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Design of a New Compressible Metronidazole Powder: Co-precipitation with Ovalbumin

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Abstract

Metronidazole powder was co-precipitated with egg albumin solution at concentrations of 10 to 40 % w/v. The batch treated with 15 % of the ovalbumin was compared with metronidazole granulated with starch. Brittle Fracture Index (BFI), crushing strength, Hausner Factor (H_f) and Carr's Index (I) were used as basis of evaluation. The effect of Avicel PH101, Emcompress and Primojel on the tableting properties of the egg albumin treated metronidazole was also investigated. The aggregation of metronidazole particles improved the fluidity and compressibility of the amoebicidal drug. The high elastic recovery behaviour of plain metronidazole was rendered plastic, having BFI of 0.4 following treatment with ovalbumin. Avicel PH101 and Primojel were found to be useful excipients in optimizing the compact strength or disintegration time of co-precipitated metronidazole (CPM) tablets at minimal concentration of 5 % each. Emcompress could also be employed with CPM at 15 % w/v in the presence of a superdisintegrant, such as Primojel. This co-processing technology may well be of economic importance in metronidazole tablet production as minimal excipients and steps are required.

Key words: Ovalbumin, co-precipitated metronidazole (CPM), fluidity and plasticity

Introduction

Over the years, there has been an increasing interest in microencapsulation technique involving the use of aqueous-based film coating solutions. Such substances are non-toxic, non-volatile and cheap, an example being ovalbumin, which has been used for microencapsulation process (1). Torrado-Duran *et al* (2, 3) employed ovalbumin in the production of microencapsulated paracetamol particles. The bitter taste of the analgesic drug was masked to some extent, fluidity and compressibility characteristics of the powder were improved and the capping tendency was greatly reduced. The tensile strength of the compacts resulting from the treated paracetamol was similar to that of tablets obtained using paracetamol granulated with Povidone or gelatin as binders.

The imidazole derivative, metronidazole, which is used in the treatment of trichomonal infections of the genito-urinary tract, intestinal amoebiasis, giardiasis and *H. pylori* associated peptic ulcer diseases exhibit poor compressibility and fluidity characteristics (4, 5). The tableting qualities of metronidazole, which exhibits high elastic recovery and capping tendency has been modified by means of granulation technique using methylcellulose and polyvinylpyrolidone as binders (5). In this investigation, metronidazole particle was co-

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precipitated with ovalbumin at different concentrations. The powder and tableting properties of the co-precipitated metronidazole (CPM) was compared with that prepared by wet granulation technique. The effect of direct compression excepients and a superdisintegrant on the compressibility and disintegration profiles of the treated metronidazole powder was also studied.

Materials and Methods

Materials: Metronidazole (Vision Pharmaceutical Co.Ltd, China), Ovalbumin solution (prepared in our laboratory, using fowl eggs obtained from a market at Idu-Abuja), Avicel PH101 (FMC Corporation, USA), Dicalcium Phosphate Dihydrate as Emcompress (E. Mendel Corporation, USA), Sodium starch glycolate NF as Primojel (Generichem Corp., USA), Maize starch (BDH chemicals, England) magnesium stearate (Hopkin and William, England). All the chemicals were used as obtained from the manufacturers or suppliers.

Methods:

Preparation of ovalbumin: A small incision was made on the shell of the fowl egg just enough to allow the withdrawal of the white liquid portion that contains ovalbumin. The collection was screened through white muslin so as to remove any debris and the clear solution was stored in a clean glass bottle, at 58 °C.

Preparation of aggregated metronidazole particles: Five batches of a mixture of metronidazole powder and ovalbumin were prepared so as to contain 10, 15, 20, 30 or 40 % of concentrated albumin respectively. In each case, 100 g of metronidazole powder was dispersed in the egg albumin solution in order to obtain a 50 % concentration of the drug in the final suspension. The suspension was stirred for 10 min and maintained at 70 °C in a water bath (Karl Kolb Scientific Model FGL 10083, UK) for 15 min with occasional stirring. As soon as the albumin was denatured, stiring was discontinued and the mass of coagulated albumin enclosing the metronidazole particles was dried at 60°C for 12 h, screened through a sieve of 300 m aperture and stored in a desiccator.

Particle properties: The bulk density was assessed by means of tapping technique using an automatic tapping equipment, Stampfvolumeter model STAV 2003 (JEF, Germany). Both bulk and tapped densities were calculated. Hausner factor (H_f) was determined using the expression: $H_f = d_t/d_b$ where d_b and d_t represent bulk and tapped densities respectively (2). Carr's index (6), expressed as percentage compressibility index (I) was calculated as $[(d_t - d_b)/d_t] \times 100$. The particle density ($d_p$) was determined using the specific gravity bottle (Model 930 Beckman Instruments, Germany) as earlier reported by Nicklasson, and Nyqvist (7). The angle of repose was determined by measuring the height (h) and radius (r) of the cone formed by the free fall of particles from a fixed position and the angle of repose was determined using the expression tan=h/r (8).

Determination of metronidazole content in co-precipitated metronidazole (CPM) particles: The different batches of the treated metronidazole particles were

analysed for drug content in accordance with the official monograph specifications (9) and assay was done using Beckman HPLC equipment.

Metronidazole granules: The granules were formulated by wet massing in accordance with the general formula; Metronidazole 400mg, Starch (disintegrant) 40 mg, Starch Paste (10% w/w) qs, and Magnesium stearate 0.75% of the dry blend. Starch paste served as the binder wet or dry screening was done using sieves of size 600 and 300 m apertures respectively.

Formulation of CPM tablets: Effect of the tableting excipients, Avicel PH 101, Emcompress and Primojel on the tableting properties of metronidazole particle, co-precipitated with 15% ovalbumin was studied. Six batches were formulated so as to contain Avicel or Emcompress at 5, 10 and 15% respectively. Another six batches were made similarly with each containing 5% Primojel as disintegrant. Batches containing either of these excipients at the stated use levels and plain matronidazole were also made. In each case, appropriate quantities of the excipients and the drug sufficient for production of 50 tablets were weighed and mixed inside a bottle for 5 min.

Compression: Different batches of the formulations were tableted to a target mass of 500 mg using the basket type tablet machine Model THP (STC Machinery Co. Ltd, China) fitted with a punch of 12 mm diameter. The tablets were produced at different compression forces of 17.5, 20.0 and 22.5 KN. The tableted samples comprised of granulated, co-precipitated or untreated metronidazole powder.

Brittle Fracture Propensity: Batches of tablets were made with co-precipitated metronidazole obtained with 15 % ovalbumin solution or that prepared by wet granulation technique. In each case, tablets were made with or without stress concentrator. The brittle fracture index (BF1) was determined in accordance with the Hiestand et al. model (10, 11) where BF1 = 0.5 ([T_s/T_o] 1) while T_o and T_s represent the tensile strength of compacts with or without stress concentrator. The average of three determinations was taken as BFI for each batch.

Evaluation of tablets: Crushing strength was determined using the Monsanto hardness tester in which the mean of 3 determinations was taken as the hardness per batch. A digital micrometer (Mitutoyo Corporation, Japan) was used for measuring the diameter and thickness of the tablets. Erweka Hardness Tester was used to determine diametral crushing strength and the tensile strength (T_s) was calculated in accordance with Fell and Newton's expression (12):

$$T_s = \frac{2P}{Dt}$$

Where *P* is diametral crushing strength, *D* is tablet diameter and *t* represents the thickness.

The Erweka dual drum friabilator was used for the friability study. The mass of 10 tablets taken per batch was noted before and after 4 min of running the equipment at 25 rpm, friability was calculated as percentage mass loss. In situations where capping or fracture occurred, friability of the formulation was not evaluated. The in-vitro disintegration time (DT) was determined in accordance with BP

specifications (9). The Erweka disintegration tester Model EP4-4 was used in which distilled water at 37 ± 0.5°C served as the disintegration fluid. Dissolution test was performed using Erweka dissolution tester Model DT. A 0.1N HCl served as emersion fluid maintained at 37 ± 0.5 °C and ran at a speed of 100 rpm. Withdrawn samples were analysed using Shimadzu spectrophotometer Model UV-160A. Five determinations were made and the mean was taken.

Results and Discussion

The results presented in Table I show that co-precipitation of metronidazole particles with ovalbumin modified the elastic behaviour of the amoebicidal agent. The untreated drug particles failed to produce stable compacts following withdrawal of the compression pressure. In contrast to this, tablets resulting from CPM were stable, robust and exhibited glossy exterior. It was however observed that the crushing strength of compacts made from CPM was within a narrow range of 29.4 to 314 N at varied ovalbumin concentrations of 10 40%. This might be due to a limited plastic flow during the compaction process irrespective of concentration of the egg albumin. Hardness of the co-precipitated metronidazole tablets at 10 to 40% w/v concentration of the protein solution is somewhat

Below the minimum average strength of 39.2N considered as adequate hardness for compressed tablets (13). Batches formulated with 10-15% of the egg protein disintegrated within 10 min whereas those made with ovalbumin at concentrations above 20 % failed to disintegrate after 60 min. The glossy appearance of tablets made from CPM is suggestive of some lubricating or coating effect due to the incorporated ovalbumin. The coating wall might have increased with concentration of the protein binder leading to corresponding rise in water repelling tendency with attendant longer disintegration time The result obtained here is similar to what had been reported earlier by Torrado-Duran *et al* (2, 3). Friability is one of the indices used for determining the hardness of tablet (13). The tablets made from co-precipitated metronidazole particles failed the friability test in spite of the high disintegration time even at concentrations of 30 % and above. This is most probably due to weak intra bonding propensity. The weak distance forces responsible for bonding (14) and the interparticulate solid bridges created during compaction appears to have assumed similar proportion irrespective of the

Table 1: Tablet properties of co-precipitated metronidazole particles

Ovalbumin (% m/v)	Hardness (N)	Disintegration time (min)	Drug content (%)
10	28.5	6.0	99.6
15	29.4	9.0	99.1
20	31.4	45	97.8
30	30.4	>60	89.5
40	31.4	>60	87.9

concentration of the ovalbumin. The average crushing strength remained steady in the region of 29.4N.
The percentage drug content in table 1 was observed to decrease with concentration of the ovalbumin and this could be attributed to increasing level of the constituent bridge between the agglomerated dry particles.

On the basis of the minimal influence of coating on the drug content at concentrations below 20%, the batch of metronidazole co-precipitated with 15% egg albumin, which had a tablet hardness of 31.4N with disintegration time of 9 min was selected. The particulate properties were compared with those of granulated metronidazole using the indirect methods as shown in Table 2.

Cohesive powders and particles with high interparticulate friction have Hausner factor (H_f) greater than 1.6 or compressibility index (CI) above 40% whereas those with H_f values of approximately 1.2 or CI less than 18% are classified as free flowing powders (15). It has also been reported that compressibility index values in the range of 18 - 22% is suggestive of fair flowability potential whereas materials having index values above 23-25% are rated as possessing poor flow potential (15, 16). In this study, it was observed that treatment of metronidazole with ovalbumin resulted in free flowing agglomerated particles, which was as good as the granulated powders, the H_F value being 1.2 in either case. Untreated metronidazole particles exhibited poor flow propensity having H_F of 1.4 and compressibility index of 25.7 %. Angle of repose generally supplies qualitative information on the flow of powder and granules (8). When the angles are more than 50^o, flow is poor, below 30^o indicate good flow and above 40^o is suggestive of irregular flow. The result obtained here in respect of the angle of repose is in agreement with the impression derived from Hausner factor or compressibility index parameters. Co-precipitated and granulated metronidazole particles showed good flow characteristics with angle of repose values of 29 and 27^o while plain metronidazole exhibited irregular flow behaviour with angle of repose above 40^o.

Brittle fracture propensity indicates the ability of a compact to relieve stresses caused by deformation. A brittle fracture index (BFI) of zero indicates no brittle behaviour but one that tends to unity, is indicative of high brittleness (17). The result of the tensile strength of compacts made with or without stress

Table 2: Some derived properties of metronidazole formulations

Parameters	Metronidazole samples		
	Co-precipitated	Granulated	Plain (untreated)
Bulk density, d_b (g/ml)	0.71	0.64	0.61
Tapped density, d_t (g/ml)	0.87	0.71	0.82
Particle density d_p (g/ml)	1.4	1.3	1.3
Hausner factor, H_F	1.2	1.2	1.4
Compressibility index, I (%)	17.9	13.79	25.70
Angle of repose, θ (degree)	29	27	43

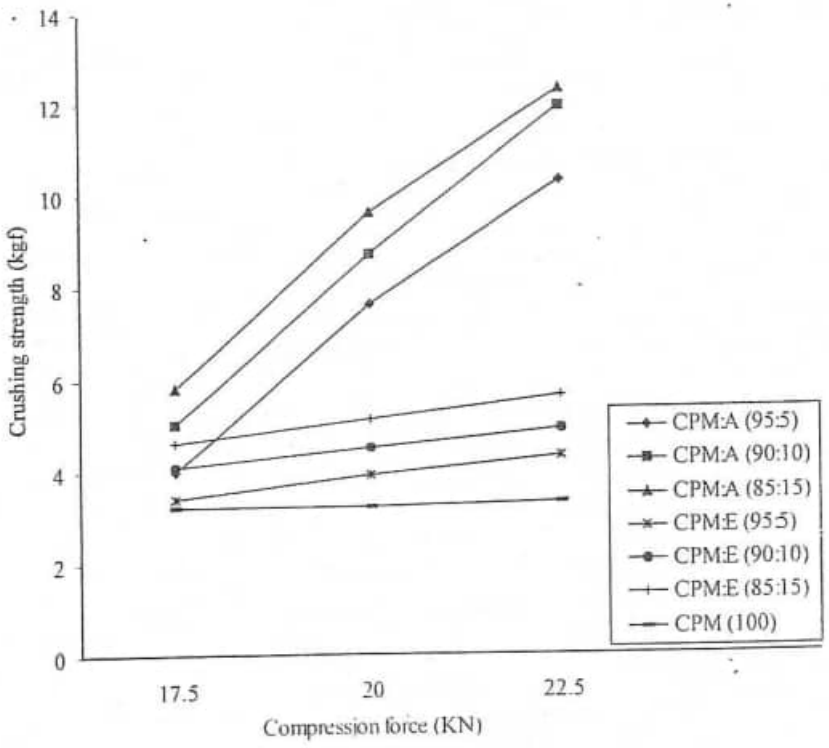
Table 3: Effect of co-precipitation or granulation on BFI of metronidazole tablets

	Tensile strength (MPa)		
Metronidazole sample	T_s	T_o	BFI
Co-precipitated	11.5	6.6	0.4
Granulated	16.6	8.0	0.5

concentrator and the calculated BFI for co-precipitated and granulated metronidazole particles are shown in Table 3.

Metronidazole powder has high elastic recovery propensity in which the BFI tends to 1 (one) under compressive load and this results in tablet failure with high lamination and capping tendency. It was noted here that co-precipitation or granulation using ovalbumin or starch paste modified the elastic recovery behaviour of the particles as evidenced in the BF1 of 0.4 or 0.5. There was no capping or lamination in both batches. Although the treatment of metronidazole particle with egg albumin modified the behaviour of the drug under compressive load, the plasticity was not optimized as evidenced from the limited compact strength of about 29.4N even at concentrations of 20 to 40%. The use of some filler-binders in

Fig. 1: Compression force profile of metronidazole formulations



A = Avicel PH101, E = Emcompress. CMP = Co-precipitated metronidazole powder

order to enhance the compact strength of CPM was therefore considered.

The effect of two direct compression excipients, Avicel PH101 and Emcompress that deforms by plastic flow or brittle fracture on the compressibility profiles of co-precipitated metronidazole particle is presented in figure 1. The tablet strength increased with concentration of the filler-binders and pressure, indicating an increasing tendency towards non-capping behaviours. While incorporation of 5% Avicel PH101 increased the crushing strength of the treated drug from 29.4 to 74.6N (150% increase in strength) at constant compression force of 20 KN, the use of Emcompress at similar concentration only increased the strength to 38.9N (30%) under the same compression force.

Table 4 shows the effect of formulation excipients on some tablet properties of co-precipitated metronidazole. All the formulations containing Avicel PH101 at concentrations of 5 - 15%, with or without Primojel showed adequate crushing strength of 56.9 to 80.4N, short disintegration time and tolerable friability values, which were below 2%. On the other hand, co-precipitated metronidazole (CPM) prepared with dibasic calcium diphosphate in the range of 5-10% concentration, with or without primojel, failed the friability test as the tablets crumbled on tumbling. The bonding strength in this set of formulations was not strong enough to withstand handling. However, at concentration of 15% of Emcompress, the hardness of the aggregated metronidazole tablets increased from 31.4 to 49.1N and friability value was as low as 1.2% at compression force of 20 KN. The batch of tablets made with co-precipitated metronidazole (without any additive), which served as the control, failed both the friability and hardness tests due to inadequate particulate bonding as postulated earlier.

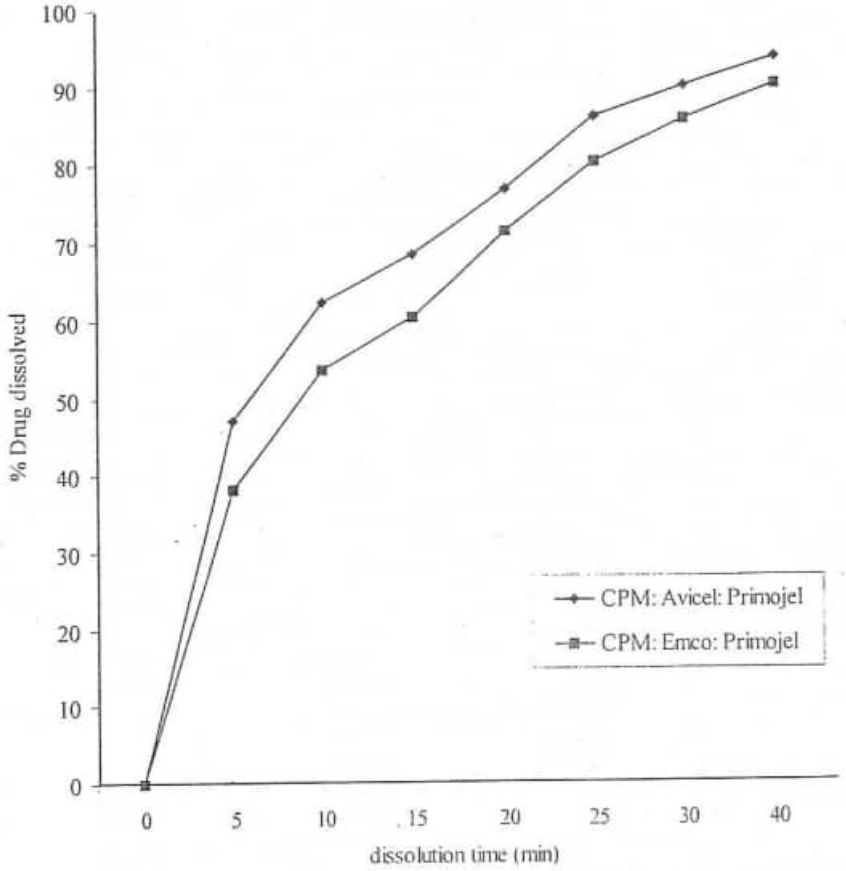
The formulations made with CPM: Emcompress in the ratio of 95:5 exhibited the highest disintegration time of 9 min. Incorporation of microcrystalline cellulose

Table 4: Effect of direct compression excipients on co precipitated metronidazole tablets

Content (% w/w)						
CPM	A	E	P	Hardness (N)	DT (min)	Friability (% loss)
100	-	-	-	31.4	9.0	NE
90	5	-	-	74.6	2.0	1.9
90	5	-	5	56.9	0.8	1.6
85	10	-	5	58.8	0.8	1.3
80	15	-	5	80.4	0.6	1.0
95	-	5	-	38 3	8.9	NE
90	-	5	5	43.2	0.9	NE
85	-	10	5	50.0	0.6	NE
80	-	15	5	49.1	0.5	1.2

CPM Co precipitated metronidazole; NE Not evaluated; DT Disintegration time; A Avicel PH101; E Emcompress; P Primojel

Fig. 2: Dissolution profile of co-precipitated metronidazole formulations



CPM Co-precipitated metronidazole: Avicel Avicel PH1101; Emco Emcompress

and/or Primojel greatly modified the water intake potential of the drug.

This is not surprising as Emcompress has no disintegration propensity whereas Avicel, which is a brand of microcrystalline cellulose has limited disintegrating property, which has been attributed predominantly to wicking mechanism of action with some swelling activities (18). Primojel is rated as one of the superdisintegrants (19, 20) because of the acclaimed extraordinary wicking potentials. The formulated tablets containing sodium starch glycolate disintegrated at fast rates. less than 40 s, compared to over 120 s in that containing MCC.

Incorporation of Primojel did not adversely affect tablet properties of CPM tablets and this is in consonance with Shangraw's report (19) that superdisintegrants do not adversely affect the compact or tablet strength of directly compressed pharmaceutical powders. It may therefore be inferred that co-precipitated metronidazole (CPM) tablets could be prepared by the incorporation of low concentrations of microcrystalline cellulose (5-15%) to enhance the tablet strength with Primojel at (5-10%) to shorten the disintegration time. On the other hand. employment of dibasic calcium diphosphate

at 15 % and above with 5% Primojel may be considered as another option in the formulation of CPM tablets. The dissolution profile of CMP tablets made with 5% Avicel PH101 or 15% Emcompress containing 5% w/w Primojel in either batch is presented in figure 2. The two formulations showed similar dissolution profiles with that containing Avicel PH101 dissolving at a slightly faster rate. The t_{50}% was 6.0 or 8.5 min for AvicelPH101 or Emcompress formulated tablets and the $t_{80\%}$ was 21.3 or 23.8 min respectively. Drug release was not impaired in either case and this makes the technique a probable option to be explored in the formulation of metronidazole tablets.

Conclusion

Treatment of metronidazole particles with egg albumin modified the tableting properties of the amoebicidal drug. The aggregated particles were found to be self-lubricating, exhibited high fluidity propensity with moderate compressibility. Therefore, addition of lubricant or glydant may not be necessary in the production of Ovamet tablets. The excipient economy and the simplicity of the technique employed here makes it a potential cost effective method to watch in the production of some pharmaceutical dosage forms. The system design may range from tablets with rapid onset of action to those having controlled release profiles.

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