ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Characterisation of metronidazole granules prepared by melt granulation and melt dispersion techniques

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ABSTRACT

To investigate the sustained release profile of Metronidazole granules prepared by melt granulation and melt dispersion techniques. Metronidazole granules have been formed by melt granulation whereby the drug powder was triturated in a melted carnuba wax followed by screening, and by melt dispersion whereby the drug and the wax were melted together and the molten mass dispersed in water, allowed to solidly by cooling, dried and then screened. Conventional granules of the drug were also formed by wet massing the powder with starch mucilage (20% w/v). The granules were characterized with respect to their particle structure (size and shape), bulk and tap densities, flowability, disintegration and dissolution profiles. The results indicated that melt granulation or melt dispersion increased the particle size and bulk density of the granules considerably but decreased their flowability and dissolution rates. The conventional granules disintegrated rapidly to their primary particles within 5 mins whereas the melt granulation and the melt dispersion system failed to disintegrate to their primary particles even after 1h (i.e. matrix property). The maximal release was in the range 93 to 96% w/w and the time to attain it (t_{∞}) were 4h (conventional granules), 8h (melt granulation) and 10h (melt dispersion system). Melt dispersion was marginally more effective than melt granulation in retarding the release of metronidazole from the granules. This was however not statistically significant.

Keywords: Metronidazole, melt dispersion, melt granulation, carnuba wax, sustained release formulation.

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ISSN: 0975-8585

INTRODUCTION

Metronidazole is used in the treatment of trichomoniasis, amoebiasis and anaerobic infections. Its half life is 6h with a peak plasma concentration of 5 -7 μg/ml attainable in 1-2h [1,2]. It is normally taken 400mg three times daily for 5 days, which is cumbersome to the patient [1,2]. Therefore, to improve compliance it is desirable to develop a sustained release formulation of the drug. One of such approaches is melt granulation which involves the trituration of drug powder with melted wax [3,4]. The advantage of this technique compared to conventional granulation is that no water or organic solvent is needed and the hydrophobic nature of the wax will confer a retard release property on the granules[4]. Recently, this technique has been used to retard the release of paracetamol using goat wax, carnuba wax and glyceryl monosterate in the melt granulation [5]. The resulting granules have a matrix (non – disintegrating property). Another approach is melt dispersion which involves dispersion of molten drug or molten drug - wax mixture in hot water followed by solidification by cooling, screening and drying [6,7]. Thus, the melt dispersion technique is more complex than melt granulation.

The aim of the present study is to compare the effectiveness of these techniques as procedures for modifying the physical characteristics of the drug particles for sustained release application.

MATERIALS AND METHODS

Materials

Carnuba wax (Halewood Chemicals Ltd, England) is a fine waxy solid with melting point of 82 - 88^{0}C, yellowish in colour and was used as the granulating agent and as the matrix former in preparing the matrix granules. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20% w/v) to produce the conventional granules. The test drug was metronidazole (Pune, India) and was received as gift from Sam Pharmaceutical Nigeria Ltd.

Wet granulation technique

A sample of the metronidazole powder (80 g) was wet - massed with 25ml of starch mucilage (20% w/v) to reach the granulation point. Hence, the content of starch binder in the resulting granules was 16.5%w/w. The wet mass was screened and then dried in a vacuum oven (Model A2904, Gallenkamp, England) at 25^{0}C for 1 h. Moisture content of the resulting granules was 2.3 ± 1.1 %w/w.

Melt granulation technique

The wax material (20g) was melted in a stainless steel container in a water bath at a temperature higher than the melting point of the wax (i.e. 90^{0}C). A sample of the metronidazole powder (80g) was then added to the melted wax and mixed well with a glass rod. The mass was pressed through a sieve of 710μm aperture size and dried in a vacuum oven

ISSN: 0975-8585

(Model A2904, Gallenkamp, England) at 25^{0}C for 0.5h to produce matrix granules. The granules were stored in an airtight container before use.

Melt dispersion technique

The wax material 20g (Carnuaba wax) and the metronidazole powder (80g) were melted together in a stainless steel container using a hot plate (Model 2103, England) at 162^{0}C. The homogeneous molten mass formed was poured gradually in water (40ml) while stirring with a mixer, 1000 rev min^{-1}. The resulting dispersion was cooled rapidly in a refrigerator to solidify. The solidified mass was pressed through a sieve of 710μm aperture size and dried in a vacuum oven (Model A2904, Gallenkamp, England) at 25^{0}C for 0.5 h to produce matrix granules of moisture content 1.9 ± 1.3 %w/w. The resulting granules were stored in an airtight container.

Particle size analysis

Samples of the conventional melt granulation or melt dispersion granules were spread thinly on a microscopic slide and viewed under the light microscope at various magnifications up to x 40. Photomicrographs of representative fields of view were taken to study particle structure (size and shape). The mean particle size (χ) was calculated using the formula:

$$\bar{x} = \frac{\sum fx}{\sum f} \quad \text{..... ..... (1)}$$

Packing property of the granules

The packing properties were determined by measuring the difference between bulk density (BD) and the tapped density (TB) using standard procedure [8]. In the procedure, a 30g quantity of granule sample was placed into 250ml clean, dry measuring cylinder and the volume, V_0 occupied by the sample without tapping was determined. After 100 taps using method described previously by Onyekweli [9], the occupied volume, V_{100} was also noted. The bulk and tap densities were calculated from these volumes (V_0 and V_{100}) using the formula. Density = Weight/Volume occupied by sample. From the data compressibility index (CI) values of the granules were calculated as [10]:

$$CI = \left\{ \left(\frac{\text{TB - BD}}{\text{TB}} \right) x100\% \right\}$$

..... (2)

Flow property of granules

The flowability of the granules was determined by measuring the angle of repose formed when a sample of the granules (40g) was allowed to fall freely from the stem of a funnel to a horizontal bench surface[8]. The radius (r) and the height (H) of the powder heap was then determined. The angle of repose (θ) was calculated using the expression:

$$\theta = \arc \tan \frac{H}{r} \qquad (3)$$

Encapsulation of the granules

Samples of the conventional or melt granulation or melt dispersion (drug content 400mg) was filled manually into plain hard gelatin capsules. The capsules were kept in airtight containers before their use in disintegration and dissolution tests.

Disintegration test

The method described in the British Pharmacopoeia BP [11] was followed using water maintained at 37 ± 0.5^{0}C as the disintegration fluid. Six capsules were used in each determination, which was carried out in triplicate and the mean results reported.

Dissolution test

The method described earlier by Okor [12] was followed. Two capsules filled with 400mg of the granules were placed in a cylindrical basket (aperture size 425 µm, diameter 20 mm; height 30 mm), which was immersed in 800 ml of leaching fluid (0.1 N Hydrochloric acid maintained at 37 $\pm$ 0.5^{0}C). The fluid was stirred at 100 rev. min^{-1} with a single blade GallenKamp stirrer (Model APP No 4B 5784A). Samples of the leaching fluid (5ml) were withdrawn at selected time intervals with a pipette fitted with a cotton wool plug and replacing with an equal volume of drug - free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analysed for content of metronidazole at λ_{max}, 315 nm (Model Spectronic 21D, Bausch and Lomb, USA). The samples were filtered before assay. The dissolution test was carried out in quadruplicate and the mean results reported. Individual results were reproducible to ± 10% of the mean.

RESULTS AND DISCUSSION

Packing and flow properties of the granules

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The results (Table 1) showed the packing and flow properties of the granules obtained by conventional, melt granulation and melt dispersion techniques. All the granules exhibited free flow (angle of repose $\leq 22^0$). The results also showed that the granules were fairly compressible by tapping. The CI values were 38% (conventional granulation), 25% (melt granulation) and 32% (melt dispersion).

Particle structure

The particles were generally irregular in shape (Fig 1) with mean particle sizes of the range 646.5 ± 8.4μm (conventional granules), 821.6 ± 9.8μm (melt granulation) and 794.3 ± 7.6μm (melt dispersion). Melt granulation thus produced bigger and irregular shape granules which may account for the lower packing of these granules upon tapping.

Disintegration test

The capsules shell disintegrated within 3mins. However, it took about 5mins for the conventional granules to disintegrate to their primary powder particles. For the granules obtained by melt granulation or dispersion, the granules failed to disintegrate to their primary particles even after 1h, thus exhibiting matrix property.

Drug release profile of the granules and their release mechanisms

The drug release profiles of the granules are presented in Fig 2. Melt granulation or melt dispersion retarded drug release rate remarkably, attributable to the hydrophobic nature of the carnuba wax used in the granulation or dispersion procedures [13, 14]. The maximum release was in the range 91 - 96% w/w of the initial amount of drug. The times to attain it (t_∞) were 4h (conventional granules), 8h (melt dispersion), and 10h (melt dispersion) (Table 2). Thus, melt dispersion was slightly more effective than melt granulation in retarding drug release from the granules, but the difference was not statistically significant ($p > 0.05$). The melt granulation system represents a particulate dispersion of the drug in the wax continuum while the melt dispersion system represents a solid solution of the drug in the wax. In spite of this difference the drug release profiles were similar (Fig 2). This observation suggests that the release-retardant effect was attributable mainly to the hydrophobic nature of the wax [13] and partly to the larger particle size of the matrix compared with the conventional granules [15].

TABLE 1: PHYSICAL PROPERTIES OF GRANULES

Parameters evaluated.	Conventional granulation	Melt granulation	Melt dispersion
Angle of repose (º)	13.31±1.2	18.8±1.5	21.6±1.4

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Bulk density (g/cm³)	0.36±0.05	0.63±0.02	0.61±0.03
Tap density (g/cm³)	0.58±0.02	0.84±0.01	0.69±0.05
Compressibility index (%)	38.21±2.1	25.0±3.2	31.5±2.2
Mean particle size (μm)	646.5±8.4	821.6±9.8	794.3±7.6
Particle shape	Irregular	Irregular	Irregular

TABLE 2: DISSOLUTION PARAMETERS (m_∞, t_∞ and m_∞/ t_∞) OF THE GRANULES

Dissolution parameters	Conventional granulation	Melt granulation	Melt dispersion
m_∞ (%)	96	93	91
t_∞ (h)	4	8	10
m_∞/ t_∞ (%h^{-1})	24	11.6	9.1

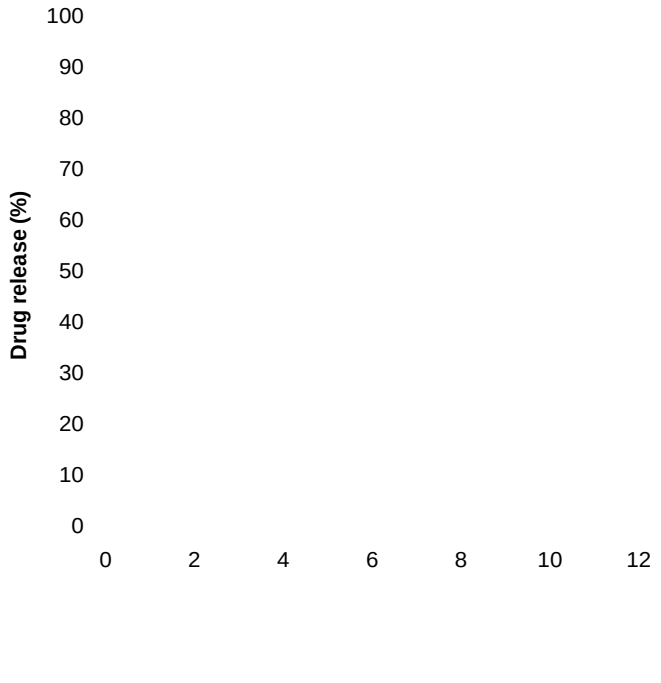

Fig 2: Effect of granulation type on the dissolution profiles of conventional granules (•), melt granulation (■) melt dispersion (▲).

ISSN: 0975-8585

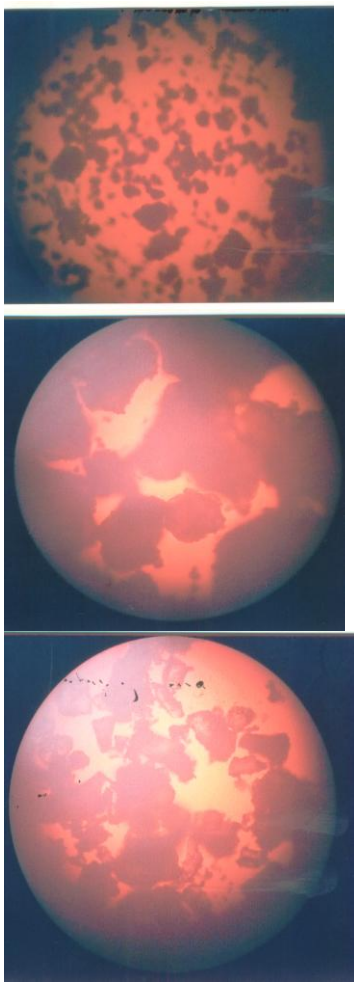

Fig 1: Photomicrographs showing particle structure of the conventional granules (a), melt granulation (b) and melt dispersion (c).

CONCLUSION

The conclusion is that melt granulation and melt dispersion techniques produced matrix granules of similar characteristics, including their drug release – retardant effect. The more complex technique of melt dispersion therefore has no obvious advantage over melt granulation in producing wax – matrix granules for sustained release applications. The free-flow nature of the matrix granules is an indication that carnuba wax is a suitable matrix former for the systems studied.

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