Research Article

Co-processed Metronidazole Granules for Tabletting: Formulation and *In Vitro* Evaluation

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ABSTRACT

The objective of the work was to produce co-processed metronidazole granules and to formulate metronidazole tablets by direct compression. Potato starch was extracted from *Ipomoea batatas*, the starch obtained was pregelatinized. Co-processed metronidazole granules were formulated using 10 % of pregelatinized potato starch and 0, 2, 4 and 6 %w/w of polyvinylpyrrolidone (PVP) as binders. The flow properties of the granules were assessed using direct and indirect methods. The tablets were formulated by direct compression using potato starch as the extra granular disintegrant (3.5 %) and magnesium stearate as lubricants. The properties of the tablets were evaluated using official and non official tests. The results of the study showed that the flow properties of the granules were good and fell within acceptable limits for good tablet production. Metronidazole granules showed fast disintegration time, good hardness and also complied with BP specification for tablets weight uniformity. The friability results were significantly lower than 1 % for all the tablets batches ($p < 0.05$). The tablet formulations showed a fast release of the drug with maximum release (T100) at 24 min in most formulations. Therefore, metronidazole tablets could be formulated by direct compression in order to enhance the oral bioavailability of this drug.

Keywords: Co-processing, metronidazole, direct compression, potato starch, pregelatinization.

INTRODUCTION

The disintegration of tablets in most cases is the rate limiting step to dissolution and overall bioavailability of drugs. Co-processing have been develop to address these issues enhance the tabletting processes by providing a new material (adjuvant or active ingredients) that could be formulated by direct compression. Co-processing was developed primarily to address the issues of flowability, compressibility, and disintegration potential, with filler–binder combinations being the most commonly tried. Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980s with the introduction of co-processed microcrystalline cellulose and calcium carbonate [1-2]. Co-processing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible adjutants [3-4]. Co-processing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients[1-2]. Co-processed materials have advantage of improved compressibility, reduced fill weight variation, high dilution potential and reduced lubricant sensitivity. Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory and improved organoleptic properties[1]. The fundamental solid-state properties of the particles such as morphology, particle size, shape, surface area, porosity, and density influence excipient functionalities such as flowability, compactability, dilution potential, disintegration potential, and lubricating potential [1].

Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques [5]. The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques [6]. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directly compressible ingredients to manufacture satisfactory tablets. In the development of directly compressible granules by the modification of a single substance, Co-processing of two or more components was applied to produce composite particles or co-processed excipients [5]. The composite particles or co-processed multi-component-based excipients are introduced to achieve better powder characteristics and tabletting properties than a single substance or the physical mixture [6]. Directly compressible adjuvants can be prepared by various methods such as physical modification, crystallization, granulation, spray drying, co-processing and co-precipitation[3]. Direct compression technique involves simply the compression of dry blend of powders that comprises the drug and various excipients. The simplicity and cost-effectiveness of the direct compression process have positioned it as a preferred alternative to other methods of tablets production [1].

Native starches have been recognized as one of the most commonly used excipients in the manufacture of tablets which can be used as fillers, disintegrants or as binders [7-8]. In recent years pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starches in the formulation of dosage forms. However, due to the limitations of native starches such as poor compressibility and flow properties, some special starch products, like pregelatinized starch were introduced [8].

Metronodazole is an antiprotozoal and anti parasitic agent that is very effective in the treatment of amoebiasis, trichomoniasis, giardiasis and many other parasitic diseases[9]. However, this drug has poor water solubility[10]. Therefore, the aim of the study is to formulate co-processed metronidazole tablets by direct compression and to evaluate the properties of tablets formulated.

MATERIALS AND METHODS

Metronidazole (Evans Pharmaceutical Ltd., England), polyvinylpyrrolidone (PVP) (Sigma–Aldrich, Germany), hydrochloric acid, lactose (Merck, Germany), maize starch, acetone, toulene, gelatin, acacia, ethyl cellulose (BDH, England), SCMC and magnesium stearate (May and Baker, England), distilled water (Lion water, Nsukka, Nigeria). Potato starch was obtained from batch processed in our laboratory. All other reagents and solvents were analytical grade and were used as supplied.

Extraction and purification of potato starch

Ipomoea batatas L. was purchased from the market of Nsukka, Enugu state Nigeria. The potatoes were cleaned by removing the soil and stones and washed with water. The bark were properly peeled and rewashed with clean water containing 1 % sodium metabisulphite. After washing, the potatoes were reduced to a fine pulp in a rasping machine of hammer mill type. The pulp was separated from the rasped potato by means of a muslin cloth and agitation was provided using hands. During screening, the water used contained 1 % sodium metabisulphite in order to avoid discolouration of the starch by oxidative enzymes. The obtained starch suspension was allowed to settle under gravity and the supernatant was decanted. The starch suspension was washed severally using three times its volume of water for 3 days with intermittent shaking and changing of water [11]. Dewatering was done using a bag with pores of about 100 mm and pressure was applied using hand. The drying of the starch was carried out under the sun.

Preparation of pregelatinized potatoes starch

The slurry of the potatoes starch were made in distilled water and the slurry was heated to a temperature of 66^{o}C to cause partial swelling of the starch granules without causing disruption of the starch granules. The starch slurry was cooled and screened using a muslin cloth. The starch was dewatered using a muslin cloth and dried in a tray dryer at 55 ^{o}C and lather passed through a 1 mm sieve [7, 11].

Preparation of co-processed metronidazole granules

Pregelatinized potato starch (10 %w/w) and metronidazole were mixed geometrically. The powder mixtures were moistened with appropriate solution of PVP. The homogeneous moist mass was then screened through a 1.0 mm sieve and dried in a hot air oven at 60°C for 20 min. Thereafter, the granules were rescreened with a 1.0 mm sieve. A control containing pregelatinized potato starch as the filler binder without PVP was also formulated [13].

Table 1: Composition of metronidazole tablets

Batch*	Co-processed metronidazole granules (mg)	Potato starch (mg)	Magnesium stearate (mg)
F1	222.0	7.0	2.0
F2	224.0	7.0	2.0
F3	226.0	7.0	2.0
F4	220.0	7.0	2.0

*F1, F2 and F3 were formulated with co-processed metronidazole containing 2, 4 and 6 % PVP; F4 was formulated with co-processed metronidazole with no PVP (control).

Micromeritic studies

Bulk and Tapped Densities

A 50 g quantity of the granules was placed in a 100 ml measuring cylinder and the volume occupied by the sample was noted as the bulk volume. The bulk density was obtained by dividing the mass of the sample by the bulk volume, as shown in Equation 1 [13-15]:

$$\text{Bulk density} = \frac{\text{Mass of Powder (M)}}{\text{Bulk volume of powder } (V_B)} \text{ -------- (1)}$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 seconds interval until there was no change in volume reduction. The volume occupied by the sample was then recorded as the tapped volume. The tapped density was calculated using the formula:

$$\text{Tapped density} = \frac{\text{Mass of sample (M)}}{\text{Tapped volume } (V_T)} \text{ ---------- (2)}$$

Flow rate and angle of repose

A funnel was properly clamped on to retort stand. The funnel orifice diameter, base diameter and efflux tube length were appropriately measured. A 30 g quantity of the sample was weighed out and gradually transferred into the funnel with the funnel orifice closed with a shutter. The time taken for the entire sample in the funnel to flow through the orifice was noted. The flow rate was gotten by dividing the mass of the sample by the time of flow in seconds.

The static angle of repose was determined using the fixed base cone method [13-15]. A 30 g of the sample was transferred into an open-ended cylinder placed on a static base cone on a horizontal surface. The cylinder was gradually withdrawn vertically and the sample formed a cone-shaped heap. The height of the sample was determined using a cathetometer; the radius was gotten by dividing the fixed diameter by two. Angle of repose (Θ) for each sample was gotten using the equation:

$$\Theta = \tan^{-1} h/r \quad \text{---------- (3)}$$

Compressibility index and Hausner's quotient

Carr's compressibility indices (%) of the lyophilized SLMs were obtained using the formula [13-15]:

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{- (4)}$$

While Hausner ratio was obtained using Equation 5:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{---------- (5)}$$

Preparation of tablets

The tablets were produced by direct compression. Co-processed metronidazole granules (10 %) were mixed with potato starch (3.5 %) as the extra granular disintegrants and magnesium stearate (1 %). Tablets were prepared by compressing the lubricated granules at 46-48 kgf in an automated F3 Manesty Single Punch tabletting machine.

Evaluation of tablets

Disintegration time test

Disintegration time test was conducted using an Erweka ZT 120 basket and rack assembly and O. I N Hydrochloric acid maintained at 37.0 ± 1.0 ^{o}C as the disintegration medium. Ten tablets from each batch were used for the test and the procedure being as stipulated in the BP, 2009 for normal release tablets [16].

Uniformity of Weight

Twenty tablets were randomly selected from each batch. The tablets were weighed individually using an electronic balance (Ohaus Adventurer, China) and the individual weights recorded. The mean weight, standard deviation and percentage deviation were calculated [16].

Tablet friability test

Twenty tablets were randomly selected from each batch of the tablet. The tablets were dedusted and weighed. The tablets were placed into the drum of the friabilator (Erweka GmbH, Germany) and rotated at 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted and reweighed. The friability result was expressed as loss of mass expressed as a percentage of the initial mass [16]. The friability was calculated from the equation below:

$$\text{Friability loss} = 100\left[1 - \frac{W}{W_o}\right] \quad \text{------- (6)}$$

where W_o and W are the initial weight and final weight of the tablets respectively.

Hardness/Crushing Strength Test

This test was carried out using a Monsanto-stokes hardness tester. Ten tablets from each batch were randomly selected. Each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of tester until the tablet integrity failed. The results were recorded in kgf.

Content of active ingredient

Beer's calibration curve for metronidazole was obtained at a concentration range of 0.1 – 0.9 mg% in 0.1 N HCl at a predetermined wavelength of 277 nm. Twenty tablets were randomly selected from each batch of the tablets. The tablets were weighed together and crushed in a mortar with a pestle. An amount equivalent to the average weight of the crushed tablet was weighed out in an analytical balance. The weighed amount was dispersed in the medium and filtered (Whatman No. 1) and an aliquot of the filtrate was assayed using spectrophotometer (Jenway 6305 spectrophotometer, Barloworld Scientific Ltd., Essex CMB 31BWL, UK). The absorbance readings were recorded and the concentration of metronidazole in each tablet was calculated with reference to Beer's plot.

In vitro release studies

The *in vitro* dissolution profile for each batch of tablet was determined using the paddle method with an Erweka DT 600 Dissolution apparatus. The dissolution medium consisted of 900 ml of freshly prepared 0.1 N HCl. The temperature of the medium was maintained at 37 ± 1 ^{o}C. A tablet from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. At various intervals, 5 ml-sample was withdrawn from the dissolution medium, filtered with a non adsorbent filter paper (Whatman No. 1) and an aliquot of the filtrate was assayed using spectrophotometer (Jenway 6305 spectrophotometer, Barloworld Scientific Ltd., Essex CMB 31BWL, UK) at 277 nm. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition. The amount of drug released at each time interval was determined with reference to Beer's plot for the drug.

Statistical analysis

Statistical analysis was carried out using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA). All values are expressed as mean ± SD. Data were analysed by one-way ANOVA. Differences between means were assessed by a two-tailed student's T-test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Micromeritic studies

The results of flow properties of metronidazole granules, potato starch, metronidazole powder and pregelatinized potato starch are shown in Table 2. The flow properties of potato starch were improved by formulating pregelatinized potato starch as shown. Also metronidazole powder was not flowable, but the flow properties were improved also by formulating co-processed metronidazole granules as shown in Table 1. The values obtained from the micromeritic studies showed that pregelatinized potato starch and co-processed metronidazole granules exhibited good flowability and values obtained were within specified limits for the production of good quality tablets.

Tablets properties

The results of tablets weight uniformity test shown in Table 3 showed that the tablets complied with BP specifications for tablets weight uniformity and deviations obtained were within the limits of 7 % specified for tablets weighing less than 250 mg [16]. The results of disintegration time of tablets also shown in Table 3 showed that the tablets exhibited fast disintegration of time range between 1.00 ± 0.07 to 2.04 ± 0.17 min for Fl and F3 tablets formulated with co-processed metronidazole containing 2 and 6 % PVP, however, the control (F4) formulated with co-processed metronidazole with no PVP had disintegration time of 3.57 ± 0.24 min. All the batches complied with BP specification for normal release tablets. The results of tablets hardness shown in Table 3 showed that the tablets hardness ranged from 5.10 ± 0.39 to 6.00 ± 0.50 kgf for batches F1 and F3 formulated with metronidazole containing 2 and 6 % PVP. However, all the tablets batches passed the test for hardness. Metronidazole tablets formulations also complied with BP specifications for tablets friability with friability results significantly lower than 1 % as shown in Table 3($p < 0.05$). Therefore, the tablets can withstand shock and vibrations during handling, packaging and transportation without compromising the properties of the tablets.

The results of the release profile of metronidazole from formulated tablets are shown in Fig. 1. The results showed that all the tablet formulations showed fast release of the drug with maximum release (T100) at 24 min for F2 and F4 batches. However, batches F1 and F3 could not reach maximum release at 24 min. Therefore, the formulations showed good release of the drug which may be due to fast disintegration time seen in all the formulations.

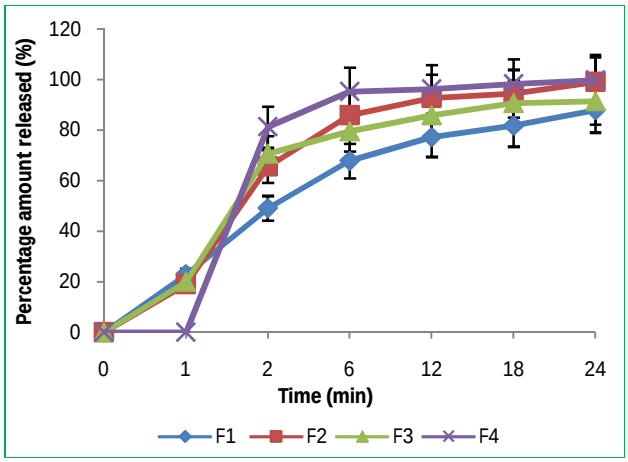

Figure 1: The release profile of metronidazole tablets prepared by co-processing. Batches F1, F2 and F3 were formulated with co-processed metronidazole containing 2, 4 and 6 % PVP; F4 was formulated with co-processed metronidazole with no PVP (control).

Table 2: Micromeritic properties of materials

Material	ℓ_B (g/ml)*	ℓ_T (g/ml)*	A.R (°)*	H.R	C.1 (%)	Flow rate (g/Sec)
Potato starch	0.60 ± 0.06	0.79 ± 0.02	52.4 ± 0.5	1.31	23.9	-
Metronidazole powder	0. 67 ± 0.08	0.85 ± 0.02	52.0 ± 0.5	1.27	21.2	-
Pregelatinized potato starch	0.56 ± 0.06	0.67 ± 0.00	39.9 ± 0.6	1.20	16.5	6.60 ± 0.19
Coprocessed metronidazole granules	0.52 ± 0.01	0.60 ± 0.01	39.9 ± 0.6	1.15	13.3	5.80 ± 0.06

Values shown are mean ± SD (*n = 3); ℓ_B and ℓ_T = Bulk and tapped densities, AR = Angle of repose, HR = Hausner's ratio, CI = Carr's compressibility index.

Table 3: Properties of metronidazole tablets

Batch/Tablet code	Weight (mg ± CV)*	Hardness (kgf ± SD)[a]	Friability (% ± SD)[a]	Disintegration (min ± SD)[a]	Drug content (mg ± CV)*
F1	240.3 ± 1.2	5.10 ± 0.39	0.50	1.00 ± 0.07	201.1 ± 0.16
F2	239.5 ± 1.8	5.40 ± 0.47	0.90	1.29 ± 0.13	201.1 ± 0.23
F3	240.1 ± 1.3	6.00 ± 0.50	0.90	2.04 ± 0.17	202.4 ± 0.12
F4	240.1 ± 2.1	5.20 ± 0.07	0.60	3.57 ± 0.24	202.2 ± 0.11

*Mean for 20 tablets, [a]Mean for 10 tablets, CV: coefficient of variation SD: standard deviation; batches F1, F2 and F3 were formulated with coprocessed metronidazole containing 2, 4 and 6 % PVP; F4 was formulated with coprocessed metronidazole with no PVP (control).

CONCLUSION

Co-processing enhances the disintegration time and the release profile of drugs. The disintegration time and the drug release profile of metronidazole were improved as shown in this work. Co-processed metronidazole granules exhibited good flow properties and therefore could be encapsulated in hard shell gelatin capsules or could be formulated as tablets for improved oral bioavailability of metronidazole.

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