PHARMACEUTICAL CHARACTERISTICS OF ALPHA AND MICROCRYSTALLINE CELLULOSES DERIVED FROM RICE (oryza sativa) HUSKS AS EXCIPIENTS IN FOLIC ACID TABLET FORMULATION

BY

NABINTU, YUNUSA ABUBAKAR

BSc. PHARM (ABU), MPSN

A THESIS SUBMITTED TO THE POST GRADUATE SCHOOL

AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

AWARD OF

MSc PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICS & PHARMACEUTICAL MICROBIOLOGY

FACULTY OF PHARMACEUTICAL SCIENCES
AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA.

DECLARATION

I hereby declare that this thesis has been written by me and that it is a record of m research work under the supervision of **Dr J.E Ojile, and Dr Y.K.E Ibrahim.**

It has not been presented in any previous application for a higher degree.

All sources of information are acknowledged by means of references.

NABINTU, Yunusa Abubakar

Department of Pharmaceutics and Pharmaceutical Microbiology

Faculty of Pharmaceutical sciences,.

Ahmadu Bello University, Zaria Nigeria.

CERTIFICATION

This thesis entitled, "Characteristics of wet and dry granulated folic acid tablets containing alpha and microcrystalline celluloses derived from rice *(ORYZA SATIVA)* husks", submitted by **NABINTU, Yunusa Abubakar**, meets the regulations governing the award of the degree of Master of Science (Pharmaceutical ~~Technology~~) of Ahmadu Bello University, Zaria, Nigeria and is approved for its contribution to knowledge and literary presentation.

External Examiner..... **Date**.....
Dr. M. A. Ibrahim
BSc. Pharm (ABU), MSc Pharm Tech.
(London), Ph.D (ABU),
Senior Lecturer and Sub-Dean,
Faculty of Pharmaceutical Sciences,
University of Jos, Jos Nigeria.

Internal Examiner..... **Date**.....
Dr. J. E. Ojile
BSc Pharm (ABU), PhD (RGU Aberdeen UK),
Senior Lecturer. Department of Pharmaceutical and
Pharm. Microbiology, Ahmadu Bello University, Zaria

Internal Examiner..... **Date**.....
Dept. of Pharm. & Pharm. Microbiology
Faculty of Pharmaceutical Sciences
Ahmadu Bello University
Zaria - Nigeria
Dr Y.K.E Ibrahim
BSc Pharm, MSc Pharm (ABU), Dr. Sc-hum (Heidelberg),
Senior Lecturer and Head of Department of Pharmaceutics and
Pharm. Microbiology Ahamadu Bello University, Zaria.

Internal Examiner..... **Date**.....
Dr. J. A. Onaolapo
BSc Pharm, MSc Pharm (ABU), Ph.D (Aston UK)
Reader, Department of Pharmaceutics and Pharm.
Microbiology. Ahmadu Bello University, Zaria.

Professor S. B. Ojo..... **Date**.....
BSc., MSc (ABU), Ph.D (W. Ontario), FNIP
Dean, Postgraduate School, Ahmadu Bello University,
Zaria, Nigeria.

DEDICATION

Dedicated to my late father, **Yuguda Muhammed.**

ACKNOWLEDGEMENT

I wish to express my profound gratitude to my supervisors, **Dr J.E Ojile and Dr Y.K.E Ibrahim.** They have given me the utmost attention possible in supervising the research and in prompt reading of the scripts with most invaluable contributions. My appreciation goes to Messrs. J.B Aina and I. Agbo, to the entire staff of the Department of Pharmaceutics and Pharmaceutical Microbiology, to the Staff of Pharmacognosy and Drug Development, to that of the department of pharmaceutical chemistry and quality control of this great university of their assistance in the laboratory work, and the staff of Centre for Energy Reach and Training for allowing us to use some of their equipment's to do part of this work.

I can not express enough, the support and encouragement of my family throughout the course of the work.

My special regards are due to my colleagues and friends, who are too numerous to mention, for their contributions and encouragement.

TABLE OF CONTENTS

KASU... ...BRAHIM LIBRARY

LIST OF TABLES

PHARMACEUTICAL CHARACTERISTICS OF ALPHA AND MICROCRYSTALLINE CELLULOSES DERIVED FROM RICE *(ORYZA SATIVA) HUSKS* AS EXCIPIENTS

NABINTU, Y.A. (2000)

ABSTRACT

As a part of the continuous search for locally sourced pharmaceutical raw materials, rice husk oryza sativa was investigated for cellulose and its derivatives. Alpha cellulose (RHAC) was extracted from rice husks using standard procedure and giving a yield of 21%.

Part of the α cellulose was subjected to depolymerisation using HCL to form rice husk microcrystalline cellulose (RHMCC) with a yield of 91%.

The obtained materials (RHAC and RHMCC) were then investigated, for their physico –chemical property and later as tablet excipients in micro-dose formulation. Folic acid formulation was used tablet. The physcio-chemical parameters measure include particle sizes (157, 79, and 64 μm); moisture content: (6,4,3%); angles of repose (50, 47 and 44°); flow rates 0.34, 0.38. and 1.20gs $^{-1}$; bulk/tapped densities: (0.13, 016 and 0.25/0.22, 0.26 and 0.39gcm^{-3}); and Carr's indices: 41, 39 and 35%. Although RHAC had the largest particle size, its highest fluidity impediment characteristics appears to be consequential on the higher more fibrous, more irregular shaped and higher porous packing nature of the material.

The diluent effect of the wet granulation process of the 3 cellulose materials which are well documented to be more porous and insoluble in binder solvents caused crumbly, softness of tablets as compared with lactose (soluble). This is possibly due to unutilized more than twice the binder volume uptake requirement by these insoluble materials.

Their tablet disintegrant functions when used intra – and extra- granularly were as effective as Maize Starch (MS). These three materials and the MS have disintegrant qualities. Unlike the MS, they produced tablets, which had higher Crushing Strength (CS), less friability values and decreased thickness on account of their higher plastic binding effects. Compared with 10:1 mixed ratio of talc/magnesium stearate as glidants cum lubricants, the tablets containing the three materials had shorter disintegration time (DT) and higher CS.

The mean granule size (MGS) comminuted from slugs of only RHMCC was slightly ($P \leq 0.05$) smaller than that of RHAC. The MGS obtained from slugs pre-mixed with the folic acid dose of only 6.7% for RHMCC was significantly smaller than that from RHAC by 13%. Irrespective of the folic acid pre-mixed binary component ratio of RHAC: RHMCC from 30 to 100%, the MGS was equal at 331 μm. These phenomena may be attributed to denser packing and consolidation of inter-particulate voids by variously sized mixed particles as shown in table 3.11. These could be further enhanced by a seemingly lubricant and glidant properties of the microscopic particles of the folic acid. The compaction force used for both consolidation and fracture would now be tailored solely for the fracture part of the compaction cycle. The same comminution force used would then produce the same MGS. The slight difference ($P \leq 0.05$) of the tablets CS lends credence to this notion. Despite the relatively adequate CS of some 4.7kg force for all the tablets with small tablet size of only 5.5 mm diameter and 75 mg weight, the DT was equal throughout at only 0.1 min but the mean friability of 2% instead of the minimum of 1% normal standard needs further attention. Therefore the celluloses appear to have a great potential as sole excipients in producing dry processed granules for direct compression.

CHAPTER ONE

1.0 INTRODUCTION

1.1 GENERAL INTRODUCTION

A major feature of the pharmaceutical industry in the West African sub-region, and indeed, the whole of tropical Africa, is its high dependence on imported inputs. Both production and quality control facilities including spare parts and consumables are imported. Even utility requirements such as standby electricity, boreholes and steam generating systems are mostly import dependent for both equipment and parts. Olukoya 1993 summarized the implications of the above thus "the total of all the above is a very significant increase in the cost of production and subsequently increases in selling prices of these products. Indeed about 85% of the cost of production of a typical pharmaceutical product manufactured locally is directly import-related. The high cost of production is imparting adversely upon the profitability of the business as there is a limit to the selling prices".

A survey of the literature shows that over the last three decades, several investigations have been undertaken to explore the suitability of substances of plant, animal and mineral origins in the sub-region as raw materials in pharmaceutical production Okahamafe 1998.

Several local raw materials have demonstrated enough potentials to warrant research and development efforts. One of the pioneering works in this area is the development of pharmaceutical grade starch from yam, cassava and cocoyam (Nasipuri,1975a 1975b and 1979a), Akande (1988) and Garr and Bangudu (1991) have also investigated and developed pharmaceutical grade starch from sorghum and millet.

Another important tablet excipient in pharmaceutical industries is cellulose and its derivatives particularly microcrystalline cellulose. A pioneer in this area is Okhamafe (Okhamafe et al 1991, 1995), who had investigated the pharmaceutical quality of cellulose from groundnut shells, maize cob, bagasse and rice husks. Other workers that investigated the pharmaceutical qualities of cellulose include Musa 1996; Musa 1999; and Audu – Peter 2000.

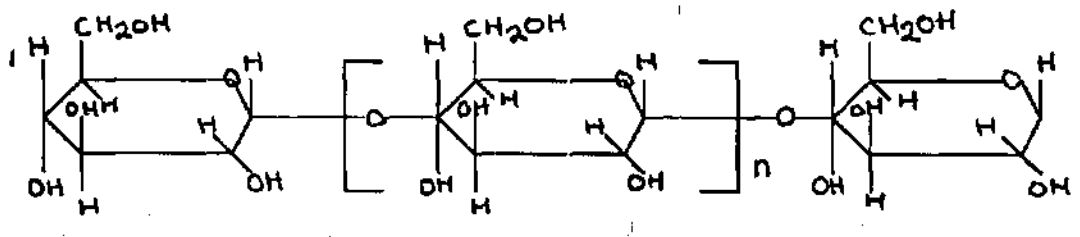
Cellulose is present in rice in high quantities (36% w/w) Bienvenido 1985. Rice of various varieties is widely cultivated and consumed in the northern part of Nigeria and in fact in the whole country. The rice husk is principally cellulose in crude form.

It is worthwhile to investigate the possibility of obtaining micro-crystalline cellulose from this wasting source and explore its potential application as tablet excipient.

1.2 CELLULOSE

1.2.1 Chemistry

Cellulose is a linear polysaccharide consisting of 1,4-linked ß, D-glycopyranoside units.



Structure of cellulose polymer where n = 2000 – 4000

Structure of Cellulose Polymer

Cellulose is the most widely distributed skeletal polysaccharide and the most abundant and chemically resistant of all substances elaborated by living cells. It is the main constituents of the cell walls of plants where it is found as a mixture of homologous polymers in association with other polysaccharides of related structures and with non-carbohydrates of which the most important is lignin (Reid and Dryden, 1940).

Cellulose can easily be converted to other related sugar molecules by treatment with different chemicals, e.g. hydrolysis of pure cellulose by concentrated mineral acids at low temperatures yields ß, D-glucose. Controlled hydrolysis will produce cellubiose. Methylation of cellulose by treating cellulose acetate dissolved in acetone with methyl sulphate and alkaline hydrolysis followed by fractionation gives mainly 2,3,6 trimethyl – D – glucopyranose (Harworth et al, 1929). Each cellulose unit contains 100 to 200 glucose units with molecular weigh between 20,000 and 40,000 because the length of the chain of cellulose is not constant. Cellulose is therefore found as a linear chain of glucose residue mutually joined by ß -1, 4-D linkage. Cellulose from various sources and from different preparations may show great differences in mean chain length as well as in the degree of homogeneity. In general, the more homogenous cellulose is, the more suitable it is for industrial purposes. Cellulose molecules thus differ in number and types of arrangement of the glucose unit in the molecules.

1.2.2. **Types Of Cellulose**

Crude cellulose may be fractionated into α, β, and γ cellulose according to their solubility in 17.5% NaOH solution (Cross et al, 1895). This treatment removes xylose and variable amount of the other non-cellulosic cell wall constituents.

ALPHA – CELLULOSE (TRUE CELLOLOSE)

This is insoluble in 17.5% of NaOH. It represents a much higher average degree of polymerisation and approximate pure cellulose.

BETA – CELLULOSE

This is the fraction precipitated from the alkaline extract by acidification.

GAMMA – CELLULOSE

This is that fraction which is alkaline soluble but acid precipitated.

Beta and gamma celluloses represent non-cellulose polysaccharides removed during treatment. The composition of this types of cellulose in rice husk (Bienvenido, 1985) is:

Alpha – Cellulose	(31.4 – 36.3)
Hemicellulose	(2.9 – 11.8)
Totaling	(34.3 – 11.8)

1.2.3 importance of Cellulose in Pharmaceuticals

Cellulose is less frequently used in pharmaceutical industries as compared with its derivatives such as micro-crystalline cellulose, methyl cellulose, sodium carboxy menthyl cellulose, ethyl cellulose, hydroxyl propyl cellulose and cellulose acetate phthalate (Remington, 1990).

1.2.4 Cellulose Derivatives

Microcrystalline cellulose is synthesised by subjecting cellulose to partial hydrolysis using hydrocholoric acid (Remington 1990. This celllulose dervative is highly indispensable in recent times in tableting formulations.

It is employed as a binder and has good disintegration and compressibility potential, hence the most used compression vehicle in tableting. A good example is the industrial microcrystalline cellulose marketed as Avicel® in four different grades namely, PH101, PH102, PH103 and PH104. Avicel® PH101 is the grade commonly used in tableting process.

Methyl Cellulose

This is the methyl ether of cellulose obtained by the reaction of cellulose with caustic soda and methyl chloride. Methylcellulose is a bulk laxative. It is also used as suspending agent, it is employed in tablet formulation where disintegration is desired to start in the small intestine in order to sustain the action of the drug or prevent any irritation in the stomach.

Hydroxypropyl methylcellulose

This is the propylene glycol ether of methylcellulose in which both hydroxy propyl and methyl groups are attached to the anhydroglucose ring of cellulose by linkages. It is also used as a bulk laxative.

Ethyl cellulose

This is an ethyl cellulose containing not less than 44% and not more than 51% of ethoxy group. It is employed as a binder and film coating of tablets.

Cellulose acetate phthalate

It is a reaction product of phthalic anhydride and a partial acetate ester of cellulose as coating materials.

Sodium Carboxymethyl Cellulose

This is the sodium salt of polycarboxymethyl ether of cellulose. It is a hygroscopic powder, which is used as suspending and binding agents. It is also used as a bulk laxative (Musa, 1999).

1.3.0 Extraction of Cellulose

Recently recorded extraction of cellulose from groundnut shell and rice husk was by Okhamefe et al (1991 and 1995) and from baggase and maize cobs by treating the materials with 3.5% nitric acid and sodium nitrite to remove lignin. Defibering was done using 2% NaOH and finally bleached with 1 in 2 dilution of NaOCl of PH 5-6.

Literative survey showed that many workers had extracted cellulose from various plant materials. This included Fremy and Turners (1968), who treated wood with chlorine, followed by aqueous potassium hydroxide to obtain crude cellulose. Much earlier, Cross and Bevan (1895) used chlorination as the first step but then extracted the chlorinated lignin with hot aqueous sodium sulphite solution.

Asplund (1939) defibred cellulose by subjecting cellulose materials to heating in a closed vessel to about 100°C without digestion. This was done without extra water beside the amount present as moisture in the material.

Ralph and Lew (1940) isolated high quality α - cellulose by treating comminuted hard wood with nitric acid of 5% or less strength for about 24 – 30 hours at a temperature of 10 –50°C.

Thereafter, it was steamed for about 45 minutes, rinsed and 2% sodium hydroxide was added and boiled for about 2 hours. The obtained materials were preliminary bleached with chlorine (about 0.6 –2% of the weight of the air dried pulp). The pulp was further treated with NaOH solution (9 – 10 times its dry weight) for 10 – 20 minutes at room temperature and finally bleached for approximately 2 hours with 0.15 – 0.3% NaOCl.

A different approach was adopted by Foster and Joachim (1940) who liberated cellulose from baggase with sodium hydroxide solution after a preliminary treatment with solvent or emulsifying agent to remove raw wax from the fibre bundles of the baggase.

Musa, (1996) also extracted cellulose from sugar-cane by chlorinating the reduced baggase in hot water with glacial acetic acid and sodium chlorite. The mixture was maintained at 70°C for 12 hours in a water bath, subsequently was washed with cold water and the holocellulose so obtained was used to proceed to the alkaline extraction stage.

In the alkaline extraction stage, the holocellulose was treated with 12% sodium hydroxide and the container was shaken gently for 30 minutes and left to stand for 24 hours at room temperature. This was filtered and the residue returned to the bottle into which one litre of 7.1% sodium hydroxide was added stirred and allowed to stand for another 24 hours. The mixture was then filtered and the residue washed with 5% sodium hydroxide and followed with cold water.

The obtained cellulose was then treated with 10% acetic acid for 10 minutes to neutralise the alkalinity impacted on the cellulose by sodium hydroxide.

Similarly, Hassan (1999) extracted cellulose from rice husk by adopting the method of Okhamafe et al (1991). This is also the method used in this work to extract the cellulose from which microcrystalline cellulose was subsequently derived.

1.3.1 RICE (ORYZA SATIVA) PLANT AS A SOURCE OF CELLULOSE FROM RICE HUSKS

Rice cereal plant (*oryza sativa)* is belongs to the grass family Graminaceae. Its origin is considered to be South eastern Asia, where it has been cultivated from prehistoric times and where million of people still subsist almost entirely on a diet of rice.

Rice is an annual plant with grass-like leaves rough to the touch, complete or less erect and hallow except at the nodes. The root-system is well adopted to a mainly aquatic life, it tends to grow horizontally and draws its nutrients from near the surface of the soil.

The inflorescence are borne on long peduncles and the boat shaped spikelets are one flowered, the sexual parts being enclosed by two glumes.

The flowers has six stamens and two feathery styles. The fruits are grain, white or reddish, dull or almost transparent and are enclosed in husks. The height of the mature plant is generally four to six feet.

Rice is an annual grass. The seeds and the husks are the edible portion. The husks of the grain has a high silicon content and is dangerous to animals. The outer skin and the kernel contains the protein and vitamins Bienvenido 1985.

The rice farm is commonly known as paddy, hence paddy fields and only when it has been harvested and the husks removed does the rice it become the rice that is sold. Rice is grown in over 100 countries on every content except in Antarctica, extending from 52 °N to 40° South and from sea level to an altitude of 3000m. However, O-glabberima is grown only in African and only on a limited scale. Asian rice now gradually takes over from African rice in Nigeria and other countries in West Africa and Africa as a whole. For instance, the reason why African rice is not better known internationally is that it does not grow very well in South East Asia where the work in major rice research facility is located.

Other reasons are that the seed tend to split if handled roughly during milling and the plant tends to have weak stock that can easily be broken by wind storms that blows towards the end of the rainy season.

1.3.2 Cultivation of Rice In Nigeria

In Nigeria, rice is grown in three major ways: dry land or upland, paddy and floating cultivation. About 40% of the rice produced in Nigeria relies on rain as the only source of water. The dry land African rice grows in highland soils wherever there is a rainy season of 4 months and minimum rainfall of700mm. It is either grown alone or interplanted with other crops. Today, varieties mature in 90-170 days. The average yield per hectare is 450-900 kg or even higher.

Paddy Areas

African and Asian rice species are grown in swampy areas of Niger Delta, River Niger and Benue tributaries. These types matures in 140-220 days. The yield is between 1000 – 3000kg per hectare.

Floating

This is planted mostly in the fadama areas of Sokoto and River Niger inland delta. The plant grows tall to keep their heads at the surface of the water where the flower and seeds set. They are often harvested from canoe and they mature between 180 – 250 days and the yield is about 1000 to 3000 kg per hectare (Noel, 1996).

Harvesting

Harvesting is done depending on the situation of the farms. On the floating farms, canoes are used while on the dry land, the manual method is used.

Depending on the variety of rice grown, care must be taken to avoid wastage due to splitting especially with the African species.

Cellulose is present in high quantity in rice heads (28 – 36%). Rice plant of various varieties is widely cultivated and consumed in the whole of Nigeria. The husk in which the seed is contained is removed and thrown away. This husk is principally cellulose. It is worthwhile to investigate the possibility of obtaining microcystalline cellulose and explore its potential application as a tablet excipient.

1.3.3 Uses of rice

Rice is nutritionally a high –energy food because of its large content of starch, though the percentages of fat and protein are low. Rice can loose a great part of its nutritive value during milling. Vitamin C content is in many cases low and most of the vitamin B content, especially of thiamine (B), is lost in milling and polishing. Where milled rice is the staple food, there is a likelihood of deficiency diseases such as beriberi; this can be avoided by under-milling, parboiling, artificial enrichment with vitamins and diversifying the diet with fish and vegetable.

1.3.4 The Milling Fraction of Rice

Dehulling separates the husk from the brown rice. Abrasive milling removes the outer tissues producing milled or polished rice and by products of bran or polish rice. The rice husks according to Bienvenido (1985) is composed essentially of many compounds as shown on table 1.2.

1.3.5 Rice Husks

The rice caryopsis is enveloped by husk, composed of two modified leaves, the palea and the larger lemuna hook – like structure. The outer surface of the husk possesses trichomes that fit between longitudinal rows of epidermal cells. The cells of the husk are highly lignified and brittle and contain cellulose.

TABLE 1.2 COMPOSITON OF RICE HUSKS (BIENVENIDO 1985)

Protein	2.0	-	2.8
Crude fat	0.3	-	0.8
Crude fibre	34.5	-	45.9
Crude Ash	13.2	-	21.0
Available carbohydrate starch	1.5		
Neutral detergent fibre	65.5	-	74.0
Pentosans	2.9	-	11.8
Hemicellulose	31.4	-	36.3
Free sugar	0.6		
Lignin	9.5	-	18.4
Cellulose	31.4	-	36.3

1.4.0 PHYSICO-CHEMICAL PROPERTIES OF PHARMACEUTICAL POWDERS

1.4.1 Particle Size Distribution

Properties of powders are directly influenced by particle sizes. Particle size is important in effective and efficient mixing of solids substances and also important in the stability of the resulting mixture. For example, there may be segregation of particles in a powder mix especially when there is great variation in the particles that compose the powder mix. This is because the smaller particles can fall through the voids between the larger particles and settle at the bottom of the mixture. If care is not taken, the result is variation in content uniformity and flowability problem of the powder mass into the die-cavity in a tablet press with its attendant problems. So to ensure proper mixing the knowledge of particle size is very important. Generally to ensure proper mixing, the component powders should have similar size distribution ranges .

1.4.2 Density

Density of solid particles affect their flow properties in physical mixtures of powders made up of components of different densities, the denser materials tend to fall to the bottom of the powder mass as a result of greater force of gravity, thus leading to powder segregation.

Therefore, knowledge of the bulk and tapped densities of particles, which give indication of the packing profile in a powder mass and also an indirect index of powder flowbility is of great value Musa 1996.

1.4.3 Flowability

The particle sizes, shapes and densities are factors which indirectly influence the flow properties of powder mass . A good flow of a powder or granulation ensures efficient mixing and yields of tablets of uniform and consistent weights.

Poor flowing powders may have to be precompressed or pregranulated. During the preformulation studies of the drug substance, powder flowability is usually evaluated most especially for macro-dose drug.

1.4.4 Hygroscopicity

Drug substances exhibit a tendency to absorb moisture, which may affect physical and chemical stability of tablets that may be produced from it. The hygroscopicity nature of such substances tends to negatively influence the flow and compression characteristics of the particles and hence the properties of the resulting tablets.

1.4.5 Compressibility

The ability of powders to form a compact under pressure is dependent on the compressibility characteristic of the drug substance especially where it forms the major component of the powder mass.

Powders which form hard compact under applied pressure without exhibiting any tendency to cap or chip may be compressed into tablets by direct compression method without any recourse to granulation. The compressibility potential of a material also determine if direct compression excipients should be incorporated for direct compression method to be employed in the production of its tablets or wet granulation process using binders should be used to produce compressible granules.

1.5 TABLETS AND TABLETING

Tablets are a solid dosage form prepared by compression of pharmaceutical powders or granules. They normally contain a unit dose of one or more medicaments. Apart from the medicinal substance called the active ingredient, a tablet contains additives (excipients) which have no pharmacological action.

The shape of tablets varies according to the shape of the die and punches used to compact ("mould") the powders.

Component of Tablets

Tablets are composed of active ingredients and additive or excipients . Excipients in tableting are all the ingredients used in producing tablets apart from the drug component. The functions of such excipients are enumerated below:-

Diluents

Usually, an inert substance is added to increase the bulk of the single dose of the active ingredient when the single dose of the active ingredient is small i.e. when the dose is equal to or less than 50 mg. This is so done in order to make the tablet of practical size for compression and handling. At times when the compression integrity of a high dose is too soft e.g. metronidazole tablet B. P. 200 mg, a larger punch and die tooling is recommended so that the formulator would have to bulk up the tablet so that the thickness of the tablets is not left too thin which makes the tablet too fragile (B. P. 1988).

A diluent should be inert, non-toxic with respect to the active ingredient and cheap Considering the quantity that is used in tablet formulation, diluents particle size should be approximately the same as that of the drug to enable efficient mixing and tableting. Diluents commonly used for tableting purpose include starch, sucrose, dextrose, mannitol, sorbitol, conventional and spray dried lactose.

Certain diluents, such as mannitol, lactose and sorbitol when present in sufficient quantity, can impart properties to some compressed tablets that mask and unpleasant taste in the mouth when chewed. Such tablets are commonly called chewable tablets.

Most tablet formulators tend to use consistently only one or two diluents such as lactose, starch, sucrose, etc. The selection is on the basis of experience. However, in the formulation of new therapeutic agents, the compatibility of the diluent with the drug must be considered. For example, calcium salts used as diluents for the broad spectrum antibiotic-tetracycline, have been shown to interfere with the absorption of the drug from the gastro-intestinal tract. Highly absorbent substances e.g. bentonite and kaolin are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be absorbed/adsorbed by such absorbent to the point where the drugs are not completely available after administration.

Disintegrants

A disintegrant is a substance, or a mixture of substances added to a tablet to facilitate its break-up or disintegration after administration. A tablet will be useless if after being swallowed does not disintegrate to release the active medicament. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid absorption into the systemic circulation.

Substances or materials serving as disintegrante have been chemically classified as starches clays, celluloses, algins or gums. The most popular disintegrants are corn and potato starch, which have been well dried and powdered. Starch has a great affinity for water and swell when moistened, thus facilitating the rupture of the matrix. However, other authors have suggested that its disintegrating action in tablets is due to capillary action rather than swelling. The spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action. 5% to 15% starch is normally used as disintegrants (Edward, 1990)

In addition to the starches, a large variety of materials have been used and are effective as disintegrants. This variety includes veegum, methyl cellulose, agar, bentonite, cellulose and wood products, natural sponge, cation exchange resins, and carboxyl-methyl-cellulose.

Cross linked poly-vinyl-pyrrolidone has been described as having superiority over corn starch and alginic acid for a number of tablet formulations made by either wet or dry granulation. Sodium lauryl sulphate in combination with starch has also been demonstrated to be an effective disintegrant.

In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as being due to an increase in the rate of wetting (Akande, 1988).

Process of incorporation of disintegrants into tablet formulations.

The disintegrating agent is usually mixed with the active ingredients and diluents prior to granulation. This is intragranular incorporation. (Shotton and Leonard, 1972). In some cases, it may be advantageous to divide the starch into two portions. One part is added to the powdered formula prior to granulation (intra-granular incorporation) and the remainder is mixed with the lubricant and added prior to compression (extra-granular incorporation).

Depending on the particular formulation, different portions of the specific disintegrant are incorporated in the tablet fabrication. However, there seems to be an optimum concentration above which disintegration time increases with further increase in proportion of disintegrants (Akande, 1988).

MODE OF ACTION OF DISINTEGRANTS

Disintegrants when incorporated in tablets were found to exert their activities through one or more of the following mode of action:

1. **Water absorption capillary theory:** This theory maintains that a disintegrant especially starch, by virtue of its relative incompressibility forms pore chains around granules. These chains form a capillary network within the tablet and the higher the concentration of the starch, the greater the number of capillaries formed. The capillaries are thought to promote the rapid absorption of water into the tablet and the subsequent disintegration of tablets. Akande (1988) has shown that starch will absorb about 20% of its weight of water in 24 hours when exposed to an atmosphere of 95% relative humidity at 27 ^{o}C. The disintegration properties of PVP is also based on the same principle. Capillary per se may not have a disintegrating effect, although under certain conditions related to pore size, it may play a part in increasing the rate at which water is introduced into the tablet matrix. Many fluids e.g. alcohol and glycerine have been found to penetrate tablet without causing disintegration.

2. **Swelling rupture theory:** Majority of disintegrants have the ability to absorb water and swell to several times their own size. If for example, starch is added to the dry granules before compression, the tablet will absorb gastric fluids causing starch to swell and mechanically disrupt the tablet. This is called the rupture theory. Water hydrates the hydroxyl group of the starch molecules causing them to move apart indicating that the slight swelling that occurs is due to the rapid hydration step and a slower sorption of water step followed by a slower sorption rate of water.

The swelling which takes a few seconds would result in significant increase in volume of the grain thereby causing sufficient force to break up the tablet (Kunle, 1988).

The antagonists of the rupture theory have countered the above statement by the observation that while many substances swell to a greater degree than the starches but are poor disintegrants, other materials do not swell, but have good disintegrating properties e.g. amylose.

In tablets containing disintegrants which are adhesive in the hydrated state (e.g. sodium carboxymethyl cellulose), the positive forces of penetration of water and swelling of particle must overcome the opposing forces of adhesion within the particles to produce tablet disintegration. When opposing forces are equal to or greater than the positive forces the result is a longer disintegration time (Khan and Rhodes 1975). Because the extent of hydration increases with the number of polar groups, one would expect higher grades (of viscosity) to produce greater swelling of particles, thus causing faster disintegration at low concentrations.

At higher concentrations however, the higher grades may become more adhesive in the hydrated state because of their higher viscosities. Thus, the opposing forces of adhesion within the particles would become dorminant, resulting in a longer disintegration time of tablets.

The mechanisms of action of disintegrating agents are complex and mediated through several unrelated phenomena. In most cases, however, the principal mechanisms of disintegrants especially starch is pressure exerted by increased volume in the presence of water, although capillary may facilitate rate of penetration of water.

3. **Evolution of Gas theory**: The basis of effervescent tablets is the reaction of carbon dioxide gas, the product of the production of sodium bicarbonate with citric and tartaric acids in the presence of water. As carbon dioxide is released within the tablets, an internal pressure develops until the tablet breaks apart and carbon dioxide dissolves or disappears from the reaction vessel.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart cohesiveness to the tablet formulation which ensures that tablets remain intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin and sugars such as sucrose, glucose, dextrose, maltose and lactose.

Natural and synthetic gums which have been used include acacia, sodium-alginate, carboxymethyl cellulose methyl cellulose, polyvinyl pyrrolidine, veegum. Other agents which may be considered as binders under certain circumstances are polyethylene glycol, ethyl cellulose, waxes, water and alcohol.

Alcohol and water are not binders in the true sense of the word; but because of their solvent action on some ingredients such as lactose and starch, they convert the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed.

Binders are mostly used in solutions, although some are used in the dry form. In some formulae, the binders are added dry and blended with the diluents and the active ingredient. They are then activated by the addition of water or other solvents.

In other methods, adhesives are dissolved or slurries in a liquid and in this form, added to the mixed powders. Binders added in solution have more adhesiveness than the identical one added dry and then moistened.

The liquid binders are used in different concentrations depending on the nature of the binder and the powdered material to be granulated. The nature, concentration and mode of incorporating the binder will influence the compression characteristics of tablets.

Therefore, these factors must be evaluated empirically for each formulation to prevent adverse effects. Jacob and Plein (1968), have shown that there was an increase in mechanical strength of Phenobarbital tablets but which simultaneously resulted in a decrease in the dissolution rate of the tablet.

High concentration of binder results in premature wear-out of the sets of punches and dies due to regular compression of such formulations. High concentrations of binder can also result in tablet capping. Too much binder may also make granules, which require heavy pressure to compact into tablets. Inadequate binding leads to formulation of extremely soft tablets. Dry binders are often used as vehicle for direct compression of tablets. The most popular dry binders are microcrystalline cellulose, amylase and polyethylene glycol.

GLIDANTS

A glidant is a substance that improves the flow characteristics of a powder mixture. The materials are always added in the dry state just prior to compression (i.e during the lubrication step). Some of the most commonly used glidants are talc and silicon dioxide.

LUBRICANTS

Lubricants have a number of functions in tablet manufacture. They improve the rate of flow of the granules, prevent adhesion of the tablet to the surface of the dies and punches, reduce interparticle friction and facilitate the ejection of the tablets from the die cavity. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid and hydrogenated vegetable oils.

Based on the three distinct functions which lubricants perform, Munzel and kagi (1954) classified lubricants as proper lubricants, glidants and antiadherents.

Lubricants (proper) are those agents that act between surfaces in relative motion to prevent friction and wear. True lubricant action is particularly required immediately after compression of the tablet within the die. It is needed to reduce the friction between the inner die wall and the tablet edge during the ejection cycle.

The absence of the lubricant, at this stage is evidenced by the severe staining of the press as it labours to eject the tablet out of the die. This is frequently audible as a characteristic grunting sound.

Another manifestation of poor lubrication at this critical stage is the presence of vertical irregular striations or "scratch" marks on the edges of the ejected tablets. Lubricants also help the granules to slip and slide to form the compact as well as facilitate the ejection of the tablets.

The most popular lubricants include metallic stearates such as calcium stearate and magnesium stearate. The most commonly used lubricants are hydrophobic substances.

Therefore, the primary problem in the preparation of water-soluble tablet formulations represent a number of compromises between compression efficiency and water solubility (King, 1975) and therefore, the optimum proportion of lubricant must be empirically selected.

Most of the lubricant materials posses both lubricant and glidant properties, since the mechanism of lubrication is adequate for both.

Ways of Incorporating Lubricants in Tablet Formulation

Lubricants are incorporated into tablet formulation in two main ways. The Lubricant should be divided finely by passing it through a 60 to 100 mesh nylon cloth onto the granulation, that is, by bottling the lubricant. After adding the lubricant the granule is tumbled or mixed gently to distribute the lubricant without breaking them down to finer particles as order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Prolonged blending of a lubricant in a granulation can affect the hardness, disintegration time and dissolution performance for the resultants tablets.

Lubricants can also be added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and reduce processing time (Kunle, 1997). In selecting a lubricant, proper attention must be given to its compatibility with the drug.

Colourants

A pharmaceutical colouring agent (colourant) is any material that is pigment or other substance made by a process of synthesis or extracted, isolated or otherwise derived from a vegetable animal, mineral or other sources that is employed solely in a pharmaceutical product to impart a colour (Pharmaceutical Handbook of Excipients, 1994).

Colouring Agents may be classified according to their origin in three major groups: synthetic organic dyes, mineral pigments and natural colourants for technical and economic reasons. The application of natural colourants in pharmaceuticals is minimal.

Colouring agents are important tablet ingredients that assist or help to give additional, desirable physical characteristics to the finished tablet. Also, compressed tablets serve functions other than making the dosage form aesthetic in appearance but help the manufacturer to control the product during their preparation, as well as serving as a means of identification to the user. The wide diversity in the use of colours in solid dosage forms makes it possible to use colour as an important category in the identification code. This helps in establishing the identity of an unknown compressed tablet in a situation arising from poisoning. Some commonly used colouring agents in use in tableting include tartrazone, burnt sugar as caramel, etc.

Pharmaceutical preparations are coloured for four main reasons:-

- to increase their acceptability to patients.
- to give warning
- to produce standard preparations for identification
- to make the tablet more attractive

METHOD OF ADDING COLOUR TO A TABLET FORMULATION

The most common method of adding colour to tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye on starch or calcium sulphate from its acqeuoes solution. The resultant powder is dried and blended with the other ingredients.

Frequently during drying, colours in wet granulations migrate resulting in an uneven distribution of the colour in the granulation. After compression, the tablet will have a mottled appearance due to the uneven distribution of the colour.

Migration of colours may be reduced by drying the granulation slowly at low temperatures in contrast to the work of Ojile et al (1980) and stirring the granulation while it is drying.

DESIRABLE PROPERTIES OF A COLOURING AGENT

A pharmaceutical colouring agent should possess some important properties before it can be used as a colouring agent. These properties include:-

- It should be compatible with the active ingredient and should not interfere with the tests and assays to which the preparations containing it are subject (Carter, 1975).
- It must be harmless to health and should have no physiological activity.
- It should be a definite chemical compound because then its colouring power will be reliable.
- It must be free from objectionable taste and odour
- It must be readily available and inexpensive.
- It should not be affected by oxidising or reducing agents or by pH changes.
- Its colouring power should be high so that only small quantities should be required.
- It should be unaffected by hight tropical temperatures, hydrolysis and micro-organisms and therefore be stable on storage.

Flavouring Agents

Flavours and sweeteners are commonly used to improve the taste of chewable tablets. Nowadays even adults hope for a palatable formulation as objectionable taste may lead to nausea, wrenching and vomiting; and would lead to refusal to take the preparation regularly or none at all. On the other hand, an attractive flavour will encourage continuation of the treatment.

Flavours are identified by sensitive taste buds of the tongue either as sweet, sour, bitter, salt and possibly metallic and alkaline, but their response is modified by additional factors such as the temperature, physical nature and special characteristics such as the astringency and potency of the flavouring material.

As many flavours are odour-related, the brain receives additional impulses into the nose which co-ordinates stimuli to produce sensation that is recognised as the flavour of a substance (Carter, 1975).

Problems of Flavouring

The acceptance of a flavour is influenced by age. In general, children like fruit flavoured formulations, adults prefer a more acid taste, while many old people find mint or wine flavour more agreeable. An ideal selected flavour must be non-toxic, soluble, stable and compatible with the formulation.

In principle, flavouring is active by masking unpleasant taste and making the formulation palatable. Often, the flavour is built upon a sweetened base, which is usually a syrup but may be a mucilage prepared from a cellulose ester or an alginate and containing a synthetic sweetener. These viscous materials give the product a better feel in the mouth.

Some commonly used ways of flavouring formulation include the use of effervescent powders, granules or tablets. These contain the medicament, a sweetener, sodium or potassium bicarbonate and citric or tartaric acid. When the preparation is dissolved in water the carbonated sweetened solution obscures the taste of salines such as potassium citrate. Flavouring is one of the most important aspects in the formulation of a chewable tablet especially for over the counter products such as magnesium trisilicate tablets.

1.5.1 Method of Tablet Preparation

Generally, three methods are used in tablet preparation namely direct compression, dry and wet granulation methods. In wet and dry granulation methods tablet production involves granulation. This is the formation of agglomerates of particles (granules) which become a permanent entity while retaining the original chemical properties of the constituents particles. The aim of granulation is to agglomerate the drug mix or ingredients, improve their flow compressibility, and avoid dust during feeding into machines.

Direct Compression Method

Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting.

The primary purpose of the granulation step was to produce a free flowing and compressible mixture of active ingredients and excipients. The availability of new excipients or new forms of old excipients particularly fillers and binders, and the invention of new or the modification of old tablet machinery have allowed the compression of tablets by the much simpler procedure of direct compression.

There are a few crystalline substances such as inorganic salts, sodium chloride, sodium bromide and potassium chloride which may be compressed directly.

The crystals are broken and passed through sieves to select the required size. They are then mixed with the diluents or disintegrants, if necessary in the dry state and the mix is ready for compression King (1975), Gunsel and Kanig (1976) and Rawlings, (1977).

Excipients of significance in direct compression technique include anhydrous lactose, spray dried lactose, micro crystalline cellulose, amylase, dicalcium phosphate dehydrate, granular mannitol and crystalline sorbitol.

The term direct compression has long been used to the compression of a single crystalline compound into a compact without the addition of other substances. Few chemicals posses the flow, cohesion, compressibility and lubricating properties under pressure to make such compacts possible, if and when compacts are formed.

Advantages of direct compression

1. **Economy:** The most obvious advantages of direct compression is economy. Savings can occur in a number of areas, including reduced processing time and thus labour costs, fewer manufacturing steps and processes, fewer pieces of equipment, less space, and a lower consumption of power.

2. **Elimination of Heat and Moisture:** In direct compression, there are obviously fewer chemical stability problems as compared to those made by the wet granulation process.

The primary cause of instability in tablets is moisture. Complete absence of heat and moisture enhance the stability of the active ingredient especially thermolabile active ingredients in the tablet.

3. **Prime Particle Disassociation:** Probably one of the latest recognised advantages of direct compression is the optimisation of tablet disintegration in which each primary drug particle is liberated from the tablet mass and is available for dissolution.

4. **Particle Size Uniformity:** This allows proper mixing of powder and uniform formulation of the active ingredients.

Dry Granulation Method

Dry granulation method refers to the granulation of powder mixture by compression and without the use of any solvent. On a relative basis, it is the least desirable of all the methods of preparing tablet granules. However, when direct compression is not possible due to the properties and dose of the drug, and wet granulation cannot be used because the drug is sensitive to moisture and heat, then dry granulation remains the only method available.

For example, this method has been useful in the granulation of aspirin and of effervescent products. The basic procedure is to form a compact of the material by compression and then to mill the compact to obtain granules.

The compacted masses are called slugs. The slugs, when comminuted, form a tableting material which now is apt to flow uniformly than the original powder. Two methods are used for dry granulation.

The more widely used method is slugging, where the power is precompressed on a granulation. The other method is to precompress the powder with pressure rolls using a machine such as the chilsonator or the Hut Compactor called nodulization.

Advantages of dry granulation

The advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for liquid binder solutions, heavy and costly mixing equipment and time consuming drying step required for wet granulation. Slugging can be used to advantage in the following situations:-

1. For moisture sensitive materials
2. For heat sensitive materials
3. For improved disintegration since powder particles are not bonded together by a binder
4. For improved blending, since there is no migration or active ingredients as might occur during the drying of a set granulation.

Some of the disadvantages of slugging are as follows:-

1. It requires a specialised heavy duty tablet press to form the slug.
2. It does not permit uniform colour distribution as can be achieved with wet granulation, where the dye can be incorporated into the binder liquid
3. Disintegration usually must taken place by means of dissolution which can take a considerable length of time, delaying drug release and possibly causing physiological problems such as have occurred in potassium chloride tablets.

Wet granulation method

Essentially, this involves wetting the powder mix with a liquid binder to form granules.

a. **Weighing:** This is the weighing of the active ingredients, diluents and disintegrant.

b. **Mixing:** Blending of the drug powders

c. **Granulation:** Involves wetting the powder mix with liquid binder to form a damp mass.

d. Screening the damp mass on an appropriate sieve to give wet granules.

e. Drying of the wet granules in oven, fluidized dryer or in open air.

f. **Dry Screening**: Screening of the dried granules through appropriate sieves.

g. Mixing of the dried granules with glidants and lubricant or extra-granular disintegrant and compressing of the lubricated granules into tablets in a tablet press.

Care must be taken not to use too much binder solution as this produces harder granules that produce tablet with mottled appearance. On the other hand if too little of the binder solution is used the resulting granules will be powdery which will give soft, easily friable granules that break down during screening and difficult to compress into tablet.

Other methods of wet granulation are:-

(a) **Pan granulation**

The process involve the use of liquid builder which is sprayed into the particles that are tumbled in an inclined rotating drum usually fitted with baffles to prevent slippage of the particles at the wall.

Spray – dried granulation

In this process a solution or slurry of the powdered mix is forced at high pressure through a nozzle or atomiser, A stream of hot gas is passed through the chamber to dry the liquid leaving clusters of spherical particles (granules) from the droplets.

Fluidized granulation

In this method, a bed of powdered particles is fluidized by a stream of hot gas through the bed. A liquid binder is sprayed into the fluidized particles. As the required consistency of granule is reached, spraying of the binder is stopped.

1.5.2 Evaluation of Tablets

The aim of any solid dosage form is to ensure that the active ingredient is delivered at or over a period of time in a desired manner and quantity to elicit its pharmacological action. To achieve this, official standards are usually set, which the tablets must conform to before they are released for consumption. These tests include weight variation, uniformity of tablet thickness, drug content, disintegration time, uniformity of diameter and dissolution rate tests as specified in British pharmacopoeia. Other non-official tests include hardness and friability tests.

(i) **Tablet Hardness Test or Mechanical Strength:** The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. A high quality tablet should resist rigour from manufacture until usage. Instruments used to measure tablet hardness include Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. A minimum hardness of 4kg is considered adequate for quality tablet. Other instruments used for measuring tablet hardness include Strong-cob hardness tester, Pfizer hardness tester and Erweka hardness tester.

(ii) **Friability test :** This is closely related to tablet hardness but differs from the fact that it measures resistance of the tablet or evaluates the ability of the tablet to withstand abrasion in packaging, handling and shipping.

This resistance may be tested by means of a tablet friability tester. A sample of twenty (20) tablets is taken at random, weighed and place in the tumbling apparatus, the drum of which is revolving at 25 r.p.m. for 4 minutes. The tablets are exposed to rolling and repeated shocks resulting from free falls within the apparatus. The tablets are then removed, dusted and reweighed. The loss in weight should not be more than 1% w/w. This loss in weight indicates the ability of the tablets to withstand this type of wear.

iii. **Weight variation test:** The weight of the tablet is the quantity of the granules which contains the labelled amount of the therapeutic ingredient. The fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine, the fill is adjusted to give the desired tablet weight.

After the tablet machine is in operation, the weight of the tablet are checked routinely to ensure that the proper weight of the tablets are being met.

The standard weight variation test requires a sample of twenty tablets to be taken and their average weight determined. The tablets are then weighed individually and deviation from the mean weight must be within the limits set by the British Pharmacopoeia Standard (B.P). U.S.P also states that not more than two of the tablets must differ by more than the percentage listed below. No tablet differs by more than double that percentage.

Sugar coated tablets are exempted from why are they exempted these requirements. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more by weight of the dosage form.

Average Weight	Percentage Difference
130mg or less	10
More than 130mg through 324mg	7.5
More than 324mg	5

ii. **Tablet thickness:** It necessary to control thickness of tablets as variation may occur from production batch to production batch. Tablet thickness can vary with no change in weight due to difference in the density of the granules, the pressure applied to the tablets and due to the speed of tablet compression. While variations in the tablet thickness could lead to packaging problems and could also affect patients acceptance due to difference in appearance. Tablet thickness is determined with a calliper or a micrometer screw gauge which measures the thickness in millimetres.

A plus or minus 5% may be allowed depending on the size of the tablet.

iii. **Uniformity of Diameter Test:** This standard is necessary for uncoated tablet and is an attempt to rationalise the diameters of tablets containing a certain dose of active medicament. Tablet diameter is determined by those of punch and die. However, wear and tear of the die may occur with time due to constant compression of a given amount of material in the given die and may result to increase in diameter of die and tablet diameter variation (Garr, 1988).

Bioavailability tests

Biological quality standard evaluation tests of tablet include disintegration tests and dissolution.

Disintegration test: Disintegration is the break up of the tablet into particles after administration. The active ingredient is usually released from the tablet matrix as efficiently as possible to allow for its rapid dissolution and absorption and pharmacological action.

Tablets formulated may not pass quality control test if it does not disintegrate within the specified time limit as such tablet if administered will not release the active ingredient for desired therapeutic action. Disintegration time test measures the time it will take a tablet to break down into small granules or particles when placed in a liquid medium. This is an attempt to evaluate the availability of the drug from active components from the tablet. Many equipment have been designed for this purpose. The equipment specified in the B. P. consists of a Perspex tube, the bottom end of which is sealed with a number 10 mesh screen.

The tube is attached to an arm and is raised and lowered at 30 cycles per minute through a water – bath thermostated at 37°C. At the top of the stroke, the mess must just break the surface, while at the bottom of the stroke the top of the tube must remain above the water level. Six tablets are placed in the tube, the machine is set in operation and the time noted.

The tablets steadily break up and the pieces pass through the mesh. **Physiological availability**. This can be determined by single assay in which active content of individual tablet is investigated by a composite test. In the latter case twenty or such other numbers as may be stated under a monograph are used for this assay. The tablets are crushed together and the mean active content determined. This tends to mask the individual variation. B.P and other official books have specified assays of different individual active content.

Colour test: This is an attempt to determine possible tablet mottling which could be an indication of inadequate mixing.

1.9 AIMS AND SCOPE OF PROJECT

There have been several attempt to source cellulose from raw materials in this country. Most of the raw materials investigated have competing demands e.g utilisation and alternative source of fuel.

Rice husk on the hand, is an abundant waste material, hardly utilised for any use, hence it is readily available and at no cost as a source for production of cellulose. Although there have been an attempt to extract α-cellulose from rice, no known attempt has been made to produce microcrystalline cellulose from this abundant waste material.

This study is therefore directed towards production of α-cellulose and microcrystalline cellulose from rice husks. The following aspects would be investigated.

- Collection, authentisation, drying and milling of rice husks obtained from Kawo Kaduna.

- Extraction of α-cellulose from the rice husks using standard produces.

- Depolymeration of the obtained α-cellulose to produce microcrystalline cellulose.

- Characterisation of the physico-chemical properties of the α-cellulose and Microcrystalline Cellulose (MCC)

- Formulation of micro-dose tablets by wet & dry granulation methods utilising α-cellulose and MCC as the sole excipients; and

- Evaluating the compact properties of resulting tablets.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 MATERIALS

The list and sources of chemicals are as follows:-

Lactose (Laboratory reagent, BDH Chemicals England);

Magnesium stearate (Hopkin and Williams Ltd, England);

Maize starch (Laboratory reagent, May and Baker, England);

Methanol (Laboratory reagent, May and Baker, England);

Sodium chlorite (Technical grade, BDH Chemicals, England);

Sodium hydroxide (Avondale Laboratories Banbury, Oxon, England);

Sulphuric acid (laboratory reagent, BDH Chemicals, England);

Talc (Analar grade, BDH Chemicals, England);

Butanol (Laboratory reagent, May and Baker Ltd., England);

Chloroform (Laboratory reagent, May and Baker Ltd., England);

Fructose (Analar grade, BDH Chemicals, England);

Folic acid (F-Hoffman-La Roche Co. Ltd., Switzerland);

Galactose (Analar grade, BDH Chemicals England);

Glucose (Analar grade, BDH Chemicals, England);

Hydrochloric acid (Laboratory reagent, BDH Chemicals, England);

Avicel® (PH 101 grade, Honey and Stein Ltd., UK);

Acetic acid (laboratory reagent, BDH Chemicals, England)

Parazone (3.5% w/v sodium hypochlorite solution, Nigerian German Chemicals Plc Lagos Nigeria).

2.2 Equipment

The list of equipment used is as follows:-

Mixer (MX-T110PN National Electric Co. Ltd., Japan);

Granule powder flowability tester (type GDT, Erweka Apparatus, Germany);

Oven (BS Size Three, Gallenkamp Ltd. England)

Light microscope (Wild Mill, Heerbrugg, Switzerland);

Hot plate (6B-85475, Gallenkamp Ltd., England);

Milling Machine (Type YL 112M-4-TH,Atlas Alzico Ltd);

Specac hydraulic press (model P/N 25.011 London, UK);

Single punch tablet press (Type EKO, Erweka Apparatebau GMBH, Germany);

Tablet disintegration test apparatus (Type TA3R, Erweka Apparatebau GMBH, Germany);

Analytical weighing balance (Mettler, Type P103, Mettler Instruments A. G., Switzerland);

Water bath (IM 840 Gallenkamp, England);

Micrometer screw gauge (Moore and Wright, England);

Suction machine; (locally fabricated from car A/C compressor);

Stainless steel bowl 5L;

Stainless steel container 50L;

Glass slides (Pyrex England);

Glass wares;

2L Erlenmeyer flask;

1000 x 50 ml Erlenmeyer flask;

1L wide – mouthed screw-cap bottles;

Whatman filter paper No.1;

Rice husks (Kaduna local) collected from a local rice mill at Hayin Banki, Zaria environment.

2.3 METHODS

2.3.1 EXTRACTION OF RICE HUSK ALPHA CELLULOSE (RHAC)

The method described by Okhamafe et al (1991) was used to extract the cellulose from rice husk with few modifications.

(i) Preliminary Treatment

Rice husks were dried at 60°C for 24 hr in the Gallenkamp oven, comminuted using the multipurpose Atlas Exclusive Alzico milling machine. The portion of the milled mass that passed through 355µm sieved mesh was collected and used for further processing.

(ii) Delignification

The material (400g) was treated with 4 litres of 3.5% nitric acid containing 40 mg of sodium nitrite for 2 hours in a 10 - litre volume stainless steel bowl immersed in a water bath set at 90°C to remove lignin in the form of soluble nitrolignins.

(iii) Washing

The mixture was washed with one litre aliquots of distilled water repeatedly and filtered until the effluent water became colourless. The suction pump was used to hasten the filtration process.

(iv) Reaction with 2% sodium hydroxide and 2% sodium sulphite

The residual product was digested with a 4L solution containing 2% each of sodium hydroxide and sodium sulphite at a temperature of 50°C for 1 hour.

This was also rinsed or washed with water repeatedly and filtered as above. The resulting holocellulose was used in the next stage.

(v) Bleaching with 1.75% sodium hypochlorite

The washed product was bleached using a 500 ml of 1.75% sodium hypochlorite solution at 40°C for 1.5 hours. This process was repeated twice. This was also washed and filtered as above.

(vi) Treatment with 17.5% w/v sodium hydroxide

The extract (holocellulose) was treated with 500 ml of 17.5% or 4.5M sodium hydroxide solution for 1 hr at 80°C to dissolve beta and gama cellulose from the mixture leaving only the required alpha cellulose which was washed and filtered again.

(vii) Further Bleaching of the alpha cellulose with 20% volume of hydrogen peroxide solution

The extraction process was completed by whitening the product with 500 ml of 20 v/v hydrogen peroxide solution for 1.5 hours at 40°C. This was also washed with distilled water, filtered, pressed and dried at 48°C for 10hr and later at 60°C for 1 hour. The product was sieved and the portion that sieved through 500, 250, 125, 75 μm was collected in pans and stored separately in a silica gel desicator.

The whole extraction process was repeated twice to obtain enough cellulose for this work.

(viii) Determination of percentage yield

The mean of the ratio of the weight of the extracted alpha cellulose to the weight of sieved crude cellulose which was expressed as a percentage gave the mean percentage yield

2.3.2 QUALITATIVE TESTS ON RHAC

The identification test for sugar and lignin described by Trease and Evans (1983) were followed in this work for the identification of the sugars that may be present in the extracted crude alpha cellulose.

(a) **Test for Lignin**

0.1g of the cellulose obtained from 2.2 (vii) was placed on a slide and two drops of concentrated hydrochloric acid were added and warmed gently until it dried up. Two drops of phloroglucinol were added and viewed under the microscope to observe any colouration change.

(b) **Identification test for Cellulose**

To 5ml of concentrated solution of zinc chloride 1ml of iodine solution was added. Three drops of this mixture was added to 0.1g of the cellulose mass placed on a petri-dish and observed for blue colouration.

(c) **Test for Sugars**

For standard test for free reducing sugars, 0.4g of the cellulose was dispersed in 4ml of distilled water in a test tube. This test tube boiled in a water bath for a few minutes. The solution was divided into two equal portions. To one portions, 5ml of equal volumes of a mixture of Fehling's solutions A and B was added and boiled for few minutes again. It was then observed for a brick red colouration.

(d) **Test for non-Free Reducing Sugar**

To the second portion of the above test, dilute hydrochloric acid was added and boiled for 10 minutes. 5ml of equal volume of Fehling's solution A and B was added and treated for 2 more minutes. It was then observed for a brick red colouration.

(e) **Test for Cellulose**

To 0.2g of alpha cellulose powder drops of iodine solution (B.P) were added followed by 66% v/v sulphuric acid. It was then observed for swelling and by blue black colouration.

(f) **Test for Starch**

5g of the cellulose was placed in a test tube and 5 ml of 5% potassium hydroxide solution was added. This was heated gently and observed for yellow colouration.

(g) **Chromatographic Finger Print Replication**

Test For Sugars

Thin layer and paper chromatographic processes were used in this test. The test solution was prepared by dispersing 0.5g of the cellulose in 50ml methanol.

System I	:	Thin layer chromatography
Absorbent	:	Silica gel G (air dried) on a glass plate.
Solvent system	:	Chloroform: Methanol (60:40)
Technique	:	Ascending

Visualization : (1) Under W at 305nm

(2) Spraying with anisaldehyde sulphuric acid reagent and heated at 105°C until sports appeared distinctly.

System II : Paper chromatography

Chromatographic paper : Whatman No.1 (20 x 20cm)

Solvent system : Chloroform methanol (60:40)

Technique : Ascending

Visualisation : Aniline phthalate spray reagent was applied, kept in the oven for 2 minutes to dry and viewed with naked eye and under W 305nm.

2.3.3 PHYSICO-CHEMICAL EVALUATION OF CELLULOSE

The cellulose obtained in 2.2 (vii) was evaluated as follows:-

(a) Particle Size Determination

0.01g of the cellulose powder was mounted in water and viewed under the Wild light microscope using the x10 objective lens. The diameter of 100 particles selected at random were measured by varying the field of view. From the values, the mean particle size and size distribution were determined.

(b) Flow Rate Determination

10g of the powder was taken and passed through the Erweka flowability tester and the time taken for the powder to pass through the orifice was recorded. This procedure was repeated twice. The mean of the three readings were calculated.

(c) Bulk density and tapped density determination

To calculate the bulk density, 10g of the powdered cellulose was allowed to flow freely into a 100ml measuring cylinder and the bulk volume noted. The cylinder was tapped 50 times on a hard table and the tapped volume was also noted. The procedure was repeated twice for both bulk volume and tapped volumes. The mean values of the three readings each for bulk and tapped volumes were calculated and recorded.

$$BD = \frac{\text{Mass}}{\text{Bulk volume}} \quad \text{Eq. 2.1and}$$

$$TD = \frac{\text{Mass}}{\text{Tapped volume}} \quad \text{Eq. 2.2}$$

Where TD is tapped density and

BD is the bulk density

(d) Carr's Index

The values obtained from bulk density and tapped density were used to calculate Carr's index (CI) which is the percentage difference between tapped density and the bulk density as described by Schwartz et al (1975).

$$CI = \frac{(TD) - BD) \times 100}{TD} \quad \text{Eq. 2.3}$$

Where CI = Carr's Index

TD = Tapped Density

BD = Bulk Density

(e) **Determination of the Angle of Repose**

This was determined using a funnel fitted firmly at a height of 10cm from a flat surface on which was placed a clean sheet of plain glass and a piece of glazed paper. 10g of the powder was placed in the funnel and allowed to flow, forming a conical heap on the base under which the paper was placed. The height of the cone was measured in centimetres and noted, while the contour of the base line of the heap was marked round to form the circle as the base of the cone formed by the powder. Two parallel lines were drawn so as to form a tangent on the circumference of the circle. The maximum perpendicular distance between the tangential points of the two parallel lines in the circle was the diameter of the circle half of which is the radius.

The angle of repose was calculated from the equation:-

$$\text{Tan } \alpha = \frac{h}{r} \qquad \text{Eq. 2.4}$$

Where α is angle of repose

h the height of the heap of the powder

and r is the radius of the circle.

(f) **Determination of Moisture Content**

1g of the cellulose powder was placed in an evaporating dish, transferred to the Gallenkamp oven and dried at 105°C until a constant weight was obtained. This was repeated twice and the mean of the three readings was calculated. The moisture content was determined as a percentage.

$$M_c = \frac{100\,(I_w - F_w)}{1_w} \qquad \text{Eq. 2.5}$$

where M_c is Moisture content

I_w the Initial weight

and F_w the Final weight

(g) **Determination of true density**

The true density of the cellulose was determined by the specific gravity bottle-method (Okhamafe et al, 1991). The weight of the specific gravity bottle filled with xylene was determined. Some of the xylene was poured out and a known weight of the cellulose was placed inside the bottle. More xylene was poured into the bottle until it was filled.

Its weight was again determined. True density, D_t was calculated from the formula;

$$D_t = \frac{w\,x\,d}{(b-w) - a} \qquad \text{Eq. 2.5}$$

where ***w*** is the weight of cellulose

d is specific gravity of xylene

a is the weight of the bottle and xylene

b is the weight of the bottle, the xylene and cellulose together.

The determination was carried out in triplicate and the mean determined.

(h) **Determination of Swelling Capacity**

The swelling capacity of the cellulose was determined by the method of Bowen and Vadino (1991). The volume V_x occupied by 5g of the cellulose placed in a 100ml measuring cylinder was noted. About 85ml of distilled water was added and the measuring cylinder agitated to disperse the cellulose. The volume of the cellulose suspension was made up to 100ml with more water and the dispersion allowed to stand for 24 hours.

The volume of the sediment V_y was noted and the swelling capacity computed thus:-

Eq 2.6

$$\text{Swelling capacity} = \frac{V_y}{V_x}$$

where V_x initial volume

where V_y volume of sediment

The mean of triplicate determination was computed as the swelling capacity.

2.5. PRODUCTION AND CHARACTERISATION OF MICROCRYSTALLINE CELLULOSE (RHMCC) FROM RICE HUSKS α - CELLULOSE

2.5.1 PRODUCTION RHMCC

The process described by King (1975) was followed. 2000 ml of Hcl in 3L stainless steel bowl was heated in the Gallenkamp hot plate to boiling temperature of about 105 °C; 200g of the extracted cellulose was added to the boiling solution and strained for 15 minutes and then the mass collected by filteration, neutralizing with aqueous ammonia solution. This was then dried at 48 °C in the oven and milled to break down the aggregates into smaller fragments with the aid of a blender.

2.5.2 Characterisation of RHMCC

Particle size determination and size distribution, flow rate, angle of repose, bulk and tapped densities. Carr's index, moisture content, true density and swelling capacity were all carried out using the same procedure described for the rice husk alpha cellulose. Characterization of Avicel^{R} was similarly carried out.

2.6 TABLET PRODUCTION

A low dose drug, using 5mg folic acid per tablet was used for the formulation.

2.6.1 Wet Granulation

The following formulations given in Tables 2.1 and 2.2 based on different applications of rice husk alpha cellulose (RHAC) and rice husk microcrystalline cellulose (RHMCC) respectively as functional excipients in tablet formulation were studied.

TABLE 2.1: WET GRANULATION FORMULATION TO COMPARE FUNCTIONS OF RHAC & RHMCC TO LACTOSE AND MAIZE STARCH

Function	F1	F2	F3	Wt Batch size of 50tablets (g)
Drug	Folic Aid	Folic Acid	Folic Acid	0.250
Diluent	Lactose	RHAC	RHMCC	2.5625
Disintegrant	Maize starch	RHAC	RHMCC	0.375
Binder	PVP in 5ml of 3.7% w/v solution	PVP in 5ml	PVP in 5ml	0.1875
Extra-granular excipients	Maize starch: Talc: Mgst 10:1 ratio	RHAC	RHMCC	0.2925
		RHAC	RHMCC	0.0825
				3.750

PVP = Polyvinyl pyrollidone

Mgst = Magnesium stearate

- Only one functional variable as a diluent, disingrant, glidant or lubricant was applied for each batch while the other ingredients in the typical formulation were adopted.

(i) **Initial Mixing**

The folic acid powder as the drug, the diluent and the disintegrant were dry mixed by trituration using the mortar and pestle. The disintegrant was first incorporated into the drug completely in geometrical proportions. Thereafter, the diluent was incorporated with the powders in the same manner.

(ii) **Wet mixing**

A 3.75% w/w binder solution was prepared by dissolving 3.750g of PVP in 100 ml of distilled water; 5 ml of this solution was used in wetting the already mixed powdered mass and kneaded with a spatula in the mortar for 5 minutes. The wet mass was then screened through a 10mm sieve mesh using the spatula. The resulting wet granules were dried in an oven at 50°C for 30 minutes. The granules were removed from the oven and re-screened through the same sieve mesh and further dried for 1 hour at the same temperature.

(iii) **Final Mixing**

Final mixing of the granules was done in the plain bottle. The extra-granular excipients (disintegrant, talc and magnesium stearate) or other substances as shown in the working formula were individually incorporated one at a time into the folic acid granules, the bottle was used to mix the substances using figure eight motion .

Thereafter, the whole mixture was transferred into a plain bottle, covered and was turned upside down for 200 times to ensure thorough mixing of the components.

2.6.7 **Dry Granulation or Pelletisation**

Folic acid tablets containing only rice husk alpha cellulose (RHAC), rice husk microcrystalline cellulose (RHMCC) and a binary mixed powder of RHAC with RHMCC respectively were prepared shown in table 2.2.

10g weight of the sole excipient was dry mixed with 0.714 g of folic acid powder using the doubling up mixing techniques in the 250 ml procelain mortar with the pestle. 2.5 g weight of the mixture each was pelletized at 10 metric tonne force using 25 mm diameter of the punch and die tooling set of the specac hydraulic pelletising machine at CERT.

The thickness of the pellets were measured. They were comminuted and passed through 1.7 mm sieve mesh and then sieved into various sieve sizes in order to calculate the mean granule size and the percentage of the fines.

TABLE 2.2: **FOLIC ACID FORMULATION BY THE DRY GRANULATION-COMMINUTION METHOD WITH RICE HUSK ALPHA CELLULOSE (RHAC), RICE HUSK MICROCRYSTALLINE CELLULOSE (RHMCC) AND THE BINARY MIXTURE AS SOLE EXCIPIENTS.**

Batch No.	Ratio of Binary Mixture		Weight of ingredients		
	RHAC	RHMCC	RHAC (g)	RHMCC (g)	Folic Acid (g)
1	0	10	0.0	10.0	0.714
2	3	7	3.0	7.0	0.714
3	5	5	5.0	5.0	0.714
4	7	3	7.0	3.0	0.714
5	10	0	10.0	0.0	0.714
6	0	10	0.0	10.714	-
7	10	0	10.714	0.0	-

Batch Size of 153 tablet each weighing 75mg

2.6.8 Compression of granules into tablets

The Erweka single punch tableting machine using 5.5 mm punch and die assembly, was used to compact 75 mg weight of the granules into tablets using 3 compaction forces; the lowest to compress and form tablets, the mid-way interval pressure and the highest possible pressure respectively.

2.7 EVALUATION OF TABLET PROPERTIES

2.7.1 Weight variation test

Ten tablets were randomly selected from each batch, weighed together and then individually on the Mettler balance. From the mean tablet weight, the percentage deviation of each tablet from the mean weight was calculated.

2.7.2 Hardness

Monsanto hardness tester was used to determine the force (kgf) required to crush one tablet. Each tablet was placed between the spindle and the anvil, held in position using the adjustable knob without exerting any pressure. The zero reading was set and the knob was carefully and slowly adjusted until that point when the tablet just fractured. The reading at which this occurs was taken. Similar readings were taken for nine other tablets and the mean crushing strength of the ten tablets calculated.

2.7.3 Tablet thickness

The thickness of the tablets was measured using the micrometer screw gauge. Each tablet was placed flatly in-between the gauge teeth and the thickness measured. The readings for ten tablets were taken in each batch and their mean calculated.

2.7.4 Friability

Ten tablets from each batch were selected, brushed and weighed together on the Mettler balance. They were then placed in the Erweka Friabilator. It was operated and allowed to run for 4 minutes at 25 rpm.

After the 100 rotations, the tablets were removed, their surface were brushed to remove fines and re-weighed on the balance. The difference in weight was determined and expressed as percentage weight loss to obtain the friability value.

2.7.5 Disintegration time

The method specified in the British Pharmacopoeia 1988 was followed. The Erweka tablet disintegration apparatus was utilized in this test. Distilled water in a beaker and thermostatically maintained at 37±0.5 °C was used as the disintegrating medium. Six tablets in each batch was placed, one each in the six tubes of the apparatus. The switch was put on and the time taken for each tablet to disintegrate and pass through the mesh at the bottom of each tube was recorded using a stop clock. The time taken for the last tablet to pass through the mesh is taken as the disintegration time for that batch. Two readings were generally taken for each batch of tablets and the average recorded.

53

CHAPTER THREE

3.0 RESULTS

3.1 PHSICO-CHEMICAL PROFERTIES OF CELLULOSE AND MICROCRYSTALLINE CELLULOSE

3.1.0 The Yields

The yield of rice husk alpha-cellulose from the milled crude was 21% and that of rice husk microcrystalline cellulose from the extracted alpha-cellulose was 91%.

3.1.1 Identification and Purity Tests on Materials

Table 3.1 shows the results of tests carried on the cellulose material obtained from rice husks. The results show that the substance was mainly cellulose with no free reducing sugars in the materials. This is also confirmed by the results of paper and thin layer chromatography (TLC) where there were no similar spots of the material compared with those of reference of standard samples of glucose, galactose, fructose and xylose (Table 3.2), meaning that the sample was devoid of the presence of these simple sugars.

3.1.2 Particulate consolidation properties of materials

The particle size distribution of the cellulose materials – rice husk alpha cellulose (RHAC) – obtained from rice husks is shown in Table 3.3 and Figure 3.2. The histogram plot of particle size distribution of the cellulose mass is slightly skewed to the left and this confirms that majority of the powder particles were medium to fine size.

MASLIM IBRAHIM LI. 132

The particle size distribution of microcrystalline cellulose (RHMCC) obtained from rice husks is shown on Table 3.4 RHMCC contains a higher proportion of finer particles than those of cellulose power (RHAC) as shown in figure 3.2. About 75% of the particles have sizes lower than 100 um with a mean particle size of 79 μm. The plot of frequency against particles size was also slightly skewed to the left. The particle size distribution pattern of Avicel® shown similar characteristics with those of RHMCC above. For example, about 80% of Avicel® was found to have particle size lower than 100um with a mean size of 63.6um (Table 3.5). The cumulative frequency curves of the cellulose (RHAC), microcrystalline cellulose, (RHMCC) and Avicel® are show in Fig. 3.3. The cumulative curve of RHMCC was very similar to that of Avicel®.

In general, the cellulose power (RHAC) was mainly composed of relatively large fibres of diverse irregular shapes, while the microcrystalline cellulose (RHMCC) was characterised by small, partly spherical structures with few longitudinal and cylindrical fibres. Avicel® power has fewer longitudinal fibrous structures.

3.1.3 Flow properties

The bulk/tapped densities in gcm-3 followed the following order:

RHAC<RHMCC<Avicel®

The Carr's index, values followed a reverse order i.e. the sequence of which is as follows: RHAC > RHMCC > Avicel®.

These values show that RHAC & PHMCC are highly compressible though slightly less compared with Avicel. Low Carr Index values generally indicate higher level of ease of consolidation.

The two celluloses produced from Rice husk are relatively comparable to Avicel, the order in decreasing values of angle of response is in the order:

RHAC > RHMCC > Avicel® as shown in table 3.6

This order indicates that RHAC is the most cohesive while Avicel® is the least. The flow rate values reveal that Avicel®, with the highest flow rate has the best flowability while RHAC and RHMCC have similar flowability (RHAC, < RHMCC <Avicel®.

TABLE 3.1: IDENTIFICATION TESTS ON RICEHUSK ALPHA CELLULOSE (RHAC)

Tests	Observation	Inference
Standard test for free reducing sugar:	Absence of brick red colouration	Absence of free reducing sugar.
Test for lignin:	Absence of red colouration	Absence of lignin
Test for Cellulose:	Blue colouration seen	Cellulose present

TABLE 3.2 THIN LAYER CHROMATOGRAPHY (TLC) TEST FOR SIMPLE SUGARS CARRIED OUT ON THE EXTRACTED RICE HUSK ALPHA CELLULOSE AS COMPARED WITH REFERENCE (STANDARD) SAMPLES.

Chromatographic Paper:	Whatman No. 1
Solvent System	n- Butanol: Acetic acid: water (4:1:5)
Spray reagent	Anisaldehyde + sulphuric acid

RHAC

Extracts	**HR_f**	**Colour reaction**	**Spots under uv (305nm)**
Reference Samples			
Xylose	1.17	Light brown	Light brown
Galactose	1.17	Brown	White Fluorescence
Glucose	1.17	Purple	White Fluorescence
Fructose	1.17	Brown	White Fluorescence
Test Sample			
RHAC	0.0	Nil	Nil
RHMCC			
Reference Sample	1.17	Light brown	Not visible
Xylose	1.17	Brown	Not visible
Galactose	1.17	Purple	Not visible
Glucose	1.17	Brown	Not visible
Fructose			
Test Sample			
RHAC	0.0	Nil	Nil

TABLE 3.3: **PARTICLE SIZE DISTRIBUTION OF RICE HUSK ALPHA-CELLULOSE**

Size range (μm)	Frequency (f)	Class mark (xi)	(Fixi)	Cumulative frequency
1-50	-	25.5	-	-
51-100	37	75.5	2793.5	37
101-150	22	125.5	2761.0	59
151-200	11	175.5	1930.5	70
201-250	11	225.5	2480.5	81
251-300	9	275.5	2479.5	90
301-350	10	325.5	3255.0	100
	Σ(fi) = 100		Σ(fixi) = 15699.0	

Mean particle size = $\frac{\Sigma(fixi)}{\Sigma(fix)} = \frac{15699.0}{100} = 156.99 \cong 159\ \mu m$

TABLE 3.4: PARTICLE SIZE DISTRIBUTION OF RICE HUSKMICROCRYSTALLINE CELLULOSE (RHMCC)

Size range (μm)	Frequency (f)	Class mark (xi)	(Fixi)	Cumulative Frequency
1-50	48	25.5	1224.0	48
51-100	29	75.5	2189.5	77
101-150	6	125.5	753.0	83
151-200	8	175.5	1404.0	91
201-250	5	225.5	1127.5	96
251-300	2	275.5	551.0	98
301-350	2	325.5	651.0	100
	Σ(fi) = 100		Σ((fixi) = 7900.0	

Mean particle size = 79.0 μm

Table 3.5 PARTICLE SIZE DISTRIBUTION OF AVICEL®

Size range (μm)	Frequency (f)	Class mark (xi)	(Fixi)	Cumulative frequency
1 – 50	60	25.5	1530	60
51 – 100	21	75.5	1585.5	81
101 – 150	10	125.5	1255	91
151 – 200	4	175.5	702	95
201 –250	2	225.5	451	97
251 – 300	3	275.5	826.5	100
	Σ(fi) =100		Σ (fixi) = 6350.0	

Mean particle size = 63.5 μm

3.1.4 Moisture Content

The moisture content of the three powders are as given in Table 3.6. The values range between 3.1 for Avicel® to 6.1 for α cellulose (RHAC). These values are generally accepted as low for polysaccharides (Balami, 1999).

RHAC X 400

RHMCC X 400

Avicel^{R} X 400

FIGURE 3.1 COMPARATIVE SIZE AND SHAPE OF RICE HUSK ALPHA- CELLULOSE (RHAC), RICE HUSK MICROCRYSTALLINE CELLULOSE (RHMCC) AND AVICEL^{R}

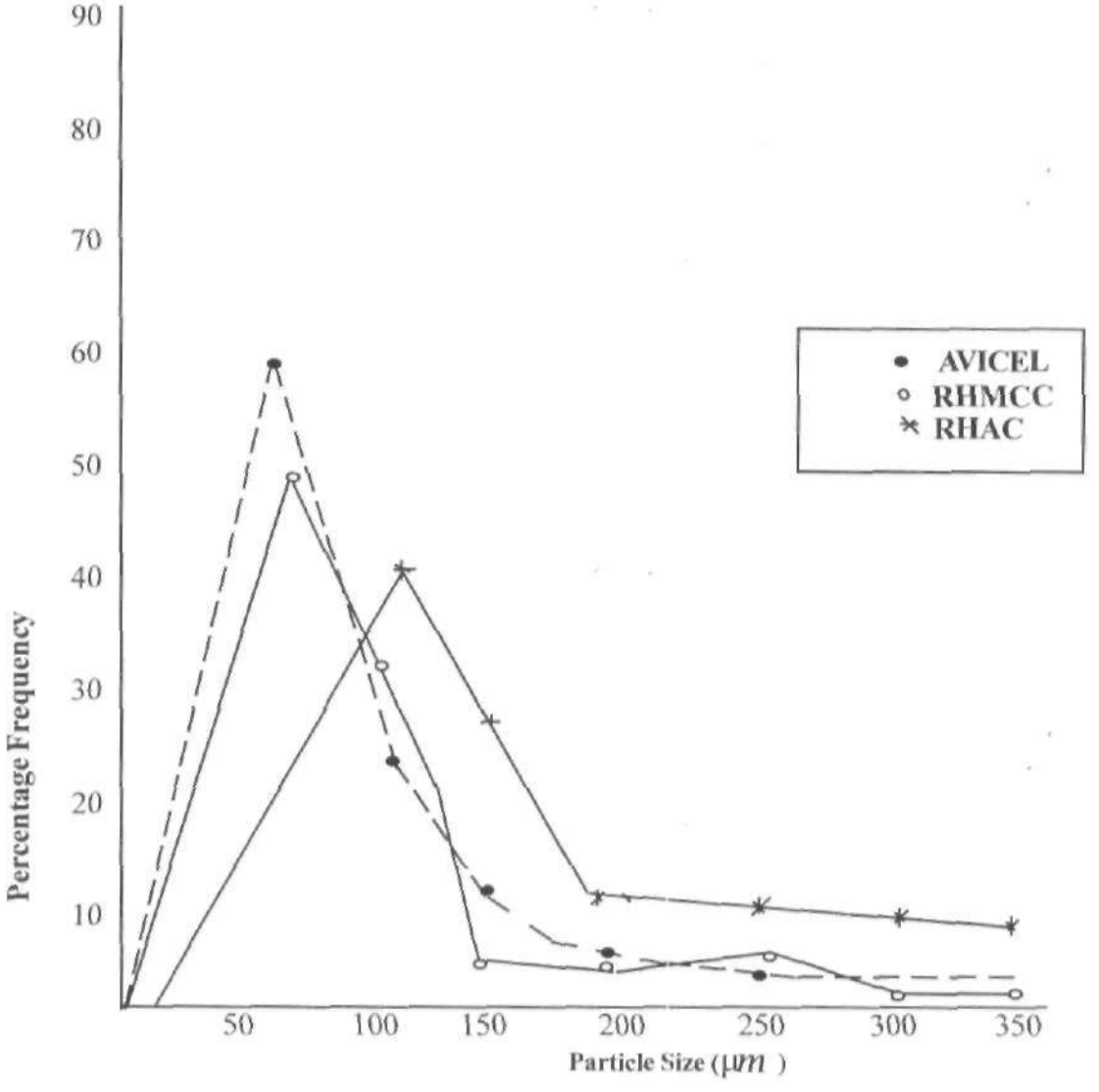


Fig. 3.2: Percentage frequency Vs particle size Distribution of Rice Husks Alpha Cellulose, (RHAC) Microcrystalline Cellulose (RHMCC) and Avicel Powders.

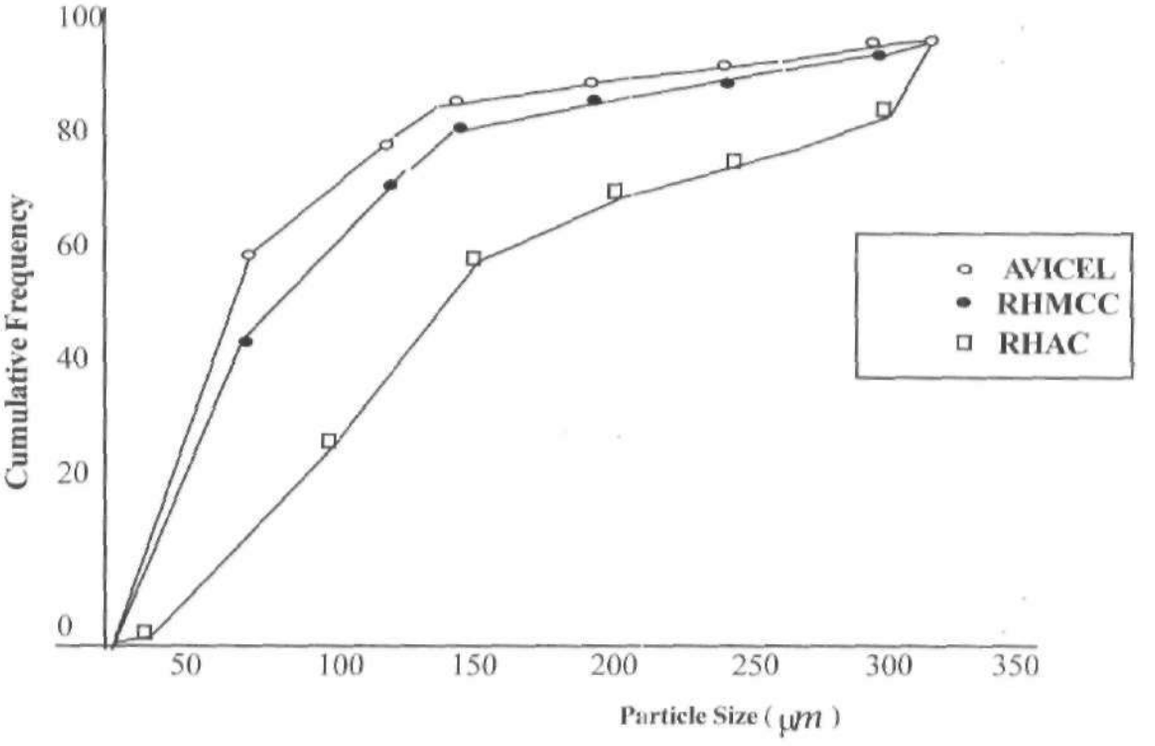


Fig. 3.3: Cumulative Percentage Frequency Vs particle size of Rice Husks Alpha Cellulose, (RHAC) Microcrystalline Cellulose (RHMCC) and Avicel Powders.

Table 3.6: **CONSOLIDATIVE PHYSICAL PROPERTIES OF THE CELLULOSES**

Parameter	RHAC	RHMCC	Avicel®
Mean particle size (μm)	157	79	64
Bulk density (g/cm^3)	0.13	0.16	0.25
Tapped Density (g/cm^3)	0.22	0.26	0.39
Carr's index (%)	40.5	38.8	34.44
Flow rate (g/s)	0.34	0.38	1.20
Angle of repose (^{0})	50	47	44
Moisture content (%) w/w	6.1	4.3	3.1

3.2 PROPERTIES OF TABLET PRODUCED BY WET GRANULATION

3.2.1 Diluent properties of Cellulose in tablets

Properties of compacts produced from granules prepared by wet granulation using Rice Husk Cellulose Powder (RHAC), Rice Husk Microcrystalline Cellulose (RHMCC), Avicel® and lactose as diluents in folic acid tablet formulation are shown in Table 3.7. Tablets could not be formed when RHAC, RHMCC and Avicel® were used as sole diluents in micro-dose formulation. So the properties of the tablets could not be evaluated.

Table.3.7: COMPACT PROPERTIES OF TABLETS, PRODUCED USING RHAC, RHMCC AND LACTOSE AS DILUENTS IN GRANULES PRODUCED BY WET GRANULATION

Parameter	Lactose	Avicel®	RHAC	RHMCC
Mean tablet weight (mg)				
Thickness (mm)	73.35± 1.36	No tablets	No tablets	No tablets formed
Hardness (kgF)	2.87± 0.08	formed	formed	
Friability (%w/w)	5.1±0.3			
Disintegration (min)	1.4			
	1.27± 0.13			

473424

Table 3.8: COMPACT PROPERTIES OF TABLETS, PRODUCED USING RHAC, RHMCC AVICEL AND MAIZE STARCH AS INTRA-GRANULAR DISINTEGRANT

Tablet properties	Intra-granular Disintegrant Effect			
	RHAC	RHMCC	Maize Starch	Avicel ®
Mean weight (mg)	73.4±1.3	73.31±1.3	74.1±1.1	73.7±1.2
Thickness (mm)	2.85±0.04	2,84±0.04	2.95±0.12	2.80±0.06
Hardness (kgf)	8.0±1.1	8.9±0.3	6.38±0.6	8.5±1.3
Friability (% w/w)	0.6	0.4	0.8	0.7
Disintegration time (min)	1.3±0.1	1.2±0.1	0.70±0.1	1.1±0.1

3.2.2 Disintegrant properties of materials in tablets

The observed characteristics of folic acid tablets formulated with RHAC, RHMCC, Avicel® and maize starch as intra-granular disintegrant are show in Table 3.8

As depicted in this table, the tablet properties of formulation containing RHAC, & RHMC were generally similar with those of Avicel, especially the thickness, hardness and disintegration values. Tablets formulated with RHAC & RHMC were generally less friable. Maize starch produced relatively softer tablets, which were slightly more friable with shorter disintegration time.

TABLE 3.9 **COMPACT PROPERTIES OF TABLETS, FORMULATED USING RHAC, RHMCC AVICEL AND MAIZE STARCH AS INTRA AND EXTRA GRANULAR DISINTEGRANTS**

Tablet properties	**Intra- and Extra-granular Disintegrant Effect**			
	RHAC	**RHMCC**	**Maize Starch**	**Avicel ®**
Mean weight (mg)	74.1±1.1	73.6±1.4	74.8±1.1	73.8±0.8
Thickness (mm)	3.10±0.11	3,09±0.20	3.80±0.09	2.96±0.09
Hardness (kgF)	8.4±0.9	8.5±0.5	6.0±0.9	8.6±0.8
Friability (% w/w)	0.1	0.3	0.5	0.1
Disintegration time (min)	0.4±0.1	0.3±0.1	0.4±0.1	0.6±0.1

3.2.3 Intra and Extra – Granular Disintegrant Properties of Materials

Tablet produced using RHAC, RHMC & Avicel as mixed intra and extra granular distegrants exhibited similar compact properties (Table 3.9) were generally harder, less friable and slightly thinner than those produced using maize starch. Basically, all the tablets disintegrated within 1 min showing that the three cellulose materials and MS behave as disintegrating agents.

3.2.4 Glidant/Lubricant Function of Materials

Extra – granular maize starch and talc with magnesium stearate in figure 3 were substituted with the materials as given in F1, F2, and F4 to determine their glidant/lubricant function. The results in Table 3.10 were obtained. It is clearly demonstrated that tablets formulated with the cellulose materials as glidant/lubricant were harder, less friable and exhibited faster disintegration time than F3.

TABLE 3.10 COMPACT PROPERTIES OF TABLETS, FORMULATED USING EITHER CELLULOCES OR MAGNESIUM STERATE WITH TALC AS LUBRICANTS/GLIDANTS

Tablet properties	**Glidant/Lubricant Effect**			
	RHAC F1	**RHMCC F2**	**Maize starch: Talc: mgst 10:2:0.1 F3**	**Avicel ® F4**
Mean weight (mg)	74.1±1.3	74.4±1.2	74.8±1.1	74.2±1.4
Thickness (mm)	2.90±0.05	2.89±0.07	3.40±0.6	2.90±0.05
Hardness (kgF)	5.1±0.8	5.0±0.6	3.0±0.4	5.3±0.4
Friability (% w/w)	0.6	0.6	0.8	0.6
Disintegration time (min)	0.2±0.1	0.2±0.0	4.5±0.7	0.4±0.1

TABLE 3.11: PROPERTIES OF MATERIALS ON PELLETISATION (DRY GRANULATIONS)

Parameter	Batch Numbers Ratio of Binary mix RHAC: RHMCC						
	No folic acid		Containing 5mg folic acid				
			1	2	3	4	5
	100% RHMCC	100% RHAC	0:10	3:7	5:5	7:3	10:0
(i) (Specific thickness of pellets (mm/mg x 10_{-3})	1.34	1.55	1.48	1.33	1.33	1.34	1.48
(ii) Mean granule size (μm)	253	271	296	332	330	330	334

TABLE 3.12: PROPERTIES OF TABLES FORMULATED FROM GRANULES PREPARED BY PELLETIZATION (DRY GRANULATIONS) OF TABLET INGREDIENTS.

Parameter	Batch Numbers						
	Ratio of Binary mix RHAC: RHMCC						
	No folic acid		Containing 5mg folic acid				
			1	2	3	4	5
	100% RHMCC	100% RHAC	0:100	30:70	50:50	70:30	100:(
i. Mean weight (mg)	incompressible	incompressible	75.4±1.4	74.5±1.1	74.7±1.0	74.7±0.6	74.8±2.2
ii. Thickness (mm)	-	-	3.63±0.11	4.15±0.06	4.20±0.0	4.33±0.08	4.65.4±0
iii. Hardness (kgf)	-	-	5.4±0.9	6.0.4±0.9	4.80.4	3.5±0.3	1.20±4.
iv. Friability (% loss)	-	-	2.20±0.2	0.4±0.2	2.0±0.3	2.4±0.3	2.3±0.3
v. Disintegration time (mm)	-	-	0.1	0.1	0.1	0.1	0.1

3.3 Sole Excipient Properties of Materials in Dry Granulated Folic Acid Tablets.

Table 3.11 and 3.12 above shows the properties of pellets, granules and tablets produced from dry granulated folic acid formulation.

3.3.1 Pellet and tablet thickness

The specific thickness of the pellets of the pure rice husk microcrystalline cellulose (RHMCC) was lower than that of the pure rice husk alpha-cellulose (RHAC) by 17%. The presence of folic acid dose despite constituting only 6.7% of the tablet weight equibriated the thickness of both materials (RHAC and RHMCC) to 1.48 units' scale which is 10% higher than the value for the pure RHMCC. It is shown that the thickness of the pellets containing three different ratios of the binary mixtures of RHAC and RHMCC admixed with the folic acid dose produced the same thickness of pellets ($P \leq 0.05$).

3.3.2: Mean Granule size of Comminuted Pellets

The variation of the mean granule size resulting from comminuted pellets followed the same pattern as with thickness of the pellets (Table 3.13 and Figure 3.2). Properties of folic acid tablets produced by dry granulation via the pelletization of pure and binary mixed cellulose materials show that the results have been treated by reference to the tablet weight uniformity, thickness, hardness, friability and disintegration time, all of which are shown on Table 3.12.

3.3.3: Tablet weight and uniformity

The mean weight was 75 mg. Although the particle sizes were different, the weight variations were all within a maximum of ±2% for the granules with higher percentage of fines while the others had variation of ±1%.

3.3.4: Tablet Thickness

Tablets produced from pure alpha-cellulose ass sole excipient had the highest value of thickness. As the ratio of microcrystalline cellulose portion increased, the thickness appears to decrease, that is, giving an inverse relationship.

3.3.5: Tablet Hardness

Tablets containing pure RHMCC as sole excipient produced a higher value of crushing strength compared with pure RHAC sole excipient content. However, the 3:7 ratio of RHAC: RHMCC produced the highest hardness value while the hardness tended to decrease with increase in RHAC content in the binary mixture.

3.3.6: Tablet Friability

The mean of the values of friability in this dry granulated process is 2% except for the tablets with the highest value of hardness (see above) for 3:7 RHAC: RHMCC which produced the least value of friability of 0.4%. It would be recalled that tablets produced by wet granulation method had values of friability which were each below 1% .

3.3.7: Tablet Disintegration Time

Irrespective of the type of the sole excipient material – whether with pure RHAC, pure RHMCC or binary admixtures of the two at different ratio – the disintegration time was 0.1 minute.

CHAPTER FOUR

4.0 DISCUSSION AND CONCLUSION

4.1 PHYSICO-CHEMICAL PROPERTIES OF RHAC AND RHMCC

4.1.1 Materials Extracted and Derived from Rice Husks

The physico-chemical tests and results on the rice husks alpha cellulose RHAC, rice husk microcrystalline cellulose (RHMCC) and Avicel® confirmed and the three materials to consist of cellulose. One would have expected that the treatment of part of the RHAC . with acid that partially depolymerised or partially hydrolyzed the alpha-cellulose would contain some traces at least of the reducing sugars. However, the comparative chromatographic test and the specific tests for reducing sugars (xylose, glucose, galactose and fructose) showed no traces of the simple sugars. This is an indication that the washing techniques would have obviously dissolved off such simple sugars due to their susceptible solubilities.

The crude rice husk cellulose was expected to contain lignin, the absence of which in the tests on the extracted material signifies that the treatment with acid to form soluble nitro-lignins and the washing procedures (Okhamafe et al, 1991) got rid of the lignins. For obtaining higher yields of alpha-cellulose, one may consider the initial and sole use of sodium hydroxide solution which is to dissolve lignin (**Adikwu and Ojile** 1999). **Balami et al** (1999) showed that alkaline hydrolysis of polysaccharides was extremely slow compared with acid hydrolysis. This means that the solubilization of beta and gama-cellulose in 17% Na OH would have as well dissolved off the lignin with little or no hydrolysis of the part of the alpha-cellulose being extracted.

By so doing, the extractive processes would have been shortened to reduce costs and the alpha-cellulose yield would have been higher than the 21% obtained. However the yield obtained is this work is within acceptable limit and compares favourably with that obtained by the earlier workers (Okhimafe et al 1991) and (Musa Hassan 1999).

4.1.2: Consolidating properties of materials

The term consolidative physical properties' used here refers to such physical properties that could affect the packing or consolidating behaviour of the particles of the materials. Such properties would include particle size and shape, true bulk and tapped densities and therefore Carr's indices, moisture content, flow rate and angle of repose.

One of the main reasons for granulation of particles for tableting apart from imbibing plasticity or compressibility, is increase in flowability. Thus, larger particles flow faster through an orifice than smaller ones. However, rice husk alpha-cellulose (RHAC) with the largest mean size of 157 μm had the lowest flow rate compared with that of the rice husk microcrystalline cellulose (RHMCC) with 79 μm size and Avicel® with 64 μm size . The RHAC, being irregular in shape with the highest area of surface rugocities could produce higher level of frictional force that impeded the ease of flow of the particles.

On the other hand, the RHMCC and Avicel® even with smaller particle size had higher flow rate as a consequence of the more spherical and smoother surfaces that could reduce such frictional force.

The observed flow rates and angles of repose which are inversely related – higher rate of flow, is in consonance with the lower angle of repose. This could relate to the level of cohesiveness of particles – the higher the angle of repose, the higher is the level of cohesiveness. The values obtained compares closely with those obtained by earlier workers ((Okhamafe et al 1991) and (Musa Hassan 1999).

Flow time as opposed to flow rate of equal weight of particles could also be inversely related to higher porosity which is less densification and Carr's' index (CI) (which is the percentage difference between the fluff or bulk density and the tapped density). A lower level of CI could also relate to the ease of consolidation of the particles during compaction. Thus the compaction energy required as a first step in consolidating and densifying the particles before fracturing and cold welding would be reduced. This could then lead to a lower compaction force on the particles in forming the tablets.

Higher moisture content more than 3% could affect the stability of hydrolysis-prone drugs (**Okhamafe, et al** 1991). Higher moisture content to a certain level would increase the densification of the particles provided (the level does not significantly affect the swelling tendency of the particles which could impede flowability). Flow characteristics and the Carr's Index (of the ease of particulate consolidation are both important factors in pharmaceutical processes like tableting, capsule filling, etc. It has been reported by Staniforth (1990) that powders with angles of repose of less than 40^0 are freely flowing while Carr's Index between 25 and 30% are indicative of very good flow properties. The Carr's Index values obtained therefore indicate good flow properties but the angles of repose obtained show inadequate flow properties of the excipient products especially the alpha-cellulose.

4.1.2 PROPERTIES OF TABLETS PRODUCED BY WET GRANULATION METHODS

4.1.3 Diluent use of material compared with lactose

The reason why the tablets produced with rice husk alpha-cellulose (RHAC) and rice husk microcrystalline cellulose (RHMCC) respectively as diluents were too soft to handle compared with those containing lactose as diluent could be due to the relatively low concentration of binder used. Since the work was a comparative one, the same volume aqueous of binder (14% v/w of PVP) was maintained in the massing process with the cellulose derivatives. Insoluble particles require a higher volume of binding liquid (**Ojile et al**, 2000)..Lactose being soluble required between 14 to 20% w/W binder uptake while insoluble powders require some 30% volume (**Allagh-Abaa et al,** 1994). Therefore the RHAC and RHMCC both being insoluble required much higher volume to compact the mass close enough in order that crystalline bridges formed could hold more particles captive in forming dried granules.

During wet granulation, wet granules can be formed as long as a solvent or a liquid is present, the particles binded together to form wet granules by capillary force generated between the interface of liquid and the solid (**Ojile et al**, 1982). When the liquid surrounds the particles as in droplets, the force of attraction is the surface tension of the liquid. When the granules are dry, any soluble component that dissolved in the binder solution formed crystalline bridges that hold the particles together. These crystalline bridges are the forces that hold the particles together as granules.

When the amount of crystalline bridges is inadequate as in this case, a lot of fines result Wells and Landride, 1993. The presence of fines lead to soft tablets even at high compaction force Garr 1991.

4.2.2. Disintegrant use of materials compared to maize starch

Maize starch has been well known for its use as a disintegrant. This was why it was compared with the three cellulosic materials, rice husk alpha-cellulose (RHAC), rice husk microcrystalline cellulose (RHMCC) and Avicel®. The fact that the tablets produced from each of the materials had disintegration time within seconds shows that these materials also have good disintegrant properties. The hardness of 8 kgf and friability of less than 1% for the cellulosic materials show their superiority to maize starch. This could be attributable to a higher level of plasticity of the cellulosic materials than the maize starch. Tablet produced using the materials both as intra-and extra-granular disintegrants were harder compared with those produced with maize starch with even shorter disintegration time of with in half a minute.

4.2.3 Glidant/Lubricant use of material compared with Talc/Magnesium Stearete

Glidants and lubricants normally employed on traditional basis are talc and magnesium stearate respectively. **Musa** (1996) used 2.2% W/W of a 10:1 binary mix as the glidant/lubricant mix which was adopted in this present formulation. These hydrophobic mix have been know to decrease tablet hardness but increase the disintegration time disintegration and friability (**Kunle et al**, 1988 and **Ibrahim,** 1997). The same results were obtained in this project.

The hardness profiles appear to result from the less frictional force generated which caused lower coesive tendencies. Cohesion is amenable to causing harder but less friable tablets. The prlong disintegration is a consequence of the hydrophobic nature of the materials, which lessens the formation of meniscus. The formation of menisci are necessary in generating capillary force for entry of disintegrating medium and this would cause shorter disintegration.

4.3 Effects of Pure and Binary Mixed Components of Cellulose Materials as Sole Excipients On Properties Of Dry Granulated Folic Acid Tablets

Specific thickness has been adapted here as a measure of plastic compressibility. The lower the value is, the more compressible the material. The mean granule size of– rice husk alpha-cellulose (RHAC) was 17% greater than that of rice husk micro-crystalline cellulose (RHMCC) possibly due to the more fibrous and irregular shape of the former. This would hold more compacted particles together during the communation process and thereby resulting in less quantity of fines

However, the pellets from RHMCC having lower specific thickness appear to show that it is more plastically compressible (by approximately 14% even though the mean granule size was 7% lower. This signifies that two similar materials may have different granule sizes but the one with finer granule size may not necessarily produce less plastically compressible tablets as has been shown here. Despite the fact that when the folic acid was admixed even the low content

of 6.7% w/w of the dose, the RHMCC content became less compressible, that is, having higher specific thickness which was equal to that of yhe tablets containing RHAC. The RHAC content did not appreciate in thickness with the admixture of the folic acid at the same level to that of RHMCC. It is possible that the small particles of folic acid got entrapped in the more irregular and more fibrous voids of RHAC in a way that did not alter, the specific thickness of the RHAC as much as it alters that of RHMCC and therefore the compressibility of compacts containing RHAC sole excipient remain the same.

All the different proportions of the binary granule mixtures of RHAC & RHMC produced the same value of specific thickness, and same mean granules size which was larger by 20% compared with that of folic acid granules containing either pure RHAC or pure RHMCC. This has shown that a mixture of components could be used to produce compound with less specific thickness than either of the two components and there produce harder (more compressible) tablets. In this investigation a binary mixture of RHAC: RHMCC in 30.70 ratio produced the highest value of hardness and the lowest friability and still disintegrated in less than 1 minute. As shown in this work, the cellulosic materials used alone or in admixtures as sole excipients still produced tablets that disintegrated in less than 1 minute. This implies that these cellulosic materials did not only act as dry binders but also functioned as disintegrants – a characteristic desired of an ideal dry binder.

4.3.1 Conclusion

In this study, micro-crystalline cellulose (RHMCC) obtained from rice husk share close similarity to Avicel® (a commercial grade microcrystalline cellulose powder) in its physcio-chemical characteristics. The particle size distribution particle shapes, flow rates and angle of repose of the two materials were closely similar but differ significantly from the extracted cellulose.

The characteristics of tablets produced from RHMCC were similar to those of Avicel®. As shown in this work, microcrystalline cellulose from rice husk showed good disintegrant, lubricant and binder properties and function also as a direct compression vehicle and could therefore be substituted for Avicel® in the production of tablets.

4.3.2 Recommendation

The cellulose should also be tested with a wider variety of drugs and ageing effects of the tablets should also be looked into.

The stability of tablets containing RHMCC to microbial contamination should also be investigated.

The scale-up of this pilot scheme should be looked into, to explore how Rice husk microcrystalline cellulose can be employed in the mass production of tablets for commercial purposes.

REFERENCES

1. Ajayi, G. O., Igwilo, C. I. Kabele, B.B., Kabele – Toge, and Okin, O. O.(1997) Evaluation of Chasmanthera dependent starch as Binder and disintegrant in tablets. West. Afri. J. Pharmacy 11:2.

2. Akande, O. F. (1988) Evaluation of millet starch as tablet binder and disintegrant. MSc Thesis, Ahmadu Bello University, Zaria. Nigeria.

3. Asplund, A. J. A (1939) Defibring of Cellulose. Aktiebolaget Defibratos, Swed. 94, 196.

4. Bienvenido O. J. And Donald B. B (1985) U.S. Grain marketing Research Laboratory Agricultural Research Service, U.S. Department of Agriculture Manhattan Kansas. Rice Chemistry and technology.

5. British pharmacopoeia (1988), Vol. I & II . Her majesty's Stationery Office. University Press, Cambridge.

6. Coffin – Beach, D. P. and Hollenbeck, R. G. (1983) Determination of the energy of tablet formation during compression of selected pharmaceutical powders. Int. J. Pharm, 17 (2-3), 313-324.

7. Cross C. F., Beivan, E. J. and Beadle, C (1895) Cellulose an out line of the chemistry of the structural elements of plants. Longmans, Green and Co. London – P. 95

8. DUCKWORTH, P. E. (1975) The Economics of direct compression A transcript of the speeches presented at the direct compression Symposium. London on 22 April.

9. Fremy, E. and Terreil, A. (1868) Extraction of Plant Cellulose. Bull Soc. Chem. France, 9,437.

10. Garr, J.S.M (1988) Tableting properties of sorghum starch. MSc Thesis. Ahmadu Bello University, Zaria, Nigeria.

11. Garr, J. S. M and Bangudu A. B. (1991) Evaluation of sorghum starch as a tablet excipient. Drug Dev. Ind. Pharm. (17 (1), 1-6.

12. Gunsel, W. C and Kainig, J. L (1976) Tablets. In: Lachman, Lieberman, H. A. and Kanig, S. L (Eds). The Theory and Practice of Industrial Pharmacy. 2nd Edition, Marcel Dekker Inc., New York, pp. 321 – 358.

13. Hatch, R.S. (1954) Bleaching and purification of wood. In: Cellulose and Cellulose Derivation Vol 2, Otts E., Spurlin, H. M. and Grafflin, M. W (Eds) Internecine, New York, p,. 589.

14. Haworth, M. M. (1929) The constitution of Sugars, Longmas, Green and Co., New York.

15. Ibrahim, M. A. (1997). The use of novel polymer from the stem bark of cissus populnea in the formulation of controlled release matrix tablets. PhD Pharmaceutical Technology, Ahmadu Bello University Zaria, Nigeria.

16. Iwuagwu, M. A., Nwaoshai, C. A and Iseghohi, F. E. (1986) Investigations into the binding and disintegrant properties of starches from selected Disoscoraecae plants. Nig. J. Pharm. Sci. 2 (2): 10 – 22

17. Jacob J. T. And Mein, E. M. (1968). Factors affecting the dissolution rate of tablets in relation to binder concentration, tablet hardness and storage condition, of Phenobarbital tablets J. Pharm. Sci 57(5) 802-805.

18. Jaiyeoba, K. T. Starches and the Nigeria Pharmaceutical industries. In: Opakunle, W.O. and Jaiyeoba, K. T. (Eds) Pharmaceutical Raw Materials Sourcing in Nigeria. Proceedings of the First Symposium of Nigerian Pharmaceutical Industry, pp. 14 – 24 (1989)

19. Joachim, L. H. and Foster, J. P. (1940) Liberating Cellulose from bagasse (to Mau's Agricultural Co, Ltd) U.S.2,181, 785, Nov. 28.

20. KHAN K. A. (1975) Disintegration properties of direct compression systems. A Transcript of the speeches presented at the Direct compression Symposium London on 22 April.

21. Khan, K. A. and Rhodes C.T. (1975a) Evaluation of different viscosity grades of sodium carboxy methly cellulose as tablet disintegrant Pharm. Acta Hely 50 (4): 99-102.

22. Kio, P.R.O (1987) Problems of raw materials in pharmaceutical productions in Nigeria. A paper presented at the annual meeting of the Nigerian Society of Pharmacognosy, University of Ibadan.

23. King, R. E. (1975) Tablets, Capsules and Pills in Remington's Pharmaceutical Sciences 15th Edition Marc Publishing Company, Easton, Pennsylvania 18042, p1576 – 1607.

24. Kunle, O. O. (1988) The effect of some local starches on the properties of granules and tablets. MSc. Thesis Ahmadu Bello University, Zaria, Nigeria.

25. MENDELL, E. (1975) Direct compression concepts, tablet disintegration capsule filling. A transcript of the speeches presented at the Direct Compression Symposium. London. on 22 April .

26. Munzel, K. And Kagi, W. (1954) Evaluation of lubricants in Tablets Manufacture. Pharm Hely 29: 53 – 71.

27. Mgbahurike, A and Igwilo, C. (1971) Binding properties of gum from Kaya senegalensis: Granules. Nig. J. Pharm., 22:41-43.

28. Musa, A. N. (1996) Physicochemical and Tableting Properties of cellulose (Treated and untreated) Derived from sugar- cane. MSc. Thesis. Ahmadu Bello University Zaria, Nigeria.

29. Musa, H. (1999). Evaluation of cellulose and sodium carboxy methylcellulose produced from rice husks in tablets. MSc Pharmaceutics, Ahmadu Bello University Zaria, Nigeria.

30. Nasipuri, R. N. (1975) The use of cassava starch as binder/disintegrant in the formulation of tablets J. Med. Pharm. Mark. 4:17 – 20.

31. Nasipuri, R. N. (1979a) Evaluation of yam starch as tablet binder and disintegrant. Part 1: Before storage Nig. Pharm., 10:162 – 186.

32. Nasipuri, R. N. (1979b) Evaluation of cocoyam starch as tablet binder and disintegrant. Pharm. Acta Helv., 54:48-53.

33. Newmann, B. S. (1967) The flow properties of powders. In: Bean, H.S., Becket, A. H. and Carless, J. E. (Eds) Advances in Pharmaceutical Sciences. Academic Press, London and New York 2:181.

34. Noel D. V. (1996) List Crops of Africa, Grains, Vol.1 National Academy Press Washington, D.C. PP 17-58.

35. Nystrom, C. and Glazer, M (1985) Studies on direct compression of tablets, xii. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. Int. J. Pharm. 23 (3), 255 - 263

36. Ojile, J. E. (1980). Factors Affecting Drug Distribution in Granules. PhD. Thesis, Robert Gordon University, Aberdeen Scotland

37. Ojile, J. E. Selkirk, A. B. and Macfarlane, C. B. (1980). Some factors affecting *solute migration in granular beds. Int. J. Pharm, 5, 207-213.*

38. Ojile, J. E, Musa H, Ibrahim Y. K. E., Onaolapo J. A. and choudhury M. K. (1999). Ellucidation of properties of cathartic bulk laxative tablets having both drug and sole excipient derived from rice husks. Accepted for publication in the Nigeria, Journal of Pharmaceutical Sciences.

39. Okhamafe, A. O. Igboechi, A. C. and Obaseki, T. (1991) celluloses extracted from groundnut shell and rice husks 1: Preliminary physicochemical characterisation. Pharmacy World Journal. 8 (4), 120 – 123.

40. Okhamafe A. O. (1998)Local sourcing of raw materials. West. Afr. J. Pharmacy, 12:2.

41. Okhamafe, A. O., Ejike, E. N., Akinronola, F. F and Ubuane- Inedegbo, A. (1995) Aspects of the tablet disintegrant properties of celluloses derived from bagasse and maize cobs J West Afr. Pharm. (1) : 8 – 13.

42. Olukoya, O.A.T. (1993) challenges of local manufacture of Oral Liquid Medicines. Proc. NIPRD Workshop on "Strategies for Local Manufacture of Oral Liquid Medicines".

43. Ott, E. (1943) Cellulose and cellulose derivatives. In: Norbert, M. Bikales and leen Segal (Eds), Cellulose and Cellulose derivatives, Part v, Wiley Inter-science Inc. New York pp, 719 – 1079.

44. Ralph, E. M. and Lew, W. C. (1940) Cellulose from hard wood. To the Board of Regents to Union of Minnesota. U.S. 2: 301 – 314.

45. Rawlins, E. A. (1977) Tablets and Capsules. In: Bentley's Textbook of Pharmaceutics. 8th Edition, Fakenham Press Ltd. Fakenham, New fork PP 105 -115.

46. Reid, D. J and Dryden, E. C. (1940) Discoverer of Cellulose. Textile colourist, 62:43 – 45.

47. Remington's Pharmaceutical Sciences (1990) 18th Edition. Mack Printing Company, U.S.A, p, 1305 – 1321.

48. Schwartz, J. B., Martin, E. T. and Dehner, E.J. (1976) Intra granular starch: Comparison of starch USP and modified corn starch J. Pharm. Sci, 64:328 – 332.

49. Shotton, E. And Leonard, G. S. (1972) The effect of intra- and extragranualr maize starch on the disintegration of compressed tablets, J. Pharm. Pharmals! 24 : 798 – 803.

50. Stamm A. J. (1964) Wood and Cellulose Science. The Ronald Press Co., New York,pp.

51. Trease, G. E. and Evans, W. C. (1983). Pharmacognosy. 12th Edition: Bulliere Tindall, London. p21 and pp 338 – 341.

52. Traisnel M. (1975) Formulation methodology in direct compression, a transcript of the speeches presented at the direct Compression Symposium. London on 22 April.

53. Udeala, O. K. and Chukwu, A. (1985) The binding property of mucuna gum in sulphadimidine and chloroquine phosphate tablets. Nig. J. Pharm. Sci., 1: 59 – 66.