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CO-PROCESSING EFFECT OF MICROCRYSTALLINE CELLULOSE/PRE-GELATINIZED MAIZE STARCH ON PROPERTIES OF DIRECTLY COMPRESSED FOLIC ACID TABLETS.

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ABSTRACT

A binary mix powder containing various proportions of microcrystalline cellulose(MCC) and pregelatinized maize starch (PGS) was obtained, pelletized into 500 mg compacts, comminuted into granules which were compressed into 75 mg tablets containing 5 mg of folic acid powder using the direct compression method. The effect of the proportion of the binary components and compaction pressure on the proportion of comminuted pellets fines, mean granule size and tablet properties, were evaluated.The proportion of MCC in the binary mix was directly related to the proportion of fines produced and indirectly related to the mean granule size, showing that MCC had a lower binding effect than MCC. Increase in compaction pressure reduced tablet thickness, increased tablet hardness and reduced friability. This is due to higher densification effect on the tablets. PGS produced tablets with longer disintegration time (13.5 mins) compared to pure MCC content (0.8 mins). This showed that MCC is a better disintegrant than PGS.

Keywords: Binary mix, Microcrystalline cellulose, Pregelatinized maize starch, Folic acid, Direct compression, Compaction pressure.

INTRODUCTION

Direct compression technique has been one of the well accepted methods of tablet manufacture. A wide range of materials from various sources has been developed and marketed as directly compressible vehicles such as lactose, starch, cellulose derivatives, inorganic substance, poly alcohols and sugar- based materials (Gohel and Jogani, 2005). In

addition to the development of directly compressible excipients by the modification of a single substance, coprocessing oftwo or more components was applied to produce composite particles or coprocessed excipients (Kulvanich*et al,* 2004).

The direct compression process is mainly influenced by the properties of the excipients. The physico-mechanical properties of the excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity and good machineability even in high-speed tableting machinery with reduced dwell times (Ravi Shankar *et al*, 2012).

Granulation processes are often employed by manufacturers to improve the processing characteristics of powders destined to be capsules or tablets.Various manufacturing techniques are used to produce these free-flowing, compressible granules including fluid – bed granulation, rotor granulation and continuous granulation (Rojas *et al,* 2010).

Starch gelatinization is a process that breaks down the intermolecular bonds of starch molecules in the presence of water and heat, allowing the hydrogen bonding sites (the hydroxyl hydrogen and oxygen) to engage more water. This irreversibly dissolves the starch granule. Penetration of water increases randomness in the general starch granule structure and decreases the number and size of crystalline regions (Jenkins and Donald, 1998).

A strong binder is required in any of these processes to produce a high quality finished granulation with the desired flow and compaction properties. However, the binding properties of the excipient must be balanced by good disintegration and dissolution properties of the finished solid dosage form.

Powder compressibility is the property of forming a stable, intact compact mass when pressure is applied to a powder bed and granulation which is the process of pharmaceutical size enlargement of powdered ingredients is carried out to confer fluidity and compressibility to powder systems (Staniforth, 2002).

Folic acid is a component of the B group of vitamins and is necessary for the normal production and maturation of red blood cells. It is also used for other conditions commonly associated with folic acid deficiency including ulcerative colitis, liver disease, alcoholism and kidney dialysis (Nordqvist, 2011).

This report describes the preparation of a binary mix containing Pregelatinized maize starch and Microcrystalline cellulose using pelletization method in various proportions. The various folic acid tablets produced were then evaluated for their tablet properties as well as the effects of the binary mix on the formulation.

MATERIALS AND METHODS

MATERIALS

Folic acid powder (Juhel Nig. Ltd); Microcrystalline cellulose (Avicel^{R}) May and Baker, Lagos; Maize starch powder (Nig.Army Small Drug Manufacturing Unit, Victoria Island, Lagos). Talc and Magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

METHODS

Production of Pregelatinized maize starch

About 500 ml of distilled water was used to wet 250 g of Maize starch powder to form a paste and 2 litres of distilled water already boiled was added to the paste, stirred until a homogenous starch mix was obtained. The product formed was transferred to a stainless tray and dried at 40 ^{o}C for 24 hrs. The dried product was comminuted to obtain small particle sizes.

Table 1: Dry mix of Pregelatinized maize starch and MCC and Folic acid powder.

Batch no	MCC (%)	PGS (g)	MCC (g)	Folic Acid Powder (g)
1	0	10	0	0.715
2	10	9	1	0.715
3	20	8	2	0.715
4	30	7	3	0.715
5	40	6	4	0.715
6	50	5	5	0.715
7	60	4	6	0.715
8	70	3	7	0.715
9	80	2	8	0.715
10	90	1	9	0.715
11	100	0	10	0.715

Formation of Pellets

From each batch, pellets were made using a pelletizing machine with a 12.5 mm punch and die assembly of ErwekaSingle Station Tablet Press at a compression force of 10 metric tonnes to give 500 mg pellets.

Granule Size Distribution

The granules were sieved using a Test sieve shaker containing 500 µm, 250 µm, 150 µm, and pan. The contents retained on each sieve mesh and pan were weighed and expressed as percentage weights. The mesh granule size was calculated as follows:

$$\text{Mean Granule Size} = \Sigma \frac{(\text{Sieve size } (\mu m) \times \%wt)}{100}$$

Compression

The granules were homogenized and compressed into 75 mg tablets using 5.5 mm punch and die set of ErwekaSingle Station Tablet Press using two compression pressures of 3.5 and 4.0 metric tonnes.

Evaluation of Tablets

All the tablets were evaluated for weight variation, hardness, friability, disintegration time and thickness. Hardness of tablets was tested using Monsanto hardness tester, friability of the tablets was determined in a Roche Friabilator while disintegration time was determined using Erweka disintegration apparatus.

RESULTS AND DISCUSSION

The current definition of direct compression is the process by which tablets are compressed directly from the powder blends of active ingredient(s) and suitable excipients.

Table 2.:Effect of MCC content in binary mix with PGS on content of percentage fines produced from comminution of pellets.

Batch	%MCC in binary mix	500µm (%)	250 µm(%)	150 µm(%)	Pan (100µm)(%)	Mean granule size (µm)
1	0	44.7	35.9	11.8	7.6	338.55
2	10	45.9	34.4	10.9	8.8	340.65
3	20	49.0	31.7	9.5	9.8	348.80
4	30	41.2	28.1	11.1	19.6	312.50
5	40	37.5	27.0	11.4	24.1	296.20
6	50	37.2	24.5	11.1	27.1	291.00
7	60	37.0	22.7	10.5	29.8	287.30
8	70	34.0	22.7	11.0	32.3	275.55
9	80	32.5	21.6	11.8	34.1	268.30
10	90	34.9	15.6	11.3	38.2	268.65
11	100	29.1	19.7	11.9	39.3	251.90

This process is mainly influenced by the properties of the excipients. A measure of the binding efficiency could be measured by (a) the percentage (%) fines (the smaller the percentage of fines, the more the binding effects, (b) the mean granule size (the larger the mean granule size, the more the binding effect).

From Table 2, we can see the effect of increase in the content of MCC expressed as a percentage of the binary mix with PGS increased the proportion of fines of the comminuted granules from the pellets. Usually, when the amount of binder is inadequate during granulation, the result would be felt by the increase in the proportion of fines. The percentage of fines could give a measure of the granulation failure as well as the pregelatinization process. It therefore follows that the increase in the proportion of fines of the comminuted granules from the pellets (Table 2) which synchronizes with increase in the content of MCC in the binary mix with PGS decreases the binding capacity of the granules (Schmidt and Rubensdorfer, 1994).

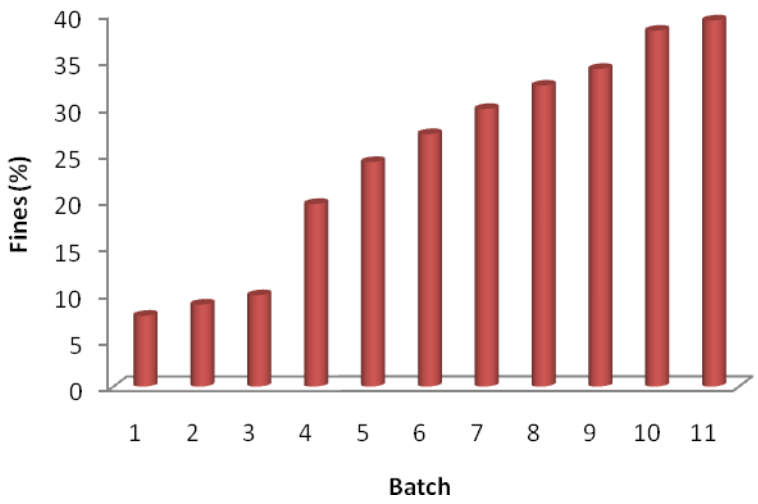

Fig 1: Effect of MCC in binary mix on fines (%)

An increase in the concentration of the content of MCC decreased the mean size of the granules comminuted from the pellets as shown in Table 2. Increase in proportion of fines would lead to a corresponding decrease in the mean granule size of the granules. This is very important because, increase in granule size can affect the consolidation and packing of granules in the tablet die before compression and this could ultimately affect the weight uniformity of the tablets (Eiseens*et al*, 2003).Fig. 1 clearly describes Table 2 where, increase in the amount of MCC led to a commensurate increase in the quantity of fines thereby

decreasing the binding efficiency of the granules.An increase in the concentration of MCC in the binary mix decreased the binding effectiveness of the granules. Larger mean granule size could affect the hardness of the tablet and lower compaction force is required to form tablets in larger sized granules than from fines (Kamal *et al;* 2008).

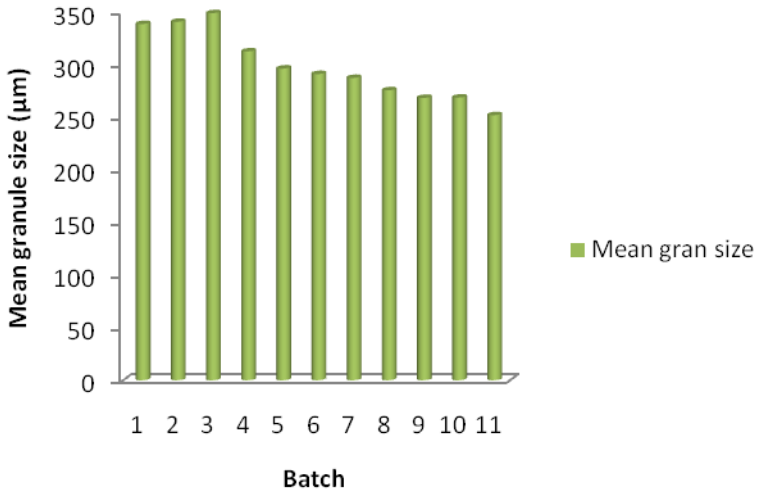

Fig 2 :Effect of MCC in binary mix on Mean granule size (µm)

Table 3: Effect of percentage (%age) of MCC with PGS on properties of folic acid tablets

Batch	%age of MCC with PGS	Compaction force (MT)	Tablet weight and % weight variation (mg ±%)	Tablet thickness (mm)	Tablet hardness (KgF)	Tablet friability (% loss)	Tablet disintegration (mins)
1	0	3.5 4.0	74.8±0.5 75.0±0.0	2.99±0.17 3.36±0.15	2.3±0.3 2.2±0.2	3.6 0.3	11.0±2.9 13.5±2.8
2	10	3.5 4.0	75.3±0.7 75.2±0.5	2.89±0.05 3.33±0.19	3.0±0.1 3.6±0.5	1.1 0.5	4.9±1.9 13.5±1.6
3	20	3.5 4.0	75.0±0.0 75.1±0.3	2.78±0.14 2.88±0.09	3.2±0.8 4.4±0.3	1.1 2.0	4.0±1.2 10.6±1.9
4	30	3.5 4.0	75±0.0 74.5±0.9	2.89±0.02 2.76±0.15	4.0±0.5 4.7±0.6	0.0 0.0	11.6±1.7 14.1±1.6
5	40	3.5 4.0	75.1±0.3 73.7±1.5	3.00±0.15 2.85±0.08	5.6±0.3 5.0±0.6	0.3 0.3	11.7±1.7 13.2±1.0
6	50	3.5 4.0	75.5±1.1 75.2±0.5	3.17±0.05 3.35±0.06	4.3±0.1 5.3±0.5	0.0 0.0	9.4±3.7 12.1±1.9
7	60	3.5 4.0	75.9±0.9 75.6±1.1	3.34±0.05 2.80±0.10	1.9±0.1 5.3±0.3	0.5 0.3	0.6±0.3 9.1±0.8
8	70	3.5	75±0.0	3.37±0.05	1.9±0.2	2.7	0.6±0.3

		4.0	75±0.0	3.15±0.20	4.4±0.8	0.5	7.2±1.1
9	80	3.5 4.0	75.3±1.3 75.4±0.8	3.81±0.10 3.40±0.28	0.7±0.3 1.7±0.2	3.4 0.5	0.1±0.0 0.2±0.1
10	90	3.5 4.0	79±0.9 75±0.0	3.90±0.05 3.32±0.03	1.1±0.1 3.0±0.1	1.7 0.5	0.2±0.0 1.3±0.3
11	100	3.5 4.0	75±0.0 75±0.0	3.31±0.11 3.16±0.06	0.6±0.0 2.5±0.2	0.3 0.6	0.1±0.0 0.8±0.3

Fig. 2 also shows a decline in the mean granule size as amount of MCC increased thereby leading to a decrease in the binding efficiency of the granules.The effect of the binary mix and compaction force on properties of folic acid tablets was evaluated. On the tablet weight uniformity, the percentage weight variations of the tablets whether at compaction force of 3.5 or 4.0 Metric tonnes were all between zero (0%) and 1.3%. No distinct pattern was observed in the variations. The allowed variation in weight of a micro dose tablet as folic acid is equal to or better less than 10%, therefore, the tablets are said to be within the pharmacopoeial standard.

There appears to be no variation with increase in compaction force. In some, it was a decrease, while others showed an increase but generally, with increase in MCC content, led to an increase in the thickness of the tablets compressed (Lewis *et al*, 2013).

The higher the level of plasticity, the thinner the tablet thickness. When the binder is highly efficient, the elastic recovery of the compact would be absent (Bolhuis et al., 2005). Since 0% MCC(100% PGS) produced much thinner tablets than 100% MCC (0% PGS), it therefore follows that as pressure was applied, PGS was more compressible than MCC provided that they have the same specific gravity.

On the tablet hardness, the higher the binding action, the higher the tablet hardness. Table 3 showed that the hardness increased with MCC content from zero (0) up to 40% at compaction force of 3.5MT and thereafter decreased. At 4.0 MT, there was an increase in hardness of the folic acid tablets from zero (0) up to 60% and thereafter decreased. This means that the increase in the concentration of MCC increased the binding efficiency of the granules in the batch.

The decrease in subsequent tablet hardness showed that there is an optimum binary mixture beyond which the efficiency of the binder inherent in the granules decreased (Brook and Marshall, 1968).

On the tablet friability, it was discovered that increase in compaction force produced tablets that were less friable. Also, an increase in the proportion of PGS produced tablets with reduced friability. This is true because increase in compaction force increases densification of the compact leading to a decrease in friability and a resultant increase in tablet hardness (Vasinee *et al*, 2004).The disintegration time was seen to decrease from 0% PGS until 30% PGS when it began to increase with increase in PGS content. The British Pharmacopoeia (B.P) set a maximum limit of 15 mins while United States Pharmacopoeia (U.S.P) is 30 mins for uncoated tablets. In all the batches examined, the disintegration varied from 0.1 min to a maximum of 14 mins which are all within the B.P standard. Tablets with high content of MCC disintegrated at the shortest time i.e from 60% at compaction force of 3.5 MT. This means that the higher content of MCC in folic acid tablet caused a shorter disintegration time. MCC produces tablet disintegration by two mechanisms: capillary or wicking due to interparticulate water and swelling due to high powder porosity (Jenkins and Donald, 1998). Generally, an increase in compaction pressure increased disintegration timeas a result of densification of the tablet matrix which would obliterate capillary forces within the disintegration medium responsible for shortening the disintegration time (Schlack*et al*, 2001).

CONCLUSION

The binary mix of PGS and MCC produced tablets with satisfactory properties like enhanced binding capacity and compressibility due to intimate association of both excipients.

The relatively poor flow properties, low bulk density, loss of compactibility and sensitivity to lubricants of MCC were masked and complemented by the increased flowability and compressibility of PGS.Also, an increase in compaction pressure gave rise to tablets with reduced tablet thickness, increased hardness and reduced friability due to higher densification effect on the tablets.

PGS produced tablets with longer disintegration time (13.5 mins) compared to pure MCC content (0.8 min). This showed that MCC is a better disintegrant than PGS.

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