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TABLETING PROPERTIES OF THERMALLY ACTIVATED COW BONE POWDER IN HIGH DOSE FORMULATION

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ABSTRACT

Activated cow bone powder was evaluated and found suitable as a diluent in the formulation of low and high dose drugs. This study was conducted in order to compare the diluent properties of dicalcium phosphate (DCP) and activated bone powder (ABP) in the formulation of high dose drugs. The mixed powders were pelletized with the specac pelletization machine, using a compaction force between 10-20 metric tonnes. A sample weight of 666 mg of the granules was used to calibrate the volumetric fill of the die using 12.5 mm punch and die set. The appropriate compression force which varied from 10-20 metric tonnes was applied to compress the granules into tablets. The formulated metronidazole tablet was evaluated for properties such as weight uniformity, thickness, crushing strength, friability, disintegration and organoplastic. Compressibility of the pellets increased with decrease in particle size fractions, and the ABP compressibility was found to be higher than that of DCP. The crushing strength of compacts formed, decreased with increase in initial particle size fraction. The disintegration times were within the acceptable time limit. The hardness of the tablets containing same formulation with ABP compared with DCP was higher in all cases. The friability values of formulations I and II of the tablets ranged between 0.4 to 0.8%, all within the value of not more than 1% standard, normally fixed by most tablet manufacturing industries. The tablet weight variations of <2% showed that the weights of the tablets were uniform. Activated cow bone powder was found to be better direct compressible diluents than the commercially available dicalcium phosphate for high dose drugs such as metronidazole.

Keywords: Formulation, Metronidazole, Activated bone powder.

INTRODUCTION

Aside the drug (active ingredients), a tablet also contains other substances called excipients, additives or adjuvant [1]. These substances are used in tablet production to impact aesthetic values, control drug release, enhance drug stability and give a suitable physical form to the tablet as well as mask unpleasant taste [2]. Banker and Anderson [3] and Rubinstein [1] have reported that the tablet is the most common oral dosage form used in this century. This might not be unconnected to the advantage the tablets affords both the manufacturers and the users [4]. Problems encountered in tablet production include capping/ lamination, chipping, sticking, picking and binding. These problems usually occur, due to improper formulation or lack of proper manufacturing processes. Various calcium phosphate salts being marketed for directly compressible purposes have been reported [5]. Roberts [6] and Adikwu [7] reported that bone is largely calcium phosphate salt in the divalent form and could possess some directly compressible properties when micronised. Emenike and his colleagues [8] recently purified and utilized cow bones for tableting purposes. Activated cow bone powder was found to be better directly compressible diluents than the commercially available dicalcium phosphate in the formulation of folic acid (low dose drug) tablets [9]. Therefore, this study was embarked upon in order to evaluate the role of activated cow bone powder as a diluent in the formulation of poorly compressible high dose material such as metronidazole.

MATERIALS AND METHODS

Metronidazole tablet formulation containing ABP/DCP as diluent

To determine the diluent characteristics of ABP in high dose drug, metronidazole formulations containing

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varying quantities of ingredients were constituted as shown in Table 1. In Formulation I, all the ingredients except magnesium stearate (lubricant) were admixed, pelletized and comminuted into granules. The lubricant was admixed as extra-granular excipient. ABP when compared to DCP was milled to 5 µm size so as to be comparable to the 4.5 µm size of DCP. This comparative diluents type effect for ABP and DCP was applied in formulation I and formulation II respectively. All ingredients were mixed, pelletized and tableted as described in folic acid formulation reported by Emenike and his colleagues [9]. However, compression forces of 10-20 metric tones were used for pelletization. A sample weight of 666 mg of the granules was used to calibrate the volumetric fill of the die using 12.5 mm punch and die set. The appropriate compression force which varied from 2-10 metric tones, was applied to compress the granules into tablets.

Mixing

The ingredients that were to be pelletized (see Table 1) were mixed together in the Z blade mixer by doubling titration mixing techniques, starting with the active ingredient. This required seven additions, each addition being mixed for one minute. The whole mixed powder was then mixed for three more minutes, making a total mixing time of ten minutes.

Pelletization

Approximately 2.5g weight of mixed powders was pelletized with the Specac pelletization machine, using a compaction force between 10-20 metric tonnes. The weight of the pellets was accurately determined with the mettler balance and the thicknesses of the pellets were measured by the micrometer screw guage. The pellets were comminuted with laboratory designed hammer mill, which hit the pellets at the same speed to crush through a 1.7 mm sieve clamped firmly to the round spouted edge of the stainless steel receptacle. The particles so produced were sieved through a stack of endecott sieves. The mean particle/granule size of the comminuted particles was estimated by relating the sieve mesh with the fraction of the weight of granules retained on the respective sieves.

Final mixing

The weight of extra-granular ingredients according to the desired percentage in Table 1 was added to the known weight of granules comminuted from the pellets in the cylindrical, planetary, tumble mixer, which was set to mix for a total of ten minutes.

Tableting

The weight of 666 mg of granules was put in the die of the 12.5 mm punch and die assembly of the Erweka single station tableting machine to calibrate the die fill volume and set the appropriate compression force which varied between 2 to 10 metric tonnes. The granules were then fed from the hopper and the tableting machine was set to form tablets at a regular rate.

Evaluation of tablet properties

Weight uniformity

Using the Mettler balance, 10 tablets were weighed together and then individually. The mean weight of the tablet and the percentage weight deviation from the mean weight was calculated. The extent of the percentage weight deviation from the mean weight was used as a measure of the tablet uniformity.

Tablet thickness

The tablet thickness was determined using the micrometer screw gauge. The mean of 10 readings was determined. Specific tablet thickness (ST) is defined as the thickness per milligram weight of the compact or tablet.

Tablet crushing strength

The crushing strength was determined with the Monsanto hardness tester. The mean of 10 readings was taken.

Tablet Specific Crushing Strength

Metronidazole tablet weighing 666mg with diameter of 12.5mm was produced in this study (Table 1). Since a comparison of the crushing strengths of a low and high dose tablet formulations is not possible because the two types of tablets (folic acid and metronidazole) had different mean weights and diameters, the crushing strengths were converted to specific crushing strengths (CSs) using this formula. CS_S = CS (kg/force) / tablet weight (mg), where CS_S is Specific crushing strength and C_s is Crushing strength.

Friability test

Friability test was carried out to determine the extent to which the tablets would withstand chipping and abrasion during transportation and normal handling. By this test, the standard used by most manufacturers is that loss in weight per 10 tablets should not be more than 1%. Ten tablets were dusted, weighed (I_w) and placed in an Erweka friabilator and set to rotate at 25 r.p.m. for 5 minutes. At the stop of the rotation, the tablets were removed and again dusted and re-weighed (F_W). The difference in weight expressed in percentage, gave the value of Friability (F). Friability (F) = $(1 - {}^{F}{}_{W}/I_W)100$ (Where F is percentage friability, Iw is initial weight of tablets, Fw is final weight of tablets).

Tablet disintegration

The *in-vitro* disintegration time of the tablets was determined as recommended by British Pharmacopoeia [10]. This is the time it takes a tablet to break up with no fragment remaining on the screen. The Erweka tablet disintegration apparatus was used for the test. One tablet was placed in each of the six tubes sealed with a 10 number mesh screen at the bottom. The tubes were lowered into a

bath of distilled water maintained at 37^{o}C. The time taken for the tablets to disintegrate was taken as the disintegration time for the batch.

Tablet organoplastic test

The tablets produced were carefully examined physically for any defects such as sticking, picking, capping, lamination, cracking, etc.

Table 1. Metronidazole tablet formulation containing ABP/DCP diluent, indicating composition of ingredients pelletized extra and intra granularly

S/No.	Ingredients	Content (%)	Formulations	
			I	II
1	Metronidazole	30.0	●200	●200
2	Diluent	44.7	●300	●300
3	MCC	20.0	●131	●131
4	SSG	5.0	●33	▲33
5	Mg. St.	0.3	▲2	▲2
Total		**100.0**	**666.0 mg**	**666.0 mg**

ABP* = activated cow bone powder, DCP* = marketed dibasic calcium orthophosphate powder
MCC = microcrystalline cellulose marketed as Vivapar®, SSG = sodium starch glycollate (super disintegrant), Mg.St. = magnesium stearate, ● = intra-granular ingredient, ▲ = extra-granular ingredient

Table 2. Comparative compressibilities of metronidazole formulation pellets using ABP and DCP as diluent

Formulation		Inverse specific thickness
I	ABP	0.80
	DCP	0.78
II	ABP	0.81
	DCP	0.80

Table 3. Comparative properties of metronidazole granule formulations using ABP and DCP as diluent

Formulation		Intra-granular			Extra-granular		
		Carr's index (%)	Flow rate (g/s)	MGS (µm)	Carr's index (%)	Flow rate (g/s)	MGS (µm)
I	ABP	24.8	5.61	441	21.0	7.12	440
	DCP	23.6	4.21	456	18.3	5.11	440
II	ABP	20.2	7.78	503	27.2	6.42	429
	DCP	22.2	7.70	478	24.0	6.31	401

Table 4. Comparative properties of metronidazole tablets using ABP and DCP as diluent

Formulation		Weight (mg)	Weight variation (±%)	Thickness (mm)	IST	CS (N)	DT (min)	Friability (% loss)
I	ABP	667	1.5	4.30	0.153	88.2	1.7±0.5	0.5
	DCP	668	1.0	4.45	0.149	78.4	1.0±1.0	0.4
II	ABP	669	2.0	4.28	0.156	71.5	1.5±0.2	0.8
	DCP	664	2.2	4.20	0.159	59.8	1.0±0.4	0.8

CS = Crushing strength, DT = Disintegration time, IST = Inverse specific thickness (10^{3}mm/mg),Formulation I & II (Table 1)

Table 5. Effect of particle size of diluent (ABP) on pellet properties of metronidazole formulations

ABP particle size (µm)	Inverse specific thickness (10^{-3}mm)
1000	0.83
500	0.80
355	0.76
250	0.79
180	0.83
90	0.81
50	0.97

Table 6: Effect of particle size of diluent (ABP) on granule properties of metronidazole formulations

ABP particle size (µm)	Carr's index (%)	Flow rate (g/s)	MGS (µm)
1000	2.5	9.55	535
500	3.3	9.45	464
355	15	9.25	462
250	18	9.18	484
180	21	9.19	480
90	18	9.98	515
50	18	9.10	541

Table 7: Effect of particle size of diluent (ABP) on properties of metronidazole tablet

ABP particle size (um)	Wt (mg)	% Weight variation (±%)	Inverse specific thickness (10^{-3}mm)	CS (N)	DT (Min)
1000	664	1.6	0.158	10.8	3.8
500	667	1.9	0.151	11.8	2.7
355	665	1.3	0.154	13.7	2.4
250	668	2.1	0.154	14.7	2.5
180	665	0.8	0.154	17.6	1.7
90	664	0.8	0.156	10.8	1.5
50	667	1.1	0.159	5.9	1.1

CS = Crushing strength, DT = Disintegration time

RESULTS AND DISCUSSION

The effects of ABP as diluent in metronidazole formulation on granules and tablet properties were studied (Table 1, 2). The pellets were compacted by 20MT force using a 12.5 mm punch and die, while 4MT force and 12.5 mm punch and die were used for the tablets. Compressibility of the pellets increased with decrease in particle size fractions. The highest compressibility was between 50 µm to 90 µm (fines), and much lower between 180 µm and 1000 µm. This is in agreement with the earlier statement that lower particle size fraction (fines) are more compressible than the larger particle sizes since they are already densely packed. Most of the energy of compression will therefore be used for rupturing of bonds and bringing the granules together for compaction unlike with the larger particle size fractions, where part of the energy will be used for densification. While for the tablets (Table 5-7), there is no appreciable difference for the different particle size fractions. This has also been stated earlier, that possibly after the first pelletization, there is no elastic recovery, so the granules become less compressible into tablets. This is attributable to the heat of activation that has destroyed the crystalline structure of the molecules and the potential for elastic recovery of the bonds. The higher the compressibility values, the harder the compact formed, so also is the crushing strength of the compacts formed. This is depicted in Table 7. The crushing strength of compacts formed decreased with increase in initial particle size fraction. This is in agreement with the compressibility trend of the various particle size fractions. The effect of the initial particle size of ABP as diluent on mean granule size (MGS) in this formulation (metronidazole), followed a similar trend as that of Folic acid formulation [9]. Between 50µm - 500µm, the MGS produced, decreased with increase in initial particle size of ABP, while between 500 µm – 1000 µm, the reverse was the case, i.e. increase MGS with increase initial particle size fractions of ABP. For the initial particle size fraction of 50 µm – 500 µm, the finer the particles, the more compressible and harder the compacts formed, which on communition give larger MGS. For the larger (granular) initial particle size fractions, which are expected to be more porous, part of the force of compression will be used to densify the granules, before rupturing them for binding together. Depending on the porosity of the granules, which is higher with larger particles [11] the force left for rupturing and binding, would be lower. This probably caused the MGS increase with increase in initial particle size fraction of ABP.

In Tables 3, 4 and 5, the marketed DCP which has a particle size of 4.5 - 5 µm (as earlier determined), which was much lower than that of ABP had lower values of pellet and tablet compressibility as well as MGS. For tablet crushing strength, the DCP also had lower values as compared to those of ABP of small particle sizes. The values of the Carr's Index, varied from 18 - 27% for the two formulations (Table 3). When the granules were mixed with extra-granular excipients, the flow rate of the granules changed. On mixing with only magnesium stearate, in formulation I, the flow rate increased but when formulation II was mixed with sodium starch glycolate and magnesium stearate, the flow rate of the granules decreased.

In the first case, the increased flow rate by the admixture of magnesium stearate was influenced by the lubricant action of magnesium stearate. This could have happened by the adsorption of magnesium stearate to fill and smoothen the cracks and crevices of granule surfaces

[12]. By so doing, the resistance to flow by friction is greatly decreased, resulting in increased flow rate. In the case of extra-granular admixture of sodium starch glycolate and magnesium stearate together, the amount of fines had increased. This is more than enough the particles could adsorb on the granules. Therefore, there is expected to be some stagnation or impedient to granule flow. In fact, this has been corroborated by the effective decrease of MGS after the admixture. The particulate flow rate on account of lower surface area to volume ratio for bigger particles, while decrease with finer particle sizes were impediments to flow, are all surface phenomenon [12]. The granule flow rate is fast enough [13] in ensuring uniformity of flow rate of granules into the die. This would assure uniformity of tablet weight, provided that the size distribution of the granules was uniform. The mean particle size of the granules was shown to be high enough (about 400µm size) for fast flow of the granules.

The weight variation of the tablets in the Table 4 was about 2%, meaning that the tablet weight distribution was highly uniform. The 2% range is within more of statistical limits of error, and could not be due to granule size effect. Tables 2 and 4 showed the compressibility of the tablets and pellets containing ABP compared with those containing DCP, ABP was slightly more compressible than DCP. The compressibility was appreciably higher, when magnesium stearate was the only extra-granular excipient, and only slightly higher when sodium starch glycolate and magnesium stearate together were the extra-granular excipients. In other words, the presence of sodium starch glycolate, more or less masked the comparative compressibility of pellets. However, in the two tableted formulations, there was no much difference between the compressibility of ABP and DCP diluents. Possibly, this is due to extra-granular content effect of the granules that were tableted.

The disintegration times of the tablets were between 1.0 minute as the minimum and 1.7 minutes as the maximum. When it is considered that the compendial disintegration timer of not more than 15 minutes is taken note of, the disintegration time was good enough, by virtue of the formulation and by the virtue of the dry granulation process which is well acknowledged to cause fast disintegration of tablets. Dry processed granules do not have aggregates of bound particles as in wet processed granules. Dry processed granules also have longer channel of capillaries than wet processed granules [11], and therefore in tablets processed from dry process granules where there are longer and narrower channels of capillaries, there will be faster entry of disintegrating fluid, by enhanced capillary forces. This leads to much faster disintegration rate experienced with dry processed tablets.

The friability values of formulations I and II of the tablets as in Table 4 range between 0.4 to 0.8%, all within the value of not more than 1% standard normally fixed by most tablet manufacturing industries. The friability of dry processed tablets on the other hand is normally higher than those processed through wet granulation [14]. This characteristic behaviour is thought to be attributable to attachment of finer particles onto the surface of the tablets, which could easily be abraded during handling and transportation as exemplified by the scooping and banging in the friability tester.

In Tables 5 and 7, it is shown that as the particle size increases from 355µm to 1000µm, for the pellets and 500µm to 1000uµm for the tablets, compressibility value increases. In contrast, as the particle size increases from 50µm to 355µm and 500µm respectively, the compressibility value decreases. This can possibly be attributed to density or porosity of the particles. The consolidation/densification initial phase of compression appears to be the rate-limiting step. The consolidation of the particles is the stage that just precedes the fracturing and binding. At that stage, larger particles have higher compact / binded solid volume to surface area ratio. So the compacting force would enhance the binding of the compacts, which is higher compressibility. The finer the particles, the less porous they become. That is to say that the particles are more closely packed together, therefore, little part of the compaction force is needed for consolidation. The higher energy of compaction left would fracture and bind more particles snugly together. This is probably why there is higher compressibility with finer particles having the same force of compaction compared to the larger particles.

The compressibility of the granules produced from pellets with different initial particle size fractions of diluents was not significantly different, especially the formulation that had intermediate particle size that were produced from ABP initial particle sizes from 180 to 500µm size which produced the mean granule size of 473µm. This could be the reason why the tablet compressibility from pellet derived granules containing initial ABP particle of 180 to 500µm particle size produced the same range of compressibility as shown in Tables 5 and 7.

Granules with mean granule size larger than 300 µm were very flowable. The flow rate of the granules by the flow meter was at least 9g/s i.e. 9000 mg/sec (Table 6). The flow rate of granules is not known to be standardized like friability or Carr's indices although these two are not compendial standards. From the Carr's index values related to flowability, the Carr's particle settling index of 3 to 21% is regarded as being excellent [13]. The significance of these values; lower Carr's index, higher mean granule size, and fast flow rate, mean that the granules being compressed into tablets will fill the die at a fast and regular rate. Provided the granule size distribution is uniform, the weight of tablet would be uniform. The tablet weight variations of less than 2% as shown on Table 7, show that the weights of the tablets were uniform. Values of Carr's index as shown in Table 6 are inversely related to the particle size, i.e decreases with increase in particle size fraction. Much of the compaction force was used for densification leaving lower force for binding and therefore softer tablets. Table 7

shows the effect of diluent particle size on tablet disintegration time. The disintegration time is shown to be directly related to the particle size, i.e. decreases with increase in particle size fractions. Tablets formed from larger initial particle size are more porous with wider pore size, known to have lower capillary force and therefore slower disintegration time.

CONCLUSION

Formulation studies showed that ABP is better directly compressible diluent than the commercially available DCP for high dose drugs such as metronidazole tablets.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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