# INVESTIGATION OF THE EFFECTS OF PROCESS AND FORMULATION VARIABLES ON THE QUALITY OF ASPIRIN TABLETS.

A low cost Aspirin tablet formulation and

Small scale manufacture of cassava starch

MUHIMBILI MEDICAL UNIVERSITY COLLEGE
LIBRARY
DSM.

BY

AMILEN HAROLD LYIMO: B.PHARM (DAR) 1980

A DISSERTATION SUBMITTED TO THE UNIVERSITY OF DAR-ES-SALAAM IN PARTIAL FULFILLMENT FOR THE DEGREE OF MASTER OF PHARMACY.

JUNE, 1994

I have read this dissertation and approved it for examination.

.....MTemu..... ..20/10/94

Dr. M.J. Temu, B.Pharm (Dar), M.Sc, PhD (KUL) Date

SUPERVISOR

**ABSTRACT**

Aspirin is generally prepared by Dry Granulation or Direct Compression method. Majority of the Pharmaceutical Industries in Tanzania utilize imported aspirin granules for direct compression. Preparation of aspirin granules by Wet and Dry Granulation was attempted. Compression of aspirin crystals directly was also explored. The quality of commercial brands of aspirin tablets was investigated and a small scale manufacture of tapioca (cassava) starch was conducted, and the resulting starch was substituted for maize starch in some of the experiments. Parameters studied were Physical characteristics of the powders, Tablet Hardness, Friability, Disintegration time and Dissolution. The properties of the cassava starch were similar to those of other starches in the British Pharmacopoeia 1988.

Cassava starch performed well as a binder and disintegrant. Granules made by cassava starch had good flow and good packing characteristics. Tablets gave very fast disintegration. Release rates of aspirin from tablets were rapid and were similar to those of the commercial brands. Storage in metal and plastic containers at elevated temperatures was experimented and the batches in plastic containers had better results.

The quality of the tablets prepared by Wet Granulation method were similar to those prepared by Dry Granulation and Direct Compression methods. Tablet prepared with cassava starch paste appeared to be harder and had better friability than maize starch paste products.

## LIST OF CONTENTS


| | PAGE |
|---|---|
| Abstract ..... | iv |
| List of Tables ..... | viii |
| List of Figures ..... | ix |
| Acknowledgement ..... | x |
| 1.0 INTRODUCTION ..... | 1 |
| 1.1 Choice of Excipient ..... | 3 |
| 1.1.1 Fillers ..... | 8 |
| 1.1.2 Binders ..... | 10 |
| 1.1.3 Disintegration Agents ..... | 14 |
| 1.1.4 Lubricants -Glidants-Antiadherants..... | 16 |
| 1.2 Process Consideration ..... | 22 |
| 1.3 Evaluation: Tablets and Capsules..... | 25 |
| 2.0 SMALL SCALE MANUFACTURE OF CASSAVA STARCH | 33 |
| 2.1 Cassava starch ..... | 33 |
| 2.2 Manufacture of starch ..... | 36 |
| 3.0 Chemical and Physical Characteristics of Aspirin ..... | 38 |
| 4.0 OBJECTIVE OF THE STUDY ..... | 41 |
| 5.0 EXPERIMENTAL ..... | 43 |
| 5.1 Materials ..... | 43 |
| 5.2 Methods ..... | 44 |
| 5.2.1 Dry Granulation ..... | 44 |
| 5.2.2 Direct Compression ..... | 45 |

5.2.3 Wet Granulation ..... 47

5.3 Granule Properties ..... 48

5.4 Tablet Compression ..... 50

5.5 Evaluation of Tablets ..... 51

6.0 Laboratory Manufacture of Cassava Starch.... 55

7.0 RESULTS AND DISCUSSION ..... 57

7.1 Physical Characterization of the Granules .. 57

7.2 Evaluation of Tablets: Commercial Brands ... 63

7.3 Evaluation of Tablets: Experimental Products. 65

7.4 Cassava Starch ..... 85

8.0 SUMMARY AND CONCLUSION..... 86

REFERENCES ..... 89

## LIST OF TABLES

PAGE

Table 1: Tablet formulation (Dry Granulation) ..... 44

Table II: Tablet formulation (Wet Granulation) ..... 47

Table III: Sieve Analysis Results ..... 58

Table IV: Moisture content, tapped, bulk densities, angles of repose of the granules ..... 61

Table V: Physical properties of the Brands of Aspirin obtained from various pharmacies in Dar-es-Salaam..... 64

Table VI: Weight variation ..... 67

Table VII: Summary of physical tests from the representative batches..... 69

Table VIII: Hardness variation with compression pressure ..... 71/72

Table IX: Drug released (%) ..... 80

Table Xa: Effect of storage at 28-30°C, 40° and 50°C on content of Aspirin ..... 83

Table Xb: Effect of storage at 28-30°C, 40° and 50°C on Tablet Hardness, Friability and Disintegration Time ..... 84

Table XI: Cassava Starch: Analytical Report ..... 85

# LIST OF FIGURES

PAGE

Figure I: Particle size distribution of the granules generated by sieve analysis..... 59

Figure II: Bulk and tapped density results ..... 62

Figure III: Effects of compression pressure on hardness ..... 74

Figure VIA: Drug Dissolution profiles:- Experimental Batches ..... 78

Figure VIB: Drug Dissolution profiles: Commercial Brands ..... 79

## ACKNOWLEDGMENT

I wish to express my sincere gratitude to Dr. M.J. Temu for her patience and encouragement throughout the entire course. Thanks to Dr. C.M. Nshimo for his continuous advise.

I would like to thank the Management of Keko Pharmaceutical Industries for granting me permission to use their laboratory facilities. My sincere appreciation to all the staff working in the Quality Control laboratory of Keko Pharmaceutical Industries Ltd., for their help and friendly cooperation throughout my course. Special thanks to Mr. S. Mlungwana, Mr. R.S. Sombi, Mr. M.S. Mmadi, Mrs. E. Mng'ong'o and Mr. Y. Mwiko for their assistance and kindness.

Thanks to Dr. M. Halphan, the Head of Department of Chemical and Process Engineering for allowing me to utilize their laboratory facilities. I would like to mention Mr. Oscar Kibazohai for his advice and help. I am also grateful to Uswege Mbamba, Alex Msorolo and Idephonce Kahemela of this department for their patience and understanding.

To George Mlavwasi my course-mate, thanks for the good stay and encouragement.

Finally I would like to thank my husband Harold, and sons Bamrom, Bremer and Brian for their love, understanding and moral support.

This project was financially supported by Elys (T) Ltd. to whom I am very grateful.

## DECLARATION

I hereby solemnly declare, that this dissertation is my original work and has never been submitted for a diploma or degree in any other University.

CANDIDATE'S SIGNATURE: .....

A.H. Lyimo - B.Pharm (Dar)

Date: 20th October 1994

SUPERVISOR'S SIGNATURE: .....

Dr. M.J. Temu, B.Pharm (Dar), M.Sc, PhD (KUL)

Date: 20/10/94

## COPYRIGHT

ALL RIGHTS RESERVED. NO PART OF THIS DISSERTATION MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT PRIOR WRITTEN PERMISSION FROM THE AUTHOR OR THE UNIVERSITY OF DAR-ES-SALAAM IN THAT BEHALF.

CANDIDATE'S SIGNATURE: .....

DATE: 20th October 1994

I dedicate this work to the memory of my mother in-law Ann-Erica.

## 1.0 INTRODUCTION

During the past years, a great advance has been made in respect to the solubility and disintegration of tablets and at the present time there are on the market many tablets closely attaining perfection. Why are there still problems in tabletting?

Advances in science and technology do not only solve existing problems but also give rise to new problems of more challenging nature.

The formulation of tablets and capsules has been, until quite recently an art consisting of a great deal of trial and error, backed up with long years of expertise by individual formulators. However within the past two decades there have been a number of developments which have necessitated a much closer look at tablet excipient, how they function, their physical and chemical properties and how they interact and react to the manufacturing process and their effect on the final product.

Possibilities of the utilization of locally available excipients are investigated taking aspirin tablets as an example. There is no information in the literature on the formulations of aspirin tablets manufactured in Tanzania, so

it is of great importance to conduct a simple trial to compare the qualities of the Tanzanian brands of aspirin tablets. Quality Assessment Drugs Programs, provide comparative data on competitive drug products to the health professions. Such a program is not there in Tanzania.

The present study is also concerned with the evaluation of cassava starch for its potential use as a binder (starch paste) and a disintegrant in tablets. An economic study for the establishment of a modern cassava starch factory with a capacity of 24 tons of dry starch per day had already been conducted by Food and Agricultural Organization (FAO)[1]. The study included the estimated required investment and working capital for the establishment and the operation of the factory as well as the estimated operating costs and the expected profitability of the project. The study singled out the tropical region as the best area of establishment because all basic industrial requirements such as water, power, transportation facilities and raw materials are available.

Such a factory was established in Mwanza, Tanzania by the National Chemical Industries but production never took off. However, the factory was not meant for the production of starch for pharmaceutical use, due to the fact that, at the time of planning there were very few pharmaceutical industries

in the country. Secondly, the use of cassava starch in pharmaceutical products is yet to be emphasized. Initially, the factory was to depend on farmers for its supply of cassava roots. Later the management discovered that, the supply was not enough, and hence they requested the government to give them a piece of land so that they could do their own cultivation. This was difficult because nobody was prepared to shift and surrender his/her piece of land.

## 1.1 CHOICE OF EXCIPIENT

There is a wide variety of ingredients utilized in making tablets. The formulation of some tablets is very simple, others much more complex. For instance, aspirin tablets contain only an active ingredient, plus a disintegrating agent, while a chewable multi - vitamin tablet may contain at least one example from each class of excipients.

It is important that the role of the active ingredient in formulation development be discussed. It should never be forgotten that the primary objective of a tablet is to deliver an accurate amount of the drug in a unit dose from which it is available for absorption and to do this with precision over millions of units. In those cases, wherein the active ingredient makes up the bulk of the finished tablet (i.e aspirin, meprobamate, antacids, sulfa drugs, etc.) the major

problem in formulation and manufacture centre around the compressibility and fluidity of the drug substance. Variation in content uniformity is not generally a significant problem. In those tablets containing highly potent drugs which make up only a small portion of the finished dosage form; compressibility and fluidity can easily be accomplished by selecting the right excipient, but major problems, however, often arise in respect to uniform distribution of the drug, (content uniformity) and dissolution.

Excipients are chosen solely for their ability to facilitate drug administration, promote consistent drug release and bioavailability, and protect the drug from degradation. One of the most important steps in the preformulation process consists of determining the compatibility between the drug and various excipients. Drugs are usually considered compatible with a given excipient as long as no chemical reactions between the two can be observed.[2]

Excipients are generally classified as binders, disintegrants, fillers or diluents, glidants, lubricants, colourants, flavours, and sweetening agents. Although there is a tendency of thinking of tablet excipient only in gross terms of their specific functionality i.e. binder, disintegrant, it is important that the fundamental properties of each excipient be

at least considered[3]. The assays specified for recognized excipients are summarized in the various pharmacopoeia. Almost without exception, the compendial assays for excipients make no mention of physical properties. The compendial assays may provide an accurate representation of the chemical quality of an excipient, but they are not useful in describing the physical characteristics associated with the various forms of the excipient.

This lack of physical characterization is a problem because most of the functionality associated with excipients is physical in nature. On weight basis, excipients generally make up the bulk of a solid dosage form; thus, the physical characterization of excipient materials is extremely important. Below, Harry G. Brittain et al[4] gave a few practical examples to illustrate how formulation problems have arisen because of lack of proper physical characterization.

(a) Stearic acid is widely used as a lubricant, although its metal salts are more effective in this regard. From time to time, formulators have encountered lots of stearic acid that fail to exhibit stearic activity. This problem can sometimes be so severe that tablets actually stick in the press and are not ejected after compression. The typical solution to this problem might be to rework the

batch, adding extra stearic acid to compensate for the inadequacy of the formulated material. Note that the performance of the stearic acid cannot be predicted on the basis of results obtained by compendial testing. In the case just cited, all materials passed the compendial (National Formulary) tests. After microscopic examination, it was discovered that, materials that performed well as tablet lubricants consisted of rounded particles, whereas materials that did not lubricate well were found to consist of sharp, angular flakes.

b) Compressible starch

Starch can be used as a diluent, binder, and/or desintegrant. Compressible starch has been specifically processed to yield an excipient material suitable for direct compression formulations. The physical properties of a compressible starch are strongly affected by its particle-size distribution, a quality that can be controlled by the manufacturer. Unfortunately, the particle size distribution of a given sample is a function not only of its processing history but also of its subsequent handling. Formulators cannot assume that the material as received consists of particles that are of the same size as those obtained at the conclusion of product isolation and purification. In a study to

evaluate handling, a sample of compressible starch was subjected to different types of physical abuse. Particle size distribution was determined after each episode. 70% of the particles was transformed into large aggregates which were destroyed by sieving. This study clearly indicate that handling the material before its analysis strongly influences an experimentally determined particle size distribution. It is unwise to accept materials on the basis of vendor certificates, because the end user cannot know the shipping history of the excipient and the possible effects of handling on the product.

c) Microcrystalline cellulose

Microcrystalline cellulose is used as a capsule or tablet diluent, but it also possesses some desintegrant properties. The effect of sourcing on microcrystalline cellulose properties was investigated. Three suppliers of microcrystalline cellulose were chosen, and product was formulated using these three materials. During comparison of the tablet disintegration times, as influenced by the tablet hardness, for the virgin materials, no noticeable differences among the sources were apparent. However during comparison of the tablet disintegration times of reworked formulations,

significant differences appeared. In a study of tablet hardness as determined by compression force, some of the virgin material were equivalent, and differences in material properties were most evident for reworked materials. Although the suppliers of the microcrystalline cellulose materials claimed complete equivalence in physical properties, differences were readily observed in product performance in a given formulation. This led to the conclusion that most critical tests for testing equivalence of excipients should be those related to performance

The different classes of excipients with few representative examples which will be used in the study are discussed below.

### 1.1.1 FILLERS

Fillers are substances used to provide bulk or weight to tablets of practical size for compression and administration. In tablets containing very low doses of active ingredients, the filler may make up as much as 90% of the total tablet weight. In other cases, such as in a simple aspirin tablet, the only filler present is starch, which functions primarily as a disintegrating agent. Fillers may also act as binders (particularly in direct compression), absorbent or drug carrier. They should be chemically and physiologically inert,

stable over long periods of time and possess desirable aesthetic properties. One of the most important considerations in choosing a filler is its hydrophilicity because this can have a major effect on how a tablet disintegrates and the dissolution of the active ingredient.

#### 1.1.1.1 STARCH

Starch is probably used in more tablet formulations than any other single substance because it acts as a filler, binder (starch paste) and most importantly as a disintegrating agent. The most commonly used type of starch in the U.S.A. is corn starch, while potato starch is widely used in Europe and rice starch in the Far East. Starch grains tend to be elastic and not highly compressible and tend to weaken tablet compacts. Starch can be hydrolysed and used as a binder in its paste form. Starch can vary widely in its functional properties, particularly its disintegrating ability because it is naturally occurring.

#### 1.1.1.2 CELLULOSE

It is a relatively inexpensive filler, used in wet granulation in the form of powdered cellulose. It appears to give strength to tablet compacts thus reducing friability. However, it is not highly compressible. A much more compressible and free flowing form of cellulose,

microcrystalline cellulose is also used in wet granulations, but its properties are much better utilized in slugging and direct compression.

Since tablet fillers are often used in large amounts their cost often plays an important role in their selection. It is important to note that while filler excipients are purchased by weight, differences in bulk, volume and compressibility often give rise to significant differences in the amount needed to produce tablets of similar size and properties.

### 1.1.2 BINDERS

Binders are materials which possess both adhesive and cohesive properties. Their purpose is to hold filler and drug particles together in agglomerates (granules). This not only provides larger particles which are free flowing, but the layers of binder tend to cohere to each other when forced together in the compression process. Binders are usually hydrophilic materials (sugars, polymeric materials) which exert strong Van der Waals forces when small percentages of moisture are present. Polymeric materials include natural polymers such as hydrolysed starch, acacia and synthetic polymers such as polyvinylpyrrolidone (PVP) and methylcellulose. Most binders are not effective when dried to zero percent moisture. Binders used in the dry state are far

less efficient because they exhibit minimal surfaces for cohesive binding. The only truly effective dry binder is microcrystalline cellulose.

Binders are usually added out of solution (water or alcohol) and are most effective in this form. However, in some cases (pregelatinized starch and PVP) the dry powder can be distributed in the drug filler mixture and then water or alcohol added to form the binder solution in situ.

The role of the binder in the structure of a granule and its effect on tabletting is excellently presented in a series of papers by Seager et al[5]. The authors used paracetamol (acetaminophen) as a drug and a hydrolysed gelatin as binder. They made tablets by roller compaction (dry granulation), wet massing and spray drying. After granulation, granules were placed in a solvent which dissolved the paracetamol but not the binder. By this extraction procedure, it was possible to examine the binder distribution in the granule using scanning electron microscopy.

Aided by resulting photomicrographs, the authors suggested that the binder was distributed in different ways in the granules depending on the granulation technique used. Roller compaction resulted in a concentration of the binder at a

limited number of points in the granule, i.e. a poor distribution. The wet massing tended to give a fairly even distribution of the binder throughout the granules, like a network. The spray drying, finally gave a high local concentration of binder at the surface of the granules. This could be considered as a poor distribution but from a tabletting point of view, a good one.

Tabletting gave the following results. The roller-compacted granulations gave the lowest mechanical strength, wet massing gave an intermediate strength and spray drying gave the highest tablet strength. The outcome was explained to be a result of the differences in binder distribution and it was concluded that concentration of the binder at the surface of the granules was advantageous to the tablet strength.

Alderborn, G et al [6] showed that it is possible to markedly affect the tablet strength by varying the process conditions during the granulation. The results indicated further that an improvement in compactability can be due to an increased degree of fragmentation of the granules during compression.

#### 1.1.2.1 STARCH PASTE

Of all the classical binders, starch paste is probably the one still most widely used. Starch paste is typically made by

suspending the starch in 1 to $1^1/_2$ parts of cold water and then adding 2 to 4 times as much boiling water with stirring. The paste may be further diluted. The concentration of starch in the final tablet on a dry basis may vary from 2 to 5%. Starch paste makes rather soft but firm granules and is an excellent carrier for dyes in solution, as migration during drying (which could cause speckled tablets) is minimal.

The most difficult aspect of utilizing starch paste is its thick consistency which give rise to problems during handling and blending. Therefore, it is relatively common to blend pregelatinized starch powder with the dry powder mix and then wet with water to granulate. This process requires 2 to 4 times as much starch on a dry basis to achieve equivalent granule and tablet hardness.

#### 1.1.2.2 POLYVINYLPYRROLIDONE (PVP)

Of all of the new polymeric substances, PVP has probably found the most extensive use as a granulating agent. It is a versatile binder which is used as a 5% solution in water or alcohol or blends of each. It can also be dry blended with powder mixes and granulated with water or alcohol <u>in situ</u>. It is usually preferable to use alcoholic solutions if the drug and/or fillers are predominantly water soluble. This process has been used extensively to manufacture oral contraceptive

tablets. It can also be used to granulate effervescent powders (out of anhydrous alcohol) and for chewable antacid tablets.

#### 1.1.2.3 MICROCRYSTALLINE CELLULOSE

It is used in levels of 5-25% as a binder filler in direct compression. It is often used in the post-granulation running powder to give added strength to compacts and in making tablets by dry granulation (slugging). It may be used in wet granulation formulations to improve overall tablet quality.

### 1.1.3 DISINTEGRATING AGENTS.

Although investigators have proposed and evaluated numerous compounds as tablet disintegrants, relatively a few are in use today and until quite recently only starch was the most widely used. The following is a list of agents employed today with the concentration commonly used in finished tablets, extent of use or area of specialization.

a) Starch (corn or potato) - most widely used: 5-10%

b) Alginic acid-limited use, effective but expensive: 5-10%

c) Microcrystalline cellulose - widely used in direct compression for binding as well as disintegrant properties: 10-20%

d) Pregelatinized starch (starch 1500) - effective both as *in situ* binder in wet granulations and as disintegrant: 5-10%.

e) Effervescent System (Sodium bicarbonate plus tartaric acid or citric acid) - used in soluble systems only.

f) Bentonite (Veegum ) - rarely used : 5 -10%

g) Ion Exchange Resins - rarely used: 1 - 5%

h) Sodium starch glycolate - one of the new super disintegrants: 4-8%

i) Cross -linked polyvinylpyrrolidone - one of the new super disintegrants:2-5%

j) Carboxymethylcellulose (Crosscarmellose) - one of the new super disintegrants: 2 - 4%

k) Soy polysaccharides - used primarily in vitamin and health food tablets.

### 1.1.3.1 NEW DISINTEGRATING AGENTS

While many factors play a role in the rate at which a tablet disintegrates or the active ingredient dissolves, the role of the disintegrating agent is paramount. While starch has been satisfactory in many respects, the increased demand for faster and faster dissolution rates and softening effect that starch has on tablets at effective concentration levels, (particularly in direct compression) has stimulated a search for newer more effective agents.

While the new super disintegrants appear to exhibit significant advantages in reducing disintegration time and increasing dissolution rates, they are not without problems. Because of their highly hydrophilic nature, they adsorb moisture and tablets containing these agents may soften when exposed to high humidities. This effect tends to decrease as the concentration in the tablet decreases. In addition it is possible that moisture labile drugs may not be as stable in formulations containing these agents because of their high attraction for water.

**1.1.4 LUBRICANTS, GLIDANTS, ANTIADHERANTS:**

Almost all tabletting materials require some degree of lubrication. A few drugs such as aspirin and excipients such as starch require no lubrication, but these are exceptions. In tablets prepared by wet granulation, lubricants are added only after the granulation has been dried just prior to compression. In direct compression tablets, they are generally added after all other ingredients have been homogeneously blended and then mixed for very short periods of time.

Through the years, lubricants have been defined in many ways which have often led to confusion. The two primary functions of lubricants in a tablet formulation are:-

1. prevent sticking to punch faces
2. ease ejection of the tablet from the die.

As a result of the above, lubricants reduce the wear on both punches and dies. The role of improved fluidity is usually called glidant effect. Glidants are most effective at concentrations that will often cause an increase in tablet weight variation. Higher concentrations of glidants (1-2%) can be used as antiadherants and function similarly to talc at these concentrations. While some lubricants such as magnesium stearate do have a glidant effect, many do not and most glidants do not have a lubricating effect.

Most lubricants will have a lubricating effect on both ejection force and sticking to the punch faces. However, some materials, such as talc seem to exert their main effect on the punch faces and have been called antiadherants.

Although lubricants are generally used in small quantities they can cause serious problems in tablet formulations. Too low levels cause filming, picking and capping of tablets as well as binding in the die cavity. Higher levels often cause an increase in disintegration times or dissolution rates due to their hydrophobic nature. In addition, because they tend to coat particle surfaces they interrupt bonding sites between

drug and/or excipient surfaces causing a weakening in the tablet structure and decreased tablet hardness. The influence of duration of lubricant and excipient mixing on the processing characteristics of powders and on the properties of compacts prepared by direct compression was studied[7]. It was found that the ejection force, hardness, disintegration, and dissolution of directly compressed tablets of lactose and microcrystalline cellulose were all significantly affected by the blending time.

Lubrication has always been one of the most complicated and frustrating aspects of tablet formulation . The lubrication of direct compression powder blends is, if anything, more complicated than that of classical granulation. In general the problems associated with lubricating direct compression blends can be divided into two categories:

(i) the type and amount needed to produce adequate lubrication.

(ii) the softening effects which result from lubrication .

As the overall mean particle size of direct compression is less than that for granulation, hence higher concentration of lubricants are often needed. The recognized need for small particle size of lubricant in granulation is of even greater importance in direct compression.

The softening effect upon compression is magnified because there are many more surfaces available to be covered with lubricant in direct compression blends. This is particularly true in direct compression fillers which exhibit almost no fracture or tear on compression. Even when all surfaces of a granulation are covered by a layer of lubricant, significant clear surfaces are formed during compression as the granules deform with shear. In most instances standard blending time in direct compression blends may or may not cover all primary surfaces. Thus length of blending becomes critical in direct compression than in preparation of tablets by granulation. If blended long enough alkaline stearate lubrications will shear off and completely cover all exposed particle surfaces.

The effect of blending time, running time and lubricant concentration on the adhesion of directly compressed tablets to the lower punch face in a rotary press were studied by Mitrevey and Ausburger[8]. Using microcrystalline cellulose-magnesium stearate blends, adhesion force tended to decrease with increased blending time or intensity of agitation. During three-hour runs with lubricated batches, both microcrystalline cellulose and lactose fillers exhibited an initial pattern in which adhesion force increased while ejection force decreased. The study also showed that the antiadhesion function of stearic acid in hydrous lactose was

comparable to that of magnesium stearate at low lubricant level (0.25%), however, at high lubricant level (1.00%) stearic acid appeared to be more efficient than magnesium stearate. Stearic acid at high concentration, generally produced lower ejection forces than did magnesium stearate, whereas at low concentration, higher ejection forces were obtained. The stearate salts are alkaline in reaction and cannot be used with some acidic drugs like aspirin. It may be necessary to avoid the alkaline stearate lubricants completely in some direct compression formulations.

In selecting a lubricant, proper attention must be given to its incompatibility with the drug agent. One of the most widely investigated drug is aspirin and the following has been reported: Different talcs carried significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. The relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminium stearate.[9]

**1.1.4.1 STEARIC ACID:**

It is not really as effective a lubricant as the stearate salts.(23) Particle size is usually much larger and blending

time and condition are not as critical. It is incompatible with some alkaline salts such as sodium saccharin, sodium phenobarbital. Many grades are available.

MUHIMBILI MEDICAL UNIVERSITY COLLEGE LIBRARY DSM

### 1.1.4.2 TALC

Talc is a hydrous magnesium silicate which has been used as an adjuvant in pharmaceutical tablet manufacture almost since its inception. Although it is difficult to demonstrate the exact role of talc in isolated test procedures, its utility somehow assist in the mechanism of lubrication and/or antiadherance is attested to by almost all tablet formulators. The angular and generally asymmetrical shape of talc would appear to negate any glidant activity. Efforts to measure an effective reduction in tablet ejection force have been inconclusive in most cases. It does appear, however, that talc will reduce the tendency of many tablet formulations to stick to the faces of the punches and thus reducing both filming and picking. Talc is often used in combination with more effective true lubricants, such as magnesium stearate.

### 1.1.4.3 FUMED SILICON DIOXIDE

Fumed Silicon Dioxide is commercially available as very fine individual particles (~0.014 um), many of which are clustered in large aggregates. It exhibits an effect by lodging on surfaces of larger filler or drug particles reducing

interparticulate friction and also acts as a moisture scavenger. It is difficult to blend and usually must be pre-blended or milled with another component. It has no lubricant properties.

## 1.2 MANUFACTURING PROCESS CONSIDERATION

The two properties essential for tablet manufacture are:

1. Compressibility
2. Fluidity.

The various pretreatments of powders in the granulation process are carried out for the express purpose of imparting these qualities to the material to be tabletted. In wet granulation the binder (usually a hydrophilic colloid) acts as a glue to aggregate smallest particles into larger ones which have less interparticulate friction and thus greater flowability or fluidity. At the same time the distribution of the binder over large surface areas provides a glue like material which in part overcomes the lack of cohesiveness that the original drug substance and filler might posses. In dry granulation (slugging) and direct compression, compressibility is dependent upon the inherent deformation and cohesive properties of the drug and filler substances.

The process of granulation (e.g. dry blending vs wet granulation, roller compaction vs wet granulation, high sheer

granulation vs fluid bed granulation) must be thoroughly considered before one makes a decision about the process. The choice depends on mechanical properties, dose of the drug substance, and size of the dosage form. Formulation screening studies are usually done in a mixer/granulator because of the small batch sizes used to screen excipients.

It is known that the ability of material to flow uniformly and reproducibly into a die cavity is the primary factor in achieving tablets of equivalent weights and therefore drug content. In addition to the two primary attributes for successful formation of compacts at high speeds, other properties are necessary if the compacts are to be released from the die and the drug or active ingredient released from the tablets. These include:

1. Lubrication
2. Disintegration or dissolution

While initial efforts at making tablets is centred mainly around formation of the compact, equal if not greater attention today is given to releasing the drug substance from the compact in an absorbable species (in solution). It is a paradox that the processes which are utilized to make a tablet with sufficient mechanical strength to withstand the rigors of handling, packaging, storage and administration are generally

counterproductive to drug release.[10] Furthermore, it has been found that the excipient most likely to cause problems with compact strength and tablet disintegration and drug dissolution, is the lubricant[11,12,13].

Due to hydrophobic nature, lubricants like magnesium stearate have a negative effect on tablet disintegration[14,15]. This effect is caused by film formation around the particles of the tablet ingredients and a consequent inhibition in penetration rate and the volume of water uptake into the hydrophobic pores. In recent work[16], it was shown that for alpha-lactose monohydrate tablets, the deleterious effect of magnesium stearate on the water penetration into tablets can be almost completely eliminated by the incorporation of a strongly swelling disintegrant. Magnesium stearate appears in more new drug products than any other excipient except water. Mats E. Johansson[17] compared the lubricating properties of powdered and granular magnesium stearate. He concluded that batch variations of magnesium stearate due to differences in specific surface area of the lubricant can be masked by using magnesium stearate in granular form. The lubrication of powdered or granular magnesium stearate is not affected by increased mixing time and mixing intensity due to large batch sizes. The tablet properties are more affected by the powdered lubricant regardless of the mixing time or batch size.

Finally, there are factors in tablet making which are less important mechanically and physiologically, but may have a significant impact on patient acceptability, and compliance. These include:

1. Physical and chemical stability
2. Physical inertness
3. Aesthetic acceptability, (color, taste, etc).

## 1.3 TABLET EVALUATION:

There are many approaches to a discussion of the evaluation of tablets and capsules. Evaluation tests are utilized for a wide range of purposes ranging from initial formulation development to final quality control procedures for the marketed product. They can also range from subjective tests such as appearance to clinical testing of bioavailability. The following is a list of properties which at one time or another are standardized and controlled by some sort of evaluation process.

Properties of tablets which are most often evaluated or controlled

1. Size and shape (determined by tooling)
2. Thickness*
3. Surface characteristics (smoothness, molting, colour)
4. Weight (and weight variation)*

5. Breaking strength (Hardness)*
6. Potency
7. Content uniformity
8. Friability
9. Disintegration
10. Dissolution

* In process control

### 1.3.1 TABLET HARDNESS

The older hardness testers suffer from a number of disadvantages. Spring fatigue with time (stokes, pfizer), non-uniform loading rate (stokes pfizer), hand operated (strong - cobb) initial load applied to grip tablet subject to operator or instrument variability (strokes, pfizer, strong - cobb).

The new generation of hardness testers eliminate most of these disadvantages. The ease of operation, reproducibility of data and accuracy of the new instruments make them highly desirable both in formulation development and quality control work.

#### 1.3.1.1 METHOD OF DETERMINING TABLET HARDNESS

Tablet hardness or strength is a measure of the tablets ability to maintain its integrity once the compression force has been removed. The term is used to describe the resistance that a compact may offer during the stress and strains of

manufacture, packaging, shipping and dispensing. The other term which better describes hardness is breaking - strength or fracture force. Three basic methods have been used to measure breaking strength:

(a) Indentation test

(b) Diametal compression test

(c) Bending or flexure test.

The hardness or crushing strength of a tablet is highly dependent upon the geometry and size of the tablet (i.e the thicker the tablet and the wider the tablet, the higher the crushing strength)[20]. While crushing strength may be useful as a quality control parameter when tablets are all approximately the same thickness, diameter, and composition, it can be very misleading in comparing the strength of compacts of different sizes and composition. Therefore, the use of tensile strength instead of crushing strength has been suggested utilizing the equation:-

$$\sigma E = 2P/\pi Dt$$

Where:

$\sigma E$ is the tensile strength,

P is the magnitude of the force applied to the tablet,

D is the diameter of the tablet and t is the thickness.

Using lactose tablets of different thickness, Newton found that within a range of compression pressures, tensile strength data gave a common regression line for all tablet thickness.[21,22]

Several other methods have been used to compare strength of compacts, but it is important to realize that the method of determining hardness or tensile strength may influence the magnitude of differences in compact strengths and can be misleading when drawing conclusion of which material gives stronger compact.

### 1.3.1.2 USE OF HARDNESS MEASUREMENT IN TABLET FORMULATION DEVELOPMENT.

Tablet Hardness or strength measurements are used in many ways in the industry. These include:

1. Determination of the basic properties of pure material (drugs or excipient)
2. To study the effect of formulation and manufacturing variables on tablet strength i.e effects of lubricants, moisture, granule size etc.
3. As a quality control specification for in process validation

Unfortunately, the methods of measuring hardness or tablet strength are so varied that it is difficult to correlate data from different laboratories. Failure to take into consideration tablet size (diameter and thickness) makes hardness data of little use except as a routine quality control parameter for a specific product. Compendial specifications are only possible where tablet size and composition is fixed. In spite of this fact, tablet hardness for many years served as the only measure of compression force applied to a tablet. It is difficult to point out a single formulation or manufacturing variable which does not influence the strength of a compact.

### 1.3.2 FRIABILITY TESTING:

Friability is a measure of a tablet ability to withstand the abrasive forces encountered in handling such as occurs in counting and packaging equipment or during transport. It is a subjective measurement depending on the test equipment. There is no official friability testing equipment and there are no official standards in the United States of America or United Kingdom.

Because friability is an in house test depending on the size, weight and geometry of tablets, little is reported on it in the scientific literature. Generally friability is related to

tablet hardness[23]. Friability can be used as end point in comparing the compressibility of different formulations and the relative dilution potential of direct compression fillers. Friability often parallels hardness. At low compression force, increasing binder has a much greater effect on friability than it does on hardness. At high compression force, increasing binder concentration has much greater effect on hardness than it does on friability.

### 1.3.3 TABLET DISINTEGRATION

Although investigators have proposed and evaluated numerous compounds as tablet disintegrants, relatively few are in use today and until quite recently only starch was the most widely used. Many theories relating to the mechanism of action of tablet disintegration have been proposed, but none has fully explained the disintegration properties of all the agents.

### 1.3.4 TABLET DISSOLUTION

Probably no area of tablet or capsule evaluation is of greater concern today than dissolution. Since its origins in the early 1960's dissolution testing has gradually replaced disintegration testing both as quality control and formulation development test[24,25]. For some drugs, dissolution has been correlated with bioavailability and has been used as means of predicting blood level profiles.

While dissolution testing produces more meaningful data than disintegration testing, it is much more complicated, time consuming, costly and controversial. It has caused numerous conflicts between industry, standard setting organisations and governmental agencies. However, it does appear that a sufficient background of experience has been gained with the method in order to assure its general implementation on a world-wide basis and the adoption of dissolution tests and specifications by all compendial organisations.

The laboratory of William A. Hanson[26] conducted a continuous series of research projects whose objective was to isolate and evaluate the extent to which some variables may be expected to interfere with achievement of consistent results from laboratory to laboratory. The observations confined principally to the standard USP basket and paddle methods. The common variables encountered are as follows: 1) excessive eccentricity of the rotating member; 2) variations in rotational velocities (rpm) and in acceleration (torsional vibration) of the rotating member; 3) temperature variations in the actual dissolution medium; and 4) external vibration that may introduce energy into the system by coupling, and hence influence flow patterns.

### 1.3.5 WEIGHT VARIATION

Weight variation tests can be effective in determining the content of tablets if:

(a) the tablets consists almost totally of the active ingredient.

(b) the active ingredient is homogeneously distributed throughout the entire powder or granule blend.

In most tablets, however, these conditions are not met and thus only by assaying the drug in individual tablets can content uniformity be assured.

## 2.0 SMALL SCALE MANUFACTURE OF CASSAVA STARCH

### 2.1 CASSAVA, TAPIOCA, OR BRAZILIAN ARROWROOT STARCH

Before discussing the manufacture and properties of cassava starch on tablet production, discussion of its botanical source and varieties is presented.

Cassava plant was originally classified botanically as Manihot utilissima Pohl of the family Euphorbiaceae. It was subsequently changed to Manihot esculenta Crantz. The plant is popularly known under a great variety of trivial names: ubi kettella or kaspe (Indonesia), manioca, rumu, yucca (Latin America), mandioca or aipim (Brazil) manioc (Madagascar and French-speaking Africa), tapioca (India, Malaysia), cassava and sometimes cassada (English - speaking regions in Africa, Thailand and Sri Lanka). The term cassava is usually applied in Europe and the United States of America to the roots of the cassava plant.

Cassava constitutes numerous varieties grouped in two main categories as: Manihot palmata and Manihot aipi, or bitter and sweet cassava. This grouping is a matter of economic convenience, as it is difficult to distinguish the two groups by botanical characteristics. However, the distinction between them rests upon the content of hydrocyanic acid in the roots, which causes toxicity. The toxicity is not a variety

constant but varies from place to place; all cassava are now regarded as varieties of Manihot utilissima, and in certain circumstances a "bitter" variety may become "sweet" and vice versa. Hydrocyanic acid content tends to be higher on poor soils and in dry conditions. According to the recognized classification, sweet, or nontoxic, roots contain less than 50 milligrams of hydrocyanic acid per kilogram of fresh matter.

At one time it was thought that the toxicity of cassava root was associated with species or variety, but the hydrocyanic acid content was found to vary markedly with growing conditions, soil, moisture, temperature and age of the plant. Certain varieties in Africa, for instance, were found to be innocuous in Dahomey and poisonous when grown in forest soils in Nigeria; the so-called bitter type from Jamaica failed to produce the toxic substance when grown in Costa Rica.[7]

The chemical composition of cassava roots differs considerably. Studies of 30 varieties in Mexico gave the following results: the dry-matter content of the roots varied between 24 and 52 percent, with a medium of 35 percent; protein content varied between 1 and 6 percent, with a medium of 3.5 percent. On the average, the tubers of the cassava plant contain 60-75% of water and 20-30% of starch, but

variations have been obtained as low as 12% and as high as 33% starch.

The following is an analysis made in Madagascar comparing the cassava root with the potato.[1]

AVERAGE COMPOSITION OF THE CASSAVA ROOT AND THE POTATO (COMMON VARIETIES AT HARVEST TIME)

| | CASSAVA (%) | POTATO (%) |
|---|---|---|
| Moisture | 70.25 | 75.80 |
| Starch | 21.45 | 19.90 |
| Sugars | 5.13 | 0.40 |
| Protein | 1.12 | 2.80 |
| Fats | 0.41 | 0.20 |
| Fibre | 1.11 | 1.10 |
| Ash | 0.54 | 0.92 |

Bitter varieties usually average about 30 percent in starch content.

Maturity differs from one variety to another, but for food the tubers can be harvested at almost any age below 12 months. From the standpoint of starch production, cassava should be considered ripe when the yield of starch per hectare is highest. An optimum age of 18-20 months was found in experiments with certain strains of the variety "Sao Pedro Preto" in tropical climate (Java).

The bitter variety yields more starch and is generally cultivated but contains more hydrocyanic acid than the sweet ones. The acid formed by the action of an enzyme on a glucoside phaseolunatin is present to the extent of 0.01 - 0.035% in the tubers of the cassava and the cortical layers of the sweet variety contain similar percentage. The interior portion of the latter, however contains only 0.004 -0.015% of the acid. On drying in the sun, the content of the hydrocyanic acid falls to 0.0017% and if oven dried to 0.0006%.[28]

## 2.2 MANUFACTURE OF STARCH

The best starch is prepared when soft water is used in the final purification; hard water often leave calcium oxalate in the starch. Basically manufacturing can be divided into four stages.

1. Washing and peeling of the roots, rasping, and staining the pulp with additional water.
2. Rapid removal of the fruit water and its insolubles and replacing this with pure water to prevent deterioration of the pulp. This stage include sedimentation, washing of the starch in tanks or on settling tables, "SILTING" and in some of the medium and large factories, centrifuging.
3. The removal of water by draining, centrifuging and drying.

4. Grinding, bolting and other finishing operation.

Owing to the composition of the cassava root, i.e. low proteins, soluble carbohydrates, fats, etc. the preparation of starch is perfectly straight forward, and without the problems associated with the manufacture of maize, wheat or other cereal starches.

The most essential factor in the production of good grade cassava starch is that the whole process, from lifting the roots to the completion of the final drying should be carried out in the shortest time possible, since deterioration due to enzyme action occurs from the time of lifting and continues throughout the process.

Cassava starch has always been prized for its clarity of solution, good gel strength (second to potato starch), the neutral flavour and light colour of products made from it, and its excellent adhesive strength.

Maize, potato, rice and cassava (tapioca) starches were evaluated with respect to their properties on direct compression.[29] Rice starch showed better compatibility compared to maize, potato and cassava starch. All starches showed adequate capacity for water uptake to act as a disintegrant. In a different study the effect of temperature

on the binding efficiency of yam starch and cassava starch paste was investigated.[30] Increase in granule size and decrease in percentage of fines were observed as the pasting temperature was increased up to a certain level. The disintegration time of tablets was found to increase with the temperature of pasting of both starches.

## 3.0 CHEMICAL AND PHYSICAL CHARACTERISTICS OF ASPIRIN

Aspirin occurs as white crystals or as white crystalline powder. It is slightly soluble in water (1:300), soluble in alcohol (1:5) and glycerin. Aqueous solubility of Aspirin may be increased by using acetates or citrates of alkali metals, although these are said to decompose it slowly. It is stable in dry air but in the presence of moisture, it slowly hydrolyses into acetic and salicylic acids.

Aspirin is sufficiently acidic in structure to produce effervescence with carbonates and, in the presence of iodides, to cause the slow liberation of iodine.

Aspirin is not hydrolysed appreciably on contact with weakly acidic digestive fluids of the stomach, but on passage into the intestine, is subjected to some increased hydrolysis.

Preferably, dry dosage forms (i.e. tablets, capsules, or powders) should be used, since aspirin is somewhat unstable in aqueous media. In tablet preparations, the use of acid-washed talc has been shown to improve the stability of aspirin.[31] Aspirin in aqueous media will hydrolyse almost completely in less than a week. However solutions made from alcohol or glycerin do not decompose as quickly. Citrates retard hydrolysis only slightly. Some studies have indicated that sucrose tends to inhibit hydrolysis. A study of aqueous aspirin suspension has indicated that added sorbitol exert a pronounced stabilizing effect.[32] Stable liquid preparations are available that use triacetin, propylene glycol, or polyethylene glycol.

The rate of absorption is dependent to a great extent on the physical characteristics of the tablet. Aspirin tablets made up of large particles are dissolved and absorbed more slowly than are tablets of ultrafine, loosely bound particles. Formulation factors such as starch content, granulation technology, compression pressure, and type and concentration of tablet lubricant can have a significant effect on the rate of absorption of aspirin by human subject. The various brands of aspirin have therefore significantly different dissolution rates. This may be the reason for the controversy regarding the relative advantages of plain and buffered products.

Contrary to common belief, there is no correlation between the disintegration time of aspirin tablets and the dissolution rate of the drug in these tablets, except that rapid disintegration is ordinarily a prerequisite for rapid dissolution.[33] Utrafine or micronized, aspirin also has an increased rate of dissolution.

## 4.0 OBJECTIVE OF THE STUDY:

About 100% of the raw materials utilized by pharmaceutical industries in Tanzania are imported. The government, under the National Drug Policy (1991)[34] intends to gradually develop self sufficiency in the production of intermediate and raw materials wherever Tanzania has a comparative advantage. The policy intends or aims at increasing the national capacity for packaging, bottling, labelling and producing excipient of proper pharmaceutical quality.

Tanzania is one of the countries implementing an Essential Drug Program (EDP). The EDP was introduced in 1984 with the assistance of the Danish International Development Aid (DANIDA) and World Health Organization (WHO) to help solve a critical shortage of drugs especially in rural areas. However, one of the long term goals of the Essential Drugs Concepts was the attainment of some degree of self sufficiency. A possible approach is the use of locally available raw materials in the local manufacture of essential drugs. Taking for example aspirin, which is one of the most widely used drugs in the Essential Drugs Program, possibilities of using locally available starch were investigated.

Cassava starch was selected in favour of maize starch due to the following reason:-The yield of maize in Tanzania does not suffice domestic use and is very much affected by the rainfall pattern, while cassava is abundantly available and grows even in areas with very little rainfall. The main idea is to device a simple formula for the manufacturing of aspirin tablets, using simple techniques and readily accessible excipients.

**a) Broad Objective**

To investigate the effect of process and formulation variables on the quality of aspirin tablets.

**b) Specific Objectives**

(i) To evaluate the quality of aspirin tablets manufactured locally by pharmaceutical industries in Tanzania.

(ii) To attempt production of aspirin using relatively inexpensive materials and processes and compare the quality.

(iii) To explore the possibility of manufacturing cassava starch from cassava roots locally.

(iv) To explore the possibility of large scale manufacture of cassava starch.

## 5.0 EXPERIMENTAL

### 5.1 MATERIALS:

The Aspirin and excipients used were USP, B,P or Eur. Ph. grade and all reagents were of analytical grade. The drug aspirin (acetylsalicylic acid) was a product from two manufacturers (Phodine 2020 crystal and Rhodine 2040 crystal of Rhone-Poulenc, France, and one manufacturer from China) with a purity of at least 100%. Aspirin from China had big crystals of regular shape and size, with very small amount of fines. Both Rhodine 2020 and 2040 had smaller crystals and more fines than the aspirin from China. Rhodine 2020 and 2040 crystal had crystals of irregular shapes needle like, probably monoclinic crystals. Rhodine 2020 had bigger crystals than Rhodine 2040. The size of Rhodine crystal was as follows: Rhodine 2020 specification was cumulative refusal at 20 mesh 0.7%, 80 mesh 68.8% and 325 mesh 99.3%. For Rhodine 2040 cumulative refusal at 40 mesh 2.7%, 120 mesh 78.0% and 325 mesh 94.5%.

The excipients used in this study were microcrystalline cellulose (batch No. 11111, Jim Royal Trading Co Taiwan) starch B.P. (maize starch, batch No. CN 4035, Cerestat G.L., Italia SPA, cassava starch manufactured locally in laboratories at the University of Dar es Salaam), Talc (Batch No 260966, Talcopharma S), colloidal silica (Aerosil$^{R}$ 200,

batch No. 2055HH12092 C5, Degussa AG, Belgium), tartaric acid (Codex[R] batch No. 1185 L100, Farmatalia Carloebra S.P.A. Milano, Italy), stearic acid (manufacturer unknown), povidone USP (plasdone[R] K-29/32, ISP Technologies, INC WAYNE NJ), and pregelatinized starch NF(starch 1500[R], batch No. 112037, Greif Bros Corporation Blue Island Illinois).

## 5.2 METHOD

**5.2.1 DRY GRANULATION:** Tablet formulation used in this method is shown in Table I.

**Table I: TABLET FORMULATION (DRY GRANULATION)**

**Granule Preparation.**

| Ingredient | % w/w of ingredient in the formulation | | | | |
|---|---|---|---|---|---|
| | 1(a.b) | 2 | 3 | 4 | 5 |
| Aspirin | 90 | 90 | 92.5 | 92.7 | 92.7 |
| Starch (maize/cassava) | 9.7 | 7 | 7.2 | 7.2 | 7.2 |
| Talc | - | 3 | - | - | - |
| Stearic acid | - | - | 0.3 | - | - |
| Colloidal silica | - | - | - | 0.1 | 0.1 |
| Granules and Excipient blending | | | | | |
| Aspirin granules | 87.9 | 87.9 | 80 | 88 | 90 |
| Microcrystalline Cellulose | 12.0 | 12.0 | 12 | 12 | 10 |
| Starch(maize/cassava) | - | - | 7.75 | - | - |
| Stearic acid | - | 0 | 0.25 | - | - |
| Colloidal silica | 0.1 | 0.1 | - | - | - |
| Tablet weight(mg) | 378 | 379 | 380 | 379 | 354 |

Formulation 1b and 5 utilized cassava starch while the rest of the batches used maize starch.

Batches of the various formulations were prepared by mixing aspirin and the excipients mentioned in a cube blender (PRS; Erweka Apparatebau, Heusenstamm FRG) for 5 minutes. Slugs were compressed using 10mm flat-faced tooling. The tablets were crushed and granulated through a 14-mesh sieve by an Erweka granulator (FGS; Erweka Apparatebau, Heusenstamm FRG). The granules were then mixed with lubricant in the Erweka cube blender for 5 minutes and then compressed into tablets using a 33 stations rotary press (model ZP-33; China) at 2500kg/in$^2$ using a 10mm flat-faced tooling. The tablets were collected into plastic containers (with snap in caps) and hardness, weight variation, friability and disintegration time tests were conducted.

### 5.2.2 DIRECT COMPRESSION

Direct compression of the three aspirin crystals was attempted using the following formulation.

| | Batch No. 6(a,b,c) |
|---|---|
| Aspirin | 84.9% |
| Microcrystalline cellulose | 10.0% |
| Starch (maize/cassava) | 5.0% |
| Colloidal silica | 0.1% |
| Tablet weight (mg) | 353 |

The experiment was conducted in triplicate.

Aspirin with large crystals (chinese) was used in batch No. 6a while 6b and 6c contained Rhodine 2020 (medium crystals) and 2040 (small crystals) respectively.

Aspirin and the various excipients were mixed in an Erweka cube blender for 5 minutes and then compressed into tablets using a 33 stations rotary press (Model ZP-33, China)at 2500kg/in$^2$ compression pressure using flat-faced punches and die. The tablets were collected in plastic containers (with snap in caps) and hardness, weight variation, friability and disintegration time tests were conducted.

### 5.2.3 WET GRANULATION

Tablet formulations used in the study are given in Table II.

**Table II: TABLET FORMULATION (WET GRANULATION)**

**Granule Preparation**

| Ingredient | % w/w of ingredient in the formulation | | |
|---|---|---|---|
| | 7(a,b) | 8 | 9 |
| Aspirin | 46.62 | 52.63 | 48.31 |
| Povidone USP | - | - | 2.66 |
| Starch paste 15%(maize/cassava) | 12.35 | - | - |
| | - | 4.21 | - |
| Pregelatinized starch | 6.99 | - | 7.25 |
| Starch(maize/cassava) | 0.70 | 0.79 | 0.72 |
| Distilled water | 0.70 | 7.89 | 7.25 |
| Granule and Excipient blending | | | |
| Aspirin | 23.31 | 26.31 | 24.15 |
| Starch(maize/cassava) | 6.99 | 7.89 | 7.25 |
| Stearic acid | - | 0.24 | - |
| Talc | 2.33 | - | 2.42 |
| Tablet weight (mg) | 369 | 348 | 341 |

Formulation 7a contained maize starch while in formulation 7b cassava starch was used instead.

**Granule preparation**

The drug (crushed into powder using mortar & pestle) and the appropriate excipients were granulated with starch paste (containing an aqueous solution of tartaric acid) or with an aqueous solution of tartaric acid (passed through a 120 mesh copper wire sieve). The tartaric acid was used specifically

to inhibit hydrolysis of aspirin because of its high affinity for water molecules/ions. The excipients and the drug were mixed in a cube blender (PRS; Erweka Apparatebau Heusenstamm FGR) for 5 minutes prior to the wet granulation. Wet granulation was conducted in a planetary mixer (U.G. Erweka Apparatebau, Heusenstamm FGR). Total mixing time for wet granulation was 20 minutes. The wet granulations were passed through a No. 16 nylon (manual) screen and dried in hot air oven (HS 61A, Czechoslovakia) at 60°C until the desired moisture level (not more than 0.5%) was obtained. Finally the dried granulation was passed through a No. 12 mesh screen.

## 5.3 GRANULE PROPERTIES

### 5.3.1 Moisture content determination

Moisture content was determined by Ultra X infra-red moisture tester (070; Utra X, Germany). 10g of the granules was used and an average of three determinations were recorded. Data is included in Table IV.

### 5.3.2 Particle-size analysis.

The particle size distributions of the materials were obtained by sieve analysis. The sieves (153105 Czechoslovia) were set one on top of another and 100g of the granules were sieved for 20min (agitation method) using automatic sieve shaker (AP 2c, Czechoslovia). Figure I and Table III show the results.

### 5.3.3 Bulk density.

The bulk density was estimated by pouring material into 250ML graduated glass cylinder. Three determinations were performed per batch. Data is included in Table IV and Figure II.

### 5.3.4 Tapped density.

The tapped density was determined by stamping method (Stampfrolumeter 86315, Engelsmann A.G. Apparatebau, Germany). Data obtained is presented in Table IV and Figure II.

### 5.3.5 Measurement of angle of repose

The powder (100g) was carefully poured into a dry glass funnel whose sealed tip (8mm diameter) was held 6cm from the working surface. The seal was removed and the powder allowed to flow onto a sheet of parchment under force of gravity. The height and diameter of the cone were measured. The mean result of six determinations was used. The angle of repose ( X°) was obtained from the equation:

$$\text{Tan } X^\circ = \frac{h}{0.5d}$$

where h is the height of the cone and d is the diameter. Data pertaining to the above calculations can be seen in Table V.

### 5.3.6 Granules and Excipient Blending

The granules and the excipients were mixed in a cube blender (PRS; Erweka Apparatebau, Heusenstamm FRG). Each mixing study

used a total load of 1 ± 0.1kg. The granules and excipients were added at the same time.

### 5.3.7 Content of Aspirin in the granules

The method below was used to determine the content of aspirin in the granules expressed as percentage. Three samples, each equivalent to the weight of one tablet, were obtained using an analytical balance (Sartorius Model 2842, Germany). The samples were dissolved in 96% alcohol (temperature maintained low by ice bath, approximately 10°C) then titrated against 0.1N sodium hydroxide solution. The method was adopted and translated into English from Chinese Pharmacopoeia by Keko Pharmaceutical Industries Ltd. This Industry has been using this method for more than ten years and claim to produce results which are comparable to the British Pharmacopoeia 1988 method. The method is simple and easier than the British Pharmacopoeia method.

## 5.4 Tablet Compression

Tablets obtained by Wet Granulation were compressed using a 16 station rotatory press (Cadmach, CMD 3 B-16 India) at different compression pressures using 10mm diameter concave punches and die. The compression pressures used were 500kg/in$^2$, 1000kg/in$^2$, 1500kg/in$^2$, 2000kg/in$^2$, 2500kg/in$^2$, and 3000kg/in$^2$. Batches 7a, 7b and 8 were compressed using the 6

compression pressures while batch 9 was compressed at 3 compression forces (2000, 2500, 3000kg/in$^2$. The rest of the batches were compressed at 2500kg/in$^2$ only using a 33 stations rotary press (model ZP-33, China). The tablets were collected into plastic containers (with snap in caps) and hardness, weight variation, friability and disintegration time tests were conducted.

## 5.5 EVALUATION OF TABLETS

During the whole experimental process, 13 batches were generated (Table VIII). Formulation 1-5 consisted of tablets made by Dry Granulation, 6a - 6c Direct Compression and 7a - 9 Wet Granulation methods. Among them, batches 1b, 5, 6a and 7b contained cassava starch.

Four commercial brands of aspirin tablets (one from Germany and three manufactured locally) were collected from various pharmacies in Dar-es-Salaam for quality comparison with the above batches. The data generated is shown in Table V and Figure VIb.

### 5.5.1 Hardness

Immediately after compression, hardness of the tablets was determined. (TBH28; Erweka Apparatebau, Heusenstamm, FRG) Values used are an average of 10 determinations. Data is

included in Tables VII and VIII. For the Wet Granulation batches 7a, 8 and 9, the effect of compression force on tablet hardness was examined.

### 5.5.2 Weight variation

Weight of 20 tablets were determined using a Sartorius balance (Sartorius excellence, Model E 1200S, Germany) and the average and coefficient of variation were calculated. Data is reported in Table VI. Batches 7a, 8 and 9 prepared by Wet Granulation method were taken as representative batches. General comparison for all batches can also be viewed in Table VII.

### 5.5.3 Friability

An Erweka (TAP; Erweka Apparatebau, Heusenstamm, FRG)) friabilator was employed to determine the friability. The sample size was 20 tablets and test time was four minutes. Percent friability was calculated. Data is shown in Table VII.

### 5.5.4 Disintegration Time

Disintegration times of the tablets were determined in Erweka apparatus (ZT6; Erweka Apparatebau Heusenstamm FRG) using the British Pharmacopoeia 1988 method. The mean of six determinations for each batch was recorded. (Table VII).

### 5.5.5 Assay of Aspirin tablets

Method in No. 2.2.7 was adopted to assay the content of acetylsalicylic acid in the tablets and the content was expressed as the percent of label claim. A total of three readings were recorded. Data is included in Table Xa.

### 5.5.6 Drug Dissolution

The dissolution rate study of two tablet samples from each group following USP, 1988 dissolution method for aspirin tablets was conducted utilizing the USP Apparatus I (basket). The equipment was a standard multiple-head dissolution unit (Dissoette, 24-6M, Hanson Research, Northridge, CA). This dissolution equipment features six round bottom flasks each containing 900ml of Dissolution medium. The rotating baskets were positioned 2.5cm from the bottom of the flask and driven at 50 rpm by the multiple drive unit. The dissolution medium in each flask was 0.05M acetate buffer having pH 4.5, maintained at 37° ± 1°C. One tablet was placed in each flask. samples were withdrawn and passed through a millipore prefilter (filter type AP), collected in test tubes and then placed in a 1.0cm cuvette after dilution of 1:50. Volume withdrawn (1.0ml) was replaced by an equal volume of 0.05M acetate buffer. Absorbance was measured at 265nm using a UV-spectrophotometer (Ce292; Cecil Instruments, England). A mean of two determinations for each batch was recorded.

Dissolution tests were terminated after 30 minutes. The mean percent dissolved at several time points were calculated. Table IX and Figure IVa show the results.

### 5.5.7 Salicylic Acid Limit Test

The British Pharmacopoeia 1988 method was used to determine the quantity of salicylic acid. The method uses colour intensity of a freshly prepared reference solution of 0.010% $^{w}/_{v}$ salicylic acid. This test was conducted on day 1, day 90 and after the elevation of storage temperatures at 40° and 50°C for one week. Physical examination was conducted on the tablets by smelling and visualization of deposition of salicylic acid on the tablet surface.

### 5.5.8 Stability Test

Stability testing was conducted on both the aspirin tablet obtained from local manufacturers and those manufactured in the laboratory. The tablets were stored in plastic and metal containers then subjected to elevated temperatures using hot air ovens at 40° (U40; Memmert, Germany) and 50°C (1119UV; Termaks, Bergen Norway) for one week. The tablets were tested physically and content of aspirin expressed as percentage of label claim. Results appear in Tables Xa and Xb.

## 6.0 LABORATORY MANUFACTURE OF CASSAVA STARCH

### 6.1 MATERIALS

Stainless steel tray -1

Plastic tray - 1

Stainless steel kitchen pots - 2

Stainless steel bucket - 1

Kitchen Grater - 1

Sieves 250um, 180um, 90um, 80um.

Filter papers

Oven (HS 61 A; Czechoslovakia)

Buchner funnel

Vacuum pump (Marius AL15; Germany)

Apex mill (1145;Apex-Mill Comminuting,England)

Distilled water

Cassava roots (collected at foot of the University of Dar-es-Salaam Hill)

### 6.2 METHOD.

Two cassava plants (identified by a Botanist) aged about 12 months were lifted and taken to the laboratory ready for the extraction of starch. The cassava roots were thoroughly washed to remove adhering soil or sand, and then peeled. Rasping was done by means of a kitchen grater (Taiwan). In separating the pulp from the free starch a liberal amount of water was added and the resulting suspension was vigorously

stirred with both hands ready for screening. The pulp was pressed out by hands and the suspension was passed through a line of arranged sieves 250um, 180um and 90um.

Purification of the starch was done by settling method where the starch was separated from soluble contaminants. The starch was washed three times before it was filtered through a paper filter using buchner filter and vacuum pump. The whole process of extraction took 3 hours. The starch was dried in hot air oven (T 1119 UV; Termaks, Bergen Norway) for four hours, milled using an apex mill (1145; Apex-Mill Comminuting, England) and then screened using 80um hand sieve. The resulting starch was analysed according to British Pharmacopoeia 1988 specifications. Data is included in Table XI.

## 7.0 RESULTS AND DISCUSSION

### 7.1 Physical characterization of the granules

#### 7.1.1 Particle-size analysis

Table III and Figure I show the particle-size distribution of the granules prepared by Wet and Dry Granulation methods. The wet granulation formulations contained starch paste (13.35%) polyvinylpyrrolidone (2.66%) and pregelatinized starch (4.21%) as binders while the dry granulation formulations contained microcrystalline cellulose (10%) as dry binder. The granules size distribution was compared with Rhone-Poulenc granules (grade 3118 Rhone-Poulenc, France). Refusal at 125um, sieves should not be less than 96%, at 710um and 1000mn sieve should not be more than 40% and 5% respectively. The results show that the values are in the same range as those of Rhone - Poulenc granules. Refusal at 125um was more than 96% for all batches. Refusal at 710um for batches 7a, 7b and 5 was 22.8%, 8.2% and 22.3% respectively. Batches 8 and 9 had slightly higher values. Refusal at 1000um, for all batches was less than or equal to 5% except for batch 8. This small difference in granule size could be due to the factor of end point determination during wet granulation due to the fact that too wet mass produces large granules while less wet mass produces small granules.

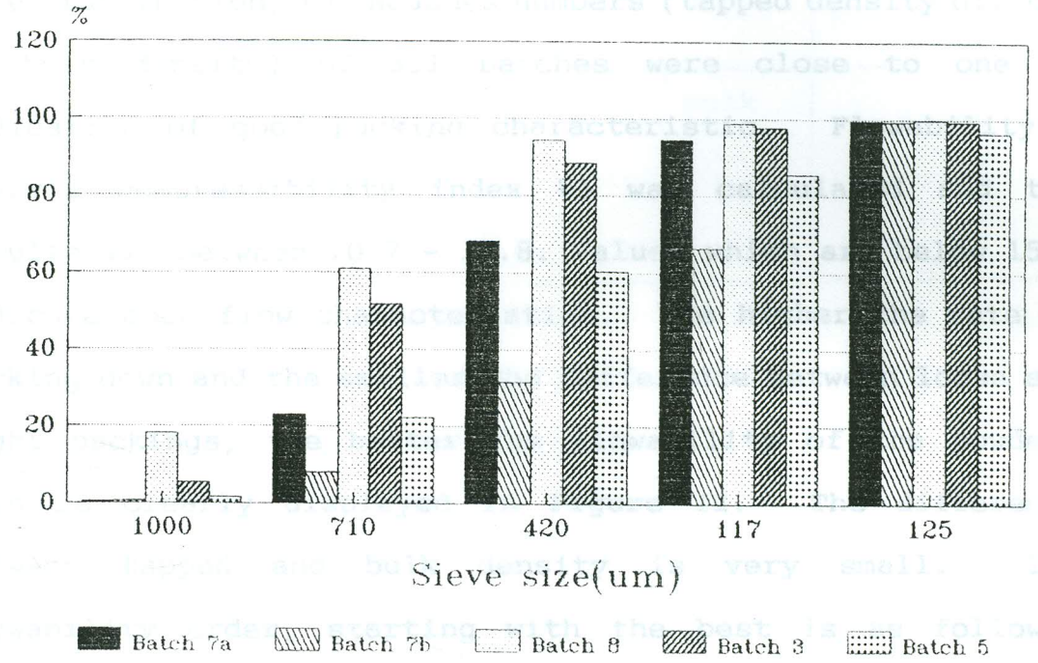
**Table III: Sieve analysis results**

**Weight of sample: 100g; Sieve time: 20min.**

| Sieve size um | Total Percent | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 7a | | 7b | | 8 | | 9 | | 5 | |
| | on | passing | on | passing | on | passing | on | passing | on | passing |
| 1000 | 0.3 | 99.7 | 0.5 | 99.5 | 18.0 | 82.0 | 5.3 | 94.7 | 1.6 | 98.4 |
| 710 | 22.8 | 77.2 | 8.2 | 91.8 | 60.9 | 39.1 | 51.7 | 48.3 | 22.3 | 77.7 |
| 420 | 68.2 | 31.8 | 31.5 | 68.5 | 94.3 | 5.7 | 88.5 | 11.5 | 60.4 | 39.6 |
| 117 | 94.5 | 5.5 | 66.3 | 33.7 | 99.0 | 1.0 | 97.8 | 2.2 | 85.6 | 14.4 |
| 125 | 99.6 | 0.4 | 99.4 | 0.6 | 99.8 | 0.2 | 99.4 | 0.6 | 96.4 | 3.6 |
| Pan | 100.0 | 0.0 | 100.0 | 0.0 | 100.0 | 0.0 | 100.0 | 0.0 | 100.0 | 0.0 |

| Formulation | Type of binder used | |
|---|---|---|
| 5 | Microcrystalline cellulose | (10.0%) |
| 7a | Maize starch paste | (12.35%) |
| 7b | Cassava starch paste | (12.35%) |
| 8 | Pregelatinized starch | (4.21%) |
| 9 | Polyvinylpyrrolidone | (2.66%) |

Figure 1. Particle size distribution of the granules generated by sieve analysis




Weight of sample:100g; sieve time:20min

| Formulation | Type of binder used | |
|---|---|---|
| 5 | Microcrystalline cellulose | (10% ) |
| 7a | Maize starch paste | (12.35% ) |
| 7b | Cassava starch paste | (12.35% ) |
| 8 | Pregelatinized starch | (4.21%) |
| 9 | Polyvinylprrolidone | (2.66%) |

### 7.1.2 Bulk and Tapped Densities

The data collected are presented in Table IV and Figure II. Despite the fact that there were some differences in particle size distribution, the Hausnes numbers (tapped density divided by bulk density) of all batches were close to one an indication of good packing characteristic. Flowability C (Carr's compressibility index %) was calculated and the results lie between 10.7 - 13.8. Values which are below 15%, indicate good flow characteristics. The higher the rate of packing down and the smaller the difference between loose and tight packings, the better the flowability of the powder. This is clearly displayed in Figure II. The difference between tapped and bulk density is very small. The flowability order, starting with the best is as follows: Formulation Nos 5, 7a, 9 , 8 and 7b.

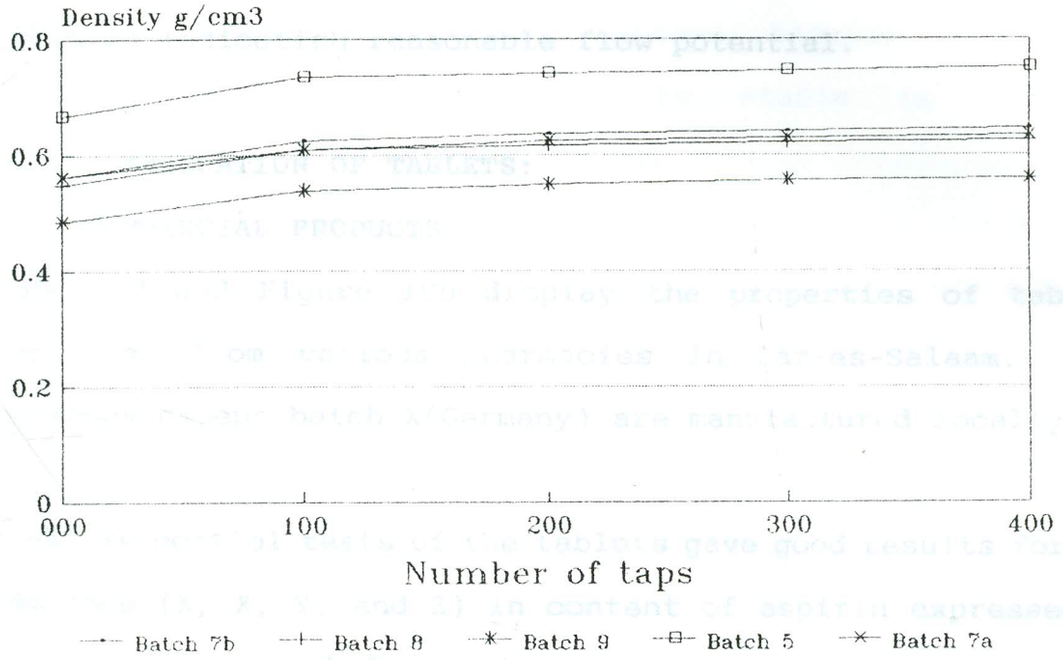
**Table IV: Moisture content, tapped, bulk densities and angle of repose of the granules generated.**

| | | | Density ($g/cm^3$) | | Hausner Number | Flowability |
|---|---|---|---|---|---|---|
| Formulation | Moisture content (%) | Angle of repose | Tapped | Bulk | | C (%) |
| 7a | 0.3 | 33.0° | 0.63 | 0.56 | 1.13 | 11.1 |
| 7b | 0.4 | 31.8° | 0.65 | 0.56 | 1.16 | 13.8 |
| 8 | 0.2 | 33.5° | 0.63 | 0.55 | 1.15 | 12.7 |
| 9 | 0.1 | 33.2° | 0.56 | 0.49 | 1.14 | 12.5 |
| 5 | 0.3 | 31.0° | 0.75 | 0.67 | 1.17 | 10.7 |

| Formulation | Type of binder used | |
|---|---|---|
| 7a | Maize starch paste | (12.35%) |
| 7b | Cassava starch paste | (12.35%) |
| 8 | Pregelatinized starch | (4.21%) |
| 9 | Polyvinylpyrrolidone | (2.66%) |
| 5 | Microcrystalline cellulose | (10%). |

The Hausner number is the ratio of tapped over bulk density while flowability is 1- the ratio of bulk over tapped density X100 S.D (n=3) ranges lies between 0.0094 - 0.89.

Figure II. Bulk and tapped density results




| Formulation | Type of binder used | |
|---|---|---|
| 5 | Microcrystalline cellulose | (10%) |
| 7a | Maize starch paste | (12.35%) |
| 7b | Cassava starch paste | (12.35%) |
| 8 | Pregelatinized starch | (4.21%) |
| 9 | Polyvinylpyrrolidone | (2.66%) |

### 7.1.3 Angle of Repose

The data obtained is shown in Table IV. Angles of repose have very little variation and are lying in the range 31.0° - 33.5°. The values of angle of repose lie between 20° and 40° (normal values) indicating reasonable flow potential.

## 7.2 EVALUATION OF TABLETS:

### (i) COMMERCIAL PRODUCTS

Table V and Figure IVb display the properties of tablets obtained from various pharmacies in Dar-es-Salaam. All batches except batch X(Germany) are manufactured locally.

Quality control tests of the tablets gave good results for all batches (X, X, Y, and Z) in content of aspirin expressed as percent of label claim, hardness, friability and disintegration time tests. The properties displayed in Table V indicate that, all tablets which are manufactured locally have good physical characteristics.

The dissolution profiles for the four batches (W, X, Y and Z) are displayed in Figure IVb. There is very little difference in the release pattern of the batches. The time (min) for 50% release of the drug is 5, 6, 6, and 7.4 minutes for batch X, Y. W and Z respectively. For 80% release, the order is the same, that is 22, 28, 28, and >30 minutes.

According to United States Pharmacopoeia 1988, 80% of the drug under study should be released within 30 minutes. Batch Z does not meet this standard. Batches W and X could be considered as standard references for the experimental products, but batch Y was chosen because of faster disintegration and proved to be stable in the two temperatures, 40°C and 50°C studied.

**Table V: Physical Properties of the Brands of Aspirin tablets obtained from various Pharmacies in Dar-es-Salaam.**

| Batch | Content (%) | Tablet wt mg (Mean ± SD) | C.V. | Hardness (%) Erweka Units | Friability (%) | D.T. (S) |
|---|---|---|---|---|---|---|
| W | 104.2 | 356.6 ± 4.6 | 1.28 | 52.9 | 0.50 | 120 |
| X | 98.1 | 338.7 ± 3.1 | 0.91 | 35.9 | 0.21 | 13 |
| Y | 101.4 | 338.4 ± 5.9 | 1.74 | 65.8 | 0.48 | 25 |
| Z | 95.8 | 307.3 ± 6.3 | 2.05 | 52.7 | 0.51 | 22 |

C.V = Coefficient of variation $\left(\frac{S.D.}{Mean} \times 100\%\right)$

D.T.= Disintegration time.

With the exception of batch X (Germany), batches W, Y and Z were manufactured locally.

## 7.3 (ii) EXPERIMENTAL PRODUCTS

### 7.3.1 Weight Variation

A one way analysis of variance was used to test if there were any significant differences in the weight of the tablets in the three batches (Wet Granulation) selected (7a, 8, and 9). The statistical data analysis appear in Table VI. At the 95% level of significance the following can be concluded. For batch 7a the differences in the mean weight is highly significant ($P << 0.05$). For batches 8 and 9 the differences in the mean weight is statistically not significant ($P > 0.05$). Batch No. 7a had granules of good particle size, and good flowability index which could be compared to the rest of the batches. The apparent weight variation could be attributed to the machine capacity (16 stations) and small batch size ($1.0 \pm 0.1$.kg).

**Table VI: Weight variation.**

Batch 7a

Analysis of Variance

| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 5 | 6311.0000 | 1262.2000 | 17.7103 | .0000 |
| Within | 114 | 8124.7000 | 71.2693 | | |
| Total | 119 | 14435.7000 | | | |

| Group | Count | Mean | S.D | S.E | 95 % C.I. for Mean |
|---|---|---|---|---|---|
| 500kg/in$^2$ | 20 | 358.7000 | 9.0035 | 2.0132 | 354.4862 To 362.9138 |
| 1000kg/in$^2$ | 20 | 364.6000 | 9.1099 | 2.0370 | 360.3365 To 368.8635 |
| 1500kg/in$^2$ | 20 | 364.6500 | 8.9341 | 1.9977 | 371.2850 To 368.8313 |
| 2000kg/in$^2$ | 20 | 374.4500 | 6.7627 | 1.5122 | 371.2850 To 377.6150 |
| 2500kg/in$^2$ | 20 | 370.5000 | 8.0557 | 1.8013 | 366.7298 To 374,2702 |
| 3000kg/in$^2$ | 20 | 380.0000 | 8.5508 | 1.9120 | 376.7981 To 384.8019 |
| Total | 120 | 368.9500 | 11.0140 | 1.0054 | 366.9591 To 370.9409 |

Batch 8

Analysis of Variance

| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 5 | 315.1667 | 63.0333 | 1.0195 | .4096 |
| Within | 114 | 7048.3000 | 61.8272 | | |
| Total | 119 | 7363.4667 | | | |

| Group | Count | Mean | S.D. | S.E. | 95% C.I. for Mean |
|---|---|---|---|---|---|
| 500kg/in$^2$ | 20 | 362.8000 | 10.5959 | 2.3693 | 357.8410 To 367.7590 |
| 1000kg/in$^2$ | 20 | 359.8500 | 9.9593 | 2.2270 | 355.1889 To 364.5111 |
| 1500kg/in$^2$ | 20 | 362.6000 | 6.8087 | 1.5225 | 359.4134 To 365.7866 |
| 2000kg/in$^2$ | 20 | 358.7000 | 5.4686 | 1.2228 | 356.1406 To 361.2594 |
| 2500kg/in$^2$ | 20 | 361.5000 | 5.4144 | 1.2107 | 358.9660 To 364.0346 |
| 3000kg/in$^2$ | 20 | 359.1500 | 7.3433 | 1.6420 | 355.7132 To 362.5868 |
| Total | 120 | 360.7667 | 7.8662 | .7181 | 359.3448 To 362.1886 |

Table VI cont.

Batch 9

Analysis of Variance

| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 2 | 24.4333 | 12.2167 | .3097 | .7349 |
| Within | 57 | 2248.5000 | 39.4474 | | |
| Total | 59 | 2272.9333 | | | |

| Group | Count | Mean | S.D. | S.E. | 95% C.I. for Mean |
|---|---|---|---|---|---|
| 2000kg/in$^2$ | 20 | 351.1500 | 6.1497 | 1.3751 | 348.2719 To 354.028 |
| 2500kg/in$^2$ | 20 | 352.7000 | 5.9657 | 1.3340 | 349.9080 To 355.492 |
| 3000kg/in$^2$ | 20 | 351.7500 | 6.7033 | 1.4989 | 348.6128 To 354.887 |
| Total | 120 | 351.8667 | 6.2068 | .8013 | 350.2633 To 353.470 |

### 7.3.2 Tablet Friability

The friability test data at 2500kg/in$^2$ compression force is included in Table VII. The friability observed lie in the range 0.24 - 0.99% weight loss. The tablets which had maize starch paste (batch 7a) had the highest, that is 0.99 percent weight loss while the formulation which contained cassava starch paste (batch 7b) had 0.54 percent weight loss indicating better binding properties compared to maize starch. Cassava starch produces a stronger gel and good adhesive strength than maize starch.[29] Polyvinylpyrrolidone produced tablets with friability of 0.24%. In comparison with starch, polyvinylpyrrolidone is a better binder. Tablets made by dry granulation had a friability range of 0.29-0.64% weight loss while tablets made by direct compression method had friability range of 0.37 - 0.50% weight loss.

The friability of most of the tablets tested was within the specified limit of not more than of 0.8% weight loss and no tablet exhibited physical defects such as capping or lamination. Value for batch 7b did not differ from the standard.

A regression analysis between hardness and friability gave a negative correlation coefficient (r) of 0.62. This clearly shows that an increase in hardness will decrease friability. The friability of four commercial brands of aspirin obtained from various pharmacies in Dar-es-Salaam was determined and ranged from 0.21 - 0.51% weight loss with the reference standard having a value of 0.48%.

**Table VII: Summary of physical tests from the representative batches.**

| Formulation | Tablet wt mg (Mean ± S.D) | C.V. (%) | Hardness (Erweka units) | Friability (%) | D.T. (s) | Content (%) |
|---|---|---|---|---|---|---|
| 1a | 371.2 ± 5.6 | 1.51 | 75.6 | 0.30 | 18 | 99.8 |
| 1b | 378.4 ± 6.7 | 1.77 | 68.6 | 0.29 | 15 | 101.7 |
| 2 | 367.7 ± 5.3 | 1.44 | 64.7 | 0.45 | 27 | 100.3 |
| 3 | 344.4 ± 5.1 | 1.48 | 48.8 | 0.40 | 10 | 98.9 |
| 4 | 376.6 ± 6.3 | 1.67 | 65.4 | 0.35 | 21 | 99.2 |
| 5 | 351.4 ± 4.9 | 1.39 | 49.4 | 0.64 | 20 | 105.6 |
| 6a | 352.0 ± 5.1 | 1.45 | 50.1 | 0.46 | 27 | 100.4 |
| 6b | 356.3 ± 5.4 | 1.52 | 44.1 | 0.37 | 20 | 100.1 |
| 6c | 358.1 ± 5.5 | 1.54 | 42.4 | 0.50 | 22 | 100.7 |
| 7a | 370.5 ± 8.0 | 2.16 | 27.2 | 0.99 | 25 | 102.4 |
| 7b | 370.4 ± 6.1 | 1.65 | 35.7 | 0.54 | 15 | 100.1 |
| 8 | 361.5 ± 5.4 | 1.49 | 37.1 | 0.31 | 249 | 101.7 |
| 9 | 352.7 ± 5.9 | 1.67 | 54.9 | 0.24 | 50 | 97.2 |

Compression pressure: 2500kg/in$^2$

C.V = Coefficient of variation ($\frac{\text{S.D.}}{\text{Mean}} \times 100\%$)

D.T.= Disintegration time.

| Formulation | Method of preparation |
|---|---|
| 1a - 5 | Dry Granulation |
| 6a - 6c | Direct Compression |
| 7a - 9 | Wet Granulation |

### 7.3.3 Tablet Hardness

Table VII show the tablet hardness values generated for each model drug formulation at 2500kg/in$^2$ compression pressure. For the Wet Granulation formulations tablet hardness ranged from 27.2 - 54.9 Erweka units. The formulation containing

polyvinylpyrrolidone produced the hardest tablets (54.9 Erweka units) followed by pregelatinized starch (37.7 Erweka units), then cassava starch paste (35.7 Erweka units), and finally maize starch paste (27.2 Erweka units). The difference between maize and cassava values are expected due to the fact that, cassava starch produces good gel and excellent adhesive strength.[29]

The tablets made by Dry Granulation method had hardness range of 48.8 - 75.6 Erweka units). Batch No. 3 had the lowest value (48.8 Erweka units) and this could be attributed to the amount of starch (approx 15%) present. The rest of the formulations contained between 7 and 9.7% starch. Previous findings indicate that starch grains tend to be elastic and are not highly compressible and tend to weaken tablet compacts.[10] All Dry Granulation formulations contained microcrystalline cellulose (12%) as binder except batch No.5 which contained 10%. The low hardness and high friability value for batch 5 might be associated with the low percentage of microcrystalline cellulose. The Direct Compression formulations produced tablets with hardness range of 42.4 - 50.1 Erweka units. All three batches (6a, 6b, 6c) contained microcrystalline cellulose 10% as dry binder, and batch No. 6c (42.4 Erweka units) consisted of aspirin with high percentage

of small crystal size while 6a (50.1 Erweka units) contained a high percentage of aspirin with big crystal size.

**Table VIII: Hardness variation with compression pressure.**

Batch 7a

Hardness
Comparison pressure
Analysis of Variance

| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 5 | 1974.5333 | 394.9067 | 18.5855 | .0000 |
| Within | 54 | 1147.4000 | 21.2481 | | |
| Total | 59 | 3121.9333 | | | |

| Group | Count | Mean | S.D. | S.E. | 95% C.I. for Mean |
|---|---|---|---|---|---|
| 500kg/in$^2$ | 10 | 20.7000 | 4.1647 | 1.3170 | 17.7208 To 23.679 |
| 1000kg/in$^2$ | 10 | 22.7000 | 6.4816 | 2.0497 | 18.0633 To 27.336 |
| 1500kg/in$^2$ | 10 | 30.2000 | 4.4422 | 1.4048 | 27.0222 To 33.377 |
| 2000kg/in$^2$ | 10 | 35.0000 | 4.1096 | 1.2996 | 32.0602 To 37.939 |
| 2500kg/in$^2$ | 10 | 27.2000 | 3.3928 | 1.0729 | 24.7729 To 29.627 |
| 3000kg/in$^2$ | 10 | 36.0000 | 4.4721 | 1.4142 | 32.8008 To 39.199 |
| Total | 60 | 28.6333 | 7.2742 | .9391 | 26.7542 To 30.512 |

Table VIII cont.

Batch 8 Analysis of Variance

| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 5 | 370.6833 | 74.1367 | 2.3407 | .0538 |
| Within | 54 | 1710.3000 | 31.6722 | | |
| Total | 59 | 2080.9833 | | | |

| Group | Count | Mean | S.D. | S.E. | 95% C.I. for Mean |
|---|---|---|---|---|---|
| 500kg/in$^2$ | 10 | 34.4000 | 5.1683 | 1.6344 | 30.7028 To 38.097 |
| 1000kg/in$^2$ | 10 | 36.2000 | 5.6332 | 1.7814 | 32.1702 To 40.229 |
| 1500kg/in$^2$ | 10 | 37.5000 | 4.1164 | 1.3017 | 34.5553 To 40.444 |
| 2000kg/in$^2$ | 10 | 38.4000 | 5.5418 | 1.7525 | 34.4357 To 42.364 |
| 2500kg/in$^2$ | 10 | 37.1000 | 3.9285 | 1.2423 | 34.2897 To 39.910 |
| 3000kg/in$^2$ | 10 | 42.5000 | 8.2765 | 2.6173 | 36.5794 To 48.420 |
| Total | 60 | 37.6833 | 5.9389 | .7667 | 36.1491 To 39.217 |

Batch 9 Analysis of Variance

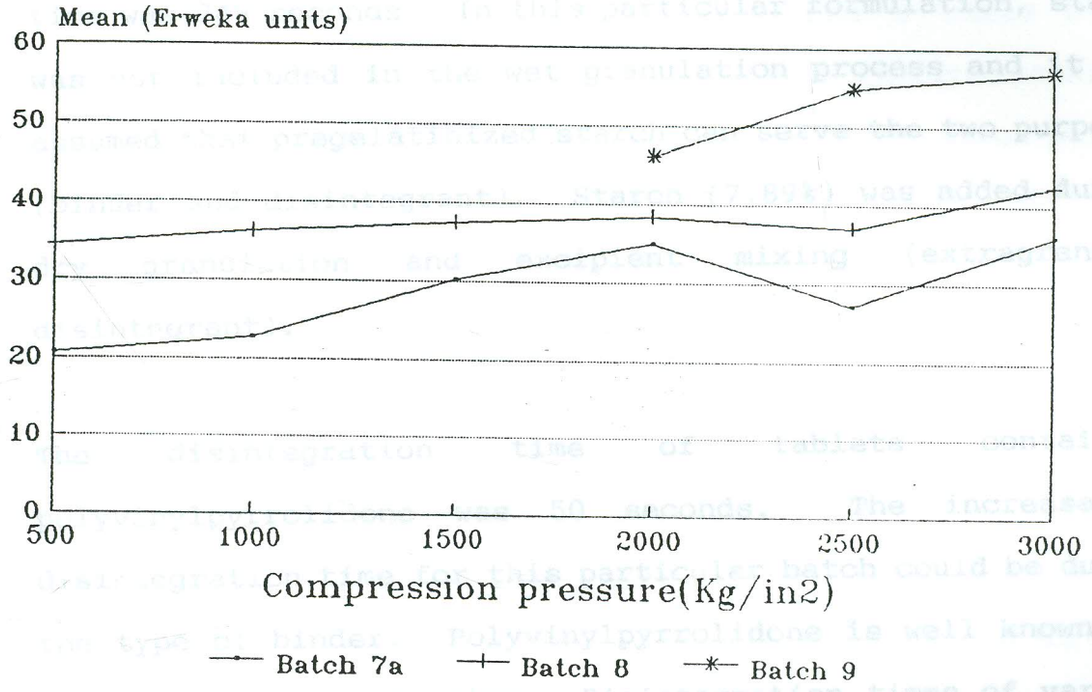
| Source | D.F. | Sum of Squares | Mean Squares | F Ratio | F Prob. |
|---|---|---|---|---|---|
| Between Groups | 2 | 677.6000 | 338.8000 | 12.2836 | .0028 |
| Within | 27 | 744.7000 | 27.5815 | | |
| Total | 29 | 1422.3000 | | | |

| Group | Count | Mean | S.D. | S.E | 95% C.I. for Mean |
|---|---|---|---|---|---|
| 2000kg/in$^2$ | 10 | 46.1000 | 6.3500 | 2.0080 | 41.5575 To 50.6425 |
| 2500kg/in$^2$ | 10 | 54.9000 | 3.6652 | 1.1590 | 52.2781 To 57.5219 |
| 3000kg/in$^2$ | 10 | 57.1000 | 7.3841 | 1.7026 | 53.2484 To 60.9516 |
| Total | 60 | 52.7000 | 7.0032 | 1.2786 | 50.0850 To 55.3150 |

### 7.3.4 Effects of Compression Pressure on Hardness

The hardness data for the three Wet Granulation batches (7a, 8 and 9) was tested using a one way analysis of variance and the results are presented in Table VIII. At the 95% level of confidence ($P = 0.05$), the difference in the means of batches 7a and 9 is statistically highly significant ($P << 0.05$). For batch 7a, the mean weight was not constant throughout the compression forces, and hence the difference in hardness mean can also be due to the mean weight difference. Considering batch 9, the mean weight was constant and thus the difference in the mean hardness due to change of pressure indicate that the particles are more tightly bound. The coefficient of correlation (r) was calculated for all the three batches, and batch 9 (+0.94) had the highest value followed by batch 8 (+0.87) and then batch 7a (+0.81). These values indicate a linear correlation between compression force and hardness. (Figure III).

Figure III.Effect of compression pressure on hardness




| Formulation | Type of binder used | |
|---|---|---|
| 7a | Maize starch paste | (12.35%) |
| 8 | Pregelatinized starch | (4.21%) |
| 9 | Polyvinylpyrrolidone | (2.66%) |

### 7.3.5 Disintegration Time

All tablets disintegrated within 30 seconds excepts the tablets which contained polyvinylpyrrolidone and pregelatinized starch (Table VII). The formulation which contained pregelatinized starch (batch 8) mean disintegration time was 249 seconds. In this particular formulation, starch was not included in the wet granulation process and it was assumed that pregelatinized starch can serve the two purposes (binder and disintegrant). Starch (7.89%) was added during dry granulation and excipient mixing (extragranular disintegrant).

The disintegration time of tablets containing polyvinylpyrrolidone was 50 seconds. The increase in disintegration time for this particular batch could be due to the type of binder. Polyvinylpyrrolidone is well known for its high binding capacity. Disintegration times of various brands of commercial aspirin tablets collected from various pharmacies in Dar-es-Salaam were determined for comparison purpose. The tablets had a disintegration range of 13 - 120 seconds. The brand having the longest disintegration time (120 seconds) is made from granules containing 100% aspirin, 8% pregelatinized starch as a disintegrant and 12% microcrystalline cellulose as dry binder. The tablets

containing cassava and maize starch had a disintegration time which was comparable to that of commercial reference standard.

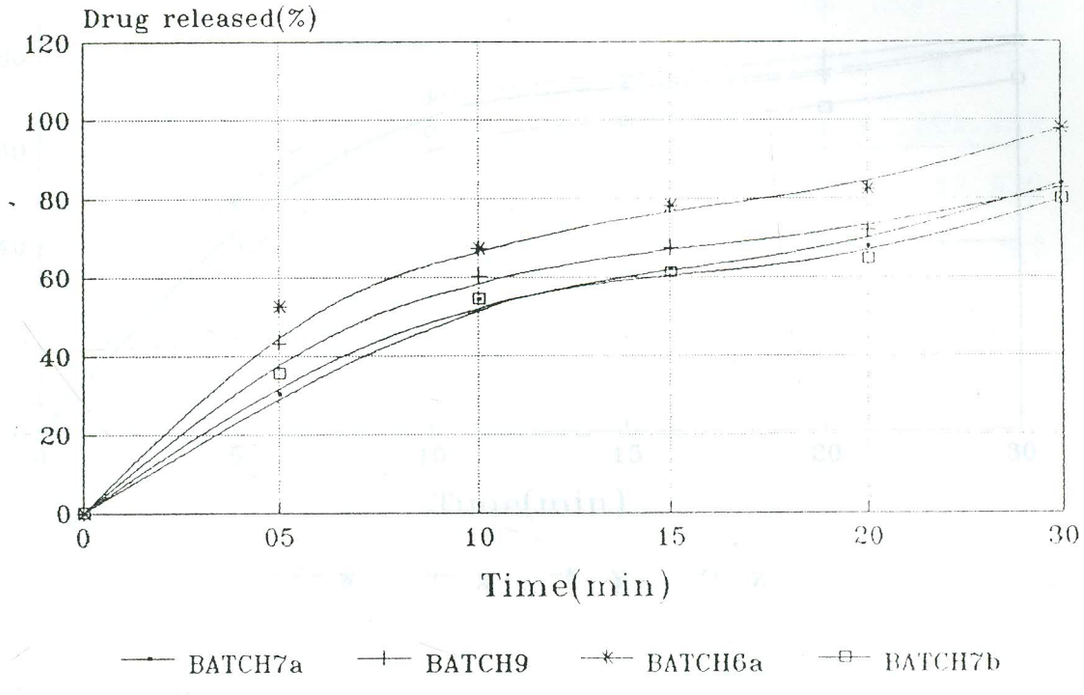
### 7.3.6 DRUG DISSOLUTION

The dissolution profiles of the tablets of four drug formulation are shown in Figure IIIa. Tablets prepared by Wet Granulation include Batch No.7a, 7b and 8 while Direct Compression is represented by batch No. 6a (microcrystalline cellulose 10% and cassava starch 5%). Dry Granulation batches were not included in the test due to inadequate laboratory facilities. Tablets prepared by direct compression showed a trend of higher drug release than the rest of the formulations.

Commercial products dissolution profile can be observed in Figure IIIb. The dissolution rates of the four batches (6a, 7a, 7b and 9) were compared with the dissolution rate of commercial brand, Y (the standard reference). The dissolution time (t50%, min) was 6.0, 9.0, 8.5 and 7.0 units for batches 6a, 7a, 7b and 9 respectively. Likewise, the dissolution time (t80%, min) in the same order was determined and as 17.5, 27.5, 30 and 27.5. Batch Y had released 50% and 80% at $6^{th}$ and $28^{th}$ minute respectively. All batches had rapid dissolution rate and complied with the United States Pharmacopoeia 1988 specification.

While more than 80% of the active ingredient in almost all experiments is completely dissolved at 30 minute points, minor differences appeared throughout the points with differences at the 30 minute point being most apparent. When considering the 30 minute points, a two way analysis of variance was used to test the mean dissolution rates of all samples considered in the dissolution profile (Table IX) with significant differences being seen ($P << 0.05$).

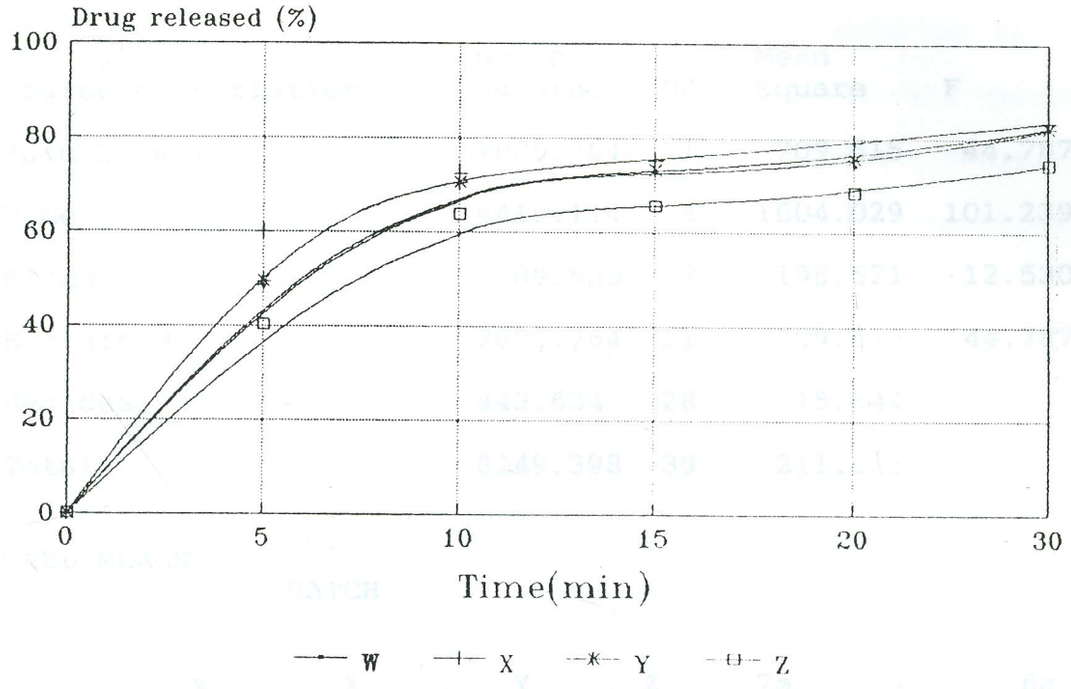
Figure IIIa. Drug dissolution profiles of batches 6a,7a,7b,and 9




| Dissolution time (min) | Formulation 6a | 7a | 7b | 9 |
|---|---|---|---|---|
| t50% | 6.0 | 9.0 | 8.5 | 7.0 |
| t80% | 17.5 | 27.5 | 30 | 27.5 |

| Formulation | Type of binder used |
|---|---|
| 6a | Micrystalline cellulose (direct compression (10%) |
| 7a | Maize starch (12.35%) |
| 7b | Cassava starch paste (12.35%) |
| 9 | Polyvinylpyrrolidone ( 2.66%) |

Figure IUB. Drug dissolution profile of commercial brands of aspirin




| | Formulation | | | |
|---|---|---|---|---|
| Dissolution time (min) | W | X | Y | Z |
| t50% | 6.0 | 5.0 | 6.0 | 7.5 |
| t80% | 28.0 | 22.0 | 28.0 | >30 |

MUHIMBILI MEDICAL UNIVERSITY COLLEGE LIBRARY DSM.

**Table IX: Drugs released (%)**

ANALYSIS OF VARIANCE

PERCENT
BY TIME (MINUTES)
BATCH

| Source of Variation | Sum of Squares | DF | Mean Square | F | Signif of F |
|---|---|---|---|---|---|
| Main Effect | 7805.764 | 11 | 709.615 | 44.787 | .000 |
| Time | 6416.114 | 4 | 1604.029 | 101.239 | .000 |
| Batch | 1389.650 | 7 | 198.521 | 12.530 | .000 |
| Explained | 7805.764 | 11 | 709.615 | 44.787 | .000 |
| Residual | 443.634 | 28 | 15.844 | | |
| Total | 8249.398 | 39 | 211.523 | | |

CELL MEANS

| | BATCH | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | W | X | Y | Z | 7a | 9 | 6a | 7b |
| TIME | | | | | | | | |
| 5 | 48.20 ( 2) | 60.10 ( 2) | 49.50 ( 2) | 40.20 ( 2) | 30.50 ( 2) | 43.20 ( 2) | 52.40 ( 2) | 35.30 (2) |
| 10 | 70.50 ( 2) | 72.50 ( 2) | 70.50 ( 2) | 63.70 ( 2) | 54.30 ( 2) | 60.20 ( 2) | 67.20 ( 2) | 54.30 ( 2) |
| 15 | 72.60 ( 2) | 75.30 ( 2) | 73.10 ( 2) | 65.50 ( 2) | 63.30 ( 2) | 67.50 ( 2) | 78.10 ( 2) | 61.20 ( 2) |
| 20 | 74.10 ( 2) | 79.20 ( 2) | 75.50 ( 2) | 68.40 ( 2) | 68.00 ( 2) | 72.10 ( 2) | 82.50 ( 2) | 4.40 ( 2) |
| 30 | 81.80 ( 2) | 83.50 ( 2) | 82.20 ( 2) | 74.30 ( 2) | 83.90 ( 2) | 82.80 ( 2) | 97.70 ( 2) | 79.70 ( 2) |

### 7.3.7 Salicylic Acid Limit Test

The major stability problem with aspirin, is the hydrolysis into salicylic acid and acetic acid. In the physical examination all batches passed except batch 9 which had acetic acid smell and deposition of salicylic acid on the tablet surface. With the exception of batch 9, all passed the salicylic acid test described in the British Pharmacopoeia 1988 at day 1, day 90, before and after the stability test. Batch 9 passed the test on day 1 only.

### 7.3.8 Stability Test

Tables Xa and Xb summarizes the effects of storage on tablet hardness, friability disintegration and content (%) at 40°C and 50°C. At both temperatures batches W, Y, 6a and 5 direct compression and dry granulation using cassava starch respectively in plastic containers had higher tablet hardness than metal containers. The wet granulation batches in both containers had lower values at both temperature except batch 9 (with PVP) at 50°C. Same behaviour was observed before the elevation of temperature in storage.

At 40°C the disintegration time of batches in metal containers were higher than the disintegration time of the batches in plastic containers. This may be attributed to the fact that metal conducts heat faster than plastic material.

At 50°C all wet granulation batches in plastic container had a good disintegration time of less than 5 minutes. The reference standard, Y had a disintegration time of 4 minutes which is in the same range with the wet granulation tablet batches. The other batches by dry granulation and direct compression in plastic containers had a disintegration of more than 15 minutes or did not disintegrate at all. All batches in metal containers at 50°C did not disintegrate within 15 minute except batch 7a.

Thus batch 7a in both containers had a good disintegration time at both temperatures. The friabilities of all batches were good.

**Table Xa: Effect of storage at 28 - 30°C, 40° and 50oC on content of Aspirin expressed as percentage of label claim.**

| | Content (%) | | | | | | Salicylic acid limit test |
|---|---|---|---|---|---|---|---|
| | 28 - 30°C | | 40°C | | 50°C | | |
| | DAY 1 | DAY 90 | | | | | |
| BATCH | P | M | P | M | P | M | |
| W | 104.6 | 104.5 | 103.9 | 104.1 | 104.3 | 104.4 | Complied |
| Y | 101.1 | 100.9 | 100.8 | 101.3 | 101.5 | 100.6 | Complied |
| 8 | 101.7 | 101.8 | 101.2 | 100.9 | 99.7 | 101.1 | Complied |
| 9 | 97.2 | 95.8 | 94.8 | 95.2 | 96.4 | 95.6 | Did not comply |
| 7a | 102.4 | 102.6 | 102.1 | 101.8 | 100.9 | 100.5 | Complied |
| 6a | 100.4 | 99.2 | 99.1 | 98.7 | 100.1 | 99.3 | Complied |
| 5 | 105.6 | 105.3 | 105.1 | 103.9 | 104.7 | 104.1 | Complied |
| 7b | 100.1 | 99.7 | 99.1 | 98.6 | 99.5 | 98.9 | Complied |

M = Metal container
P = Plastic container

| Formulation | Type of binder used |
|---|---|
| W | Microcrystalline cellulose (12%) |
| Y | Unknown |
| 8 | Pregelatinized starch (4.21%) |
| 9 | Polyvinylpyrrolidone (2.66%) |
| 7a | Maize starch paste (12.35%) |
| 6a | Microcrystalline cellulose (10%) |
| 5 | Microcrystalline cellulose (10%) |
| 7b | Cassava starch paste (12.35%) |

Table Xb: Effect of storage at 28 - 30°C, 40° and 50°C on Tablet Hardness, Friability and Disintegration time.

| | Friability (%) | | | | Disintegration time (min) | | | | Hardness (Erweka units) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 40°C | | 50°C | | 40°C | | 50°C | | 40°C | | 50°C | |
| BATCH | P | M | P | M | P | M | P | M | P | M | P | M |
| W | 0.33 | 0.19 | 0.21 | 0.11 | 3.83 | 4.25 | >15 | >15 | 69.5 | 62.1 | 71.3 | 73.1 |
| Y | 0.31 | 0.21 | 0.23 | 0.18 | 2.83 | 3.17 | 4.0 | >15 | 75.1 | 60.8 | 81.1 | 68.3 |
| 8 | 0.34 | 0.37 | 0.32 | 0.40 | 2.35 | >15 | >15 | >15 | 51.6 | 61.5 | 57.0 | 55.4 |
| 9 | 0.21 | 0.21 | 0.18 | 0.15 | 3.0 | 15.17 | 3.27 | >15 | 62.2 | 71.7 | 60.9 | 75.8 |
| 7a | 0.08 | 0.21 | 0.78 | 0.62 | 0.5 | 3.33 | 0.67 | 2.25 | 40.4 | 48.6 | 42.2 | 47.1 |
| 6a | 0.20 | 0.18 | 0.11 | 0.08 | 2.17 | >15 | >15 | >15 | 57.5 | 50.2 | 74.5 | 53.1 |
| 5 | 0.23 | 0.14 | 0.64 | 0.08 | 2.33 | 3.15 | >15 | >15 | 72.8 | 59.9 | 83.8 | 65.5 |
| 7b | 0.26 | 0.16 | 0.47 | 0.03 | 0.5 | 2.17 | 3.47 | >15 | 46.4 | 64.7 | 62.5 | 68.8 |

M = Metal container
P = Plastic container

| Formulation | Type of binder used |
|---|---|
| W | Microcrystalline cellulose (10%) |
| Y | Unknown |
| 8 | Pregelatinized starch (4.21%) |
| 9 | Polyvinylpyrrolidone (2.66%) |
| 7a | Maize starch paste (12.35%) |
| 6a | Microcrystalline cellulose (10%) |
| 5 | Microcrystalline cellulose (10%) |
| 7b | Cassava starch paste 12.35%) |

## 7.4 Cassava starch

The quality analysis data for cassava (Tapioca) starch as specified in the British Pharmacopoeia 1988 are included in Table XI. The product passed all the tests under cassava starch.

**Table XI: Cassava starch: Analytical Report**

| Determinations | Specifications | Results |
|---|---|---|
| Description | Very fine white powder which creak when passed between the fingers. | Passed |
| Solubility | Insoluble in cold water | Passed |
| | insoluble in ethanol (96%) | Passed |
| Identification | A.Heat to boiling 1g in 50ml of water for 1min and cool; gives thin cloudy mucilage and transparent. | Passed |
| | B.1ml of mucilage mix with 0.05ml of 0.005M Iodine. A dark blue colour is produced, disappears, on heating reappears on cooling. | Passed |
| Loss or drying: | not more than 15.0% | 10.5% |
| Sulphated ash: | not more than 0.6% | 0.1% |
| Acidity: | not more than 2.0ml of 0.1M NaOH | 0.1ml |

This product complied with the specifications of cassava starch British Pharmacopoeia 1988.

## 8.0 SUMMARY AND CONCLUSION

Laboratory production of cassava starch was successful and the starch obtained had properties which was comparable to other starches in the British Pharmacopoeia 1988.

The binding and disintegration capacity of the cassava starch was investigated. It produced tablets of equal or better strength than maize starch. Disintegration was fast and dissolution rate was rapid and comparable to maize starch. Thus locally produced cassava starch by the outlined method can be used as a binder and disintegrant in tablets.

Cassava starch has light colour and thus produced tablets of fairly lighter colour than maize starch products.

A quality analysis was carried out on four commercial brands of aspirin, three being locally manufactured. With the exception of one which failed the dissolution test, all had good physical qualities, rapid disintegration and adequate dissolution rate. All faired well in stability tests, and one was taken as reference standard.

The properties of the tablets produced in the laboratory were similar to those of the reference standard.

Wet Granulation of aspirin tablets using aqueous solution of tartaric acid was attempted and compared to Dry Granulation and Direct Compression, the commonly used processes. The process produced granules similar to those produced by Dry Granulation and those of Rhone-Poulenc (France) granules. Tablets made by Wet Granulation method had lesser mechanical strength but the friability could be compared to those made by Dry Granulation, Direct Compression methods and the standard. Disintegration time was fast for all processes. Dissolution rate was good, and comparable to the standard. Direct compression exhibited a higher release rate due to reduced particle size.

Stability Test were conducted at elevated temperatures at 40° and 50°C in plastic and metal containers. The results were based on physical properties and content of aspirin expressed as percentage of label claim.

The wet granulation batches proved to be more stable than those prepared by Dry Granulation and Direct Compression. All products stored in plastic containers were the most stable.

Direct compression of aspirin crystals which potentially is a low cost in terms of manpower and power consumption savings process, produced tablets of good quality. However, the

excipients involved are quite expensive. Wet Granulation can be considered as one of the processes for manufacturing aspirin tablets. However, economical points of view, power consumption and manpower have to be considered because of the costs involved in this process.

The Mwanza plant may be converted or used to manufacture cassava starch of pharmaceutical grade if an improvement is made in the manufacturing process to comply with Good Manufacturing Practice (GMP).

**REFERENCES**


1. Grace, M.R. Cassava Processing. Food and Agriculture Organization of the United Nations, Rome, 1977.

2. Akers, M.K. Preformulation Testing of Solid Oral Dosage Form Drugs. Can J. Pharm Sci. 11: 1-10, 1976.

3. Lieberman H. A., Lachman L., Schwartz J.B. Pharmaceutical Dosage Forms: Tablets second edition, revised and expanded. Marcel Dekker, INC. 1989.

4. Brittan, H. G., Clifford J. Sachs, and Kenneth Fiorelli Physical Characterization of Pharmaceutical excipients: Practical Examples. Pharmaceutical Technology 15(10): 38-52, 1991.

5. Seager H., Burt I., Ryder J., Murray S., Beal N. Relationship between granule structure, process of manufacture and tableting properties (proceedings) J. Pharm. Pharmacol 30 Suppl: 23P, 1978.

6. Alderborn G. Int. J. Pharm. Ind. 46, 310, 1984.

7. Shah, A.C. and Mlodozeniec, A.R. Mechanism of surface lubrication: Influence of duration of lubricant-Excipient mixing on processing characteristics of powders and properties of compressed tablets. J. Pharm Sci, 66(10): 1377-1382 Oct. 1977.

8. Mitrevej, K.T. and Augsburger, L.I. Adhesion Tablets in a Rotary Tablets Press. II. effects of Blending Time, Running Time, and Lubricant Concentration. Drug Dev. Ind. Pharm. 8(2): 237-281, 1982.

9. Remington's Pharmaceutical Sciences, 18th Ed. Mack Publishing Company; Easton, Pennsylvania 18042, 1990.

10. Manudhane, K.S. ,Contractor, A.M., Hyo Y. Kim, and Shangraw, R.F. Tabletting properties of a directly compressible starch J. Pharm Sci 58(5): 616-620, 1969.

11. Iranloyo, T.A. and Parrot, E.L. Effects of compression force, particle size and lubricant on dissolution rate J. Pharm Sci 67(4): 535-539, 1978.

12. Chowhan, Z.T. and Li-Hua Chi. Drugs Excipient Interactions Resulting from powder mixing III: Solid state properties and their effects on drug dissolution. J. Pharm Sci 75(6): 534-531, 1986.

13. Chowhan, Z.T. and Li-Hua Chi. Drugs Excipient Interactions resulting from powder mixing IV: Role of lubricants and their effects on In Vitro dissolution J. Pharm Sci 75(6):542-545, 1986.

14. Ganderton D. The effect of distribution of magnesium stearile on the penetration of a tablet by water. J. Pharm Pharmacol Suppl 21 9S, 1969.

15. Lerk C.F. , Bolhuis, G.K. and de Boer, A.H. Effect of Microcrystalline Cellulose on Liquid Penetration in Disintegration of Directly Compressed Tablets. J. Pharm Sci 68: 205, 1979.

16. Van Kamp H.V., Bolhuis G.K., de Boer A.H., Lerk C.F., Lie-A-Huen L. The role of water uptake on tablet disintegration. Design of an improved method for penetration measurements. Pharm. Acta helv 61: 22, 1986.

17. Mats E. Johansson. Summary of a dissertation at the faculty of Pharmacy, Uppsala, Sweden 1985 Acta Pharm Suec 23(2): 128, 1986.

18. Brook, D.B. and Marshall, K.. Crushing strength of Compressed Tablets 1: Comparison of Tablets J. Pharm. Sci., 57(3): 481, 1968.

19. Bavitz, J. , Bohidar, N.R., Karr, J.I. and Restaino, F.A. Performance of tablet breaking strength testers 1: Intralaboratory comparison and prediction. J. Pharm. Sci., 62(9): 1520, 1973.

20. Frank W. Goodhart, Draper, J.R., Dancz, D., and Ninger, F.C. Evaluation of tablet breaking strength testers J. Pharm Sci, 62(2): 297, 1973.

21. Ridgeway K., Lazarou C., Thorpe E.E. The properties of tablets manufactured on an automatically - controlled rotary machine. J. Pharm. Pharmacol, 24:(4) 265-71, 1972.

22. David, S.T., Augsburger, L.L. Flexure test for determination of tablet tensile strength.
J. Pharm. Sci., 63(6), 933-936, 1974.

23. Mendez, R. and Suva Roy. Tabletting Excipient. Part I
Pharmaceutical technology 2 (3):32, 1978.

24. Underwood T.W. and Cadwallader, D.E. Influence of various starches on dissolution variability rate of salicylic acid from tablets.
J. Pharm Sci., 61: 239-243, 1972.

25. Chowhan, Z.T. Tablets - to - tablet dissolution variability and its relationship to the homogeneity of a water soluble drug.
Drug Dev. Ind. Pharm. 8(2): 145-168.

26. Hanson, W.A. Solving the puzzle of random variables in dissolution testing.
Reprint from Pharmaceutical Technology 1977.

27. Grace, M.R. Cassava Processing. Food and Agriculture Organization of the United Nations, Rome, 1977.

28. Knight J. The Starch Industry, Oxford, Pergamon Press, 1969.

29. Bos C.E. Native starch in tablet formulations: properties on compaction
Pharmaceutisch weekblad - Scientific edition 9(5): 274-82, 1987

30. Eradiri O. Nasipuri R.N. Temperature effects on the binding efficienty of starch pastes.
J. Pharmazie (JC:p4d) 40(3): 183-5, 1985.

31. Gold G. and Campbell,J.A. Effect of Selected U.S.P. Taks on Acetylsalicylic Acid Stability in Tablets.
J. Pharm Sci 53(1): 52 1964.

32. Blaug S.M. and Wesolowski J.W.
J. Am. Pharm A (Sci Ed) 48: 691, 1959.

33. Levy, G. Comparison of Dissolution and Absorption Rates of Different Commercial Aspirin Tablets
J. Pharm Sci 50(5): 388, 1961.

34. Master Plan for The Pharmaceutical Sector 1992 - 2000, Ministry of Health Government of Tanzania Mainland, 1991.

MUHIMBILI MEDICAL UNIVERSITY COLLEGE
LIBRARY

MED. THS
RM 666
.A82
.L9
1994