EVALUATION OF CELLULOSE AND SODIUM CARBOXYMETHYLCELLULOSE PRODUCED FROM RICE HUSKS IN TABLETING

BY

MUSA, Hassan

MARCH, 1999

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MARCH, 1999

DECLARATION

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

It has not been presented in any previous application for higher degree. All sources of information are acknowledged by means of references.

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CERTIFICATION

This Thesis entitled, Evaluation of cellulose and sodium carboxymethylcellulose produced from rice husks in tableting, submitted by **MUSA, Hassan** meets the regulations governing the award of the degree of Master of Science (Pharmaceutics) of Ahmadu Bello University, Zaria and is approved for its contribution to science and literary presentation.

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DEDICATION

This work is dedicated to Allah (S.W.A.), my parents and my friends whose self sacrifice opened up the path of learning.

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ABSTRACT

Cellulose and sodium carboxymethylcellulose (SCMC) derived from rice husks have been evaluated as tablet ingredients.

Rice husk, an agricultural waste of the first order, found abundantly and freely, was evaluated for its high components of cellulose and as an alternative source of raw material for the synthesis of sodium carboxymethyl- cellulose, an important pharmaceutical necessity.

Alpha-cellulose was extracted from rice husks by using standard extraction procedures which include delignification, digestion, bleaching and washing. Part of the rice husks alpha cellulose (RHAC)so extracted and chloroacetic acid were used as the main raw materials in synthesising the SCMC. The rice husks gave and alpha cellulose yield of 23%w/w, while the alpha cellulose in turn gave yield of 92%w/w SCMC. The ellucidation of the physico-chemical properties such as pharmacognostic characterisation, particle size and size distribution, particle shape, bulk and tapped densities, Carr's indices, moisture content, flow rate, angle of repose of the RHAC and the SCMC was undertaken. The SCMC was denser with higher flow rate than RHAC.

The SCMC is a multi-purpose ingredient as well as possessing a cathartic bulk laxative property. The tablets absorbed many times its weight of water resulting in formation of gelatinous layer around the tablets which did not disintegrate even after 60 minutes. Thus the compendial limit of the disintegration time does not apply here. The stimulation of gastro intestinal tract (git) peristalsis by bulkiness and the gelatinous lubricative action of the swollen tablets are thought to produce the laxative action. When RHAC was used as the sole excipients, the tablets had a higher bulk forming effect as compared to the conventional multi-excipient tablet formulation used in the study.

SCMC in paracetamol tablet formulation was evaluated as a disintegrant compared to maize starch, as a binder compared to gelatin and as a glidant/lubricant compared to talc/magnesium stearate. The properties of SCMC weresimilar to those of the compared standards and apart from the glidant/lubricant effect that was the same, the other standard excipient materials were slightly superior SCMC.

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ABBREVIATIONS

B.P.C.	-	British Pharmaceutical Codex
U.S.P.	-	United States Pharmacopoeia
Mg	-	Milli gramme
mm	-	Milli Metre
KgF	-	Kilogram Force
W/W	-	Weight by Weight
PH	-	Hydrogen - ion - Concentration
°C	-	Degree Centrigrade (Celsius)
%	-	Percentage
g	-	gramme
ml	-	Millilitre
µm	-	Micro-metre
V/V	-	Volume by Volume
N	-	Normal Solution
ɣ	-	Gamma
ß	-	Beta
α	-	Alpha
HCl	-	Hydrochloric Acid
r.p.m.	-	Rounds (revolutions) per Minute
B.P	-	British Pharmacopeia
Kg	-	Kilogramme
NaOH	-	Sodium hydroxide
RHAC	-	Rice Husk Alpha-Cellulose
SCMC	-	Sodium CarboxymethylCellulose

CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 RICE HUSKS AS A WASTE PRODUCT

Rice husk is the shell covering the rice seed which is usually milled or removed as an agricultural waste after harvesting.

Although the African rice grain is always white, most types have red husks whose removal is labourious, unlike the Asian species which is easy to be milled. Millers prefer it because its grains are less brittle and therefore easier to mill.

African rice, when compared with its Asian cousin, is better at tolerating fluctuating water depths, excessive soil iron content? low levels of management, infertile soils, harsh climates, and late planting (a valued feature in Nigeria erratic climate where the rains are often tardy). Also, there are some types that mature much more quickly than the common rice planted in emergencies when food stocks are getting low. These can save lives.

Asian rice performs best on alluvial soil types and temperatures of between 30-35°C.

Components of Rice Husks: Rice Husks composes of lignin, pentosans, hexosans, α-cellulose, ß- cellulose, ɣ-cellulose and other materials.

Pharmaceutical and other uses of rice:-

1. Rice is grown primarily for human consumption as a source of calories, vitamins, proteins and

minerals.

2. As an important component of baby foods.

Non competitive use of rice husks

Unlike other agricultural wastes such as maize cobs, groundnut shells and sugar cane chaff which are used as fuel, the rice husks has no use. Rice husks cannot be used as fuel because it produces only smoke. They are known to be used for smoking fish which is a good way for food preservation in rural areas.

Due to its abrasive effect, it is not used for ruminant animal feeds. Binder may be utilized to compact the husks into sheets that could be used as heat and electrical insulators as well as being used as ceiling boards. But this has not also been thought off. So rice husks is really an agricultural waste of the first order.

This is to say that sources of rice husks is available abundantly and freely. Rice grain millers would be too happy for the scavenging effect if any users of the husks wish to remove the husks for whatever use the "scavengers" wish to utilise.

Rice husks are a source of high components of cellulose. This project is well concerned with extraction of alpha cellulose from the rice husks.

1.2 AVAILABILITY OF RICE IN THE WORLD IN GENERAL AND NIGERIA IN PARTICULAR.

The largest world producers of rice are China, India, Indonesia, Malaysia, Thailand and Vietnam which are all in Asia. These account for some ninety percent (90%) of the world production for feeding some 2.7

billion inhabitants.

Rice is one of the important cereal grown in Nigeria. It is grown primarily for human consumption in swampy, riverine, uphill and Fadama areas as it grows well in the presence of sufficient water and other necessary requirements for its growth and development.

Large quantity of rice from both African and Asian varieties are cultivated in Fadama areas of Sokoto, Kano, Niger State, Borno State near Lake Chad and Benue River around Makurdi and Gboko. It is also grown on large floating fields of delta areas of Sapele in Delta State and some riverine states of Nigeria.

Rice is also cultivated by dryland and paddy farming in the Northern Nigeria especially around Plateau, Benue, Niger and Kogi States which mostly constitute the Middle belt area. Such type of cultivation is even more common in the Southern part of Nigeria where high rainfall is recorded per season.

..2.1 **PRODUCTION OF RICE IN NIGERIA**

Asian rice (Oryza Sativa) is now grown widely in Nigeria. Infact it is the biggest cereal after maize, millet and sorghum in terms of cultivation land area (hectares). Its demand is ever rising as population, standards of living, urbanization, international travel and the search for easy to prepare foods increase. At present, Nigeria and other West African

countries consume a quarter of the world's rice exports.

Asian rice now gradually takes over the position of African rice in Nigeria and other countries. For instance the reason why African rice is not better known internationally is that it grows poorly in the Phillipines where the world's major rice research facility is located. Another reason is that it is susceptible to plant fungi and parasitic diseases. It is difficult to remove the husks. The plants tend to have weak stalks, and late season windstorms can sometimes topple them (dislodging).(Noel, 1996).

Agronomy

As with Asian rice, African rice is grown in Nigeria in three major ways-dry land (or upland), paddy, and floating dry land.

About 40 percent of the rice produced in Nigeria relies on rain as the only source of water. Nigeria and other West African countries still grow a small but significant amount of dry land African rice. Almost all of the area employs the Asian species.

The dryland African rice thrives in light soils wherever there is a rainy season of at least 4 months and minimum rainfall of 760mm. It is often interplanted with millets, maize, sorghum, cassava or cotton. Today's varieties mature in 90 - 170 days. The average yield is 450 - 900kg per hectare, but can go as high as 1,680kg per hectare.(Noel, 1996).

Paddy Areas

The African specie can be seeded into damp soil or transplanted to fields under water. These types matures in 140 - 220 days. The yield ranges from 1,000 to 3,000kg per hectare.

Floating

In the River Niger's inland delta, in Mali and Nigeria, farmers grow various forms of floating African rice. These plants lengthen prodigiously to keep their head at the surface of the flood waters, where they flower and set seed.

The areas of most intense cultivation of both species of rice in Nigeria is the floating fields especially on the Sokoto Fadamas (flood plains) and River Niger inland delta.

Floating varieties can utilize deeply in undated basins where nothing else can be raised. They ripen in 180 - 250 days to yield between 1,000 to 3,000kg per hectare, depending on the amount of rainfall early in the growing season and on the eventual depth of the subsequent floods, (Noel,1996).

HARVESTING AND HANDLING

As soon as the crop is ready or mature enough, harvesting is carried out depending on the cultivation area. Floating one is harvested from canoes. African rice is handled like its more famous Asian cousin. Great care is taken in harvesting as its grains tend

to split. Also it is more difficult to hull as mentioned ealrier.

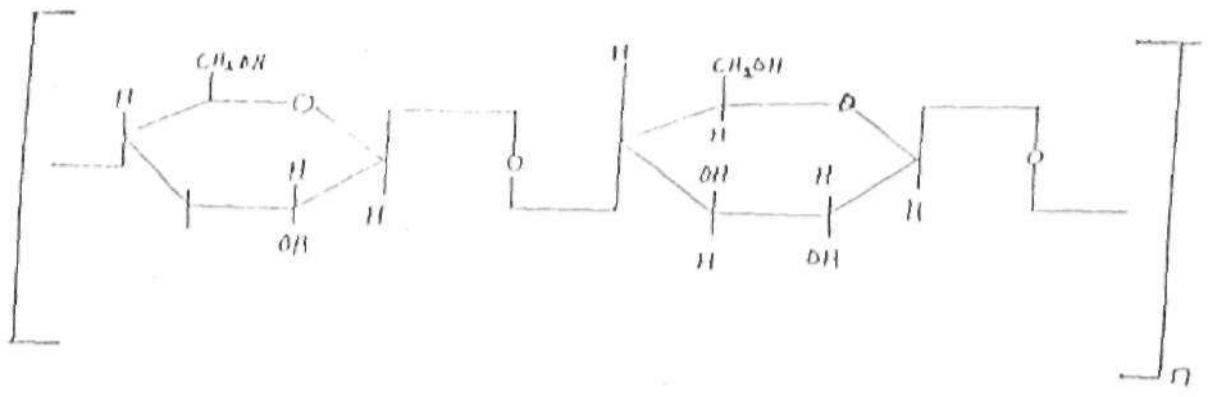
1.3 CELLULOSE AND ITS DERIVATIVES

1.3.1 Cellulose:

Cellulose is the major constituent of the cell wall of most plant and therefore provides the backbone structure of plant materials. It is perhaps the most abundant phytochemical compounds on earth.

Chemistry: Celluloses are the most complex, high molecular weight polysaccharide carbohydrates. They are the chief constituent of the frame work of plants. They give no colour with iodine and are not soluble in ordinary solvents. They consist of long, straight chains of glucopyranose units linked by ß-(1 ----> 4) bonds. They are not subject to attack by the digestive enzymes of humans because of the ß-linkage. Thus they are an important source of bulk in the diet (Martin, Mayes and Rodwell, 1981).

Structural formula of cellulose



Empirical formula $(C_6H_{10}O_5)_n$ n = 1500

Molecular weight = 243,000

Empirical formula $(C_6H_{10}O_5)_n$ n = 1500

Molecular weight = 243,000

Cellulose also occur in association with other polysaccharides of related structure and with non carbohydrate substances of which the most important is lignin. Other substances occurring with cellulose for example, are the hemi celluloses. These are also high molecular weight polysaccharides but are considerably less complex, more soluble and more easily hydrolysed than cellulose.

In rice the husk covering the rice seed is made up of cellulose, lignin and other materials.(Musa, 1996) The cellulose is extracted by treatment with different chemicals and the lignin can be removed in the form of soluble nitro-lignins. cellulose is readily converted to other related sugar molecules by treatment with different chemicals. For example, hydrolysis of the purest form of cellulose by concentrated mineral acids at low temperature or dilute acids at higher temperature yields ßD glucose. Controlled hydrolysis will however yield cellubiose.

Each cellulose unit contains 1,000 to 2,000 glucose units with molecular weight between 200,000 to 400,000, because the length of the chains of cellulose is not constant. Cellulose is therefore, composed of a linear chains of glucose residues mutually joined by ß-1,4 D-linkage.

It was found that cellulose from various sources

from different preparations may show great differences in mean chain length as well as in the degree of homogeneity in general.(Musa 1996) The more homogeneous cellulose is, the more suitable it is for industrial purposes. Cellulose molecules, thus differ in number and type of arrangement of the glucose unit chain in the molecule.

Types of Cellulose

Cellulose obtained from crude source from plants may be fractionated into α-, ß-, and γ-cellulose depending on their solubility in 17.5% sodium hydroxide solution (Musa, 1996). This treatment removes xylose and variable amounts of the other non cellulosic cell wall constituents.

α-Cellulose: This is insoluble in 17.5% sodium hydroxide. It has much higher degree of polymerization than the other celluloses.

ß-Cellulose: ß-cellulose is precipitated from the alkaline extract by acidification.

γ-Cellulose: γ-cellulose fraction is alkali soluble but not precipitable by acid.

Powdered cellulose is purified and mechanically disintegrated cellulose is prepared by processing α-cellulose obtained as a pulp from fibrous plant materials. It exists in various grades and exhibits degrees of fineness ranging from a free flowing dense powder to a coarse, fluffy, non flowing material. It

is used as a gell binding tablet diluent and disintegrating agent (Ewart, 1990).

1.3.2 CELLULOSE DERIVATIVES

Cellulose derivatives of pharmaceutical and medicinal importance include carboxymethyl-cellulose, cellulose acetate phthalate, ethyl cellulose, hydroxy-propyl methylcelulose, methyl-cellulose, oxidized cellulose, sodium carboxymethyl cellulose (SCMC), etc.

1. Sodium Carboxymethyl cellulose: This is the sodium salt of a polycarboxymethyl ether of cellulose. It is a hygroscopic powder that is used as a suspending agent, a thickening agent, a tablet excipient, and a bulk laxative. It is also used in varying proportions with microcystalline cellulose to give suspending agents with different viscosities. The usual cathartic dose of sodium carboxymethyl-cellulose is 1.5g taken with water 3 times a day (Trease & Evans, 1983).

Proprietary products such as Dialose[TM] (Docusate potassium or sodium) is used for constipation with a dose of 300 to 500mg daily in divided doses and also used for ear wax removal, Diet Trim[TM] Carmollose Satiam is used as a tablet excipient and a suspending agent, (Reynolds, 1996).

Bulk forming laxatives and mechanism of Action

Most bulk forming laxatives are natural, semi-synthetic polysaccharides and synthetic cellulose

derivatives that dissolve or swell in the gastro-intestinal fluid to form emolient gels, which facilitate the passage of the intestinal contents and which stimulates peristalsis (Curry Jr., 1986).

2. **Cellulose acetate phthalate (CAP)**

   This is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains not less than 19% and not more than 23.5% of acetyl groups and not less than 30% and not more than 36% of phthalyl groups. It is a free flowing, white powder and is used as a tablet coating agent also used in the aesthetic, enteric and controlled release coating of tablet and pellets.

3. **Ethyl cellulose** is an ethyl ether of cellulose containing not less than 44% and not more than 51% of ethoxy groups. It is a free flowing white powder. Ethyl cellulose is a tablet binder, (Tyler, Brady, and Robbers, 1981).

4. **Hydroxy Propyl Methyl Cellulose (HPMC)** is the propylene glycol ether of methyl cellulose in which both hydroxy propyl and methyl groups are attached to the anhydroglucose rings of cellulose by ether linkages. It contains not less than 19% and not more than 30% of methoxy groups and not less than 3% and not more than 12% of hydroxy

propyl functions. It occurs as a white fibrous or granular powder. Hydroxy propyl methyl ~~cellulose~~ is used as a suspending agent, a thickening agent, and a tablet excipient. Ophthalmic solutions such as aqua flow Goniosol(R) (Hypromellose) use 0.2 to 2.5% w/v HPMC to prolong the action of medicated eye drops and is employed in alkaline eye drops as artificial tears to prevent damage to cornea in patients with Kerato conjunctivitis sicca or Keratitis and also for Dry eye (Reynolds,1996).

5. **Oxidized Cellulose**: This contains not less than 16% and not more than 24% of carboxyl groups. It is usually available in the form of sterile pads, pledgets and strips for its use as a local hemostatic. Oxycel(R) (Oxidised cellulose) is used as an absorbable haemostatic when applied to bleeding surface.

6. **Microcrystalline cellulose** is a purified partially depolymerized cellulose prepared by treating α-cellulose, obtained as a pulp from fibrous plant material with mineral acids. It is used as a diluent in the production of tablets .

1.4.0 TABLET EXCIPIENTS

Pure drugs are seldom administered to patients. They are usually formulated into a variety of dosage forms. Such dosage forms include solid dosage forms

e.g. powders, tablets and capsules, semi solid dosage forms e.g. pastes, ointments, gellies, creams and liquid dosage forms e.g. lotions, syrups, elixirs, suspensions, liquid emulsions, etc.

Excipients (additives or adjuvants) are indispensable in pharmaceutical formulation. Without them, very few products would be suitable or convenient for administration. Among other applications, excipients as pharmaceutical aids, are used to impart aesthetics to drug products, enhance drug stability, control drug release, mask an unpleasant taste and give a suitable physical form of drugs. It is believed that the number of important tablet excipients currently in extensive use is about twenty five but their range of properties is such that they meet the needs of the six major excipient categories: diluents, disintegrants, binders, colourants, lubricants, sweeteners, (Okhamafe,1992).

1.4.1. *Types of excipients used in Tableting*

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

1. **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. This is so done in order to make the tablet of

practical size for compression and handling.

A diluent should be inert, non toxic with respect to the active ingredient and cheap, considering the quantity that is used in the tablet formulation. Its 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, sorbitol, and inositol, when present in sufficient quantity can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. 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 to the point where they are not completely available after administration.

2. **Disintegrants**

A disintegrant is a substance, or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. A tablet will be useless if after being swallowed does not disintegrate and/or release the active medicament. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid absorption. Substances or materials serving as disintegrants have been chemically classified as starches, clays, celluloses, alginates 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 swells when moistened, thus facilitating the rupture of the matrix. However, others 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 disintegrant (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, alginic acid, guar gum, citrus pulp and carboxyl methyl cellulose. Cross linked poly vinyl pyrrolidine(pvp) 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 also has 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. The utilisation of intra-granular disintegrant is based on the assumption that much finer particles are recovered during disintegration than when the disintegrant is incorporated extra-granularly (Shotten 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 proportions of the specific disintegrant are incorporated in the tablet fabrication. In general, the higher the percentage of disintegrant in the tablet composition, the shorter is the disintegration time. 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 are found to have the following mode of action.

a.) **Water absorption capillary theory**: This theory maintains that a disintegrant especially starch, by virtue of its relative incompressibility forms 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°C. The disintegration properties of PVP is also based on the same principle.

Capillary per say 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 glycerin have been found to penetrate tablet without causing disintegration.

b.) **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. 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 exposed the observation that while many substances swell to a greater degree than the starches they are poor disintegrants, similarly, 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 particles must over come 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 concentration. At higher concentrations however, the higher grades because of their higher viscosities may become more adhesive in the hydrated state. Thus the opposing forces of adhesion within the particles would become dormant, 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 capillarity may facilitate rate of penetration of water.

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

3. **Binders**

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

Natural and synthetic gums which have been used include acacia, sodium-alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethyl cellulose methyl cellulose, polyvinyl pyrrolidine, veegum and larch arabo galactam. 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 slurried 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).

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 formation 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.

4. **Glidants**:

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

5. **Lubricants**:

Lubricants have a number of functions in tablet manufacture. They improve the rate of flow of the tablet granulation, prevent adhesion of the tablet material 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 performed, 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 table 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 60μm to 100μm mesh nylon cloth onto the granulation, that is, by bolting the lubricant. After adding the lubricant the granule is tumbled or mixed gently to distribute the lubricant without coating the granules too well or 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 of the resultant tablets (Akande, 1988).

Lubricant 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 (Akande, 1988).

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent.

6. **Colourants**

A pharmaceutical colouring agent (colourant) is any material that is a 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 Hand-book 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, in compressed tablets they serve functions other than making the dosage form aesthetic in appearance, 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, and to produce standard preparations for identification.
- to mask non problematic potential change.

Method of adding colour to a tablet formulation:

The most common method of adding colour to a 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 aqueus 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 since rapid results in component migration as reported by Ojile et al (1980). The slow drying should be accompanied by occasional turning of the granule bed.

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 not interfere with the tests and assays to which the preparations containing it are subjected(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 are required.
- It should be unaffected by light temperature variation, hydrolysis and microorganisms, and therefore be stable on storage.

7. **Flavouring Agents**

Flavours and sweetners 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, retching and vomiting; and would lead to refusal to take the preparation regularly or to total non-compliance. 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 pungency of the flavour material.

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

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 sweetner, 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 tablet. No disintegrant is required as the tablet is chewed before swallowing and the tablets are rationally flavoured.

Traditionally pharmaceutical flavours have been

natural oils such as oils of peppermint, wintergreen, clove, anise, lemon peel, orange and fennol or solids such as menthol. Another popular form of flavour widely used by the industry is spray dried, flavoured powders prepared by making emulsion of one or more flavour oils in water with acacia, gelatin or dextrins as the emulsifier. The oil in water emulsion is sprayed and dried to form a fine powder of low bulk density.

More recently flavours are available as adsorbed powders in which flavour oils and other liquid components e.g. esters, aldehydes, distilled fractions of oils are adsorbed onto various adsorbents.

Flavours are desirably stored in polythene bags enclosed in metal or heavy duty plastic containers with well sealed lid to minimize escapes of volatile components, as well as entry of moisture from the air. Most appropriate storage conditions are from 15°C to 30°C and below 40% to 45% relative humidity.

1.5.0 **Tablet and Tablet Production**

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods. They have been in widespread use since the later part of the 19th century.

Tablets remain popular as a dosage form till date because of the advantages afforded both to the

manufactures and the patients. These advantages include:

- Simplicity and economy of preparation.
- Stability and convenience in packaging, shipping and dispensing.
- Accuracy of dosage, compactness, portability, blandness of taste, and ease of administration.
- Tablets are most frequently discoid in shape, they also may be round, oral, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

1.5.1 Type of Tablets

The types of tablets in use for medicinal purposes nowadays include:

1. **Plain compressed tablets**: These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, lubricants, diluents and in many cases, colourants.
2. **Coated tablets**: These are subdivided into four types:
   (a) ***Film Coating Tablets (FCT)***. These are compressed tablets which are covered with a thin layer or film of a water-soluble

material. A number of polymeric substances with film forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of a greatly reduced time period required for the coating operation.

(b) ***Enteric Coated Tablets (ECT)***: These are compressed tablets coated with substances that resist disolution in gastric fluid but disolve in the intestine. Entreric Coatings can be used for tablets containing drug substances which are inactivated or destroyed in the stomach, for those which irritate the mucosa or as a means of delayed release of the medication.

(c) ***Sustained Release Coated tablets or Controlled Release Coated Tablets***: These are coated tablets that are formulated to release the drug slowly over a prolonged period of time. Hence these dosage forms have been referred to as "Prolonged Release" or "Sustained Release" dosage forms. Such tablets may be those that release the drug in a relatively steady controlled manner and those that combine a numbers of mechanisms to release pulses of drug such as repeat action tablets, double compressed or layered

tablets.

3. **Buccal Tablets**: These are placed in the buccal pouch where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal. Certain steroids are presented in this way e.g. ethisterone tablets and progesterone tablets.

4. **Chewable Tablets** are tablets designed to be chewed rather than swallowed. The widely used antacid tablets and some vitamin tablets are of this type. They are hard and do not need any disintegrant but may have good mouth feeling and may be flavoured, coloured. They are not meant for children or old people without teeth.

5. **Effervescent Tablets**: In addition to the drug substance, a base such as sodium bicarbonate and an organic acid such as tartaric or citric acid are included. In the presence of water, these additives react liberating carbon dioxide which acts as a disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.[6]

6. **Solution Tablets** are also tablets to be dissolved in water for administration, either orally or by external application, or by parenteral injection. The term solution tablet or solvella in British

Pharmaceutical Codex is to designate a tablet that is to be dissolved in water to form a solution for external use (Aulton, 1988).

7. **Sublingual Tablets** are tablets to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into the alimentary tract. Glyceryl trinitrate tablets are used in this way. The B.P. (1988) states that they dissolve slowly in the mouth. The USP xviii gives a disintegration time of 2 minutes for such tablets. Sublingual tablets are absorbed into the circulation to bye-pass the liver. Such tablets should be highly soluble, not bitter in order not to cause salivation and should not be bulky, not more than 300mg (Aulton,1988).

8. **Lozenges**: These do not disintegrate readily and are intended for slow solution in the mouth, usually to produce a local action on the throat. Their disintegration is by erosion in the mouth.

9. **Implants**: These may be made by heavy compression but are normally made by fusion. They are inserted subcutaneously by means of a minor surgical operation and are slowly absorbed. They are packed singly in sterile containers. Official examples are deoxycortone acetate implants and testosterone implants (Carter,

1972).

1.5.2 Properties of Good Tablets

Tablets, manufactured by whichever method of compression, have the following attributes or properties.

1. The tablet must be sufficiently strong and resistant to abrasion to withstand handling during manufacture, packaging, shipping and use. This property is measured by two tests, the hardness test and the friability test which are tests designed by the manufacturers.
2. The drug in the tablet must be bioavailable. This property is monitored by two tests, the disintegration test and dissolution test.
3. The tablets must be uniform in weight and in drug content of individual tablets. This is measured by the weight variation test and the content uniformity test.
4. The tablets must be elegant in appearance and must have the characteristic colour, shape and other markings that identify the product.
5. The tablets must retain all of the functional attributes, which include drug stability and efficacy.

1.5.3 Manufacture of Compressed Tablets

The design and formulation of a tablet usually involves a series of compromises on the part of the formulator, since producing the desired properties

such as resistance to mechanical abrasion or friability, rapid disintegration and dissolution frequently involves competing objectives. The correct selection and balance of excipient materials for each active ingredient combination in a tablet formulation to get the desired formulation practically is not a simple goal to achieve.

Tablet formulation and design may be described as the process where-by the formulator ensures that the correct amount of drug in the right form is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point.

Compressed tablets are made by compressing fine crystals, free flowing powders and granules in a die between punches. Materials to be tableted must have certain physical properties including:
Cohesiveness i.e. tendency of its individual powder to stick together (compressibility) and lubrication (lubricity), ability to flow freely (fluidity). Very few of the pharmaceutical materials have some of these properties, and methods of tablet formulation and preparation are being developed to impart these properties to materials to be compressed. This process is referred to as granulation.

There are generally three main methods of tablet manufacture. The choice of methods depends upon the properties and dose of the drug (active ingredient),

choice of equipment and relevant practical and regulatory concerns.

1. 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 Rawlins, (1977).

Excipients of significance in direct compression technique include anhydrous lactose, spray dried lactose, micro crystalline cellulose, amylose, dicalcium phosphate dihydrate, 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 possess the flow, cohesion, compressibility and lubricating properties under pressure to make such compacts possible. If and when compacts are formed disintegration usually must take 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.

Direct compression is now used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including diluents, disintegrants, and lubricants) which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary.

The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles which possess both flowability and compressibility for example, Avicel, Emcompress, Cellutab, and Emdex. Sta-rx 1,500 The commercially available binders or vehicles are however more costly than lactose, starch, sucrose etc. Hence granulation method is preferred to save cost. In the case of direct compression (DC) of macrodose tablets,

tablet strength greater than 50mg as in the case of Vitamin C tablet and sodium bicarbonate tablets, knowledge of tablet ingredient compressibility and flowability are necessary. Microdose tablets having strength of 50mg and less such as in folic acid 5mg tablet, the choice of the diluent must be such that it is non-reactive, compressible with inherent binding action (plastic) and have good flowability.

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 is obvious fewer chemical stability problems as compared to those made by the wet granulation process. The primary cause of instability in tablets is moisture. Complete absent of heat and moisture enhance the stability of the active ingredient especially thermolabile active ingredients in the tablet.
3. *Prime Particle Dissociation:* Probably one of the latest recognised advantages of direct compression is the optimization of tablet disintegration, in which each primary drug

particle is liberated from the tablet mass and is available for dissolution(Akande, 1988).

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

1.5.5 **Limitation of Direct Compression**

1. The choice of excipients for their properties is extremely critical in formulating direct compression tablets.
2. Direct compression excipients often cost more than comparable fillers or diluents used in granulations.
3. Many active ingredients are not compressible in either their crystalline or amorphous forms. Thus, in choosing a vehicle it is necessary to consider the dilution potential of the major diluent, binder i.e. the proportion of active ingredient that can be compressed into an acceptable compact utilising that diluent filler. For the reasons mentioned above granulation method is preferred.

2 **Granulation Methods**

This consist of two methods: Dry granulation and Wet granulation methods as shown in the Figure 1.1 below:

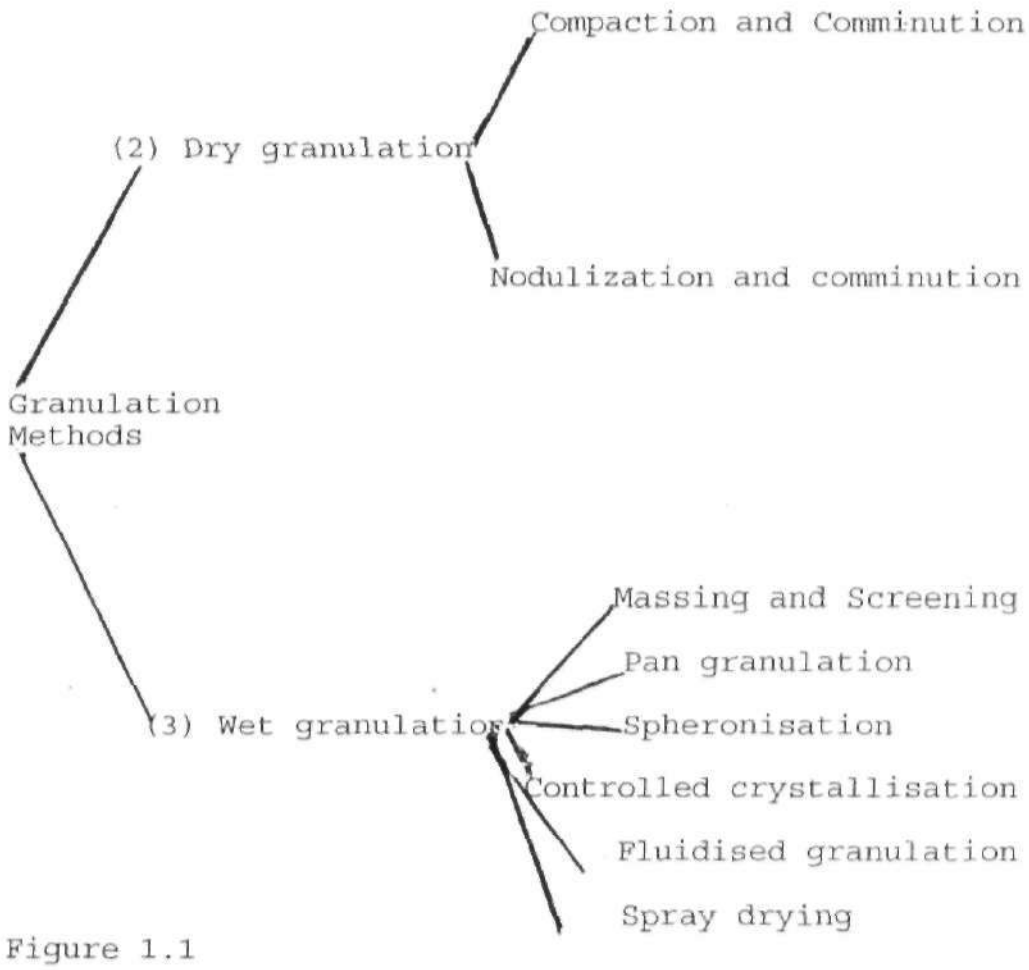


Figure 1.1

3 **Dry Granulation Method**

Dry granulation method refers to the granulation of a 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 granulation. 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 process is called compaction and comminution. 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 powder 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 Hutt Compactor called nodulization.

Sometimes, the slugs are screened, slugged again, screened once more and then compressed into tablets when a single slugging is not sufficient to confer granulator properties on the material and tablets cannot be formed.

Advantages of dry granulation ****s*im tz:¥«. "wr*

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 granulating 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 solubility, as with anhydrous soluble materials that tend to set when wet.
5. For improved blending, since there is no migration of 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 specialized 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. A pressure roll press such as the chilsonator can not be used with insoluble drugs since this may retard the dissolution rate.
4. The process tends to create more dust than wet granulation, increasing the potential for cross contamination.

Wet Granulation Method

The oldest and still the most widely used method of tablet preparation is the wet granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablet. Wet

granulation is done in order to improve the flow and compressibility of powders that would otherwise be unsuitable for making tablets. In wet granulation there are six main ways of making the wet granules before compression into tablets. These are:

a) **Massing and screening**: This can be done with a ribbon mixer, sigma mixer double z-blade mixer or even planetary mixer. The dry powder and the binder solution are mixed in any of the mixers, pouring in the binder solution and the portion of the dry powder with continuous mixing untill equilibrium granular stage is reached. The wet mass is the force screened using a comminuting machine or a reciprocating granulator to form wet granules which are then dried. The granules are then passed through a sieve or dry force-screened.

b) **Pan granulation**: Dry mix is fed into the pan with flight to churn the powder. As the pan is rotated, the binding fluid is sprayed from a nozzle into the dry mix. On contact with the liquid droplets two or more particles will bind together by pendular linkage to form agglomerates. Further infringement of the binder being sprayed in, will cause two or more agglomerates to bind together to form larger agglomerates. The rotating action of the pan forms round, spherical granules. The granules

are dried either by heating the pan or forcing in hot air through the spraying nozzles.

c) **Spheronization**: The wet mix is massed with either excess binder liquid or for a much longer time or both to form a plastic mass which is force-screened through a sieve. The worming or spagetti-like strands are prevented by a chopper to form short cylindrical granules which are spheronised into compact spherical granules by the rotatng action of the marumerizer.

d) **Controlled crystallisation**: The particle size of the crystals depends on the temperature of the solution from where the crystals are formed. For instance larger particle size of sulphadimidine were formed by dissolving the sulphadimidine in sodium hydroxide solution. Addition of hydrochloric acid would form sulphadimidine whose particle size depends on the temperature of the solution (Ojile, 1980).

e) **Spray granulation**: Solution or slurry is sprayed into a hot chamber which is maintained hot by forcing into the chamber, hot fluidised air. The liquid vapourises living clusters of particles. Two or more of such clusters would impinge on themselves to agglomerate by pendular linkage as long as the surfaces are wet.

f) **Fluidized granulation**: The powder particles are

fluidised into the chamber. A binding liquid is sprayed into the chamber through an atomiser. Two or more particles are held together by pendular linkage as long as the particles are wet. Two or more agglomerates will impinge together to form larger particles. The formation of granules and drying occurs simultaneously.

Before dry compaction became a viable process wet granulation was for all practical purposes, the only method available. However, it entails labourious material handling, as well as several processing steps, and therefore it is costly, especially on the large scale. The steps in the wet method are weighing, and mixing of the drugs and excipients, preparation of binder solution, mixing of the binder solution with powder mixture to form wet mass, coarse force-screening of wet mass using 6 to 12 mesh screen, drying of moist granules, screening of dry granules through 14 to 20 mesh screen, mixing of screened granules with lubricant and/or disintegrant, and tablet compression.

1.6 PROBLEMS IN TABLET MANUFACTURE

The production of imperfect tablets having certain noticeable defects causing them to be rejected is annoying and costly. It indicates a lack of proper formulation or difficulties with one or more processing steps, such as lack of control of one or more of the unit processes of manufacturing or

fluidised into the chamber. A binding liquid is sprayed into the chamber through an atomiser. Two or more particles are held together by pendular linkage as long as the particles are wet. Two or more agglomerates will impinge together to form larger particles. The formation of granules and drying occurs simultaneously.

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incorrect tablet press setting or operation. The imperfections resulting from any of the above situations may result to the following: binding, sticking, filming, picking, capping, laminating, chipping and cracking.

1.6.1(a) **Binding**

Binding is generally due to insufficient lubrication. The resistance of the tablet to ejection due to adherence to the die wall is called binding in the die. Tablets compressed with sufficient lubrication have smooth, glossy edges or sides. When lubrication is insufficient, tablets have rough sides or edges with vertical scratches or score marks caused by the abrasion on ejection. Tablets often crack or chip as a result of binding. The edges of such tablets are also light in colour in the case of coloured tablets, with excessive binding, the tablets are cracked and may crumble apart. Preliminary tests should therefore be run on new formulations to assure adequate lubrication, compression studies should be done to help avoid this problem. Thus the remedies for binding may include:

1. Increase lubrication
2. Use more efficient lubrication
3. Improve method of addition of lubricant, such as by screening the lubricant through an 80 mesh sieve and mixing first with a portion of the fines.

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4. decrease moisture or regranulate

5. Modify granulation; reduce granule size

6. Increase punch - die clearance

1.6.2(b) **Sticking**

Also referred to as filming or picking which is usually due to incompletely dried or improperly lubricated granules. Either of these will allow some of the granules to stick to the punch faces. These are usually small fragments from the tablet face at first, but the condition becomes progressively worse with larger and larger pieces of tablet being picked from the face as compression continues. Tablets may chip or break if picking occurs on the lower punch or may pull apart from the upper punch. The remedy for sticking, filming or picking is to control the moisture in the granules. Moisture analysis should be done on all granules, and preliminary tests should be carried out on new formulations to establish maximum tolerated moisture in granules.

Filming or sticking may be caused by rough or scratched punch faces and nicked punch tips, especially with bisected punches which have been run closely face to face, with letters or designs that may be too sharp, or with a concavity too deep for the granules. Filming may also be caused by oily or waxy materials or too little lubrication. The remedies for sticking, filming and picking include:

1) Increase proportion of binder in the granulation.

2) Decrease moisture content of the granulation.

3) Change or increase the lubricant.

4) Add an adsorbent, such as microcrystalline cellulose, silica gel, silica aerogel, or aluminium hydroxide.

5) Clean punch faces with 5% light mineral oil in isopropanol or 5% low viscosity dimethyl polysiloxane in trichloethylene.

6) Polish punch faces on lathe with jewellers rouge or fine emery cloth or chromiom plate punches.

1.6.3(c) **Lamination and Capping**

Lamination is caused by the same factors that cause capping but at exaggerated conditions and high speed. Capping is the defect in which the top or upper segment of the tablet is cracked around the edge or separated as a cap. It is usually due to air entrapped in the granulation which is compressed as the punches move together to apply pressure, and which then expands when the pressure is released. This occurrence is common with granules having a large percentage of fines. Very often new punches and dies have a tendency to cause capping because of the close fit between punch and die wall. The standard clearance of 0.001 inch is sufficient to cause capping. Excess moisture in the granules or excess lubrication, as well as too little lubrication, may produce capping.

Lamination differs from capping in that tablets split or crack on the sides by air expansion when

pressure is released - causing the tablets, when ejected to come apart or separate in layers.

Lamination and capping defect in tableting may be overcome by employing the following measures:

i. Remove some or all of the fines through a 100 to 200 mesh screen.
ii. Increase or change lubricant.
iii. Improve granulating procedure.
Iv. Increase binder or wetting of the granulation.
v. Add dry binder such as microcrystalline cellulose.

1.6.4(d) **Chipping and Cracking**

Chipping refers to the defect in which pieces are broken or chipped out of the tablet. This may occur on the faces but usually occurs on the edges. It may be due to sticking or to damaged punches or incorrectly set lower punch resulting in dipping of tablets at the "knock off" point.

Cracking refers to tablets that are cracked anywhere, but often in the centre of the top. Cracking is due to expansion as distinguished from capping or laminating. It may also be due to binding or sticking. Remedies for capping and cracking include:

i. Replace or reface nicked or chipped punches.
ii. Improve granulation by increasing binder.
iii. Polish punch tips.
iv. Remove some or all fines.

v. Reduce granule size.

vi. Reformulate to attempt to eliminate expansion of tablets.

1.6.5(e) **Tablet Expansion**

Expansion of the tablet immediately after compression is a contributing factor to many tablet defects and often goes unrecognized as such. Often capping may be experienced even when working with granules which are considered perfect from the stand point of granule size, quantity of fines and uniformity of granules. Such capping is often caused by expansion of the tablet immediately following compression. Expansion varies greatly with different types of materials.

1.7 EVALUATION OF TABLETS

The tablet solid dosage form is manufactured or formulated in such a way that the active ingredient or component is therapeutically bioavailable after administration and is well designed in order to release the therapeutic component to the desired site so as to achieve adequate necessary pharmacological action. Some quality standards have been set for compressed uncoated tablets. These quality standards include:

1. Physical standards.
2. Bio-availability standard.
3. Chemical standard.

Accordingly, tests to ensure compliance with

these standards have to be carried out.

1.7.1 PHYSICAL STANDARDS

Physical quality evaluation tests for manufactured tablets include tablet hardness test, friability test, weight variation test, tablet thickness test, and uniformity of diameter test.

a) **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 force of 4kg is considered adequate for quality tablet. Other instruments used for measuring tablet hardness include Strong-cobb hardness tester, Pfizer hardness tester and Erweka hardness tester.

b) **Friability Test:** This is closely related to tablet hardness but differs from the fact that it measures or evaluates the 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 placed in the tumbling apparatus, the drum of which is revolved 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 percent loss in weight indicates the ability of the tablets to withstand this type of wear.

c) **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. When the tableting machine is in operation, the weights of the tablets are checked routinely to insure that proper weight of the tablets are being produced.

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. Coated tablets are exempted from 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
130mg to 324mg	7.5
More than 324mg	5

d) **Tablet Thickness** is necessary to control thickness of tablet as variation may occur from production batch to 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. Whole 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 caliper 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 tablets.

e) **Uniformity of Diameter Test:** This standard is necessary for uncoated tablet and is an attempt to rationalize 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 and may result to increase in diameter of die and tablet diameter vâriation (Garr, 1988).

1.7.2(ii) **BIOAVAILABILITY STANDARDS**

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

a) ***Disintegration Test:*** *Disintegration is the* breakup 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, absorption and pharmacological action. Tablet well formulated do not pass quality control test if they do not disintegrate within the specified time limit as such tablet if administered will not release the active ingredient for the 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.

Six tablets are usually 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.

To pass the test, all the tablets must pass through the mesh in 15 minutes except otherwise stated in the individual tablet monograph.

b) **Dissolution Test:** This is another important bioavailability evaluation test for evaluating the quality of formulated tablets. Tablets with very long dissolution time above the specified limits have low bioavailability and are almost pharmacologically inactive.

Dissolution is the process by which a solid of only fair solubility characteristics enters into solution. A tablet must be in solution before it can be ready or bioavailable for absorption and then produce the desired pharmacological action. The disintegration test as a means of predicting drug availability, fails because of its inability to distinguish between fast and slow dissolving particles.

In an effort to overcome this problem, the U.S.P

has introduced a dissolution test.

In vitro dissolution test is carried out mainly for two purposes:

i. To ensure batch to batch uniformity in the release of active ingredient.

ii. To ensure that the active ingredient in the tablet is totally released on time.

The dissolution rate of tablet samples can be determined with a dissolution equipment which consists of four main parts:

1. A water bath
2. A covered vessel, one litre in volume.
3. A variable speed motor
4. A cylindrical stainless steel basket.

The temperature of the equipment bath is maintained at 37±0.5°C and the dissolution medium is specified in the individual tablet monograph. 900ml of the medium is poured into the covered vessel and one tablet is placed in the basket, situated 2.0cm above the bottom of the vessel and rotated at the rate specified in the monograph.

In vitro dissolution test compared to in vivo dissolution is usually reproducible. The problem however lies in the interpretation of result. The dissolution test should be able to discriminate between different formulations. Parameters that may affect dissolution test include pH of dissolution medium , temperature and intensity of agitation. Ionic

strength, presence of surfactants, etc.

The formulation factors that affect dissolution rate of tablets include particle size, amount of binder, lubricant and compression pressure. Other factors include method of granulation, the size, density, moisture content and age of granules, diluents, disintegrants, solubility and crystalline state of the drug on dissolution.

There are many different types of dissolution apparatus currently in use, both official and unofficial. These include Rotating Disk Method, Oscillating Tube Method and Beaker Method by Levy and Mayes. These methods differ in intensities or degree of agitations of the dissolution medium, geometry of apparatus, surface area generation, sink or non sink condition etc. No single dissolution rate test equipment yet has the ability of providing similar biological or physiological condition as found in the invivo or gastro intestinal tract (G.I.T) rather it only provides an invitro control procedure to eliminate variations among production batches, by measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions in an invitro test (Garr and Bangudu, 1991).

1.7.3(iii) **Chemical Standards**

Chemical tests for quality control of tablets include active content uniformity test, colour test,

stability tests etc.

a) **Active Content Uniformity Test:** In order to ensure that every tablet contains the amount of drug substance intended, within acceptable limit of variation among tablets within a batch, the U.S.P. and other official books include the *content uniformity test for tablets due to the* increased awareness of 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. The B.P and other* official books have specified assays of different drugs

b) **Colour Test:** This is an attempt to determine possible tablet mottling which could be an indication of inadequate mixing.

1.8 AIM AND SCOPE OF THE PROJECT

This is to source an important raw material in tableting. The raw material is pure cellulose with its derivative (sodium carboxymethyl cellulose).

The source of the raw material (cellulose) is from rice husks. Rice husks are preferred to other

rich sources of cellulose e.g sugar cane chaff, maize cobs, groundnut shells, saw dust, etc. all of which have competitive uses especially as fuel but rice husks have none of these uses. Instead, any attempt to burn rice husks produce an unpleasant intensity smoke as the husks hardly burn into flames.

Alpha-cellulose will be produced from the rice husks using standard extraction techniques. While some of the alpha cellulose would be retained for its excipicient's use in tableting, sodium carboxymethyl cellulose would be produced from the remaining cellulose.

The possible use of sodium carboxymethyl cellulose as a bulk forming laxative tablet will be explored as a high dose tablet compared with paracetamol tablet and its excipients properties in tableting of high dose tablets would alsobe elucidated.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 MATERIALS:

Rice husks were obtained from a rice mill at Tudun Wada Zaria, Kaduna State Nigeria. Nitric acid, chloroacetic acid, sodium nitrite, sodium sulphite, sulphuric acid, galactose, xylose, maltose, sucrose, arabinose, glucoronic acid sodium carboxymethylcellulose standard and glucose used were Analar grades or analytical reagent grades manufactured by BDH Chemicals Ltd, Poole, U.K. Sodium hydroxide, butanol, Chloroform, maize starch, methanol, paracetamol (May and Baker England), Magnesium stearate, gelatine, and talc were manufactured by (Hopkin and Williams Ltd. England) Sodium hypochloride was sourced from the Nigerian German chemicals and hydrogen peroxide were sourced through NovoPharm Brian Munro Nigeria Limited.

2.2 EQUIPMENT

The various pieces of equipment utilised in the project work include stainless steel bowl of 12 litres capacity and Gallenkamp oven (BS size 3, England). Water bath (IM 840) and hot plate (6B-8547E) (Gallenkamp Limited, England). Tablet disintegration test apparatus (Type 273), tablet friability tester (Type TA3R), flowability tester (Type GDT), and single stroke tablet press

(Type AR 400) were manufactured by Erweka Apparatebau GMBH, Germany. Blender/Mill(MX-THOPN) was produced by National Electric Co. Limited Japan. Light microscope (Model Wild MII) was made by Heerbrugg Switzerland. Milling Machine (Type YL 112M-4-TH) was from Atlas Exclusive Alzico Limited Italy. Other equipment include micrometer screw gauge and Vernier caliper (Moore and Wright, England), Endecott test sieve shaker (manufacturers, England), weighing balance (Type P163)by Metler Instruments, A.G. Switzerland, vacuum pump by GEC Mech Ltd Newcastle Staffs England, heater coil (STC), Japan; and Monsanto hardness tester by Manesty Machines Ltd Speke Liverpool England. Glass- wares used includes: 50ml burette, sincted glass funnels, funnels, 2L, 50ml and 100ml Erlenmeyer flask, beakers, and glass slides were produced by Pyrex England.

2.3 METHODS

2.3.1 EXTRACTION OF CELLULOSE FROM RICE HUSKS AND YIELD

The method adopted was similar to the one described by Okhamafe et al (1991) for extraction of cellulose from rice husk, an agricultural waste product. However few modifications were made.

i. *Preliminary treatment of size reduction and sieving:* The rice husk was dried at 60°C for 24 hours in the Gallenkamp oven. It was milled with a milling machine and sieved using Endecott test

sieve shaker. Cellulose was extracted from the fraction of the milled rice husks retained by 250μm sieve mesh.

ii. *Reaction with nitric acid and washing to remove lignin and other soluble matter:* 400g of the milled rice husks was treated with 4 litres of 3.5% nitric acid containing 40mg of sodium nitrite for 2 hours in a 12 litre-volume stainless steel bowl immersed in the water-bath at 90°C. This is to remove lignin in the form of soluble nitrolignins. The nitro lignin was washed off by repeated washing and filtering with distilled water using suction pump which hastened the filtration rate of the washed liquid from the material.

iii. *Reaction with 2% sodium hydroxide and 2% sodium sulphite:* The residue was then treated with 4 litres of 2% each sodium hydroxide and sodium sulphite at a temperature of 50°C for 1 hour. Again it was washed and filtered repeatedly with distilled water. This is to digest the materials

iv. *Bleaching with sodium hypochlorite:* The washed residue of the material rice husk was then bleached with 500ml of 1 in 1 dilution or 1.75% sodium hypochlorite solution, the bleaching was conducted at 40°C for 1.5 hours. Two more further bleaching steps were carried out and the material

was washed and filtered. The resulting holocellulose was set for the next process.

v. *Treatment with 17.5% w/v sodium hydroxide:* The holocellulose was then treated with 500ml of 17.5% sodium hydroxide solution for ½ hour at 80°C to dissolve off beta-and gamma-cellulose and other susceptible soluble materials leaving the required alpha-cellulose.

The α-cellulose was then washed and filtered.

vi. *Final bleaching or whitening with 20% vol. hydrogen peroxide:* The α-cellulose extraction was completed by whitening with 500ml of 20% volume hydrogen peroxide at 40°C for 1.5 hours.

The obtained cellulose was filtered, pressed and air dried at room temperature for 48 hours, and then dried in the Gallenkamp oven at 60°C for 1 hour.

The dried cellulose was then milled in Moulinex blender mill 2 and sieving with Endecott test sieves and shaker. The fractions retained by 125μm, 150μm, 250μm and 500μm sieves were obtained and stored at room temperature in a silica gel desicator.

The extraction was repeated thrice with 500g of the rice husk using 5/4 of the quantities of the chemicals used in the first initial extraction.

Determination of percentage yield

The percentage yield of the material which has been confirmed to be cellulose (α-cellulose) was

determined by obtaining the weight of the α-cellulose after all extraction procedures. The mean of the three yields was then calculated and the percentage yield determined.

2.3.2 SYNTHESIS/PRODUCTION OF SODIUM MONOCHLORO-ACETATE FROM CHLORO ACETIC ACID

Sodium monochloroacetate as a raw material for production of sodium carboxymethyl cellulose was obtained by reacting chloro acetic acid with sodium hydroxide. 29ml of 1N sodium hydroxide solution from a 50ml burette neutralised 2g of chloro acetic acid dissolved in 2ml of distilled water in a 100ml cornical flask using the methyl orange indicator. The resultant solution contained sodium monochloroacetate. The water was evaporated and the solid obtained was recrystallised and tested for purity and identity. The process was repeated with 20g of chloro acetic acid.

Identification Test for Sodium Monochloroacetate:

Test: 1g of the compound sodium monochloro acetate was dissolved in 3ml of distilled water.

Test with P^H Paper: To one portion of the sodium mono chloro acetate in a small test tube the solution was tested with P^H paper for possible colour change.

Test with Sodium bicarbonate: A solution of sodium bicarbonate was introduced into the test tube containing sodium monochloro acetate on a slanting position for possible reaction.

2.3.3 **Synthesis/Production of Sodium Carboxymethyl CelluloseSCMC) and Yield**

300g of alpha-cellulose produced in section 2:3:1 by the method of Okhamafe et al, (1991), was made alkaline with 0.5m NaOH in 12 litres stainless steel container. 0.1165g of sodium monochloroacetate was added, stirred and heated on a boiling water bath for 1 hour to form a homogenous much less dense mass which was filtered and dried in the Gallenkamp hot air oven at 65°C until a constant weight signifying that complete drying has been achieved.

Determination of Percentage Yield

The percentage yield of the material, sodium carboxymethyl cellulose, produced from rice husk was determined as in the case of cellulose derived from rice husk i.e. by obtaining the weight of the material after all extraction/synthesis production process. The percentage yield was then calculated.

2.3.4 **CHEMICAL EVALUATION TESTS ON THE EXTRACT**

. Trease and Evans (1983) methods and identification tests for cellulose, sugars and lignin were followed in this research work for the characterisation of the constituents of the powdered extract and the results are given in table 3.2.

Test for lignin

0.1g of the powdered extract was placed on a glass slide and moistened with concentrated hydrochloric

acid followed by gent warming until the liquid content dried off. Some drops of phloroglucinol was added and the slide was placed under a microscope using 8 x 7 = 42 magnification and examined for any colouration.

Test for sugars

Standard test for free reducing sugars: 0.4g of the cellulose extract was dispersed in 4ml of distilled water in a clean boiling test tube which was boiled for a few minutes on a water-bath and then allowed to cool. To one portion of the dissolved and boiled sample, 5ml of equal volumes of a mixture Fehling's solution I(A) and II(B) was added and boiled for a few minutes. Any brick red colouration would indicate a positive result.

Test for non free reducing sugar

To second portion of the sample dissolved in distilled water, dilute hydrochloric acid was added and boiled for 10 minutes. 5ml of equal volumes of mixture of Fehling's solution I(A) and II(B) was added and heated for 2 more minutes. The first heating in the presence of dilute hydrochloric acid was to hydrolise any non free reducing sugar to a reducing one which would be available for reaction with the mixture of Fehling's I(A) and II(B) solution to form brick red precipitate.

Test for Cellulose

i. To 0.2g of the alpha-cellulose extract powder few

drops of N/50 iodine solution were added followed by 66% v/v sulphuric acid. It was then observed for swelling followed by any blue black colouration on the white tile.

ii. 0.3g weight of the powdered cellulose extract was put on a white tile. Few drops of solution of chlor-zinc iodine (Zinc chloride potassium iodide in water) was added. Any blue or purple colouration and then swelling were observed and noted.

Test for starches

Test for soluble starch: 5mg weight of the powder was placed in a test tube. 5ml of 5% potassium hydroxide solution was added, heated gently and observed for any canary yellow colouration.

Chromatographic test for sugar:

Chromatographic techniques were employed to test the chemical content of the cellulose obtained from rice husks. The rice husk test cellulose was prepared by dispersing 0.4g of the powdered cellulose in 40ml of distilled water. Also the reference sugar solutions were also prepared by the same method and at the same concentration. The reference sugars employed in this research work include galactose, xylose, maltose, sucrose, arabinose, glucoronic acid and glucose, each in a concentration of 0.4g in 40ml of distilled water.

System I: Thin layer chromatography (TLC)

Absorbent: Silica gel G (air dried) on a

glass plate

Solvent system: Chloroform: Methanol (60:40)

Technique: Ascending

Visualisation: (i) Placing in iodine tank for some minutes and later visualising with naked eye.

System II: Paper chromatography

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

Solvent system: Chloroform Methanol (60:40)

Technique: Ascending

Visualisation: Analine phthalate spray reagent was applied, kept in the oven for 2 minutes to dry and viewed with naked eye under day light.

2.3.5 PHYSICAL TESTS

1. Particle Size Analysis

Microscopic method: In the determination of particle size by microscopic method, 0.02g of the powdered cellulose obtained from rice husks was mounted in water and observed under a wild M_{11} light microscope (magnification x 10). 100 particles were selected at random and their diameter measured by varying the field of view. From the values, the mean particle size and size distribution were obtained.

The powder particles sizes of SCMC standard and SCMC synthesised were similarly determined.

2. **Flow Rate**

To determine the time taken for the powdered cellulose to flow, 10g of the powder retained by 125μm sieve mesh was taken and passed through the Erweka flowability tester. The time taken for the 10g of the powdered cellulose to flow was recorded. This procedure was repeated twice using 2 other 10g powders of the same sample. The mean (average) of the three readings was recorded. Similar experiment was done with equal quantities of SCMC standard and sodium carboxymethyl cellulose derived from rice husks.

3. **Bulk Density and Tapped Density Determination:**

10g of the cellulose powder was weighed using the Metler balance. The powder was transferred into a clean 100ml capacity measuring cylinder and the bulk volume was noted. The cylinder was tapped 50 times on a hard top table and the tapped volume was also recorded. This procedure was repeated using another two sets of 10g of the powdered cellulose retained by 125μm sieve and each of the three sets of reading were recorded and the mean of the three sets of readings were calculated:

$$\text{Bulk Density} = \frac{\text{Mass}}{\text{Bulk Volume}} \quad \text{.....Eqn i}$$

4. **TAPPED DENSITY**

$$= \frac{\text{Mass}}{\text{Tapped Volume}} \quad \text{....Eqn ii}$$

5. **CARR'S INDEX**

Determination of Carr's Index (CI) which is the percent difference between the tapped density and the bulk density: Having obtained the bulk and tapped densities of the material above, Carr's Index (CI) can easily be determined. According to Schwartz et al (1975),

Carr's Index (CI) =

$$\frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times \frac{100}{1}$$

.....Eqn iii

$$CI = 100\ (TD - BD)/TD$$

Where CI = Carr's Index

TD = Tapped Density

BD = Bulk Density

The Bulk densities, tapped densities and Carr's indices of SCMC standard and SCMC synthesised were similarly determined.

6. **DETERMINATION OF THE ANGLE OF REPOSE:**

A clean funnel was clamped on a retort stand. The perpendicular height of the tip of the funnel should be 10cm from a flat table surface on which was placed a clean sheet of plain glass and a plane piece of glazed paper.

10g of the cellulose was accurately weighed on the Metler balance. This was poured into the funnel the opening of which was blocked with a piece of smooth cardboard paper to prevent the powder from falling. When the timing was to commence the cardboard

was removed to allow the powder to flow out onto the plane paper. A powdered heap was made. The height of the tip of the heap of powder was measured as Hcm. The contour of the baseline of the heap was marked round to form the circle of the cone heap. 2 parallel lines were constructed so as to form a tangent on the circumference. The maximal perpendicular distance between the tangential points of the parallel lines in the circle was the diameter of the circle, half of which is the radius R.

The angle of repose of the powdered heap was calculated from the equation:

$$\text{Tan } \alpha = \frac{H}{R} \quad \text{.....Eqn iv}$$

Where α is the angle of repose.

H is height of the heap of powder

R is the radius of the heap base.

The angle of repose of SCMC standard and sodium carboxymethyl cellulose powder synthesised were similarly determined.

7. **DETERMINATION OF MOISTURE CONTENT**

To determine the moisture content of the cellulose powder obtained from rice husk, 3g of the cellulose powder was taken in an evaporating dish of known weight, which was then transferred into the Gallenkamp oven and dried at 105°C until a constant weight was obtained. That was after all the moisture

with the powder had evaporated, the constant weight was noted and the moisture content as a percentage of the original weight of the powder taken was obtained. The experiment was repeated twice with the cellulose powder.

$$\%Mc = 100\ (I_w - F_w)/_{IW} \text{.....Eqn v}$$

Where M = Moisture content

I_w = Initial weight of the powder taken

F_w = Final weight of the powder after *drying to constant weight.*

The moisture content of the SCMC standard and *sodium carboxymethyl cellulose synthesized* were also determined in like manner.

2.3.6 **Tests on synthesised Sodium Carboxymethyl Cellulose**

1. **Identification Tests for Sodium Carboxymethyl Cellulose**:

2g of sodium carboxymethyl cellulose was taken in a beaker placed with a stirrer 25mm above the water surface. 160ml of distilled water was added and stirred for 30 minutes avoiding undue aeration of the solution. The solution was diluted with 200ml of distilled water, mixed and allowed to stand for 16 hours. The following tests on the solution were undertaken:

a) To 10ml of the solution, dilute hydrochloric acid was added and adjusted to acid pH of 0.5 and observed for colour development.

b) 10ml of the solution was also boiled for 5 minutes and observed for colour development.

c) To 10ml of the solution, 10ml of a 1% solution of calcium chloride was added and observed for colour development.

2 ***Determination of Solubility and Hygroscopicity***

SOLUBILITY

Some quantities of Sodium Carboxymethyl Cellulose and RHAC were dissolved in separate containers of distilled water until saturated solutions were formed with constant stirring. The solutions or suspensions were allowed to settle for 2 hours, and then filtered using filter paper whic was initally saturated with the solution or suspension and funnel 10 ml of the filtered solutions were taken in the evaporating dishes of known weights. The dishes were placed in a Gallenkamp oven at 110°C until all the liquid evaporáted. The dishes were allowed to cool and the final weight of the dishes noted. The solubility of SCMC and RHAC at room temperature of 23°C were then estimated. Solubility = $S = 100(\underline{K_2-K_1})/10$..**Eqn vi**

where k1 is initial weight of empty evaporating dish

k2 is the final weight of evaporating dish.

3. **Hygroscopicity:**

2g of sodium carboxymethyl cellulose was exposed to atmospheric condition by placing in an evaporating dish and left for 24 hours but weighted at 8 hourly

interval.

Hygroscopicity = [W3 - (W2 + W1)/w2]100 .....Eqn vii

where W1 is the initial weight of the evaporating dish

W2 is the initial weight of the powder taken

W3 is the final weight of the dish plus the powder.

2.3.7 **TABLET PRODUCTION**

The sodium carboxymethyl cellulose synthesized was subjected to the following tablet formulations:

1. As an active ingredient functioning as a cathartic bulk laxative by preparing tablets containing 500mg of sodium carboxymethyl cellulose per tablet.

   An attempt was made to produce cathartic laxative tablets with all ingredients derived from rice husks alpha-cellulose following the pelletisation path-way.
2. As a disintegrant intra and extra granular in paracetamol tablets as compared to maize starch.
3. It cannot be used as a diluent since in a higher amount, it has some physiological activity e.g. as a laxative.
4. As a binder in paracetamol tablets as compared to gelatin.
5. As a lubricant/glidant 2.2% w/w in paracetamol formulation as compared to the mixture of talc and magnesium stearate.

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The tablets were produced by the following techniques:

1. **WET GRANULATION METHOD**

The production followed the steps outlined below: weighing, mixing, wet mixing or massing, screening the damp mass, drying, dry screening, lubrication and compression. The screening of the damp mass was done using 1.0 mm sieve mesh, while drying of the wet granules was done at 48°C for 2 hours.

Compression:

The weight of granules containing 500mg of the active ingredient was weighed. This was transferred into the die of 12.5mm diameter punch and die tooling of the Erweka single stroke tableting machine. The appropriate compression pressure was adjusted from 4 metric tonne units upwards until adequate hardness was achieved. The compression was started until some 40 tablets were produced for tests to ellucidate the properties of the tablets.

In this work an attempt has been made to evaluate the functional properties of sodium carboxymethyl cellulose derived from rice husk in tablet formulations so as to act as a bulk laxative (ingredient) disintegrant, a binder and as a lubricant/glidant.

Table 2.1: formulae of Products for studying various pharmaceuticals properties of SCMC

Study	Amounts of ingredients per tablet (mg):									
	Formulation Number	SCMC	PCM	Maize starch as			alpha cellulose	Talc	Magnesium Stearate	Production technique
				Binder	Lubricant	Disintegrant				
Comparing SCMC and PCM as active ingredients	F1 F2	500mg -	- 500mg	5%w/v 5%w/v	7.8%w/w 7.8%w/w	60mg 60mg	- -		0.2%w/w	wet granulation
Pelletisation Properties of alpha cellulose	F3	500mg	-				70mg	2% w/w 2% w/w		pelletisation
SCMC Tablets with only ingredients from rice husk	F4	500mg					75mg			Wet granulation
Disintegrant properties of SCMC compared to starch	F5 F2	60mg -	500mg 500mg	5%w/v 5%w/v	7.8%w/w 7.8%w/w	- 60mg	-	2% w/w 2% w/w	0.2%w/w	wet granulation
Binder properties of SCMC compared to gelatin	F6 F7	5%w/v -	500mg 500mg	5%w/v 5%w/v	7.8%w/w 7.8%w/w	60mg 60mg	-	2%w/w 2%w/w	0.2%w/w 0.2%w/w	Wet granulation
Glidant properties of SCMC compared to Talc & mag. Stereate	F8 F2	2.2% -	500mg 500mg	5%w/v 5%w/v	7.8%w/w 7.8%w/w	60mg 60mg	-	2% w/w	0.2%w/w	wet granulation

2.4 EVALUATION OF TABLET PROPERTIES

Quality control tests to study the properties of the tablets produced were conducted as follows:

2.4.1 Weight Variation Test

10 Tablets were weighted as a whole and individually using the Mettler balance. The mean and percent standard deviation were calculated.

$$\%SD = 100 \times S.D$$

where %SD = Percent Standard deviation.

S.D = Standard deviation.

2.4.2 Determination of variation in tablet diameter

The diameter of 10 tablets respectively was measured using the vernier caliper. Each tablet was placed in between the caliper teeth and the diameter measured. The mean and the standard deviation (SD) were calculated.

2.4.3 Tablet Thickness Variation Test

To determine tablet thickness the Micrometer Screw gauge was used. 10 tablets were picked randomly from each batch. Each tablet was placed in between the micrometer screw gauge spindle and the diameter reading was obtained in millimeter. The mean tablet diameter and the standard deviation (SD) were calculated.

2.4.4 Friability Test

10 tablets were randomly picked from each batch, brushed carefully and lightly until any surface powder

was removed. The 10 tablets were weighed (x gm) accurately using the Metler balance. They were placed inside the Erweka friabilator which was operated to scoop and drop the tablets through a distance of 6 inches, at 25rpm for 4 minutes. The tablets were removed, dusted and weighed again (y gm). The difference in weight was determined and expressed as percentage weight loss.

$$Friability = 100(x - y)/x$$

2.4.5 Tablet Hardness Test

The hardness of 10 randomly picked tablets from each batch was measured using the Monsanto hardness tester. Each tablet was placed between the spindle and the anvil, held in position using the adjustable knob. The knob was screwed gradually from zero until the tablet was fractured. The instrument measures the force required to break the tablet. The force is generated by a coil spring applied diametrically to the tablet. The force required to break each of the ten tablets was recorded and the mean crushing strength ($Kalin^2$) determined.

2.4.6 Tablet Disintegration Time Test

Disintegration time of tablet was determined using a device described in United States Pharmacopoeia (U.S.P) adopted in British Pharmacopoeia (B.P). The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom. The bottom of each tubes is covered with a mesh. 6

tablets were randomly picked from each batch and one tablet placed inside each tube immersed in a 1 litre beaker containing distilled water which in turn is immersed in a water bath thermostatically maintained at 37°C. The assembly of tubes move up and down in the beaker. The volume of the water was such that on the upward stroke the wire mesh remains at least 2.5cm below the surface of the water and descends to not less than 2.5cm from the bottom on the down ward stroke. The time taken for each tablet to disintegrate and pass through the mesh was noted and the time taken for the last tablet to disintegrate was considered as the disintegration time for the batch. The test was done in duplicate for each batch and the average reading recorded.

CHAPTER THREE

3.0 RESULTS

3.1 PERCENTAGE YIELD

TABLE 3.1:Percentage Yield of Cellulose and Sodium Carboxymethyl Cellulose Produced from Rice Husk

Material	Percentage yield
Rice Husk cellulose (RHAC)	23.9% w/w
Sodium Carboxymethyl Cellulose (SCMC)	92.2% w/w

The percentage yield of sodium carboxymethyl cellulose was very high, 92.2% w/w compared with that of rice husk cellulose with the percentage yield of 23% w/w.

3.2 CHARACTERISATION OF ALPHA CELLULOSE AND SODIUM CARBOXYMETHYL CELLULOSE DERIVED FROM RICE HUSK:

TABLE 3.2: RESULTS OF VARIOUS IDENTIFICATION TESTS ON RICE HUSK α CELLULOSE

TEST	OBSERVATION	INFERENCES
1. **Test for Lignin**	Some few traces of red colouration were observed	Scanty presence of lignin

2. **Test for Sugars**

TEST	OBSERVATION	INFERENCES
2 Test for Free reducing sugar	No yellow precipitate or red precipitation produced No brick red colouration seen	Absence of free reducing sugar from the Sample Free reducing sugar absent.

TEST	OBSERVATION	INFERENCES
b) Test for Non-free reducing	Dark red precipitate produced.	Presence of non free reducing sugar confirmed.

3. **Test for Cellulose**

TEST	OBSERVATION	INFERENCES
Sample +N/50 iodine solution	Black colouration was Observed on the white tile.	Cellulose present
Sample + Zinc chloride + Potassium iodide	Immediately black Colouration on the white tile was observed.	Presence of Cellulose in sample the Confirmed.

4. **Test for Starches**

TEST	OBSERVATION	INFERENCES
5% Potassium hydroxide solution + heat	No canary yellow colour seen.	Starch absent from the sample.

5. Chromatographic Tests

Table 3.3: Chromatographic Characterisation by thin layer chromatography carried out on the cellulose obtained from rice husk

Absorbent: silica gel (air dried) on a glass plate.
Solvent system: chloroform methanol (60:40)
Spray reagent: iodine vapour in iodine tank.

EXTRACTS	COLOUR REACTION		R_f Value
Reference samples			
Galactose	Brown		0.4
Arabinose	"		0.5
Xylose	Light Pink		0.46
Maltose	"		0.48
Sucrose	"		0.40
Glucoronic acid	"		0.20
Glucose	Brown		0.59
Test Sample	Three spots were seen		
Hydroysed cellulose Suspension	L_1	Dark brown	0.5
	L_2	Pink	0.56
	L_3	Brown	0.72

Table 3.4: Characterisation of Paper Chromatography Conducted on the Cellulose produced from rice husk.

Chromatographic Paper: Whatman No. 1
Solvent System: Chloroform: Methanol (60: 40)
Spray Reagent: Aniline pthalate spray reagent.

EXTRACTS	COLOUR REACTION	R_f
Reference samples		
Galactose	Light brown	0.51
Xylose	Dark brown	0.65
Arabinose	Pale brown	0.66
Glucose	Brown	0.59
Test Sample		
Hydrolysed Cellulose Suspension	Deep Pink	0.87

6. Particle size analysis and shape.

TABLE 3.5: Particle Size Distribution of Cellulose Powder derived from rice husk.

Size Range μm	% Frequency f	Class Mark X_1	F_1X_1	%Cumulative Frequency
1 - 50	0	25.5	0	0
51 - 100	9	75.5	679.50	9
101 - 150	27	125.5	3388.50	36
151 - 200	18	175.5	3159.00	54
201 - 250	32	225.5	7216.00	86
251 - 300	10	275.5	2755.00	96
301 - 350	4	325.5	1302.00	100
	100		18500	

Mean particle size $= \frac{\sum fx_1}{\sum f} = \frac{18500}{100} = 185\mu m$

Most particle ranges 100μm to 250μm

Shape: Long flattened, regularly shaped, cylindrical particles of different sizes with fibres of different sizes are shown in fig. 3.5.

TABLE 3.6: Particle Size Distribution of SCMC standard and Sodium Carboxymethyl Cellulose Derived from Rice Husks

Parameter	SCMC Standard						
Size range	Classmark x1	% Frequency F1	F1x1	% Cummulative frequency	% frequency	f1x1	% cummulative frequency
11-20	5.5	10	55	10	13	201.5	13
21-30	25.5	25	637.5	35	30	765.0	43
31-40	35.5	30	1065	65	20	710.0	63
41-50	45.5	13	591.5	78	19	864.5	82
51-60	55.5	4	222	82	5	277.5	87
61-70	65.5	5	327.5	87	6	393.0	93
71-80	75.5	5	377.5	92	5	377.5	98
81-90	85.5	8	684	100	2	171.0	100
91-100	95.5	0	0	100	0	0	0
Mean Particle size	$\approx \frac{\sum f1x1}{\sum f} = \frac{3960}{100} = 39.60\mu m$ SCMC has a finer particle size ranging between 10μm-50μm with less larger partilce 60μm-90μm				Mean Particle size $\approx \frac{\sum fx}{\sum f} = \frac{3760}{100} = 37.6\mu m$ SCMC has a finer particle size ranging between 10μm-50μm with less larger partilce 60μm-90μm		
Shape	Shape: Spherical with different sizes, oval and few are polygonal.				Shape: Spherical with different sizes, oval and few are polygonal.		

Mean particle sizes obtained from the calculations above differs from that obtained from the graphs Fig 3.2 and Fig 3.4 because of difference in methods

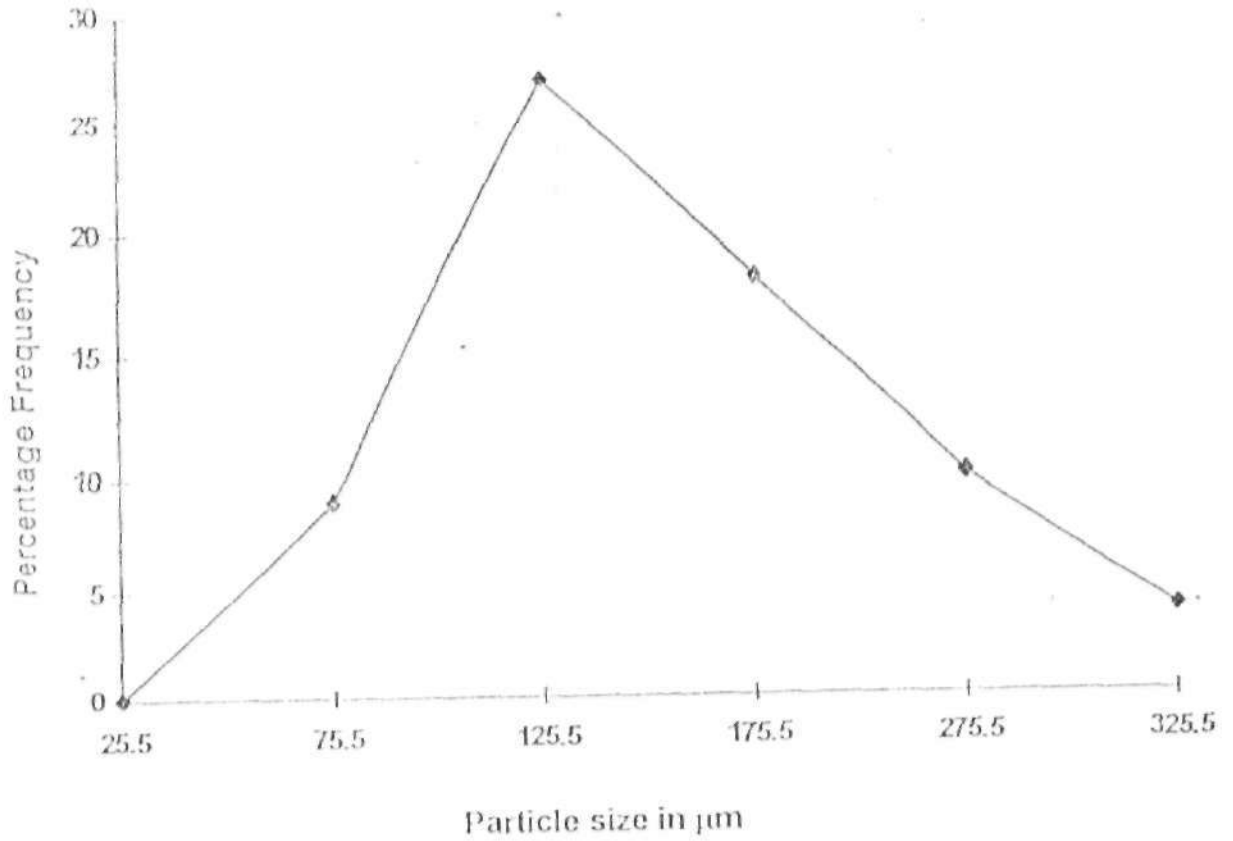


FIG. 3.1: Percentage Frequency Vs Particle Size Distribution of Cellulose Powder Derived from Rice Husk

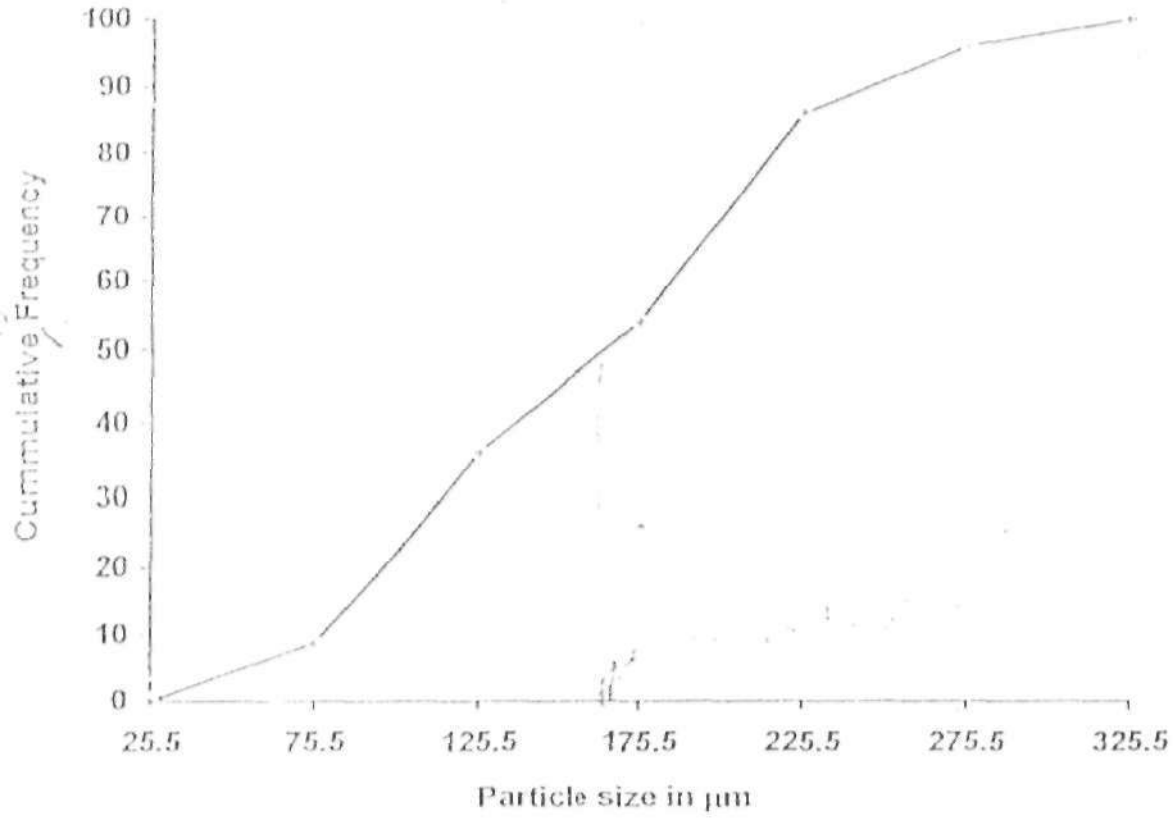


FIG 3.2: Cumulative Percentage Frequency Vs Particle Size of Cellulose Powder Derived from Rice Husk

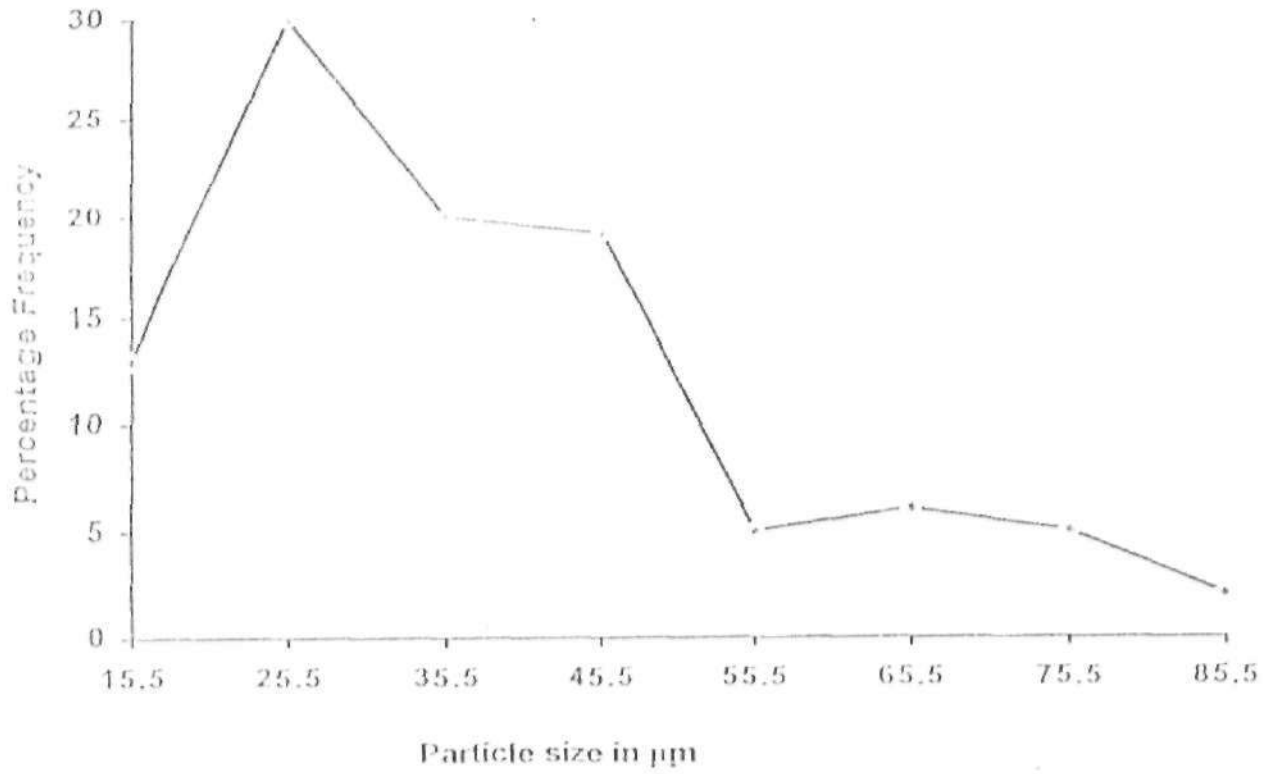


FIG 3.3: Percentage Frequency Vs Particles Size Distribution of Sodium Carboxymethyl Cellulose Powder Derived from Rice Husk

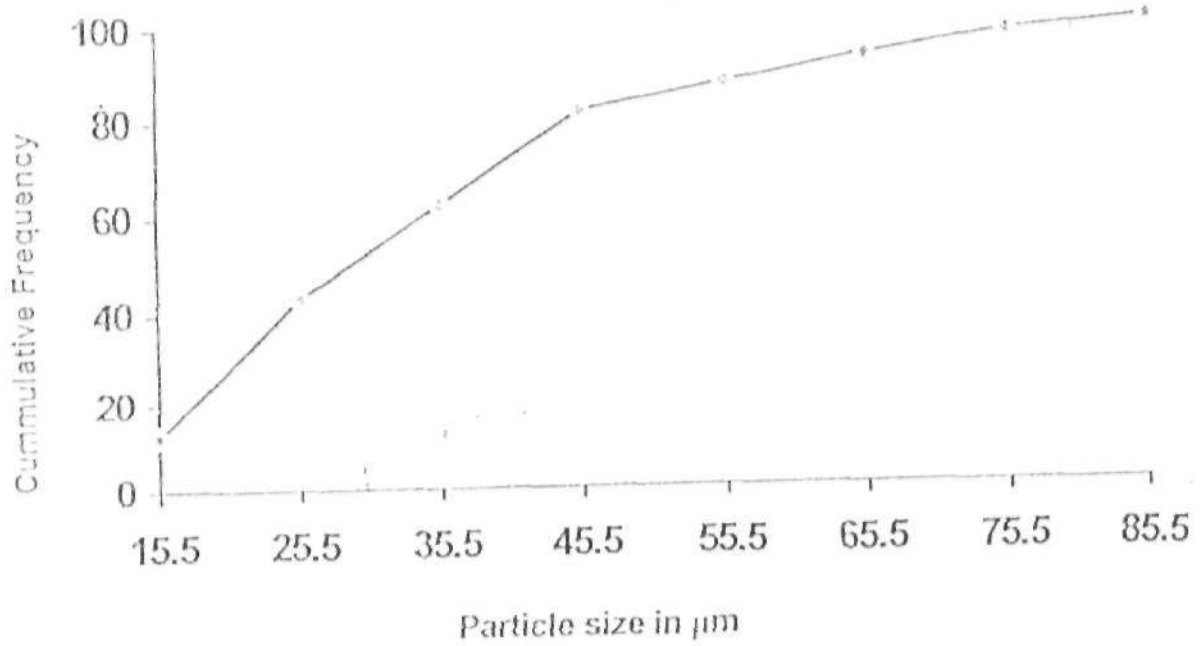
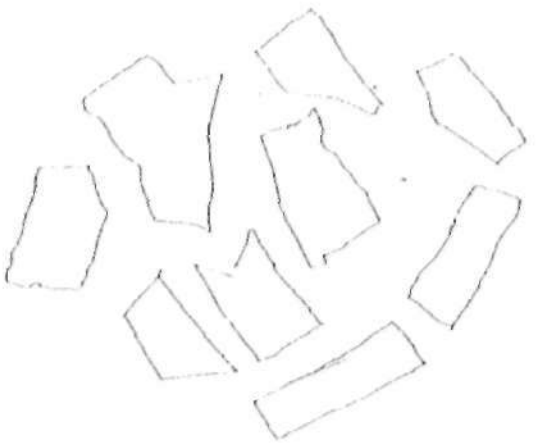


FIG 3.4: Cumulative Percentage Frequency Vs Particle Size of Sodium Carboxymethyl Cellulose Derived from Rice Husk



Particles of Rice Husk Cellulose (X40)

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Particles of Sodium Carboxy Methyl Cellulose (X40)

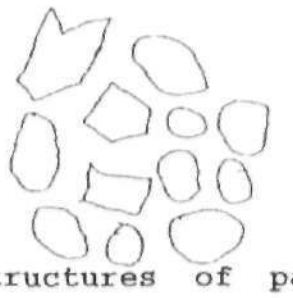


FIG 3.5: Morphological Structures of particles of Cellulose Powder and Sodium Carboxymethyl Cellulose Derived from Rice Husk under Light Microscope M_{11} with Objective X 40

Rice husk cellulose as viewed under light microscope M_{11} with objective X40 shows long, flattened, cylindrical particles of different sizes.

Particles of sodium carboxymethyl cellulose as seen under the same microscope are spherical with different sizes, some are oval and few are polygonal.

Rice husk cellulose mostly have flattened larger sized structures that are irregularly shaped, with fibres of different sizes as shown in the figures 3.5 above.

7. **Flow Properties**

TABLE 3.7: Flow parameters of alpha SCMC standard, cellulose, and sodium carboxymethyl cellulose powders derived from rice husks

FLOW PROPERTIES	RHAC	SCMC synthesised	SCMC Standard
Bulk density (g/cm^3)	0.169	0.188	0.179
Tapped density (g/cm^3)	0.233	0.303	0.350
Carr's Index (%)	27.47	37.95	48.86
Flow rate (g/sec)	0.226	0.253	0.260
Angle of Repose (o)	58.4 ± 0.2	48.4 ± 0.5	45.90±0.3

8. **MOISTURE CONTENT**

Table 3.8: ***Moisture Content of Cellulose and Sodium Carboxymethyl Cellulose Derived from Rice Husks***

Powder	Moisture Content
Rice Husk cellulose (RHAC)	6.41% w/w
Sodium Carboxymethyl Cellulose Synthesised	9.8% w/w
SCMC Standard	9.3%w/w

9. **HYGROSCOPICITY**

RHAC, SCMC standard and SCMC synthesised absorbs 6.41%w/w, 9.3 %w/w and 9.8%w/w moisture respectively at room temperature at room temperature of about 37°C kept for 24 hours and relative humidity of about 80%.

10. **Solubility**

RHA Cellulose 0.8%w/v at 23°C

SCMC synthesised 15.2%w/v at 23°C.

SCMC standard 14.5%w/V at 23°C

11. Chemical Identification Tests on Sodium Carboxymethyl Cellulose derived from RH

TABLE 3.9: **RESULTS FOR CHEMICAL TESTS**

TESTS	*OBSERVATION*	*INFERENCES*
Test for SCMC	Fine white precipitate was produced	Presence of methyl cellu lose hence SCMC confirmed
	No precipitate was produced	Distinction between methyl celluLose and ethylCellulose hence present Of SCMC
	No gelatinous precipitate was produced	Distinction from sodium alginate hence SCMC Present.

Tablet 3.10: Tableting Properties for studying of various pharmaceutical properties of SCMC

					Disintegrants		Binders		Lubricants	
Tablets Properties	500mg SCMC Tablets F1	500mg Paracetamol tablets F2	SCMC Tablet by Pelletisation F3	SCMC Tablets with only ingredients Rice Husks F4	SCMC Synthesised F5	Maize Starch F2	SCMC Synthesised F6	Gelatin F7	SCMC Synthesised F8	Magnesium Stereate+ Talc F2
Mean tablet weight (mg)	638±0.5	635±0.5	Stone hard slugs were formed	636.3± 0.3	635.5± 0.4	635± 0.5	631.0 ±0.5	633.7± 0.51	630.4±0. 5	635.9±0.4
Tablet Diameter (mm)	12.5	12.5		12.5	12.5	12.5	12.5	12.5	12.5	12.5
Tablets thickness (mm)	6.11	5.94		7.90	5.94	5.94	6.60	6.10	6.11	5.94
Tablet Hardness (kgf)	3.80	5.10		6.00	6.00	5.10	3.90	5.10	4.90	5.10
Friability %w/w	0.5	0.46		0.26	0.24	0.46	1.00	0.37	0.90	0.46
Disintegration time (min)	>60	0.82± 0.04		>60	21.16± 2.71	0.82± 0.04	28.67 ±1.63	0.92± 0.26	0.7± 0.1	.082± 0.04
Tablets Appearance									Smooth, shinny, no pitted surface no adhesion unot punches and dies surfaces no tablet grunting ejection noise	Smooth, shinny no pitted surfaces , no adhesion unto punches and dies surfaces

CHAPTER FOUR

4.0 DISCUSSIONS AND CONCLUSIONS

4.1 *DISCUSSIONS*

4.1.1 Characterisation of alpha Cellulose and Sodium Carboxymethyl Cellulose Derived from Rice Husk

The untreated crude sugar cane chaff and rice husks are mainly composed of alpha-cellulose, ß-cellulose, ¥-cellulose, lignin, molasses, mineral material matter, carbohydrates, reducing sugars, Nitrogen etc, (Musa, 1996).

The various extraction procedures were meant to solubilise all the other materials so as to be washed and filtered out to leave a residue expected to contain pure α cellulose.

Test were conducted to ensure that the α-cellulose that was so extracted is pure. Table 3.2 shows that the extract contained little or no lignin, no free reducing sugar, no starch but confirmed the presence of non free reducing sugars.

The identification test for cellulose clearly shows that the material consists mainly of cellulose. Further more two chromatographic techniques tests made using reference standards of xylose, maltose, glucose, glucoronic acid, arabinose, galactose, sucrose and maltose showed no identical spots for these materials and therefore indicative of their absence in this extracted cellulose.

The mean particle size and size distribution as shown in Table 3.5 is 185μm. These compare to 157μm of α-cellulose extracted from sugar cane chaff (Musa, 1996). This similarity is not too surprising as the cellulose from the two plants are in the same botanical family of Gramineace.

The lower yield of some 23% w/w against that from sugar cane, chaff of 28% w/w, (Musa,1996) appears to show that there is a higher percentage of other materials in the rice husk than in the sugar cane chaff.

Particle size distribution of SCMC Standard and sodium carboxymethyl cellulose derived from rice husks was compared with α-cellulose derived from the same source. The production of sodium carboxymethyl cellulose from α-cellulose derived from Rice husks is partly a depolymerisation action, a methylation action, and carboxylation action. These has led to the mean particle size of sodium carboxymethyl cellulose to be 37.6μm (Table 3.6) as compared with the 185μm of the α cellulose (Table 3.5).

The flow properties of the two derivatives of rice husks and SCMC standard are shown on Table 3.7. The tapped density are about the same at 0.2g/cm^3 for alpha cellulose while that of sodium carboxymethyl cellulose synthesised is 0.3g/cm^3 and SCMC standard 0.35g/cm^3. The implication of this is that the sodium carboxymethyl cellulose is slightly denser after being tapped. This confirmed by the higher values of Carr's Index of SCMC (38%) as compared to the value for alpha cellulose (27%)

Carr's Index gives percentage ratio between the tapped and the bulk density. The higher the particles consolidation the higher Carr's Index.

Some authors put the Carr's Index as showing the level of compressibility or percentage compressibility (Akande, 1988). However, since no compression has been applied at all, it is to show the level of consolidation which the particles can attain just before being compressed or compacted into tablet. Being denser the sodium carboxymethyl cellulose has a slightly higher flow rate of some 0.3g/sec as compared with 0.2g/sec for the α cellulose. The angle of repose for the faster flow rate is 48° degrees for sodium carboxymethyl cellulose as compared with 58° for the α cellulose.However the flow properties of SCMC standard was almost similar with that of SCMC synthesised (Table 3.7).

The higher yield of sodium carboxymethyl cellulose is a consequence of chemical addition by methylation and carboxylation.

Moisture content when kept for 24 hours at room temperature of 37°C during the hot season at relative humidity 80% for rice husk cellulose, sodium carboxymethyl cellulose synthesised and SCMC standard were 6.4% w/w, 9.8% w/w and 9.3% w/w respectively (Table 3.8). Sodium Carboxymethyl cellulose is hygroscopic but not deliquescent i.e. does not absorb water to the extent of forming a solution.

Identification test for sodium carboxymethyl cellulose. The British Pharmaceutical Codex (1994) shows the identification test for sodium carboxymethyl cellulose which was confirmed and shows the distinction test between methyl cellulose and ethyl cellulose and the product sodium carboxymethyl cellulose. The Pharmaceutical Codex also shows the test for a possible adulterant of sodium carboxymethyl cellulose which could be sodium alginate, (Table 3.9). This adulterant was found to be absent.

4.2 TABLETING PROPERTIES OF α-CELLULOSE AND SODIUM CARBOXYMETHYL CELLULOSE DERIVED FROM RICE HUSK

Tableting By Direct Compression.

An effort or attempt has been made to see wether direct compression method can be employed in the case of materials like alpha cellulose and sodium carboxymethyl cellulose. This would have saved alot of time and cost as a result of not following the long and costly tableting stages.

4.2.1 Sodium Carboxymethyl Cellulose as a Cathartic Bulk Laxative.

When a material has some physiological or pharmacological action it is to be avoided as much as possible for use as a diluent. Sodium carboxymethyl cellulose with a dose range from 500mg to 1.5g behaves as an active ingredient as a cathartic when taken with plenty of fluid. This physiological activity has necessitated formulation into a high dose tablet

containing 500mg in the tablet. In this instance three of the tablets could be taken with plenty of water as a Cathartic bulk laxative. Three formulation options were undertaken.

Firstly, the formulation made use of the wet granulation method. Secondly, direct compression of the sodium carboxymethyl cellulose after dry mixing with the disintegrant was undertaken. However the compacts of this latter method were so soft that they crumbled manually between the fingers. Thirdly, pelletisation of the dry mix with 10% of the α-cellulose was performed to be communited through an appropriate sieve mesh and to dry mix with 10% of the rice husk cellulose before final compression into tablets. This third option was thought to be feasible as all the dry processes would encourage faster tablet disintegration time (Anzah, 1997 and Popoola, 1997). The wet processing method of the first option produced tablets which could not disintegrate even after 60 minutes even though the other properties were quite adequate (Tabel 3.10)formulation F1. Any disintegration for plain compressed tablets that goes beyond 30 minutes is grossly unacceptable for purposes of bioavailability even by pharmacopoeial standards.
SCMC tablets were produced by wet granulation by just moistening the dry mix and using multi-excipients compared with the same wet method but using only water as the binder and using the alpha-cellulose as the sole excipient. The tablets from both alternatives have

similar properties.

Table 3.10, formulation F4 shows that the α-cellulose sole excipient formulation produced thicker and harder tablets which bloated more bulky with gelatinous peripheries during the disintegration time (DT) test; but both types remained undisintegrated even after 60 minutes. The weight uniformity and friability for both types were similar. The increased peristalsis by the bloating; the easier passage of gastro-intestinal (git) contents by the gel and lubricant actions of the tablets outer layer; and the git fluid retention due to increased viscocity; are all thought to exert the cathartic bulk laxative action which undergo slow erosion instead of distintegrating. (Ojile, et al, 1999).

Formulation of sodium carboxymethyl cellulose Tablets using only ingredients derived from rice husk by Dry granulation.

Table 3.10, formulation F3 shows that the pellets turned into plastic, stone-hard slugs. They were too hard to be comminuted. The attempt made to chip out pieces from the slugs resulted into adhesive, fibrous and elastic pieces. This shows that, at very high pressure the particles were forced together within a distance of about 30 Angstrom when the Vander Waals forces covalent bond etc. become very prevalent and very strong (Ojile, 1980).

At a lower compression pressure of about 10, 12 and 13 metric tonnes of the Specac pelletising machine only soft slugs crushable in between the fingers could be

formed for a dry mix such as this. This appears to show that this compaction force could not bring the particles of the powdered mix so intimately enough for the Vander Waals forces to met the particles together.

Formulation of Sodium Carboxymethyl Cellulose Tablets with only ingredients derived from Rice Husks by Wet granulation Method.

The former formulation made by the wet method earlier discussed above contained multi-excipient ingredients such as maize starch as a disintegrant, maize starch mucilage as a binder, dry maize starch as a glidant with disintegrant effect and a mix of talc and magnesium stearate as glidant and lubricant. The disintegration time went far beyond one hour. The tablets were still bloated which could produce the cathartic bulking effect by inducing the increased peristalsic rate which is amenable to the laxative action.

In this section, due considerations to effective management of available resources and the production of more porous tablets to ease the influx of fluid into the tablet matrix to hasten the bulking or bloating effect were given, α-cellulose was used as the sole excipient to sodium carboxymethyl cellulose which is soluble in water to form a gel. Thus only pure water was used to activate binding properties of SCMC. The alpha-cellulose extracted from rice husks in this project was used as the

disintegrant intra granularly and extra granularly. Also no other glidant and lubricant were added in this formulation as the glidant and lubricant properties of sodium carboxymethyl cellulose have been established in this project already as discussed above.

Although the disintegration time went beyond 60 minutes a lot of the tablet have been dissolved by erosion. A lot of the tablet remaining in the tablet disintegration test machine had split into two or more gelly-like bloated pieces. These desirable characteristics were not available in the former formulation. Since the hardness, friability and weight variation are very much within the acceptable limit, this formulation gives better desirable properties for use in this cathartic bulk laxative function.

EVALUATION OF SODIUM CARBOXYMETHYL CELLULOSE PLAYING THE ROLE OF OTHER EXCIPIENTS BESIDES ACTING AS ACTIVE INGREDIENT

Since sodium carboxymethyl cellulose acts physiologically and pharmacologically as cathartic bulk laxative at the dose from 500mg and above, its use as playing the role of other functional excipients should not be more than 10% of the total tablet weight. For instance magnesium ion could increase the peristalsic action of the git when used in high dose. However Magnesium stearate has been frequently used as a lubricant in many tablet formulations.

As a consequence of producing a viscous solution as

with polyvinyl pyrrolidone (PVP) and gelatin binders, the SCMC was investigated as a binder. As the particle of sodium carboxymethyl cellulose are fine coupled with its low bulk density and its high flow rate (Table 3.7) it was also investigated for use as glidant/lubricant.

4.2.2 THE USE OF SODIUM CARBOXYMETHYL CELLULOSE AS A DISINTEGRANT

Maize starch is a popular disintegrant. Sodium carboxymethyl cellulose was used as a disintegrant (compared with the maize starch) in the formulation of paracetamol tablet produced by wet processing method. The tablet weight variation is shown on Table 3.10,formulations F5 and F2. Tablet produced were within plus or minus 0.4% with both formulations. The tablet thickness and hardness were similar while the friability was better for sodium carboxymethyl cellulose (i.e 0.2%) as compared with 0.5% with the formulation containing maize starch.

However the disintegration time was a long as 21 minutes for sodium carboxymethyl cellulose but within less than one minute for the formulation with maize starch. For purposes of bioavailability effect maize starch is superior to sodium carboxy-methyl cellulose.

4.2.3 THE USE OF SODIUM CARBOXYMETHYL CELLULOSE AS BINDER COMPARED WITH GELATIN IN PARACETAMOL TABLET

Table 3.10 formulations F6 and F7 shows that the properties of the tablets produced have a very good acceptable weight variation was only within 0.5%

deviation for both formulations. The thickness of tablets was about 7 mm with sodium carboxymethyl cellulose as compared to 6 mm for the tablets containing gelatin. The lower the thickness of a tablet, the more it is said to deform plastically, i.e,. the more it is more compressible. The tablet hardness is slightly lower for sodium carboxymethyl cellulose being 4 kgf as compared with 5 kgf with tablets containing gelatin binder. Although 4 kg force is acceptable by many industries is higher for large sized tablets as there, higher hardness values are more acceptable. The friability of the talets were 1.0 and 0.4 using SCMC and gelatin as binders respectively, both values are still acceptable by many manufacturers. Again the tablet disintegration time of 29 minutes is considered very long when compared with less than 1 minute disintegration in tablets containing gelatin. Therefore, on the whole assessment, sodium carboxymethyl cellulose is not superior to gelatin as a binder in the formulation for paracetamol tablets.

4.2.4 THE USE OF SODIUM CARBOXYMETHYL CELLULOSE AS LUBRICANT/GLIDANT IN PARACETAMOL TABLETS

Since 7.8% w/w of maize starch was admixed extra granularly in both formulations, it is more appropriate to say that sodium carboxymethyl cellulose present at only 2.2% w/w and dried talc cum dried magnesium stearate also present at 2.2% w/w are functioning more like lubricant than glidants. Normally glidants are present in higher concentrations so as to fill and smoothen the

crack and crevices of granules so as to reduce inter-particulate frictional forces which are necessary in promoting flowability.

The tablets produced were examined for defects such as having pitted surfaces or adhessional patches on the punches and dies or lack of shinny surfaces or lustre to the tablet surfaces.

In Table 3.10, formulations F8 and F2 it is seen that the tablets in both formulations were produced without any grunting noise, they had shinny tablet surfaces with no pitted surfaces and no adhesion of powder to surfaces of the dies and punches. These are the properties that a good lubricant must have on the tablet properties. For the other usual tablet properties, the weight variation were the same, the tablet thickness and the hardness, were the same. The friability was below 1% and the disintegration time was within 1 minute. So *in this formulation, sodium carboxymethyl cellulose acts* as a lubricant comparable to a combination of magnesium stearate and talc used at level of 2.2% w/w.

4.3 CONCLUSIONS

The alpha cellulose extracted from rice husks gave a yield of 23% w/w while the yield for sodium carboxymethyl cellulose synthesised from the alpha cellulose was 92% w/w.

The mean par`ticle size of the alpha cellulose was 185μm. Test performed on the alpha cellulose extracted

showed that it was pure alpha-cellulose devoid of materials such as galactose, xylose, starches, glucose, arabinose, gamma (γ)-Cellulose, Beta (ß)- Cellulose and other extraneous matter.

Characterisation of sodium carboxymethyl cellulose derived from rice husks showed that the chemical identification of sodium carboxymethyl cellulose were positive. The mean particle size was 37μm.

The rheological properties of the two products were such that sodium carboxymethyl cellulose has a higher bulk density, higher tapped density, higher Carr's Index, higher flow rate but less angle of repose than the rice husk alpha cellulose.

Sodium Carboxymethyl Cellulose is hygroscopic within 24 hours at 80% relative humidity examined. Sodium carboxymethyl cellulose will absorb as much as 10% moisture while rice husks alpha-cellulose absorbs only 6% w/w of moisture.

On tableting characteristics,sodium carboxymethyl cellulose and α cellulose would hardly form a compact on their own. Sodium carboxymethyl cellulose compacts at higher pressures but it has higher flow rate than α cellulose . The low bulk density makes the compact to be almost floatable in water. It has the following properties in tableting: It can be used as a disintegrant, as a binder, as a glidant and as a lubricant. With suitable formulations, it can also function as a high dose ingredient, acting as a cathartic

bulk laxative. When compression force of up to 15 metric tonnes is applied the compact forms stone hard, plastic tablets which is difficult to break even with a hammer on concrete slabs.

A formulation was devised in preparing a cathartic bulk laxative tablet whereby sodium carboxymethyl cellulose and alpha (α)-cellulose produced in this project became all the ingredients that were needed in the formulation.

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APPENDICES

Appendix 1

TABLE A1. Sodium Carboxymethyl Cellulose as a Major Component Compared with Paracetamol

COMPONENTS	*WEIGHT PER TABLET*	*QUANTITIES PER BATCH*	
		BATCH G_1	BATCH G_2
Sodium Carboxymethyl Cellulose	500mg*	20,000mg	-
Paracetamol	500mg	-	20,000mg
Maize Starch	60mg	2,400mg	2,400mg
Binder			
Maize Starch 5% w/v	13mg	520mg	520mg
Lubricants			
Dried Maize Starch 7.8% w/w	= 49.7mg	1988mg	1988mg
Dried Talc 2% w/w	= 12.7mg	508mg	508mg
Dried Magnesium Stearate 0.2% w/w	= 1.3mg	52mg	52mg
		25,468mg	25,468mg

Weight per tablet = 25,468mg ÷ 40 = 637mg

* Either of the two was used in each formulation

Appendix 2

TABLE A2. Formulation of Sodium Carboxymethyl Cellulose for Tablet production by Pelletisation, Comminution, Mixing and Compression as cathartic laxative

Material	Weight/Tablet	Weight/Batch Size Of 30 Tablets
Sodium Carboxymethyl cellulose derived from Rice husk	500mg	15,000mg
Alpha cellulose drived from Rice Husk	70mg	2,100mg
		17,100mg
Excipients		1,900
Total		19,000

3g each of the dry mix was accurately weighed on the Metler balance and pelletised with Specac (model 25.011 England) hydraulic pellitiser using 10-15 metric tonne force.

Appendix 3

4. FORMULATION OF SCMC TABLET WITH ONLY INGREDIENTS FROM RICE HUSKS AS CATHARTIC LAXATIVE

TABLE A3.

COMPONENTS	WEIGHT/TABLET	WEIGHT/BATCH SIZE OF 40 TABLETS
Sodium Carboxymethyl Cellulose	500mg	20,000mg
Rice husk Alpha Cellulose	75mg	3,000mg
		23,000mg

The active ingredient SCMC and excipient RHAC were dry mixed and 6ml distilled water was added. The mixture was screened through 1.7mm siev mesh, dried at 500C for 1.5hours in the Gallenkamp oven. To the dried granules weight 23,000 mg, 10%w/w rice husk alpha-cellulose 23,000 x 10/90 = 2556 mg was added mixed throughtly and compressed to tablets.

Weight of 1 tablet = 23,000 + 2,55 mg/40
= 638.9 mg

Appendix 4

TABLE A4. Use of SCMC disintegrant compared with maize starch

COMPONENTS	QUANTITIES PER TABLET	QUANTITIES PER BATCH	
		BATCH H_1	BATCH H_2
Paracetamol	500mg	20,000mg	20,000mg
Disintegrant			
Sodium carboxymethyl cellulose	60mg*	2,400mg	-
Maize Starch	60mg*	-	2,400mg
Binder			
Maize Starch Mucilage	5% w/v	5% w/v	5% w/v
Lubricants			
Dried Maize Starch	7.8% w/v	7.8% w/w	7.8%w/w
Dried Talc	2%W/W	2%W/W	2%W/W
Dried Magnesium Stearate	0.2% w/w	0.2% w/w	0.2% w/w

* Either of the two used in each formulation

Appendix 5

TABLE A5 Formulation Containing Sodium Carboxymethyl Cellulose as a Binder Compared with Gelatin in Paracetamol 500g tablets:

2

COMPONENTS	QUANTITIES PER TABLETS	QUANTITIES PER BATCH	
		BATCH K_1	BATCH K_2
Paracetamol	500mg	20,000mg	20,000mg
Maize Starch	60mg	2,400mg	2,400mg
Binder			
Sodium Carboxymethyl Cellulose	5% w/w*	5% w/w	-
Gelatin	5% w/w*	-	5% w/w
Lubricants			
Dried Maize Starch	7.8% w/w	7.8% w/w	7.8% w/w
Dried Talc	2%w/w	2%w/w	2%w/w
Dried Magnesium Stearate	0.2% w/w	0.2% w/w	0.2% w/w

* Either of the two was used in each formulation.

Appendix 6

TABLE A6: **Formulation Containing Sodium Carboxymethyl Cellulose as a Lubricant Compared with Dried Mix Talc with Magnesium Stearate Combination in Paracetamol 500g tablets:**

COMPONENTS	QUANTITIES PER TABLETS	QUANTITIES PER BATCH	
		BATCH M_1	BATCH M_2
Paracetamol	500mg	20,000mg	20,000mg
Maize Starch	60mg	2,400mg	2,400mg
Binder			
Maize Starch Mucilage	5% w/w	5% w/w	5% w/w
Lubricants			
Dried Maize Starch	7.8% w/w	7.8% w/w	7.8% w/w
Sodium Carboxy Methyl Cellulose	2.2% w/w*	2.2% w/w	-
Dried Talc	2%w/w	-*	2% w/w
Dried Magnesium Stearate	0.2% w/w*	-	0.2% w/w

* One was used in each formulation

Appendix 7

TABLE A7: TABLET PROPERTIES OF SODIUM CARBOXYMETHYL CELLULOSE AS A LAXATIVE CONTAINS 500MG PER TABLET

	ACTIVE INGREDIENTS	
TABLET PROPERTIES	SCMC tablets (F1)	Paracetamol tablets (F2)
Mean Tablet Weight (mg)	638 ± 0.5%	635 ± 0.4%
Tablet Diameter (mm)	12.5	12.5
Tablet Thickness (mm)	6.11	5.94
Tablet Hardness (KgF)	3.80	5.10
Friability (% w/w)	0.50	0.46
Disintegration Time (Minute)	>60	0.82 ± 0.035

Appendix 8

TABLE A8 **Formulation of sodium carboxymethyl cellulose tablets using only ingredients derived from Rice husk by pelletisation.(F3)**

The pellets turned into stone-hard slugs which could not even be broken by a hammer on a concrete slab. The pellets (slugs) were too stone hard to be comminuted through a sieve by hammer mill.

Appendix 9

TABLE A.9: Formulation of sodium carboxymethyl cellulose Tablets with only ingredients Derived from Rice Husk. (F4)

TABLET PROPERTIES	SODIUM CARBOXYMETHYL CELLULOSE 500mg TABLET
Mean Tablet Weight (mg)	636.3 ± 0.3%
Tablet Diameter (mm)	12.5
Tablet Thickness (mm)	7.90
Tablet Hardness (KgF)	6.00
Friability (% w/w)	0.26
Disintegration time (min)	By 60 minutes some of the bloated tablets got split into 2 parts with gels around them.

Appendix 10

Table A. 10 Comparison between SCMC and maize starch as Disintegrants in paracetamol tablet formulation

TABLET PROPERTIES		DISINTEGRANTS	
		Sodium Carboxymethyl Cellulose (SCMC) (F5)	Maize Starch (F2)
Mean Tablet Weight	(mg)	635.5 ± 0.4%	635.9 ± 0.4%
Tablet Diameter	(mm)	12.5	12.5
Tablet Thickness	(mm)	5.94	5.94
Tablet Hardness	(KgF)	6.00	5.10
Friability	(% w/w)	0.24	0.46
Disintegration time	(Min)	21.16 ± 2.71	0.82 ± 0.035

Appendix 11

Table A.11: Characteristics of sodium carboxymethyl cellulose as a binder compared with Gelatin in 500mg Paracetamol tablets.

TABLET PROPERTIES		BINDERS	
		Sodium Carboxymethyl Cellulose (SCMC) (F6)	Gelatin (F7)
Mean Tablet Weight	(mg)	631.0 ± 0.5%	633.7 ± 0.5%
Tablet Diameter	(mm)	12.5	12.5
Tablet Thickness	(mm)	6.60	6.10
Tablet Hardness	(Kgf)	3.90	5.10
Friability (% w/w)		1.00	0.37
Disintegration time	(Min)	28.67 ± 1.63	0.92 ± 0.26

Appendix 12

Table A. 12: The tableting properties of sodium carboxymethyl cellulose as a glidant/lubricant compared with magnesium stearate and Talc in 500mg Paracetamol tablets.

	LUBRICANTS	
TABLET PROPERTIES	Sodium carboxymethyl cellulose (F8)	Magnesium stearate + Talc (F2)
Tablet Appearance	Smooth, shinny, no pitted surfaces no adhesion unto punches and dies surfaces no tablet grunting ejection noise	Smooth, shinny, no pitted surfaces, no adhesion unto punches and dies surface
Mean tablet weight (mg)	630.4 ± 0.8%	635.9 ± 0.4%
Tablet Diameter(mm)	12.5 6.11	12.5 5.94
Tablet Thickness(mm)	4.90 0.90	5.10 0.46
Tablet Hardness(Kgf)	0.70 ± 0.10	0.82 ± 0.035
Friability (%w/w)		
Disintegration time (min)		