato, and yam respectively.

Table 3.4.0 and Figs. 3.4.0.1, 3.4.0.2 show
tablet properties after crushing and recompression.
It appeared as if a certain deterioration had taken
place. The hardness for the starch compacts of maize,
cassava, potato and yam were found to be 4.0kg, 5.0kg,
4.0kg and 4.8kg respectively. The corresponding
disintegration times were 47 seconds for maize,
45 seconds, 165 seconds and 222 seconds for cassava,
potato and yam respectively.

Since starch swelling is dependent on the nature
of the granule structure, it is not surprising that
mechanical injury such as milling or crushing causes
increased swelling, hence decreased disintegration
time and hardness. The crushed and recompressed
compacts undergo marked swelling, even in cold water.

It has been suggested that compression may cause
more permanent deformation, that the deformed starch
grains are energy-rich and that this energy is released,
when the grains are exposed to water (158). The
energy-rich starch grains swell rapidly in water,
unlike undeformed grains, which require more heat in
order to swell. This seems to explain why reworked
compacts become energy-richer and swell more rapidly
than the original compacts.

Starch consists chiefly of two polymers; amylose and amylopectin linked together through alpha glycosidic bonds. The proportions of these components differ from specie to specie as mentioned earlier on. It has been shown that the amylose fraction acts as an effective disintegrant in dry or slurry form, whereas amylopectin provides the binding power of starch paste (155). It has also been shown by Kwan and Milosovich (156 ) that amylopectin is also an extrememly effective disintegrant in insoluble system, if not tied up as a binder.

Granule structure differs from specie to specie. Starch grain consists of both crystalline and amorphous regions. The crystalline regions hold the granules together and limit the amount of distortion which a granule can undergo on swelling, while the amorphous portion easily absorb water and swell. The extent of gelatinization of normal starch, depends to a large extent on the starch structure Katz (157) described the cereal starches as A-pattern; potato and other tuber starches as the B-pattern, and tapioca starch as the C pattern, which is a mixture of A and B patterns superimposed. Some of the crystallinity is destroyed on gelatinization to amorphous pattern which probably explains

the water solubility of pregelatinised starch.

It appears from the results obtained in this study, that variation in the observed hardness of the various starch compacts probably depends on the varying amylose/amylopectin composition.as well as the varying crystallinity from specie to specie.

From the diagrams of crushing strength in kilograms of compacts against applied pressure for the compacts obtained before and after reworking (Figs. 3.4.0.3 - 3.4.0.6), it was possible to calculate the reworking potentials of the various starches. The reworking potential (R.P) has been obtained from the equation $R.P = \frac{A1}{A_2} \times 100$ where $A_1$ is the area under recompression curve and $A_2$ is the area under the first compression.

Results have shown that R.P for compacts prepared with various blends of plain and pregelatinised cassava; potato, yam and maize starch, were found to be 45, 32.3, 37, and 40 respectively.

Thus the reworking potential of cassava starch is comparable to that of maize and by far better than those of potato, and yam starches. This quality coupled with its easy availability and cheapness could serve to single out cassava as the most promising source of directly compressible filler-binder in this country.

## Table 3.4.0

### Compact Properties of some starches blended with 80% W/W pregelatinised counterparts at bulk density 1.27

| Starch Type | COMPACT | PROPERTIES | | | | |
|---|---|---|---|---|---|---|
| | Before crushing | | | After crushing | | |
| | Hardness | D.T. in sec | Friability in % w/w | Hardness in kg | D.T. in sec | Friability in % w/w |
| Cassava | 5.8 | 360 | 0.23 | 5.0 | 45 | 1.28 |
| Potato | 5.8 | 240 | 1.01 | 4.0 | 165 | 8.5 |
| Yam | 6.5 | 240 | 0.46 | 4.8 | 222 | 0.425 |
| Maize | 7.5 | 55 | 0.54 | 4.0 | 47 | 1.526 |

\*    D.T.  =  Disintegration Time

Key for Fig. 3.4.0.1 and 3.4.0.2

     X  Maize.

     ▫  Yam.

     △  Potato

     ○  Cassava

Fig 3.4.0.1 - Disintegration Time and Hardness of Some Starch Compacts obtained from various Sources (before Reworking)



Crushing Strength in Kg

Disintegration Time in Seconds
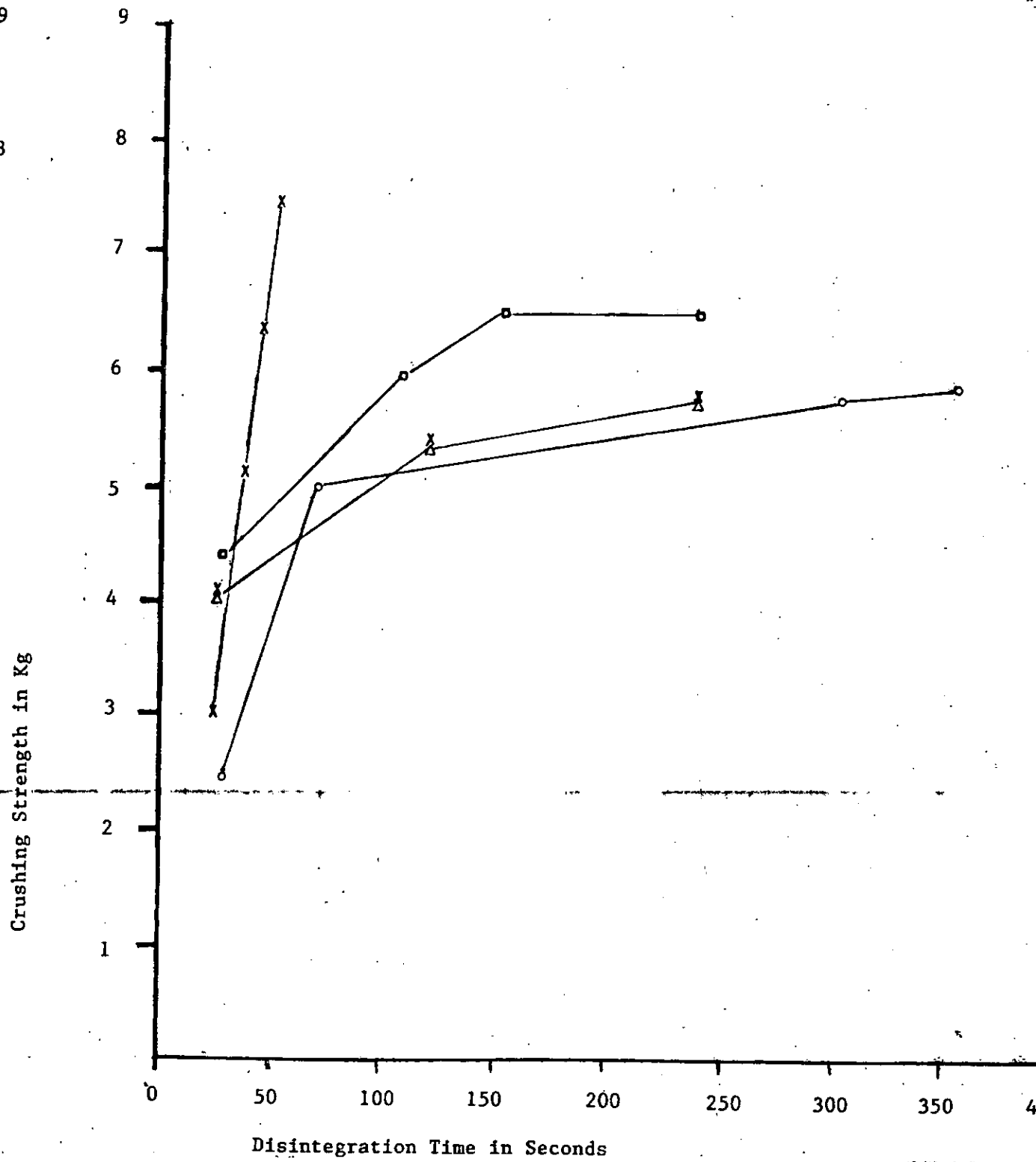
Fig 3.4.0.2 · Disintegration Time and Hardness of Starch Compacts
obtained from various Sources (after reworking)



Crushing Strength in Kg

Disintegration Time in Seconds
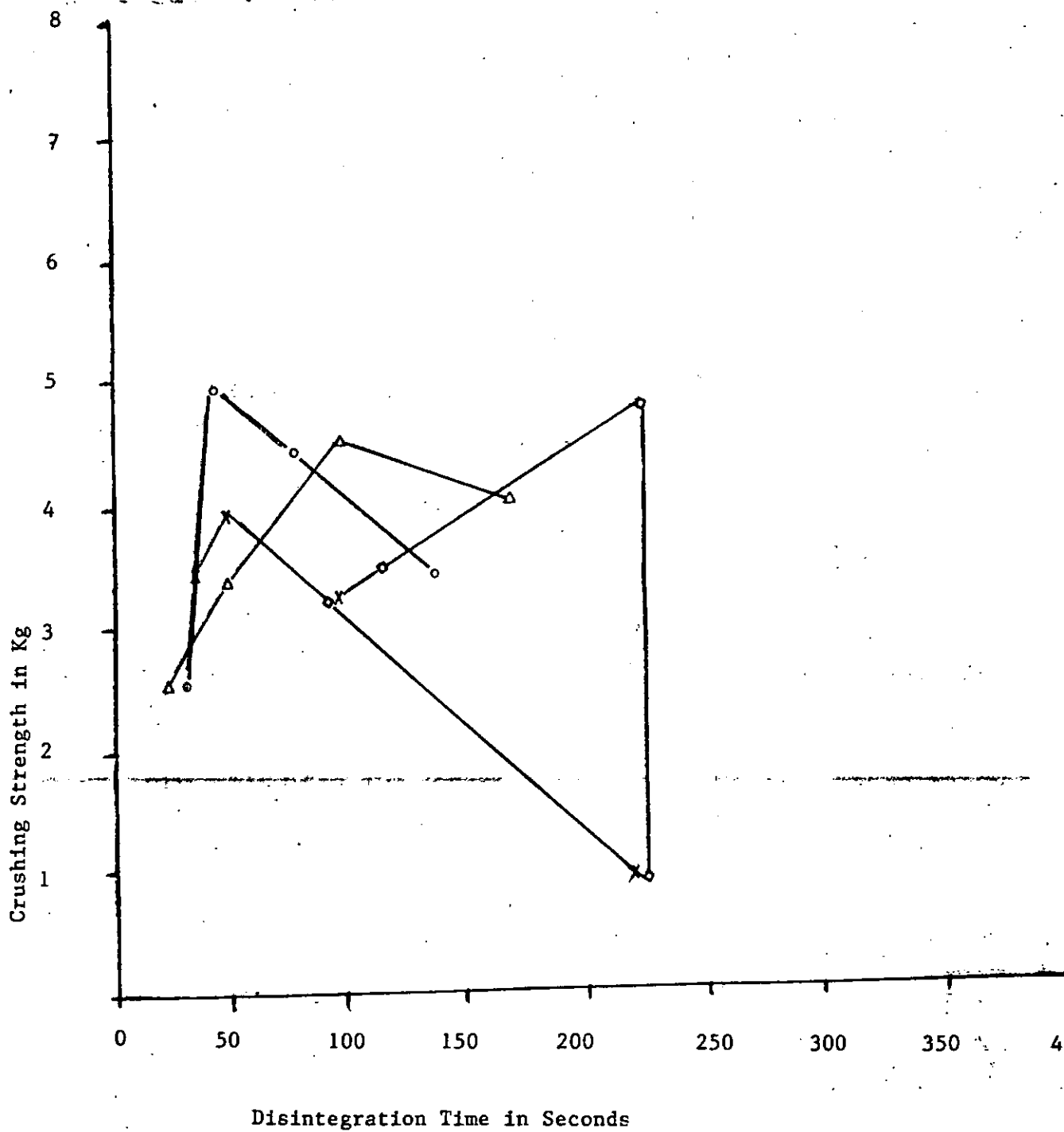
Key for Figs 3.4.0.3 ------- 3.4.0.6

Before Reworking

o   Cassava starch

□   Yam-starch

△   potato starch

X   Maize starch

After Reworking

●   Cassava starch

■   Yam starch

△   Potato starch

X   Maize starch.

Fig 3.4.0.3 The reworking Potentials of Pregelatinised Cassava Starch Compact



Crushing Strength in Kilograms

Applied Pressure in Kg cm$^{-2}$
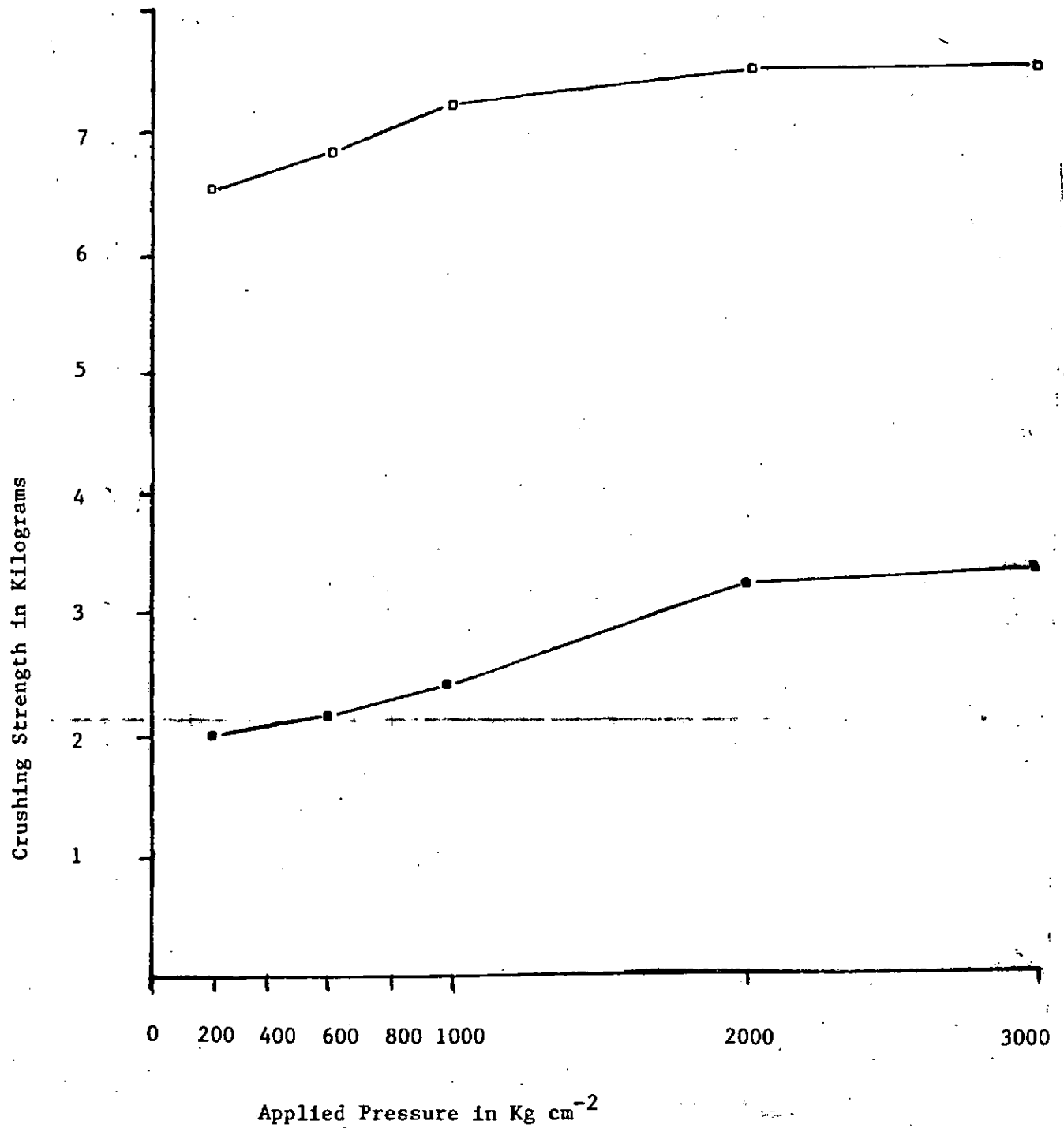
Fig 3.4.0.4    The Reworking Potentials of Pregelatinised Yam Starch
               Compacts.
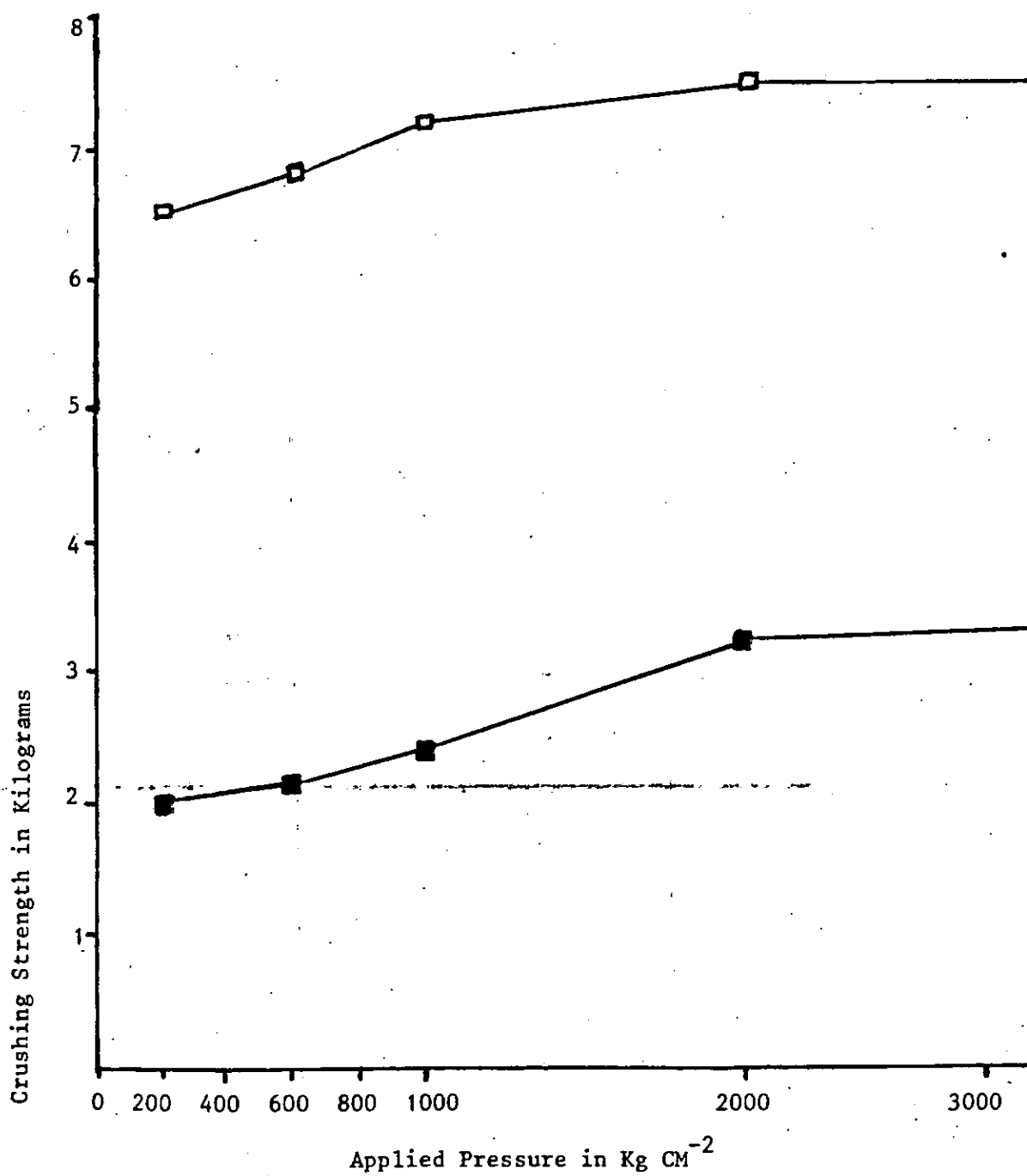
Fig 3.4.0.5    The Reworking Potentials of Potato Starch Compacts



Crushing Strength in Kilograms

Apllied Pressure in Kg cm$^{-2}$
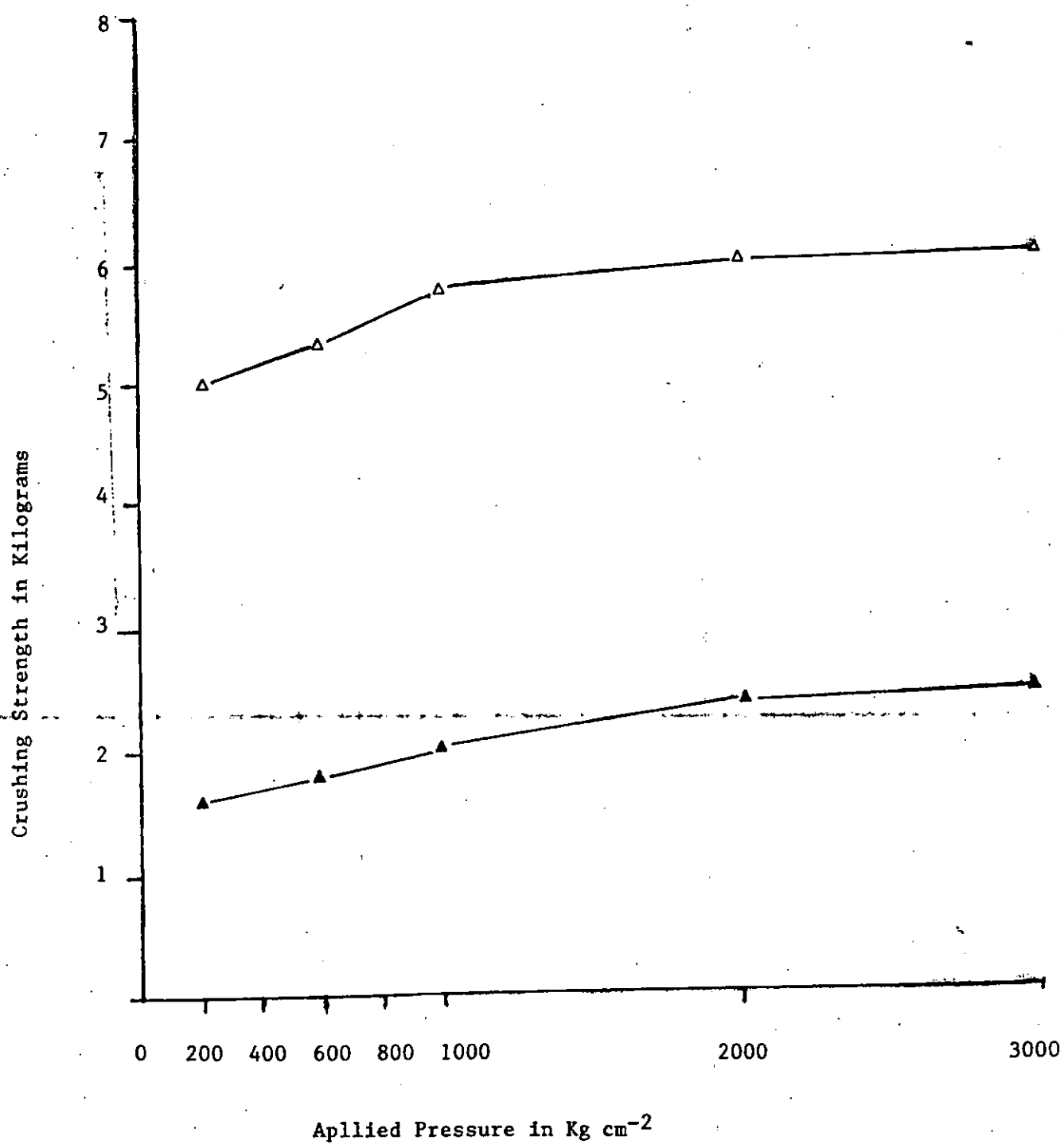
Fig 3.4.0.6 - The Reworking Potentials of Pregelatinised Maize Starch Compacts
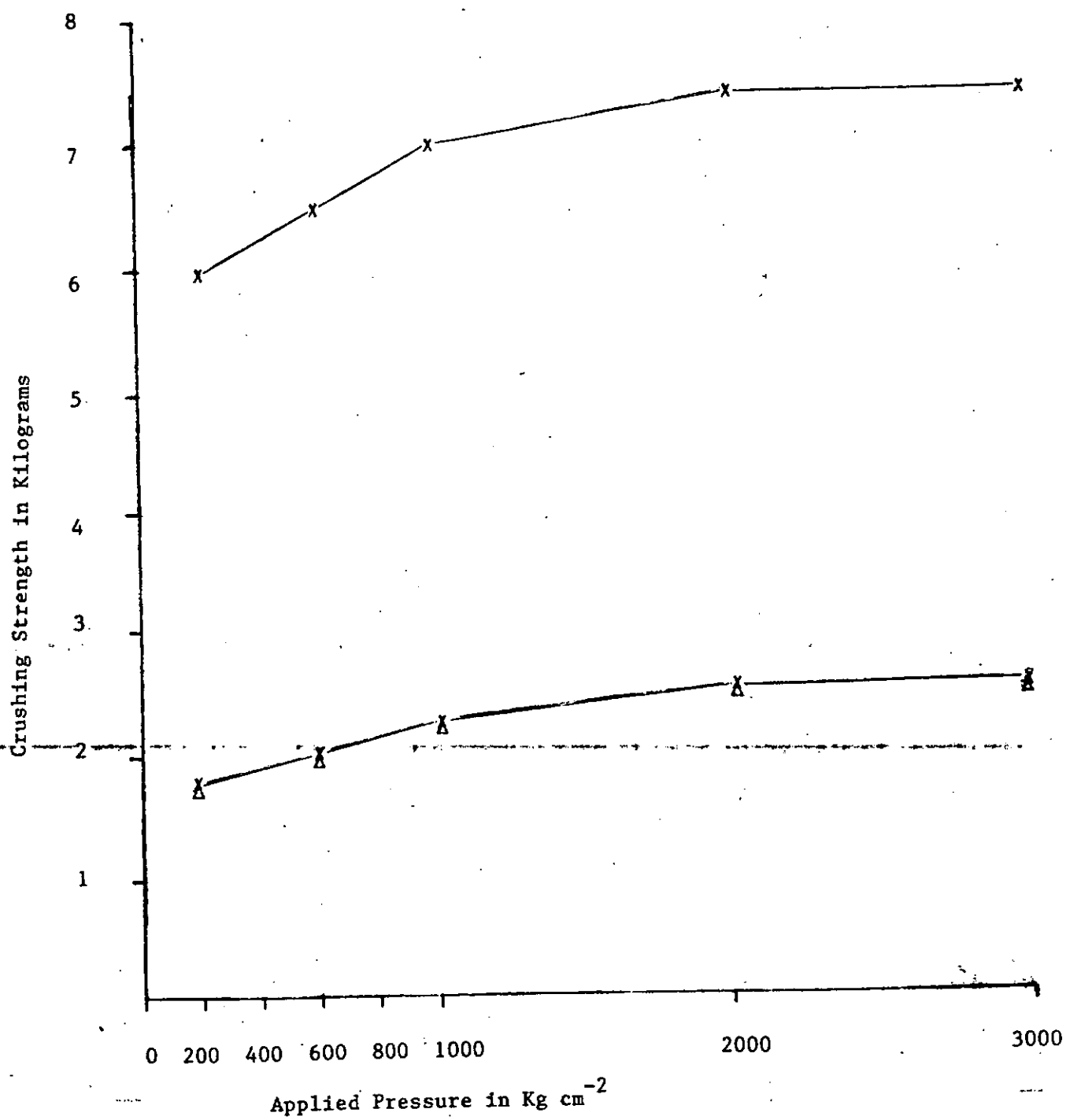
### 3.4.1.1. The effect of the concentration of pregelatinised starch on the crushing strength of cassava starch compacts

The results obtained on the crushing strength of the compacts were found to fit the general equation (Log $Y$ = MB + C), with a correlation coefficient of ) 0.90, where $Y$ represents the crushing strength, B the bulk density of the compacts, M, the slope and C, the intercept. Values for crushing strength at a particular bulk density of 1.27 for all compacts were computed (1.27 chosen because it involved minimum extrapolation).

Equations of Best fit were computed for all the compacts and are given in Table 3.4.1.1. The values obtained for crushing strength were plotted against the concentration of the corresponding pregelatinised starch.

Fig. 3.4.1. showed the results obtained using various particle sizes, 120 μms, 180 μms, and 250 μms of starch pregelatinised at 68° - 70°C and 98° - 100°C. Results showed that as the concentration of pregelatinised starch increased, the crushing strength of most of the compacts increased reaching a

maxima at between 60% W/W and 80% W/W concentration
of pregelatinised starch and then decreased.   These
increases obtained in the crushing strength of the
compact are probably due to the combined binding -
diluent effect of the pregelatinised starch.   This
observation is in line with the work done by
Eriksson 1964 (117) when he studied the disintegration
and hardness of starch-lactose tablets.   He found
that the best disintegration and hardness properties
for starch-lactose tablets are obtained when the
starch component is kept relatively  low (20%).   A
possible explanation is that like lactose, pregela-
tinised starch has some soluble extractives  ( 2 ).
This soluble portion was probably optimum when the
pregelatinised/plain starch ratio was 80 : 20.   Thus
pregelatinised-starch-can be described as a binder-
diluent and diluent-disintegrant, unlike plain starch
which is just a diluent-disintegrant.

The binding effect exhibited by pregelatinised
starch can be described as sugar-like.   This is in
line with the work done by Nelson et al. (136).
These workers were able to rank binders in order of
hardness imparted to tablets as well as to classify

them functionally as exhibiting sugar-like or gum-like behaviour. Binders possessing sugar-like behaviour showed maxima in hardness versus concentration curves. The sugar-like binders examined by Nelson et al (136).

Dextrin, Dextrose Fructose, Lactose, Mannitol, Raffinose hydrate, Rhamnose, Sucrose and Xylose. Increasing the concentration of gum-like binders gave increasingly hard tablets but the rate of increase in hardness decreased. The gum-like binders studied by Nelson et al were acacia, gelatin, methyl cellulose, pectin, sterculia and tragacanth. The property of binding material to adhere to itself and the substrate with which it is mixed is a quality that is related to degree of increase in hardness (136). With 100% W/W pregelatinised starch there was a fall in the compact crushing strength. This result is in line with the work done by Wells and Langridge (56) who obtained good tablets from microcrystalline-dicalcium phosphate dihydrate mixtures. The tensile strength of the tablets increased with increasing proportions of microcrystalline cellulose up to a maximum at all compaction pressures used.

The mechanism by which the binary blend of

pregelatinised/plain starch formed good compacts
may also be related by their modes of deformation.
According to Wells and Langridge (56) Microcrystalline
Cellulose undergoes plastic deformation and the
mechanical strength of its compacts is largely
controlled by hydrogen bonding. In like manner,
pregelatinised starch (pgs) possibly exhibited
plastic deformation, while the plain starch (pcs)
exhibited brittle fracture.

Table 3.4.1.1

Equation of Best Fit (where Y = Crushing Strength, M = Slope, B = Bulk density, C = Intercept)

| Batch No. | Log Y = MB + C | Correlation Coefficient |
|---|---|---|
| 1 | Log Y = 6611B - 4.28 | 0.84 |
| 2. | Log Y = 32,000B - 35.5 | 0.95 |
| 3. | Log Y = 25,023B - 24.9 | 0.78 |
| 4. | Log Y = 46,727 B - 52.2 | 0.90 |
| 5. | Log Y = 27,457 B - 27.2 | 0.98 |
| 6. | Log Y = 9, 554 B - 3.9 | 0.92 |
| 7. | Log Y = 32,633B - 35.1 | 0.95 |
| 8. | Log Y = 70,000B - 83.25 | 0.95 |
| 9. | Log Y = 55,000B - 63.9 | 0.92 |
| 10. | Log Y = 28,182B - 28.7 | 0.82 |
| 11. | Log Y = 35,158 - 36.5 | 0.95 |
| 12. | Log Y = 47,586B - 51.9 | 0.92 |
| 13. | Log Y = 34,545B - 39 | 0.96 |
| 14. | Log Y = 61,765B - 73.6 | 0.93 |
| 15. | Log Y = 34544B - 38.1 | 0.97 |
| 16. | Log Y = 31,667B - 35 | 0.96 |
| 17. | Log Y = 31,598B - 34.2 | 0.78 |
| 18. | Log Y = 69,545B - 82.1 | 0.75 |
| 19. | Log Y = 55,143B - 63.0 | 0.92 |
| 20. | Log Y = 22,892B - 20.4 | 0.78 |
| 21. | Log Y = 37,857B - 41.5 | 0.93 |

| Batch No. | Log Y = MB + C | Correlation Coefficient |
|-----------|----------------|-------------------------|
| 22. | Log Y = 26090B - 26.6 | 0.90 |
| 23. | Log Y = 30909B - 31.5 | 0.67 |
| 24. | Log Y = 342.86B - 36.2 | 0.72 |
| 25. | Log Y = 27,778B - 26.5 | 0.76 |
| 26. | Log Y = 35,294B - 37.7 | 0.97 |
| 27. | Log Y = 23,729B - 24.8 | 0.84 |
| 28. | Log Y = 33,252B - 36.3 | 0.97 |

### 3.4.1.2  The effect of pregelatinised starch particle size on the crushing strength of cassava  starch

Considering next, the effect of particle size
of the pregelatinised starch on the crushing strength
of compacts, Tables 3.4.1.2 and 3.4.1.3 show
that the sequence in crushing strength obtained for
the compacts made with starch pregelatinised at
68° -70°C is 120 ums ) 180 ums ) 250 ums.  The sequence
for compacts made with starch pregelatinised at
98° - 100°C  is 180 ums ) 120 ums ) 250 ums.  The
120 ums starch pregelatinised at 98° - 100°C appeared
to be further weakened by milling and excessive
heating.  Compacts containing 250 ums in all cases
were comparatively the weakest.  A possible explana-
tion for this is the well-known relationship between
solubility and particle-size.

$$S = f \infty \ exp. \ \left(\frac{2 \gamma M}{rpRuT}\right)$$

where S is the solubility of a spherical crystal of
radius r, $f$ is the solubility of an infinitely
large crystal (r = $\infty$), M is the molecular weight,
P is the density, $\gamma$ is the crystal - solvent
interfacial tension.  It has been shown that if an
equal mixture of 1.0 µ and 10.0 µ particles are
considered, the corresponding times for the dissolution
of the 1.0 µ and the 10.0 µ particles would be
approximately a thousand times greater. (12)

Since the pregelatinised starch used in this study serves both as a diluent and binder, and since preliminary studies have shown that pregelatinised starch is slightly soluble in cold water, part of it dissolves in the water-binder to form a glue holding the other starch particles together.

Liquid binders have more adhesiveness than identical dry binders or partly wetted binders. Since the dissolution rate of the very fine particles of $1.0\mu$ could be a thousand times greater than the same mass of a mixture containing $10.0\mu$, this means that pregelatinised starch having the fine particle sizes probably dissolved more quantitatively and more quickly than the coarser sizes and form stronger adhesive than the identical size of coarser particles. This has probably explained why compacts of 180 ums were having the highest crushing strength followed by 250 ums. Complications probably occurred for the 120 um size due to segregation of the various particle size during the mixing of the dry powders, as a result of gravitational effects on the agitated beds of powders. Nevertheless, the difference between the crushing strength obtained for 120 ums and 180 ums was not significant.

Table 3.4.1.2

Crushing strength in kilograms of compacts made
using various particle sizes of starch pregelatinised
at 68 - 70°C at bulk Density 1.27.

| Concentration of pregelatinised starch in % W/W | Crushing strength of compacts made using various particle sizes of pregelatinised starch. | | |
|---|---|---|---|
| | 120 µms | 180 ums | 250 µms |
| 0 | 4.11 | 4.11 | 4.11 |
| 20 | 5.25 | 6.35 | 4.90 |
| 40 | 5.95 | 5.65 | 4.79 |
| 50 | 6.27 | 5.95 | 5.76 |
| 60 | 7.04 | 7.09 | 5.75 |
| 80 | 8.4 | 8.13 | 4.39 |
| 100 | 6.57 | 8.49 | |

Table 3.4.1.3

Crushing strength in kilograms of compacts made
using various particle sizes of starch pregelatinised
at 98 - 100°C at bulk density 1.27.

| Concentration of pregelatinised starch in % W/W | Crushing strength of compacts made using various particle sizes of pregelatinised starch. | | |
|---|---|---|---|
| | 120 µms | 180 ums | 250 µms |
| 0 | 4.11 | 4.11 | 4.11 |
| 20 | 5.8 | 5.91 | 5.32 |
| 40 | 7.6 | 6.55 | 5.93 |
| 50 | 7.5 | 7.73 | 4.88 |
| 60 | 8.2 | 7.37 | 5.01 |
| 80 | 8.1 | 8.76 | 4.49 |
| 100 | 7.5 | 7.08 | 2.31 |

## The effect of pregelatinization temperature on the crushing strength of cassava starch compacts

This study takes into consideration the temperature at which starch was pregelatinised. The photograph (Fig. 3.3.1.4) showed the structures obtained for the starch grains at the two temperature ranges studied.

It has been shown that pregelatinised starch contained some cold water solubles ( 2 ), which probably dissolved in the water binder during the granulation phase to form stronger, more viscous liquid bonds between the starch particles. It is assumed that the starch completely pregelatinised at 98° - 100°C contained more of cold water solubles than that obtained for 68° - 70°C. The result is the formation of harder compacts with starch pregelatinised at 98° - 100°C.

## Table 3.4.1.4

Showing the effect of pregelatinization temperature
on the crushing strength of cassava starch compact
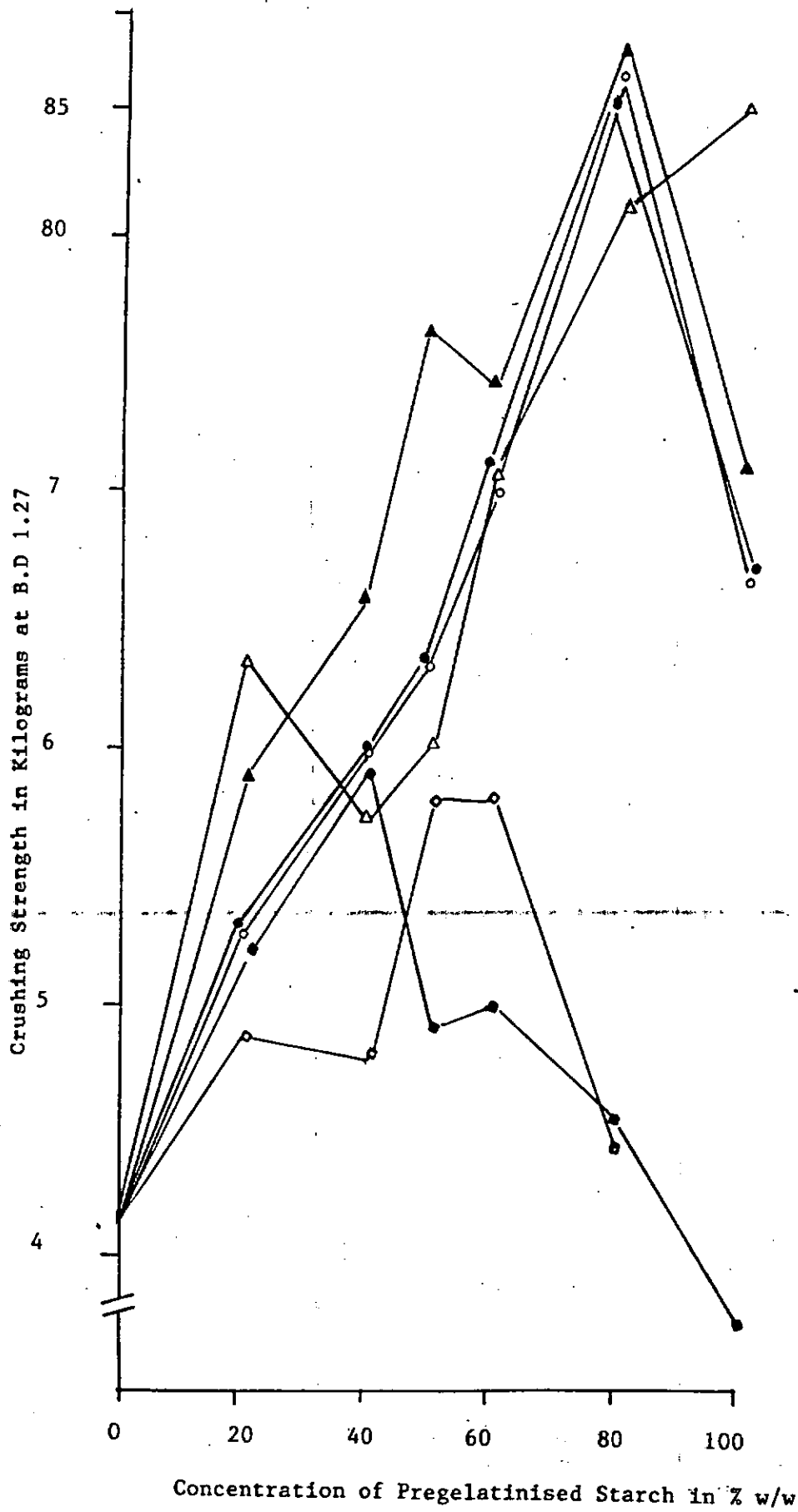using 120 ums pregelatinised starch.

| Concentration of pregelatinised starch in % W/W | Crushing Strength in Kilograms | |
|---|---|---|
| | 68° - 70°C | 98° - 100°C |
| 0 | 3.6 | 3.6 |
| 20 | 5.8 | 6.1 |
| 40 | 6.3 | 6.6 |
| 50 | 7.8 | 8.0 |
| 60 | 8.3 | 8.5 |
| 80 | 8.5 | 8.8 |
| 100 | 6.1 | 6.3 |

Table 3.4.1.5

Showing the effect of pregelatinization temperature
on the crushing strength of cassava starch compact
using 180 um  pregelatinised starch.

| Concentration of pregelatinised starch in % W/W | Crushing Strength in Kilograms | |
|---|---|---|
| | 68° - 70°C | 98° - 100°C |
| 0 | 3.6 | 3.6 |
| 20 | 4.4 | 7.0 |
| 40 | 7.3 | 7.2 |
| 50 | 7.9 | 8.2 |
| 60 | 7.9 | 7.8 |
| 80 | 7.8 | 8.0 |
| 100 | 7.0 | 7.3 |

Table 3.4.1.6

Showing the effect of pregelatinization temperature
on the crushing strength of cassava starch compact
using 250 ums pregelatinised starch.

| Concentration of pregelatinised starch in % W/W | Crushing Strength in Kilograms | |
|---|---|---|
| | 68° - 70°C | 98° - 100°C |
| 0 | 3.6 | 3.6 |
| 20 | 5.6 | 6.2 |
| 40 | 6.3 | 6.95 |
| 50 | 5.7 | 5.8 |
| 60 | 5.2 | 5.3 |
| 80 | 3.2 | 3.7 |
| 100 | 2.8 | 3.2 |

## Key for Figs 3.4.1 ------ 3.4.3.

    o =     120     μms starch pregelatinised at 68 - 70°C

    Δ =     180     μms starch pregelatinised at 68 - 70°C

    □ =     250     μms starch pregelatinised at 68 - 70°C

    ● =     120     μms starch pregelatinised at 98 - 100°C

    ▲ =     180     μms starch pregelatinised at 98 - 100°C

    ■ =     250     μms starch pregelatinised at 98 - 100°C

Fig 3.4.1
The effect of the concentration of the pregelatinised starch
on the crushing strength of cassava starch compacts



Concentration of Pregelatinised Starch in % w/w

### 3.4.2.1 The effect of pregelatinised starch concentration on the friability of cassava starch compacts

In all the compacts compared, there was a decrease in friability as the concentration of the pregelatinised starch increased. Approximately, 0.0% W/W friability was obtained for compacts containing 60% - 100% W/W pregelatinised component.

The compacts containing less than 60% W/W pregelatinised starch appeared to lose the firmness required in compacts. The plain cassava starch did not appear to adhere to itself or to the pregelatinised starch in the blend. This results in weaker points within the compacts and fine cracks around the agglomerates, leading to higher friability at lower concentration of pregelatinised starch.

This is in contrast to the case when 100% W/W and 80% W/W pregelatinised starch were granulated with water and compressed. The presence of agglomerates or even isolated plain cassava starch were not possible because all the composite ingredients of the compact are well enbeded in the partially soluble pregelatinised starch which on drying, probably crystallized out, thereby forming better and stronger bonds.

This study suggests that compact friability improved by increasing the pregelatinised content of the compact to 80% W/W and 100% W/W. This improvement in tablet friability is due to a better bonding, fewer weak points, and better homogeneity of the pregelatinised starch within the compact, since the major excipient (pregelatinised starch) is partially soluble ( 2 ).

Like the observations of Wells and Langridge (56), with 100% W/W micro crystalline cellulose (MC), 100% pregelatinised starch were slightly friable, more friable than compacts containing 80% W/W pregelatinised starch (Fig. 3.4.1.2), especially in the blend containing 250 ums pregelatinised starch.

Shotton and Ganderton 1961 (121) in their studies on the compact behaviour of paracetamol reported that the capping of the tablets at the stress loci was due to the die wall pressure and the elastic axial recovery after removal of the axial pressure. This capping was prevented by the addition of stearic acid which weakened the bonding area and allowed elastic recovery to take place partially at the expense of the bond. In like manner, 20% W/W

and 40% W/W plain starch, coating the surface of the 80% W/W and 60% W/W pregelatinised mass in the compacts could serve as a lubricant and this serves to reduce the die wall pressure. The slower elastic axial recovery after removal of the axial pressure, result in the formation of stronger compacts than the blend containing 100% W/W pregelatinised mass, since plain cassava starch itself has a lubricating effect (19).

### 3.4.2.2 The effect of Pregelatinised starch(pgs) particle size on compact friability

Table 3.4.2.1., 3.4.2.2 and Fig. 3.4.2.1 show the effect of pregelatinised starch particle size on compact friability at various concentrations of the pgs.

The results showed that compacts made with 180 ums pregelatinised starch were the least friable when compared with values obtained for 250 $\mu$ms and 350 $\mu$ms. The larger particle sizes were probably too heavy for the 180 ums particles size of the plain starch used in the composite blend, resulting in segregation of the larger particle sizes. However, blending 180 $\mu$ms sized pgs with the 180 $\mu$ms sized plain cassava starch (pcs) formed a homogeneous, well-blended mass, resulting in better bonding and better compact friability. The larger particle sizes of 250 $\mu$ms, 350 pgs did not appear to adhere to itself or to the plain starch in the blend. This again formed weaker points within the compacts resulting in the formation of cracks around the agglomerates. Higher compact friability was thus obtained.

In like manner, independent motion appeared
to set in when the very fine particle size of
120 um pgs was blended with the 180 um plain starch.
The larger particle sized plain starch in the
agglomerate could migrate to the bottom of the die
under light pressure, thus breaking the bonding
effect of the pgs. This could result in the
formation of fine cracks around the agglomerates
leading to a higher friability of the compact.
Thus more uniform blending and better compact
friability were obtained for same particle size
180 ums of the composite blends.

Table 3.4.2.1

Friability values of compacts at bulk density
1.27 using various particle sizes of starch
pregelatinised at 68 - 70°C.

| Concentration of pregelatinised starch in % W/W | Friability in % W/W of compacts made using various particle sizes of pregelatinised starch | | |
|---|---|---|---|
| | 120 ums | 180 ums | 250 ums |
| 0 | 0.9 | 0.9 | 0.9 |
| 20 | 0.18 | 0.11 | 0.11 |
| 40 | 0.085 | 0.06 | 0.11 |
| 50 | 0.25 | 0.12 | 0.22 |
| 60 | 0.00 | 0.00 | 0.19 |
| 80 | 0.00 | 0.00 | 2.0 |
| 100 | | | |

Table 3.4.2.2

Friability values of compacts at bulk density 1.27 using various particle sizes of starch pregelatinised at 98 - 100°C.

| Concentration of pregelatinised starch in % W/W | Friability in % W/W of compacts made using various particle sizes of pregelatinised starch. | | |
|---|---|---|---|
| | 120 μms | 180 μms | 250 μms |
| 0 | 0.9 | 0.9 | 0.9 |
| 20 | 0.19 | 0.5 | 0.48 |
| 40 | 0.2 | 0.05 | 0.15 |
| 50 | 0.3 | 0.025 | 0.09 |
| 60 | 0.00 | 0.01 | 0.01 |
| 80 | 0.00 | 0.0 | 0.01 |
| 100 | 0.00 | 0.02 | 0.02 |

### 3.4.2.3     The effect of pregelatinization temperature on the friability of cassava starch compact

Table 3.4.2.3 compared   the friabilities of compacts made using starch pregelatinised at 68° - 70°C and 98° - 100°C.

Friability appeared to be higher with compacts made with starch pregelatinised at 68° - 70°C. The friability of 50% W/W (180 ums) starch pregelatinised at 98° - 100°C was found to be 0.025% W/W while the friability for the same batch pregelatinised at 68° - 70°C was 0.12% W/W.

Fig. 3.3.1.4 showed the characteristics of the starch mass obtained when pregelatinised at 68° - 70°C and 98° - 100°C. At 68° - 70°C, the starch mass still retained some intact starch grains while at 98° - 100°C, all the original starch grains completely lost their identities like striations, shape and staining effect. Pregelatinised starch (pgs) have been described to contain 12% W/W cold water solubles ( 2 ). Thus, completely pregelatinised starch obtained at 98° - 100°C contained a higher percentage of cold water solubles than the

partially pgs. During the wet granulation phase of the two blends, it is probable that the starch pregelatinised at 98° - 100°C yielded more cold water solubles to the water binder, thereby increasing the binding effect of the water and the viscosity. The result is therefore improved tablet friability due to better bonding at the pregelatinization temperature of 98° - 100°C.

Fig 3.4.2     - 210 -

The friability in % w/w of compacts made at bulk density 1.27 versus the concentration of pregelatinised starch

Friability of Compact in % w/w

4.0
3.0
2.0
1.0
.5
.8
.2
.6
.5
.4
.3
.2
.18
.16
.14
.12
0.1
.08
.06
.04
.02

0        20        40        60        80        100

Concentration of Pregelatinised Starch in % w/w
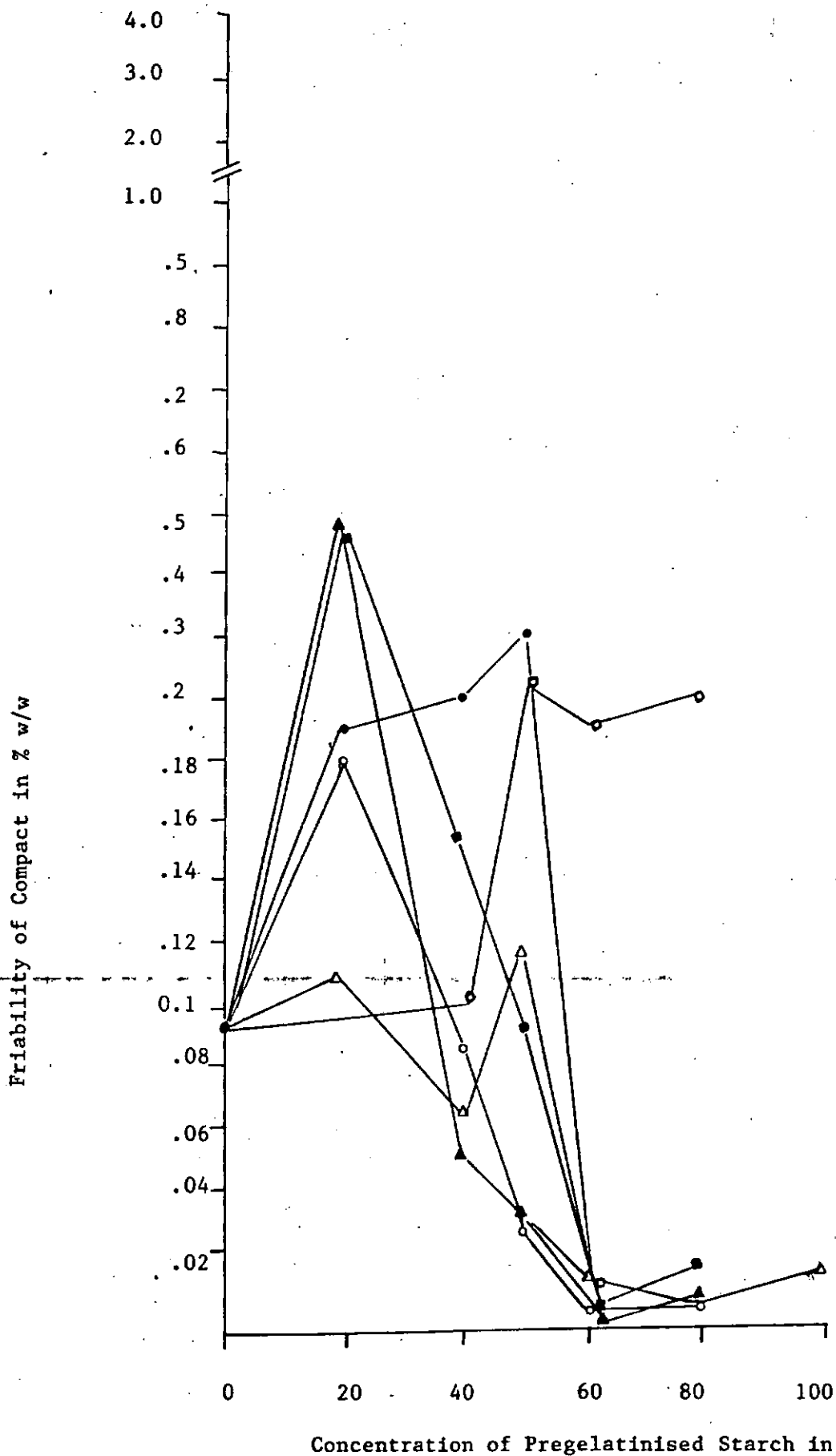
Table  3.4.2.3

Friability .values of compacts at bulk density

1.27 using 180 ums starch pregelatinised at

68° - 70°C and 98° - 100°C.

| Concentration of pregelatinised starch in % W/W | Friability in % W/W of compacts made using starch pregelatinised at | |
|---|---|---|
| | 68 - 70°C | 98 - 100°C |
| 0 | 0.99 | 0.99 |
| 20 | 0.11 | 0.10 |
| 40 | 0.06 | 0.05 |
| 50 | 0.12 | 0.025 |
| 60 | 0.00 | 0.01 |
| 80 | 0.00 | 0.00 |
| 100 | - | 0.00 |

## 3.4.3.1.

### The effect of pregelatinised starch concentration on the Disintegration Time of cassava starch compacts.

The disintegration time (D.T) for all the compacts at a bulk density of 1.27 is given at tables 3.4.3.1, 3.4.3.2. and Fig. 3.4.3.1. For all the formulations, the disintegration time decreased to a minimum at about 60% W/W pregelatinised starch (pgs) concentration, and then increased. In this study, 40% W/W plain cassava starch (pcs) in the matrix of the compact appeared to form the required continuous contact with itself for maximum disintegration for plain/pregelatinised cassava starch compacts. As the concentration of the pregelatinised starch increased, there occurred an increase in disintegration time for compacts containing 80% W/W and 100% W/W pregelatinised starch, probably because there is not much swelling, capillary action, absorption of water and pressure exertion in the compact blend.

This observation fell in line with the work done by Patel and Hopponen who studied the effect of starch concentration on the disintegration rate of aspirin tablet (137). They argued that where contact

of starch grains was continuous in the interparticle
spaces of aspirin tablets, disintegration was rapid
and effective even when void spaces were  eliminated.
where contact was not continuous, disintegration was
slower, and appeared to depend on the degree of
contact between starch grains and aspirin particles
and on the size of interparticle spaces.

In line with this argument one would expect
100% W/W pcs to exhibit the least D.T. Pregelatinised
starch contains  some cold water soluble (2) which
probably increased the hydration ability of the plain
cassava starch in the compact; the higher the con-
centration of the pgs in the compact, the more
hydrated the pcs.  60% w/w pgs probably provided
the optimum concentration required for disintegration
of such compact blend.

The mechanism of action of disintegrants have
been proposed in many theories by many authors.
There is as yet no general agreement on what con-
stitutes the mechanism of action.  Generally, the
concepts that were put forward by various workers as
the mechanism by which starch acts as disintegrants
are as follows:

    1.   Swelling

    2.   Capillary action,

3.    Wettability and Absorption of water.

4.    Hydration.

5.    Deformation

6.    Particle repulsion theory.

Starch contains two fractions in its molecules;
amylose,   amylopectin.   Amylose is responsible for
disintegration.   Amylopectin is responsible for
binding action.   Pregelatinised starch contains
mainly amylopectin, as reported before.

It was believed that starch absorbs water and
swell within the tablet matrix on coming  in contact
with water (137, 138).   Disintegrating agents
which are thought to act by this mechanism include
starch, cold water soluble starch, carboxymethyl
cellulose.

However, there has been opposition to this view.
It is argued that swelling of starch is so minimal
compared with the tablet size, that swelling alone
cannot account for the rapid disintegration.
Curling (139) contended that starch does not act
by swelling, rather by capillary action, drawing
water into the tablet.

Ingram and Lowenthal  (140) determined that
starch grains were deformed by pressure and did
not regain their original shape when exposed to

water nor swell significantly when moistened. On the other hand Hess 1978 (141) has shown with the aid of photomicrographs that disintegrant particles deform during tablet compression and that the deformed particles returned to their normal shapes when exposed to moisture. Fuhrer investigated the deformation of potato starch granules and found that not only did those granules return to their original size, but in some cases, the swelling capacity was improved when the granules were extensively deformed during compression (142).

Some believe that the heat generated by the wetting of the ingredients when the tablet is immersed in water causes the air to expand, pushing the tablet apart. Matsumaru was the first to propose that the heat of wetting of disintegrant particles could be a mechanism of action (143). He observed that starch granules exhibited slight exothermic properties when wetted and purported that this was the cause of localized stress resulting from capillary or expansion.

Lowenthal and Wood (144) postulated that the mechanism of action of starch is by hydration of the hydroxy group of the starch molecules causing them to move apart. They found this by using a

scanning electron microscope and observing the location and structure of starch grains in tablets.

Another theory of tablet disintegration attempts to explain the swelling of tablets made with "nonswellable" starch. Ringard and Guyot-Hermann have proposed a particle/particle repulsion theory based upon the observation that particles that do not seem to swell may still disintegrate tablets (145).

Although their study is not supported by adequate data, this mechanism appears to support some of the findings of this study. Pregelatinised starch though a dry tablet binder (124) still disintegrated, though at a longer time than the plain cassava starch. Amylopectin which is the major component of pregelatinised starch contains phosphate ester group in its molecule (146). This influences the physical properties of amylopectin; the charged nature and its migration in an electric field (147). This mechanism and some others found in the pregelatinised starch are probably slower in disintegration action than the wicking, absorption of water and pressure exerted by the plain starch.

Table 3.4.3.1

Disintegration Time in seconds of cassava starch
compacts made using various particle sizes of starch
pregelatinised at 68 - 70°C at bulk density 1.27.

| Concentration of pregelatinised starch in % W/W | Disintegration Time in seconds of compacts made using various particle sizes of pregelatinised starch | | |
|---|---|---|---|
| | 120 μms | 180 μms | 250 μms |
| 0 | 23 | 23 | 23 |
| 20 | 16.0 | 23.8 | 21.2 |
| 40 | 8.8 | 19.5 | 16.3 |
| 50 | 8.6 | 14.5 | 15.7 |
| 60 | 8.2 | 9.4 | 8.3 |
| 80 | 21.3 | 25.1 | 11.3 |
| 100 | – | 227.7 | 306.5 |

Table 3.4.3.2

Disintegration Time in seconds of compacts made
using various particle sizes of starch pregelatinised
at 98 - 100°C calculated graphically at bulk
density 1.27.

| Concentration of pregelatinised starch in % W/W | Disintegration Time in seconds of compacts made using various particle sizes of pregelatinised starch | | |
|---|---|---|---|
| | 120 μms | 180 μms | 250 μms |
| 0 | 23 | 23 | 23 |
| 20 | 17.7 | 22.0 | 16.3 |
| 40 | 9.0 | 12.0 | 13.5 |
| 50 | 9.4 | 10.5 | 6.6 |
| 60 | 7.4 | 8.0 | 5.9 |
| 80 | 65.3 | 253.0 | 37.0 |
| 100 | 302.2 | 869.7 | 1052.3 |

Fig 3.4.3 — The disintegration time of compacts in seconds made at bulk density 1.27 versus the concentration of pregelatinised starch
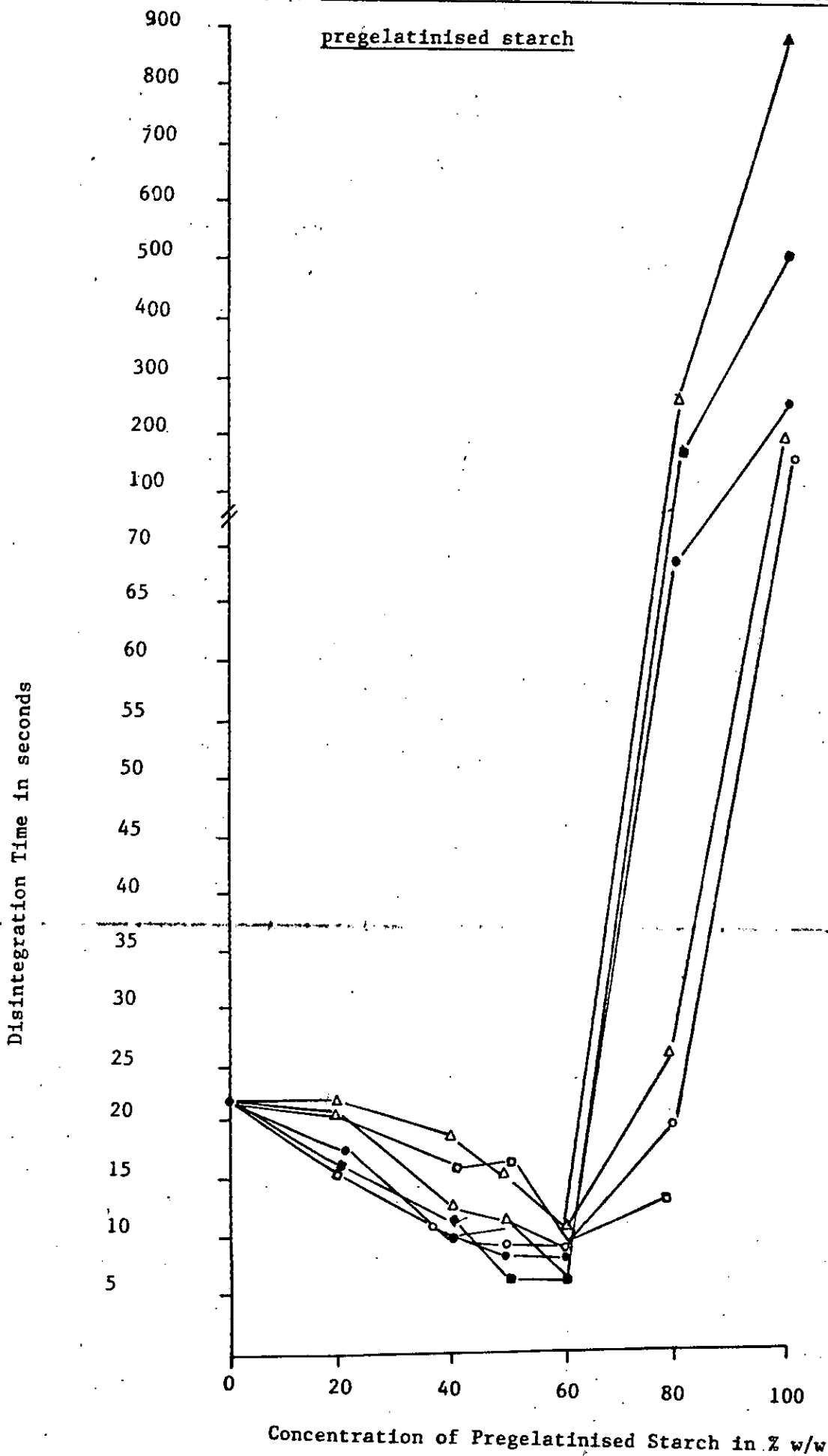
### 3.4.3.2

### The effect of the particle size of pregelatinised starch on the disintegration rate of cassava starch compact

The particle size of the plain cassava starch (pcs) used to blend with all the various particle sizes of the pregelatinised starch (pgs) studied, was 180μms. So this study compared the disintegration time of compacts made using the particle sizes 120μms, 180μms and 250μms of the pregelatinised starch as composite blend for 180ums plain cassava starch. Results obtained are seen in Tables 3.4.3.1, 3.4.3.2 and Fig. 3.4.3.1.

Considering compacts made from simple materials i.e. 100% pcs (180μms) 100% (120μms) pgs, 100% (180μms) pgs and 100% (250μms) pgs, the mechanism of disintegration appeared to be different (Tables 3.4.3.1, 3.4.3.2). The ease of solution of very fine particle sizes appeared to be the operating mechanism. Results showed that 100% (120μms) pregelatinised compact had the disintegration time of 302.2 seconds while 100% (180μms) pgs, and 100% (250μms) pgs were 869.7 and 1052.3 seconds respectively. (Table 3.4.3.2) This observation is in line with the school of thought that the dissolution rate of very

fine particles of 1.0 μ could be a thousand times greater than the same mass of a mixture containing 10.0μ (12).

However, plain cassava starch (pcs) at 180 μms had a much lower disintegration time (23 seconds) when compared with pgs (180 μms) showing that pcs is a better disintegrant.

Compacts containing portions of 120 μms, and 250 μms blended with 180 μms pcs, disintegrated more readily when in contact with the disintegeration medium, than compacts containing 180 μms pgs. Reason being that the particle sizes 120μms being lighter, and 250 μms being heavier than the component 180 ums pgs, segregated out during the mixing stage of the powders, resulting in loosely held components. These components therefore separate out easily in contact with water. On the other hand, compacts containing 180μms pregelatinised starch, being the same with that of the plain cassava starch blended uniformly with it. The components become tightly held together to form strong compacts.

Generally, results showed that the DT for compacts containing 250 μms was the least compared with compacts made with 120μms and 180μms. Thus the physical characteristics of disintegrant; pregelatinised

starch in this study, obviously have some relation-
ship to the mechanism of disintegrating action
such as swelling and water uptake.

Smallenbroek and co-workers evaluated the
effect of particle size of starch grains on their
ability to disintegrate tablets (148). They con-
cluded that starch grains with relatively large
particle sizes were more efficient disintegrants
than were the finer grades. Those authors theorised
that this behaviour resulted from increased swelling
pressure. Rudnic and co-workers investigated the
effect of particle size of cross-linked polyvinyl
pyrrolidone (PVP) on disintegrant efficiency (149).
They found that the larger particles swelled to a
greater extent and at a faster rate than did the
finer particles. Because they also found a remar-
kable correlation between the rates of swelling and
the amount of water uptake for this disintegrant,
they postulated that particle size plays a key
role in the overall efficiency of commercial sources
of sodium starch glyconate. The effect of particle
size on disintegration of compacts was also reported
by List and Muazzan (150, 151) as well as by
Gissinger and Stamm (152). List and Muazzan related

the increase in disintegration efficiency to the
greater swelling force, while Gissinger and Stamm
concluded that this phenomenon was related to the
rate of swelling.  Sakr and Elsabbagh reported that
for guar gum a finer grade of material was a better
disintegrant than was a coarse grade (153).  Those
findings were especially valid when relatively low
levels of guar gum (less than 2%) were used.  Thus
it seems evident that both the rate and the force
of disintegrant action may be dependent upon the
particle size of the disintegrant (the pgs in this
study).

### 3.4.3.3

### The effect of pregelatinization temperature on the disintegration rate of cassava starch compacts.

Tables 3.4.3.1, 3.4.3.2 and Fig. 3.4.3.1 compared the disintegration time for compacts made at 68° - 70°C and 98° - 100°C.

Generally Disintegration Time (DT) was faster for starch batches pregelatinised at temperature of 98° - 100°C than at 68° - 70°C. This may be due to the fact that at pregelatinization temperature of 98° - 100°C, the starch has been completely denatured. Thus the mechanism of action by hydration manifested more at this high temperature range. The hydroxyl groups of the starch molecules increase and cause the compacts to move further apart (144).

Other mechanisms like wicking, swelling, capillary action, wettability, Absorption, particle repulsion, and even particle deformation probably become more exaggerated to various degrees at these higher temperature ranges than at the lower ranges of 68° - 70°C.

Ingram and Lowenthal (140), Hess (141) and Fuhrer (142)

studied deformation of granules during compression,
They found that not only did deformed granules
return to their original size when exposed to mois-
ture, but in some cases the swelling capacity was
improved when the granules were extensively deformed.

## 3.4.4        HECKEL PLOT

Figs 3.4.4.1 a,b,c and Fig 3.4.4.2 a, b, c, show the plots of Ln $\frac{1}{1-D}$ versus applied pressure for powder blends containing 120 µms, 180 ums and 250 ums of pregelatinised starch at pregelatinization temperatures of 68 - 70°C and ·98° $\pm$ 100°C respectively. It is seen that the compaction behaviours of the powders were similar irrespective of the particle size of pregelatinised starch or the pregelatinization temperature used.

The powders containing 20% - 100% of pregelatinized starch were approximately rectilinear up to a pressure of about 1000 kg/cm$^2$ after which they dropped slightly exhibiting a small 'kink'. The rectilinear portions probably represent particle rearrangement as well as plastic or elastic deformation. At the onset of compression the particles slip past each other leading to closer packing. As the compressional pressure is increased, larger voids become filled due to elastic/plastic deformation also producing closer packing.

However when the applied pressure exceeds
1000 kg/cm², it seems resistance to packing sets in
which is very significant with the plain cassava starch.

The quantities $K_H$ and $A_H$ are constants for the
materials and are the slopes and intercepts respectively
of the extrapolated linear portion of the plots. $K_H$ is
the reciprocal of the yield pressure of the material
and $A_H$ is a constant for the movement of the particles
during the initial stages of compaction. These
quantities are shown in Table 3.4.4.1.

Key for Figs 3.4.4.1 a,b,c and 3.4.4.2 a,b,c.

● No Pregelatinised starch

○ 20% Pregelatinised starch

⊙ 40% Pregelatinised starch

△ 50% Pregelatinised starch

○- 60% Pregelatinised starch

x 80% Pregelatinised starch

z 100% Pregelatinised starch

Fig 3.4.4.1 a

Heckel plot showing $\ln \dfrac{1}{1 - D}$ of compact versus applied pressure
for 120μms starch pregelatinised at $68^{\circ} - 70^{\circ}C$
(D = Bulk Density of Compact



IN $\dfrac{1}{1 - D}$

Applied Pressure in $Kg/cm^{2}$
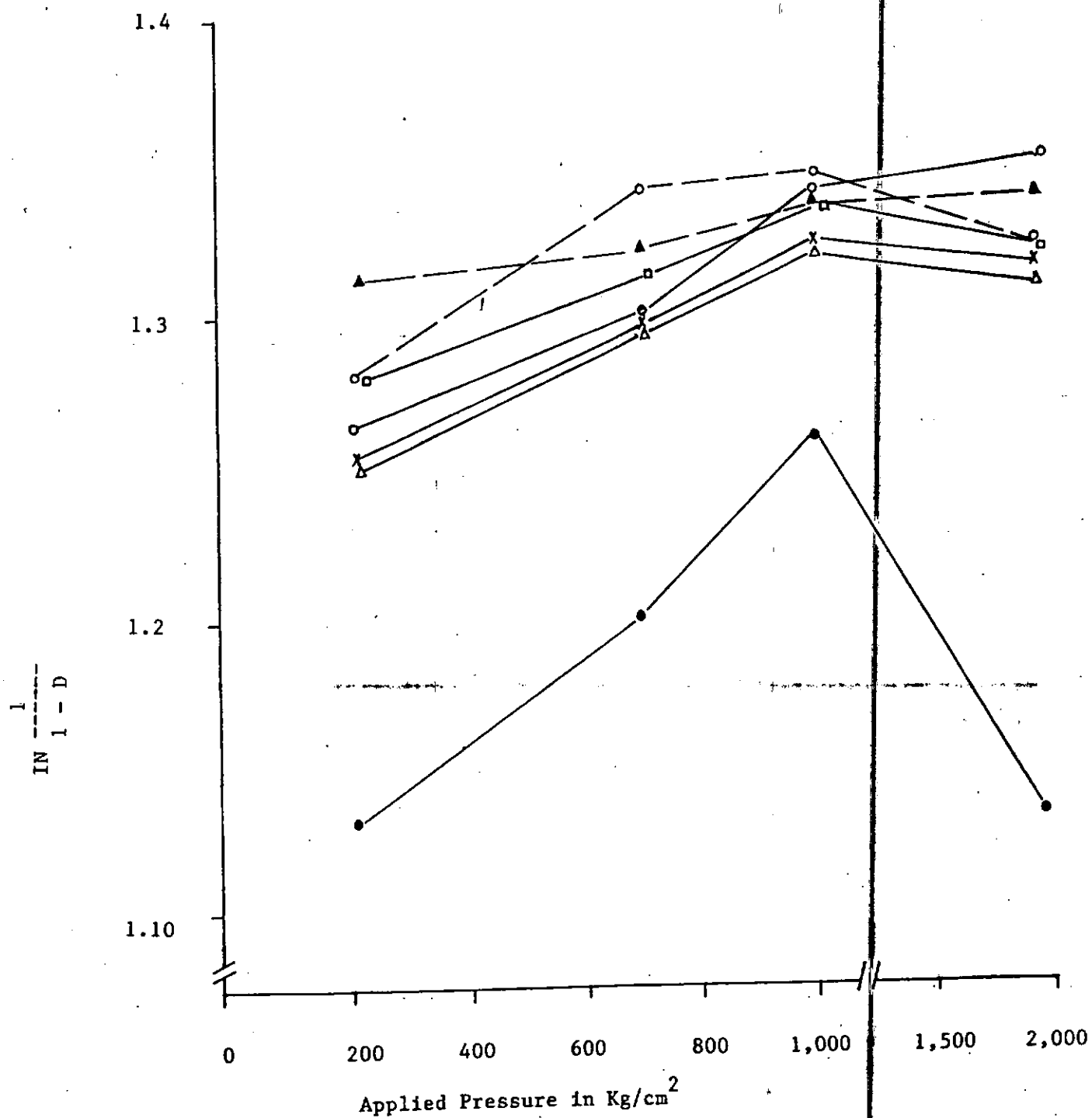
Table 3.4.4.1

SHOWING YIELD STRENGTH AND YIELD PRESSURE

OF COMPACTS CONTAINING 80% W/W, 100% W/W

OF (180 μms) STARCH PREGELATINISED AT

$68^{\circ} - 70^{\circ}C$ AND $98^{\circ} - 100^{\circ}C$.

| Concentration of pregelatinised starch | 80% W/W | | 100% W/W | |
|---|---|---|---|---|
| Pregelatinization Temperatures | $60^{\circ} - 70^{\circ}C$ | $98^{\circ} - 100^{\circ}C$ | $68^{\circ} - 70^{\circ}C$ | $98^{\circ} - 100^{\circ}C$ |
| Slope K | $1.12 \times 10^{-4}$ | $0.70 \times 10^{-4}$ | $1.12 \times 10^{-4}$ | $0.70 \times 10^{-4}$ |
| Yield Strength in Kilograms | 26,786 | 42,857 | 26,786 | 42,857 |
| Mean Yield Pressure in kg cm$^{-2}$ | 8,929.00 | 14,286.00 | 8,929.00 | 14,286.00 |

Fig 3.4.4.1(b) - Heckel plot showing in $L_n \dfrac{1}{1 - D}$ of compacts

versus applied pressure for 180mms starch

pregelatinised at 68 - 70°C



Applied Pressure in Kg/cm²

Fig 3.4.4.1 c

Hecke₁ plot showing ln $\frac{1}{1-D}$ of compacts versus applied pressure for

250µms ⁻ starch pregelatinised at 68 – 70 $^0$C



IN $\frac{1}{1-D}$

Applied Pressure in Kg/cm-2

Fig. 3.4.4.2 (a) — Heckel plot showing $\ln \frac{1}{1-D}$ of compact versus applied pressure for 120 $\mu$ms ; starch pregelatinised at 98°C - 100°C



Applied Pressure in Kg/cm²
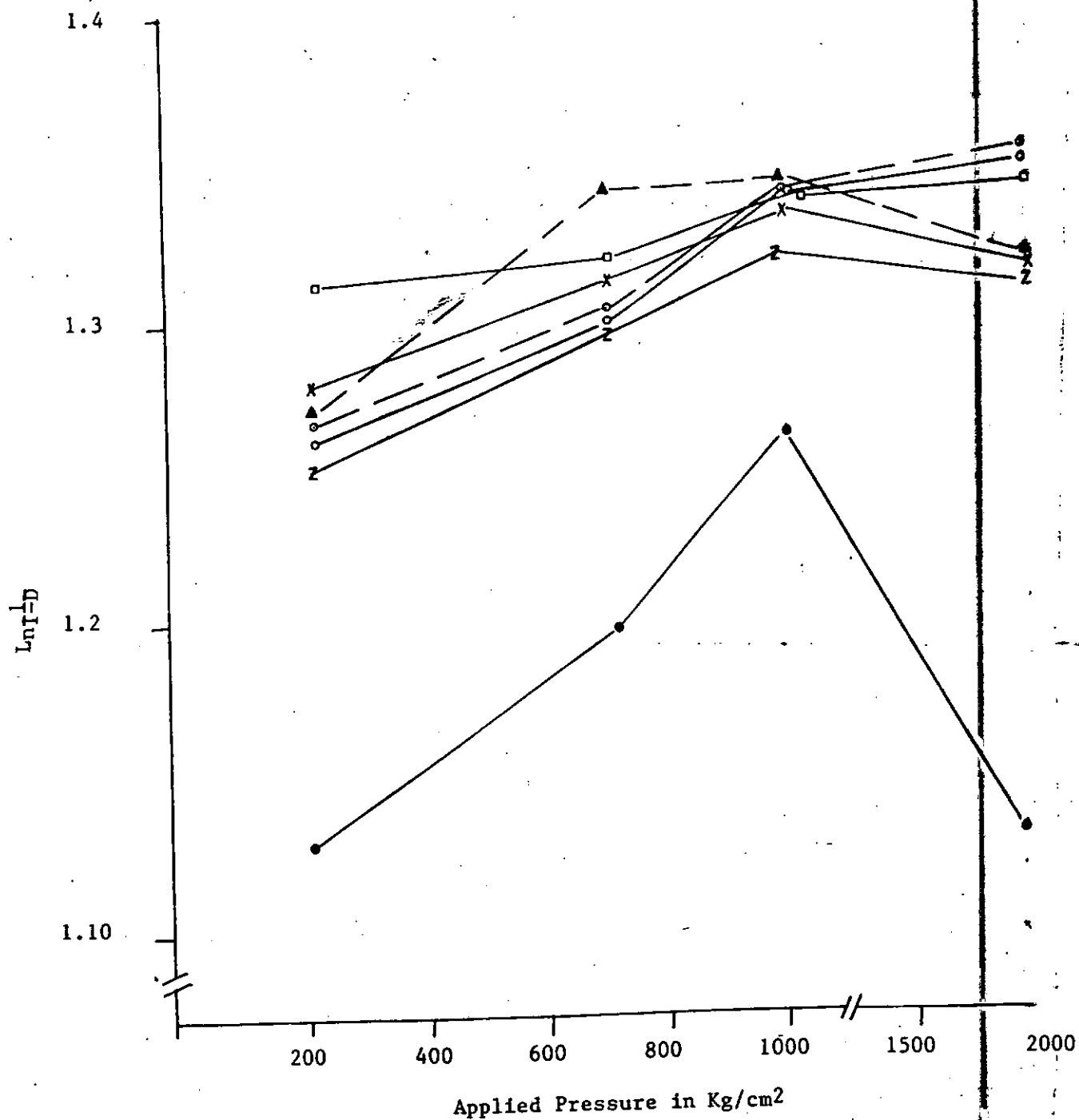
Fig 3.4.4.2 (b)

Heckel plot shows in $\dfrac{1}{1-D}$ versus applied pressure for 180 mm starch

pregelatised at $98^{\circ} - 100^{\circ}C$ (D = Bulk Density of Compact)
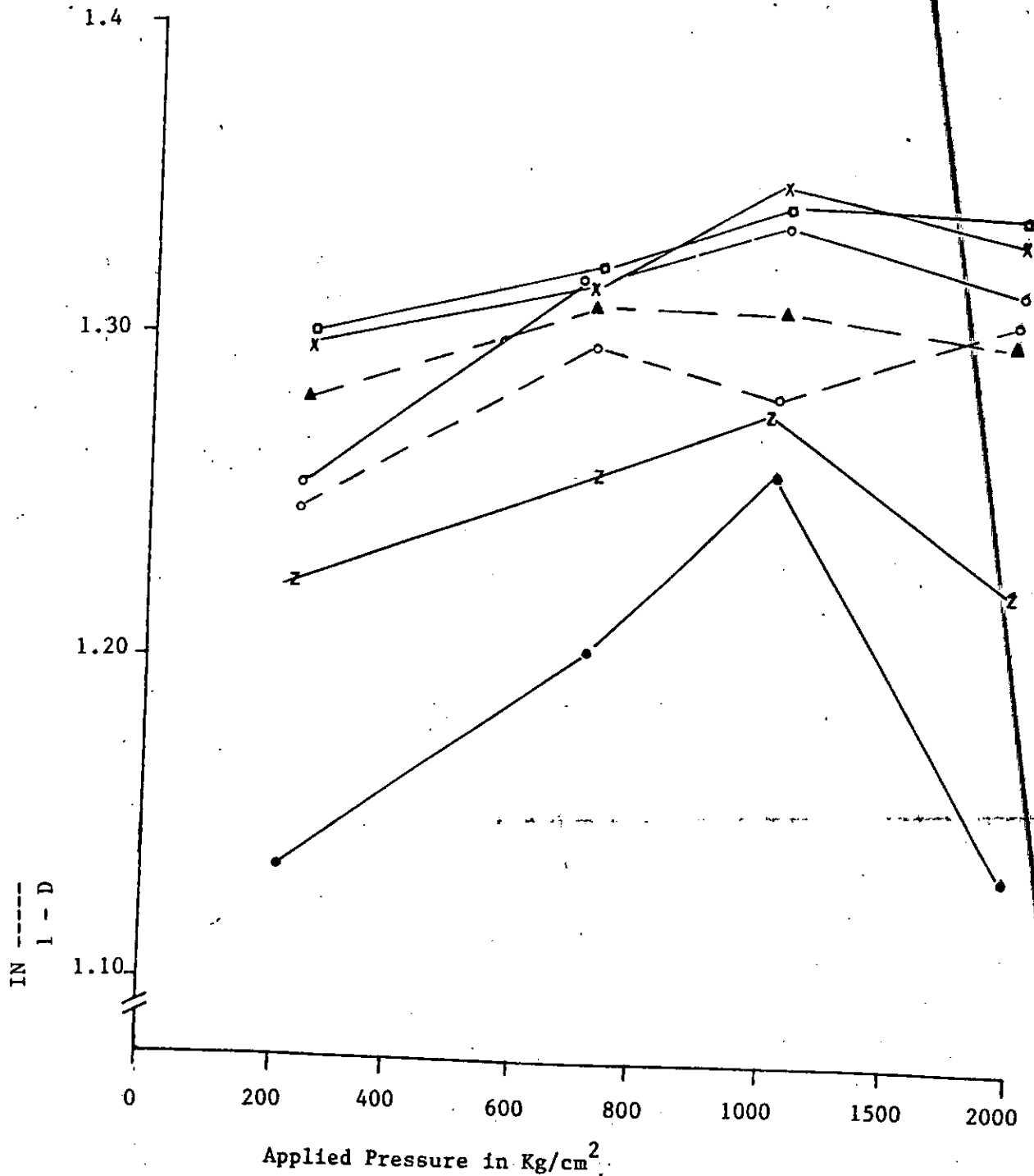
Fig 3.4.4. 2 (c)

Heckel plot showing $\ln\dfrac{1}{1-D}$ of compact versus applied pressure

for 250 $\mu$ms starch pregelatinised at $98^0$ $-100^0$C
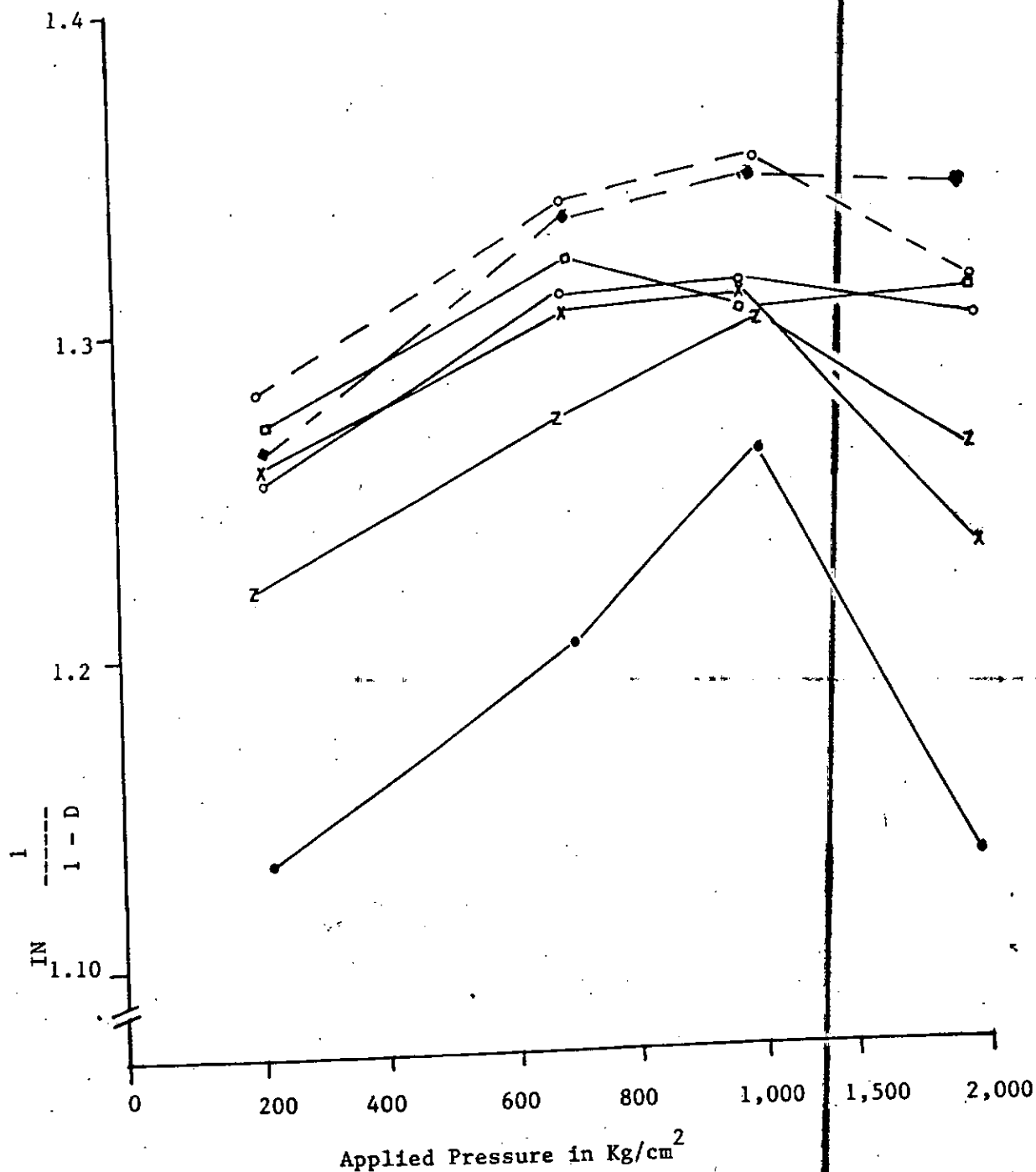
### 3.4.5 The tabletting properties of modified cassava starch

Modified cassava starches $MCS_1$, $MCS_2$, pgs, containing 60% W/W, 80% W/W and 100% W/W (180 ums) pregelatinised starch respectively were compared with plain cassava starch (pcs), Avicel pH 102 ($M_1$) and spray dried lactose ($M_2$), as diluents for making 50 mg paracetamol tablets as described in section 2.

Tables 3.4.5.1 - 3.4.5.2, show the dissolution profiles of 50 mg paracetamol in 500 mg compacts of the various diluents compressed at a constant pressure of 1000 kg cm $^{-2}$. This result shows that tablets containing pregelatinised starch had their t50% within 1 minute.

One possible explanation for the quick release of paracetamol from these compacts could be due to the fact that pregelatinization of starch promotes wetting of the paracetamol. It has been shown (2) that the release of poorly soluble hydrophobic drugs from capsules can be improved significantly by the creation of a hydrophilic surface by intensive mixing of the hydrophobic drug with a

small amount of a solution of a hydrophilic excipient.
Their data indicated that the hydrophilic material
is mechanically distributed over the hydrophobic
surface.

The creation of hydrophilic capillaries in
a tablet allowed the rapid penetration of the
dissolution fluid, resulting in a dispersion of
well-wetted particles so that the maximum surface
area of the powder was exposed to the dissolution
medium.

In all instances, the dissolution of parace-
tamol was fastest in compacts containing pregelati-
nised starch, followed by compacts containing plain
unpregelatinised cassava starch. Generally, starch
is a very good disintegrant. Starch used as a diluent
expands quickly to release the medicament. Pre-
liminary studies showed that plain cassava starch
is not water-soluble. The swelling ability of pure
starch to release medicament is probably slower than
the hydrophilicity of pregelatinised starch coupled
with a probable swelling ability.

t50% for compacts containing 60% W/W, 80% W/W
and 100% W/W pregelatinised starch was found to be

less than 1 minute, while that of 100% plain cassava starch was 1.5 minutes. t50% for spray dried lactose (M$_2$) was 8 minutes and that of Avicel pH 102 (M$_1$) was nearly 60 minutes.

It is therefore seen that various diluent types did significantly affect the rate of dissolution of the paracetamol tablet (Figs 3.4.5.1).

This result confirmed previous work. Manud hane et al. 1969 (15) showed that compressible starch appears to have many advantages over starch USP because it is much more effective as a dry binder, yet gives equivalent or faster disintegration and dissolution times. It has also been shown that compressible starch contains a relatively high amount (12%) of cold water solubles (135) and this property could be a possible reason for the faster dissolution of paracetamol containing pregelatinised starch diluent.

Compacts containing 60% W/W pregelatinised starch showed the fastest release rate. The presence of 40% W/W plain cassava starch probably aids more rapid disintegration for easy dissolution than the compact containing 100% W/W pregelatinised starch.

On the other hand; compacts containing
80% W/W pregelatinised starch contained 20% W/W
plain cassava starch.  This reduction in the quantity
of PCS that would have aided .... the disintegration
probably caused the reduced dissolution rate.  Least
of the dissolution rate for tablets containing pgs
was that containing 100% pgs, since there was no
plain starch to effect swellability and disinte-
gration.

The compacts containing spray dried lactose
(SDL) showed a faster release of paracetamol than
obtained for Avicel pH 102.  A possible explanation
is that lactose, containing many large granules,
allows a more porous and loose mound net work to
form, enabling the dissolution medium to circulate
easily through the mound.  The slower dissolution
rate of Avicel pH 102 could be due to a more compact
mound, as a result of the much smaller granule size
of the micro-crystalline cellulose.  The compact
mound would make it more difficult for the dissolution
medium to transverse  and circulate.

At any rate, all the diluents appeared to
pass the B.P. disintegration test for uncoated

tablets by disintegrating within 15 minutes. $MCS_1$, $MCS_2$ compacts disintegrated within 1 minute, while it took 100% W/W pregelatinised starch tablets nearly 7 minutes.

Spray dried lactose compacts containing 50mg paracetamol disintegrated within 1 minute, while the tablet containing Avicel pH 102 disintegrated in about 9 minutes.

The crushing strength of tablets made with $MCS_1$, $MCS_2$ and pgs were found to be 7.0kg, 7.8kg and 7.7kg respectively (Table 3.4.5.3). This degree of hardness was as obtained for the plain diluent compacts (section 3.4.1).

The crushing strength for SDL tablet was 3.60kg while that of Avicel pH 102 was more than 10.0kg. This is in agreement with previous works (9). Avicel pH 102 is the most compressible of all the direct compression fillers in the market today (2). The micro crystalline particles are held together by hydrogen bonds. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness (9). The compressibility

of spray dried lactose on the other hand is not good enough. Spray dried lactose, unlike the microfine particle sizes of MC, contains a mixture of large crystals of lactose monohydrate and spherical aggregates of smaller crystals loosely held together by glass or amorphous material.

Thus the crushing strengths of tablets made with $MCS_1$, $MCS_2$ and pgs were much better than obtained for SDL ($M_2$) but less than that obtained for MC ($M_1$).

The friability of the tablets for all batches were compared. Avicel pH 102 had the least friability of 0% in all the studies conducted, followed by modified cassava starch and least with spray dried lactose.

Table 3.4.5.1

## Dissolution Profile of paracetamol Tablet using the Various Diluents

| Time in Minutes | Concentration of Paracetamol in the various paracetamol tablets using the various diluents in % W/W. | | | | | |
|---|---|---|---|---|---|---|
| | 100 % W/W Plain Cassava Starch | PGS | $MCS_1$ 60:40 | $MCS_2$ 80:20 | $M_1$ | $M_2$ |
| 1 | 41 | 60 | 52 | 61.2 | – | – |
| 2 | 62.5 | – | 93.3 | 75.5 | 11.0 | 3.5 |
| 4 | 55.0 | 73.5 | 93.3 | 82.0 | 14.5 | 41 |
| 6 | – | 57.0 | – | – | 18 | 46 |
| 8 | – | 61.0 | 62.5 | – | 20 | 47 |
| 10 | 68.5 | 60 | 59 | 79.1 | 26 | 54 |
| 40 | – | 59 | – | 73.9 | 38.0 | 57 |
| 60 | 60.0 | 65 | 60 | 71.9 | 52.0 | 67 |
| 90 | 66.0 | 55 | 62.0 | 66.5 | 61.2 | 58 |
| 120 | 66.0 | 57 | 62.2 | 62.9 | 64.7 | 56.5 |

Fig 3.4.5.1

Dissolution profile of paracetamol from compacts made at
$1000Kg/cm^2$ prepared from varied direct compression fillers
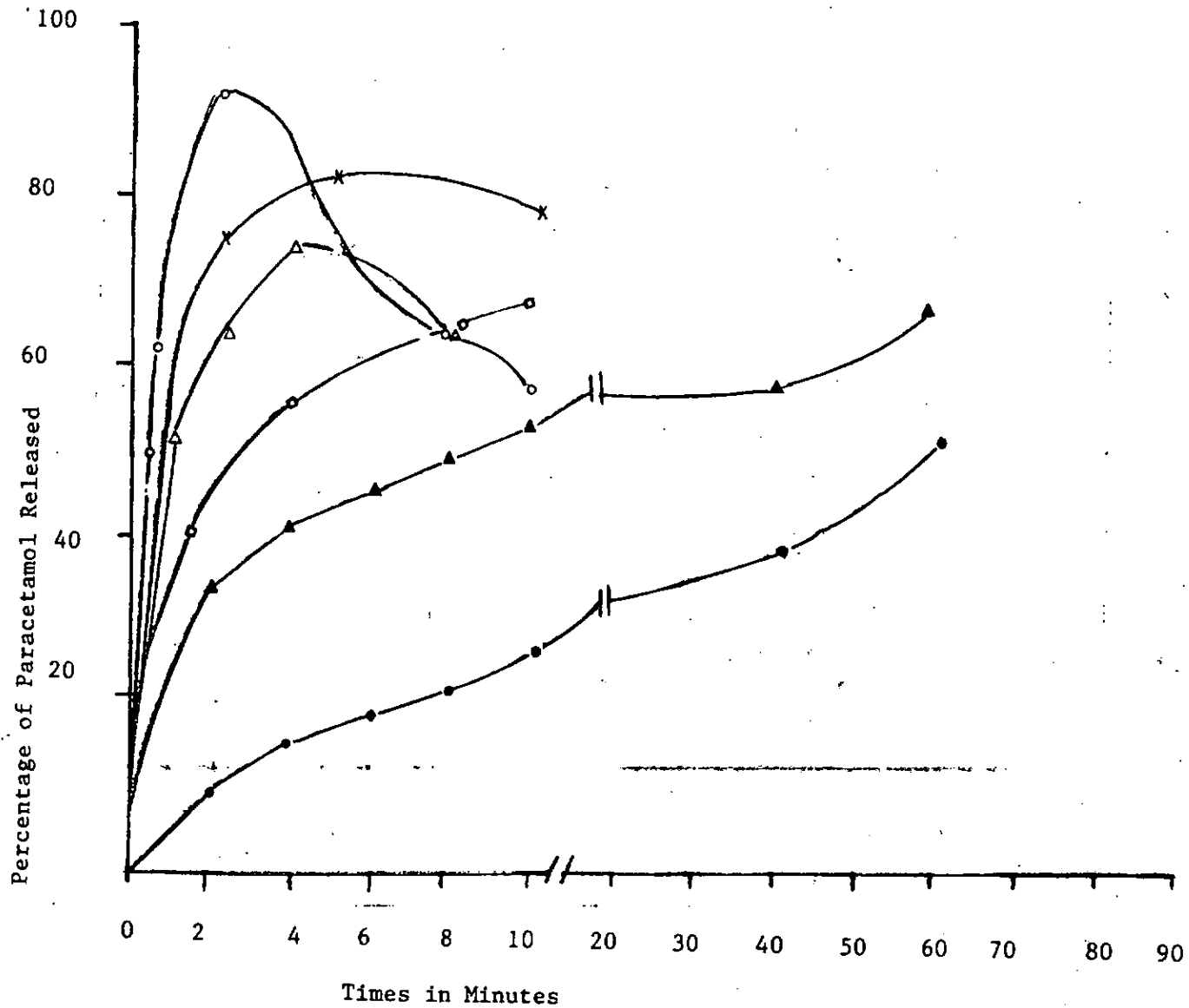


KEY

| | | |
|---|---|---|
| ▫ | = | 100% Plain Cassava starch |
| ▫ | = | 60 : 40 pregelatinised/plain cassava starch |
| ✕ | = | 80 : 20 pregelatinised/plain cassava starch |
| △ | = | 100% pregelatinised cassava starch |
| ▲ | = | spray dried Lactose |
| ● | = | Avicel PH 102 |

## Table 3.4.5.2

T50% values of Paracetamol tablets made using

PCS, PGS, $MCS_1$, $MCS_2$, M1 & $M_2$

| DILUENT | Dissolution Medium | T50% in Minutes |
|---------|-------------------|-----------------|
| (PCS) | 0.1NHCl | 1.5 |
| $MCS_{(1)}$ | 0.1NHCl | 0.5 |
| $MCS_{(2)}$ | 0.1NHCl | 0.5 |
| PGS | 0.1NHCl | 0.5 |
| $M_1$ | 0.1NHCl | 58.0 |
| $M_2$ | 0.1NHCl | 8.2 |

## Abbreviations

| | | |
|---|---|---|
| $MCS_{(1)}$ | = | Modified cassava starch (60% W/W pregelatinised starch) |
| $MCS_{(2)}$ | = | Modified cassava starch (80% W/W pregelatinised starch) |
| $M_1$ | = | Avicel pH 102 |
| $M_2$ | = | Spray dried lactose |
| PCS | = | Plain cassava starch |
| PGS | = | 100% pregelatinised starch. |

Fig 3.4.5.2

Plot of t50% of paracetamol in the various concentration of Pregelatinised
starch tablets



KEY

o  =  60 : 40 Pregelatinised/Plain Cassava Starch

x  =  80 : 20 Pregelatinised/plain Cassava Starch

Δ  =  100% Pregelatinised Cassava Starch

□  =  100% Plain Cassava Starch

Concentration of Pregelatinised Starch in Tablet in % w/w
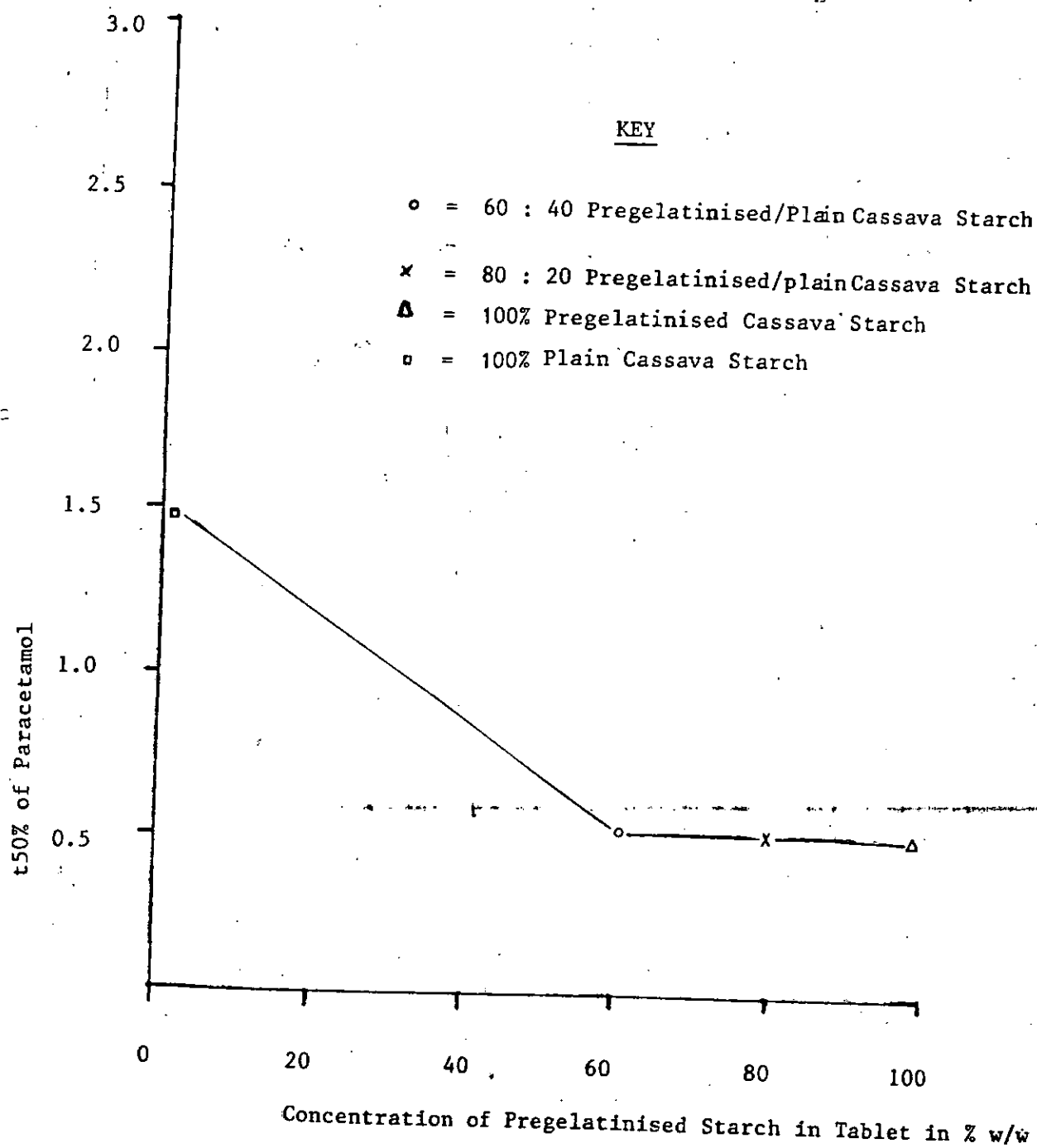
## TABLE 3.4.5.3

### COMPARISON OF COMPACT PROPERTIES OF MODIFIED CASSAVA STARCH AND SOME COMMERCIAL PRODUCTS AT BULK DENSITY 1.27

| FORMULATION | PLACEBO COMPACTS | | | PARACETAMOL TABLETS | | |
|---|---|---|---|---|---|---|
| | Crushing Strength in Kg | Friability in % W/W | D.T. in Seconds | Crushing Strength in Kg | Friability in % W/W | D.T. in Seconds |
| Plain Cassava Starch (PCS) | 4.9 | 1.4 | 17.5 | 3.6 | 1.16 | 15.0 |
| M.C.S.(1) | 7.3 | 0.0 | 0.0 | 6.6 | 0.0 | 13.0 |
| M.S.C.(2) | 7.7 | 0.05 | 47.0 | 7.9 | 0.0 | 84.0 |
| 100% Pregelatinised Starch (Pgs) | 7.8 | 0.1 | 360.0 | 7.8 | 1.5 | 300.0 |
| $M_1$ | >10.0 | 0.0 | 523.0 | >10.0 | 0.0 | 150.0 |
| $M_2$ | 3.10 | 100.0 | 24.0 | 3.0 | 100.0 | 22.5 |

**Abbreviations**

D.T. = Disintegration Time; $M_1$ = Avicel pH 102; $M_2$ = Spray dried lactose, PCS = Plain Cassava starch; Pgs 100% W/W Pregelatinised starch; MCS (1) Modified Cassava starch (60:40); MCS (2) Modified Cassava starch (80:20).

## 4. GENERAL DISCUSSION/CONCLUSION

### INTRODUCTION

Direct compression as a tabletting procedure is dependent upon the development of suitable materials which in themselves are both highly fluid and cohesive (2). Direct compression offers a number of advantages, particularly in regard to ease, economy of manufacture and increased product stability. Since the majority of drugs lack either sufficient bulk, satisfactory compression character- istics or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation. Manihot Utilissima (cassava) grows abundantly in Nigeria. The starch obtained from it is white, tasteless and inert. Though the plain starch lacks fluidity and compressibility, it seems promising if this could be converted to a directly compressible tablet diluent because of its cheapness and local availability.

In this study, cassava starch was processed from the caryopsis of Manihot utilissima and purified using a published method. The standard starch was modified by wet granulation using many

variables with the hope of acquiring expected granular
properties.  Formulation variables like the effect
of binder type and binder concentration were
utilized.  Although starch granules were obtained
by these methods, the fluidity, compressibility
and other properties of such granules were not
adjudged to be enough to use them as direct compre-
ssible filler binder.  To improve on the fluidity
and compressibility of plain cassava starch, the
effect of pregelatinization of part of the starch
as composite blend for the plain  cassava starch
(pcs) was studied.  The plain cassava starch was
pregelatinised at two temperature ranges; 68° - 70°C
and 98° - 100°C.

The pregelatinised starch grains (pgs) at these
two temperature ranges were then characterized
under the plain and polarized light of the microscope
and the photomicrographs were taken.  Pregelatinised
starch being a dry tablet binder (124) was used
as composite blend with plain cassava starch in this
study to serve both as a dry binder and diluent.
Various concentrations of pregelatinised cassava
starch made at the two pregelatinization temperature
ranges, were blended with  plain cassava starch at

20% W/W, 40% W/W, 50% W/W, 60% W/W, 80% W/W and
100% W/W. This study also used various particle
sizes of the pregelatinised starch, 120ums, 180ums,
250ums, to blend with the plain cassava starch.

Using 40% W/W water at 28°C as the granulating
fluid, the composite powders were granulated by
massing and forced screening through mesh 16. The
dry granules obtained were evaluated. The granula-
tion parameters considered include granule size,
crushing strength, friability, granule densities,
and the flow characteristics. This study is
necessary because a single granulation property
can influence many different tablet properties (52),
and for successful direct compression of tablets,
the characteristics of the binder-fillers must be
accurately defined. Since the quality of the final
tablet is the ultimate goal of this formulation
study, the granulations obtained were subjected to
compaction at various pressures; 200kg $cm^{-2}$, 700kg $cm^{-2}$,
1000kg $cm^{-2}$ and 2000kg $cm^{-2}$. The compacts obtained
were evaluated. The compact properties studied
include: the crushing strength, friability and
disintegration time (DT) at the bulk density of 1.27.

Three of the formulations; $MCS_1$, $MCS_2$, pgs

containing 60% W/W, 80% W/W and 100% W/W

pregelatinised starch were compared with Avicel

pH 102, $M_1$, and spraydried lactose, $M_2$ as directly

compressible diluents. These diluents were made

to contain 50mg paracetamol in 500mg size of tablets.

The t50% of paracetamol in the various diluents

was determined and compared.

Generally, the results showed that as the

volume of the binder solution increased, the mean

granule size increased, bulk densities decreased.

The smaller granules were able to form a closer and

more intimate packing than were the larger granules.

As the amount of water used to granulate the powder

increased, bed porosity went through a maximum

value between 45% to 70% to 68%. The region of

poor packing was found with binder volume of between

50 - 55% W/W where the bed porosities were 69% and

70.38% successively.

Hausner Quotient which is the ratio of the bulk

and loose densities could be used to predict powder

flow property. Results showed the Hausner Quotient

range of between 1.16 - 1.45, meaning that as the

binder volume increased, the Hausner Quotient reduced.

This means that the latter granulations experienced

low interparticulate friction, since they become

larger and more spherical. On the other hand, low binder volumes formed high interparticulate cohesion as the particles were much smaller in size.

The percent compressibility of a powder is another useful method of measuring flow property. Generally granulations were found to become more flowable as the binder volume was increased up to a certain point and then decreased. The granulations showed excellent flow behaviour and percent compressibility (14.0%) when the binder volume was 70% V/W.

The average granule strength was found to increase and the granule friability decreased as the binder volume increased. Davies and Gloor (33, 34) showed that increasing the amount of water used to granulate lactose caused densification by rapidly eliminating larger pores, reducing mean-pore diameter and increasing granule strength.

To study the effect of temperature on granular properties, same volume of water at various temperatures was used as the binder to prepare the pure starch granulations. The granulations obtained showed larger average granule size and granule strength with water added at elevated temperatures. The bulk densities decreased as the temperature increased. Granulation

obtained at room temperature had the least flow rate. This is because the larger granules formed at higher binder temperature were probably more spherical and were able to flow more evenly than the smaller cohesive granules formed at lower binder temperature. When the temperature of the water added was above the gelatinization temperature of cassava starch (59.3°C), the starch gelatinizes at the immediate vicinity (134). Though later dispersed, the higher viscosity of the binder fluid in this vicinity simultaneously led to the increase in the granule size, and granule strength of the resulting granulations.

The bulk densities decreased slightly as the temperature increased since the average granule size increase as the temperature increased. The smaller granules obtained at the lower temperatures packed into a closer packing, and formed enhanced bulk densities and reduction of granule porosity.

When pregelatinised cassava starch was blended with various proportions of plain cassava starch and granulated using 40% V/W water as binder, the granulation properties varied in the various formulations. Pregelatinised starch has been described as a dry tablet binder (124). In the presence of the

water added as the granulating fluid, portions of the pregelatinised starch dissolved to increase the concentration and the viscosity of the water binder. This dissolution continued until probably no free water was available to form liquid bridges. The binding mechanism therefore could be due to forces of adhesion and cohesion in bonds with restricted movement. These forces may be due firstly, to the strength of adhesion at the surface of contact between the thin layer of water, and the insoluble starch particles, and secondly, to the cohesive strength imparted by that portion of pregelatinised starch which went into solution in presence of water.

The greatest effect binder concentration has on the granule is its effect on granule hardness and strength after drying. The higher the binder level, the stronger the granule after drying. The granules obtained with highly concentrated pregelatinised starch were very strong. Carr's percent compressibility decreased as the concentration of the pregelatinised starch component increased, meaning that the granules became more flowable as the concentration increased. The Hausner Quotient reduced as the concentration of pregelatinised starch increased and so the granules could be described as

being more spherical and more flowable. Blends
containing highly concentrated pregelatinised
starch formed highly porous beds, the granules being
probably more spherical than the low concentrated
granulations. The bed porosities of all the cassava
starch granulations were found to range between
57 - 66%. At 40% W/W pregelatinised concentrations,
the bed porosities of all the blends were least,
and highest at 100% W/W pregelatinised concentration,
meaning that the granules were able to pack into
closest volumes at 40% W/W pregelatinised starch
concentration. Results also showed that the particle
sizes of the pregelatinised starch contributes its
quota to the granule growth. It is easier to bind
smaller particles to one another than to bind larger
particles because the tensile strength of liquid
bridges is inversely proportional to the diameter
of the particles (52). Thus the smaller particle
sizes formed larger average granule sizes than the
larger ones.

Previous workers have shown that a definite
relationship exists between granule strength and
granule size (i.e Surface Area) and that within
limits, the relation, granule strength = K x surface
Area is applicable (52). The granules obtained with

120 ums particle size of the pregelatinised starch showed the least granule friability and largest granule strength.

Granules produced with 120ums particle sized pregelatinised starch were much stronger, owing to the large number of bonds formed per unit volume. Also, due to the enhanced surface area of the finer particle sizes exposed to the solvent action, more of the pregelatinised starch dissolved in the water binder than the coarser grade, causing enhanced viscosity and ~ enhanced granule size. In like manner, the bed porosity increased as the particle size of the pregelatinised starch (pgs) decreased, because the granules of the finer grades tended to be more spherical than the coarser grades. Turning next to the effect of pregelatinization temperature on the granular properties of cassava starch, results showed that pregelatinization temperature T influences the drying time and the attrition of the granulation. This was seen to affect the particle size distribution and average granule size of the granulation. Granule size and granule strength were greater using the starch pregelatinised at 98° - 100°C. Studies showed that the gelatinization of cassava starch was incomplete at 68° - 70°C.

As the gelatinization temperature increased, there was a rise in viscosity. Thus the granules obtained using starch pregelatinised at 98° - 100°C became stronger and bigger with the least friability due to the strong cohesive forces obtained as the larger portions of the soluble contents went into solution. For the same reason, the fluidity increased and the die fill improved, as the pregelatinization temperature increased from 68 - 70°C to 98 - 100°C.

Reworking potential is the ability for compacts to undergo reworking without losing its compressional characteristics, and this is one of the ideal properties of a direct compression diluent. The plain starch-pregelatinised blend compacts of maize, potato, yam and cassava were prepared and evaluated. The reworking potential of cassava starch was found to be comparable to that of maize and by far better than those of potato and yam starches. This quality coupled with its easy availability and cheapness could serve to

single out cassava starch as the most promising
source of directly compressible filler-binder in
this country. The variation in the observed
reworking potentials and other physical properties
of the compacts probably depend on the varying
amylose/amylopectin composition as well as the
varying crystallinity from specie to specie.

The results obtained on the crushing

strength of        compacts were found to

fit the general equation (Log Y = M B + C)

with a correlation coefficient of ⟩ 0.90,

where Y represents the crushing strength,
B the bulk density of the compacts, M,
the slope and C, the intercept values
for crushing strength at a particular bulk
density of 1.27 for all compacts.  The
values obtained for crushing strength were
plotted against the concentration of the
corresponding pregelatinised starch.

Results showed that as the concentration
of pregelatinised starch increased, the
crushing strength of most compacts increased,
reaching a maxima at between 60% W/W and
80% W/W pregelatinised starch, and then
decreased.  This increase  obtained in the crushing
strength of the compact are probably due to the fact

that the pregelatinised starch in the blend, acts
both as a diluent and binder.  At between 60 - 80%
W/W, the binding capacity appeared to be maximum
after which the binder capacity is reduced.  This
behaviour is classified functionally as exhibiting sugar-
like,      unlike gum-like, behaviour (136).  The
mechanism by which the binary blend of pregelatinised/
plain starch formed good compacts may be related by
their modes of deformation.  According to Wells and
Langridge (56), Microcrystalline Cellulose (MC)
undergoes plastic deformation and the mechanical
strength of its compacts is largely controlled by
hydrogen bonding.  In like manner, pgs possibly
exhibited plastic deformation, while the pcs exhibited
brittle fracture (2).

The sequence in the crushing strength obtained
for the compacts made with starch pregelatinised at
68° - 70°C is 120$\mu$ms ) 180$\mu$ms ) 250$\mu$ms.  The sequence
for compacts made with starch pregelatinised at
98° - 100°C is 180$\mu$ms ) 120$\mu$ms ) 250$\mu$ms.  The 120$\mu$ms
starch pregelatinised at 98° - 100°C appeared to be
further weakened by over heating.

It has been shown that pregelatinised starch
contained some cold water solubles (2, 135) which

probably dissolved in the water binder during the granulation phase to form stronger, more viscous liquid bonds between the starch particles. It is to be assumed that the starch completely pregelatinised at 98° - 100°C contained more of cold water soluble fraction than that obtained for 68° - 70°C. The result is the formation of harder compacts with pregelatinised starch made at 98 - 100°C.

In all the compacts compared, there was a decrease in friability as the concentration of the pregelatinised starch increased. Approximately, 0.0% W/W friability was obtained for compacts containing 60% W/W - 100% W/W pregelatinised component.

The compacts containing less than 60% W/W pgs appeared to lose the firmness required in compacts. The pcs did not appear to adhere to itself or to the pgs in the blend. This results in weaker points within the compacts leading to higher friability at lower concentration of pgs. This study suggests that compact friability improved by increasing pregelatinised content of the compact to 80% W/W and 100% W/W. Not withstanding, blending 180ums sized pgs with the 180ums plain cassava starch (pcs), formed a homogeneous, well-blended mass, resulting in better bonding and better compact friability.

Friability appeared to be higher with compacts
made with starch pregelatinised at 68° - 70°C. The
starch completely gelatinised at 98° - 100°C
probably contained a higher percentage of cold water
soluble portions (2, 135) thereby increasing the binding
effect of the water binder and the viscosity. The
result is improved tablet friability due to better
bonding at the pregelatinization temperature of
98° - 100°C.

For all the formulations the disintegration time
of the compacts decreased to a minimum at about 60%
W/W pregelatinised concentration and then increased.
In this study, 40% W/W plain cassava starch (pcs) in
the matrix of the compact appeared to form the required
continuous contact with itself for maximum disinte-
gration for plain/pregelatinised cassava starch
compacts. The mechanisms for disintegrating action
of many disintegrants have been proposed. The con-
cepts that are put forward by various workers
include; swelling (137), capillary action (139),
Deformation (140, 141, 142), wettability, Absorption
of water and Hydration (144), and particle repulsion
theory (145).

However, there is as yet no general agreement
on what constitutes the mechanism of action of starch

as a disintegrant. Because of the different chemical make-up of plain starch and pregelatinised starch, most of these mechanisms may be operative in their blends.

For quick and effective disintegration, there must be effective swelling, water absorption, and good pressure release. The compacts containing 40% W/W plain cassava starch and 60% W/W pregelatinised starch appear to have these properties in the proper proportions. Of the particle sizes of the pgs studied, 180ums appeared to form more uniform and harder compacts, being of the same particle size with the other component of the blend (pcs). Compacts containing 100% W/W 120ums particle size disintegrated easily in contact with the disintegration medium, so also werethe compacts-containing 100% W/W 250ums pgs. All the compacts disintegrated within 15 minutes, the specified disintegration time for uncoated tablets. However, the result shows that 100% W/W pgs (250ums) disintegrated fastest. Generally, relatively large particle sizes were more efficient disintegrants than were the finer grades. This behaviour probably resulted from increased swelling pressure (149). Thus it is evident that the

rate and the force of disintegrant action of pre-
gelatinised starch may be dependent upon the particle
size.

However, 100% W/W pcs (180ums) had a much lower
DT (23 seconds) when compared with 100% W/W pgs
(at 180ums), showing that pcs is a better disinte-
grant. However, the compact containing 100% W/W pgs
at particle size of 120ums produced DT that fell
between the particle size of 180ums and 250ums.
Reason is the segretation of particles during mixing
and inconsistent bonding within the compact due to
the non-uniformity of particle  sizes of pcs, and
pgs in the blend.

Generally, DT was faster for starch batches
pregelatinised at temperature of 98 - 100°C than at
68° - 70°C. This may be due to the fact that at
pregelatinization temperature of 98° - 100°C, the
starch has been completely denatured and being more
hydrophilic, the hydration of the hydroxyl group
of the starch molecule cause them to move apart (144).
Being more wettable, it absorbs more water and
dissolves faster than the partially pregelatinised
counterpact at 68° - 70°C.

The tablet formulations containing pregelati-
nised starch at the concentrations of 60% W/W, 80% W/W

and 100% W/W were named $MCS_1$, $MCS_2$, pgs consecutively and were compared with 100% W/W plain cassava starch (pcs), Avicel pH 102 ($M_1$) and spray dried lactose ($M_2$) as directly compressible diluents for making 50mg paracetamol.

The dissolution profile of the paracetamol in the various diluents shows that tablets containing pregelatinised starch had their t50% within 1 minute. One possible explanation for the quick release of paracetamol from these compacts could be due to the fact that pregelatinization of starch promotes wetting of the paracetamol. It has been shown that the release of poorly soluble hydrophobic drugs from capsules can be improved significantly by the creation of a hydrophilic surface by intensive mixing of the hydrophobic drug with a small amount of a solution of a hydrophilic excipient (2).

The report indicated that the hydrophilic material is mechanically distributed over the hydrophobic surface. The creation of hydrophilic capillaries in a tablet allowed the rapid penetration of the dissolution fluid, resulting in a dispersion of well-wetted particles so that the maximum surface area of the powder was exposed to the dissolution medium.

In all instances, the dissolution of paracetamol was fastest in compacts containing pregelatinised starch, followed by compacts containing plain unpregelatinised cassava starch. The hydration ability coupled with some other operating mechanisms for disintegration appeared to be slower with plain cassava starch than in the pregelatinised starch.

$t50\%$ for tablets containing 60% W/W, 80% W/W and 100% W/W pgs was found to be less than 1 minute, while that of 100% pcs was 1.5 minutes. $t50\%$ for tablets containing spray dried lactose ($M_2$) was 8 minutes and those containing Avicel pH 102 ($M_1$) was nearly 60 minutes. Thus the compacts containing SDL ($M_2$) showed a faster release of paracetamol than obtained for Avicel pH 102. A possible explanation is that lactose containing many large granules allows a more porous and loose mound network to form, enabling the dissolution medium to circulate easily through the mound.

The slower dissolution rate of Avicel pH 102 could be due to a more compact mound, as a result of the much smaller granule size of the MC; the result obtained for MC compact was somehow disappointing. Though MC has been reported to be the

most compressible of all the directly compressible
diluents in the market, the disintegration time has
been described as been good (10). The crushing
strength of $M_2$ was 3.60kg while that of $M_1$ was more
than 10.0kg. The MC are held together by hydrogen
bonds. The hydrogen bonds between hydrogen groups
on adjacent cellulose molecules account almost
exclusively for the strength and cohesiveness (10).
The compressibility of $M_2$ on the other hand, is not
good enough. Spray dried lactose unlike MC contains
a mixture of large crystals of lactose monohydrate
and spherical aggregates of smaller crystals loosely
held together by glass or amorphous material.
However, the crushing strength of tablets made with
$MCS_1$, $MCS_2$ and pgs were much better than obtained
for $M_2$ but less than that obtained for MC ($M_1$).

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## APPENDIX

Batch Description

| No. 1 | 100% W/W plain Cassava Starch |
|---|---|
| 2 | 20% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 3 | 40% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 4 | 50% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 5 | 60% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 6 | 80% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 7 | 100% W/W 120 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 8 | 20% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 9 | 40% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 10 | 50% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 11 | 60% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 12 | 80% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 13 | 100% W/W 180 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |
| 14 | 20% W/W 250 $\mu$ms starch pregelatinised at $68^{\circ} - 70^{\circ}$C |

| Batch No. | Batch Description |
|---|---|
| No. 15 | 40% W/W 250 µms starch pregelatinised at $68^\circ$ – $70^\circ$C |
| 16 | 50% W/W 250 µms starch pregelatinised at $68^\circ$ – $70^\circ$C |
| 17 | 60% W/W 250 µms starch pregelatinised at $68^\circ$ – $70^\circ$C |
| 18 | 80% W/W 250 µms starch pregelatinised at $68^\circ$ – $70^\circ$C |
| 19 | 100% W/W 250 µms starch pregelatinised at $68^\circ$ – $70^\circ$C |
| 20 | 20% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 21 | 40% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 22 | 59% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 23 | 60% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 24 | 80% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 25 | 100% W/W 120 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 26 | 20% W/W 180 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 27 | 40% W/W 180 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |
| 28 | 50% W/W 180 µms starch pregelatinised at $98^\circ$ – $100^\circ$C |

| Batch No. | Batch Description |
|-----------|-------------------|
| 29 | 60% W/W 180 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 30 | 80% W/W 180 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 31 | 100% W/W 180 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 32 | 20% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 33 | 40% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 34 | 50% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 35 | 60% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 36 | 80% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 37 | 100% W/W 250 µms starch pregelatinised at $98^o$ – $100^oC$ |
| 38 | Spray-dried lactose |
| 39 | Avicel pH 102 |

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## SYMBOLS AND ABBREVIATIONS

| | | |
|---|---|---|
| $^{o}C$ | = | Degree Centrigrade. |
| $\mu$, $\mu ms$ | = | Microns, Millimicrons |
| W/W | = | Weight in Weight. |
| V/W | = | Volume in weight. |
| W/V | = | Weight in Volume |
| % | = | Percentage. |
| $P_B$ | = | Bulk Density of powder |
| Pg | = | Apparent/particle Density of powder |
| Ln | = | Natural logarithm. |
| D | = | Bulk density of powder at pressure. |
| Do | = | Bulk density of powder at zero pressure. |
| MYS | = | Modified yam starch. |
| MCS | = | Modified cassava starch. |
| < | = | greater than |
| = | = | equal to |
| > | = | Less than |
| P | = | Breaking load. |
| D | = | Diameter |
| T | = | Thickness |
| S | = | Tensile strength. |
| R.P | = | Reworking Potentials. |
| M | = | Molar |
| B.P | = | British Pharmacopeia. |

| | | |
|---|---|---|
| g | = | gramme |
| ml | = | Millilitre |
| Fig. | = | Figure |
| Kg. | = | Kilogramme |
| Cm | = | Centimetre |
| N | = | Normal |
| Hcl | = | Hydrochloric acid |
| mg | = | Milligram |
| e.g. | = | Example |
| $\alpha$ | = | alpha |
| B | = | Beta |
| ( | = | bed porosity |
| Sec. | = | Second |
| Temp. | = | Temperature |
| T | = | Change in Temperature |
| BD | = | Bulk Density of Compact. |
| o | = | 120ums cassava starch pregelatinised at 68 - 70°C. |
| $\Delta$ | = | 180 ums cassava starch pregelatinised at 69 - 70°C. |
| o | = | 250 ums cassava starch pregelatinised at 68 - 70°C. |
| ● | = | 120 ums cassava starch pregelatinised at 98 - 100°C. |
| ▲ | = | 180 ums cassava starch pregelatinised at 98 - 100°C. |
| ● | = | 250 ums cassava starch pregelatinised at 98 - 100°C. |

| | | |
|---|---|---|
| $A_1$ | = | Area under recompression curve |
| $A_2$ | = | Area under the first compression curve |
| X | = | Plain maize starch |
| ⌀ | = | Plain yam starch |
| ⌂ | = | Plain potato starch |
| ○ | = | Plain cassava starch. |
| Y | = | Crushing shing strength of compact. |
| M | = | Slope |
| C | = | Intercept |
| $MCS_1$ | = | Modified cassava starch containing 60% W/W |
| | | pregelatinised starch. |
| $MCS_2$ | = | Modified cassava starch containing 80% W/W |
| | | pregelatinised starch. |
| $M_2$, SDL | = | Spray dried Lactose. |
| $M_1$, MC | = | Microcrystalline cellulose, |
| | | Avicel pH 102. |
| Pgs | = | Pregelatinised starch. |
| Pcs | = | Plain cassava starch |
| S | = | Solubility |
| r | = | radius |
| ∞ | = | Infinite |
| δ | = | gammar |
| KH | = | Slope in Heckel plot. |
| $A_H$ | = | Intercept in Heckel plot. |
| | = | Plain cassava starch in Heckel plot. |
| ○ | = | Blend containing 20% W/W pregelatinised starch in Heckel plot. |

⊙         =    Blend containing 40% W/W pregelatinised

               starch in Heckel plot.

◊         =    Blend containing 50% W/W pregelatinised

               starch in Heckel plot.

□         =    Blend containing 60% W/W pregelatinised

               starch in Heckel plot

X         =    Blend containing 80% W/W pregelatinised

               starch in Heckel plot.

Z         =    100% W/W pregelatinised starch in Heckel plot.

t50%      =    Time taken for 50% W/W medicament to dissolve.

<         =    Less than.