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Full Length Research Paper

Effect of particle size of granules on some mechanical properties of paracetamol tablets

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Solid dosage forms are invariably multiparticulate systems of heterogenous particle size distribution. The purpose of this study was to investigate the effect of particle size distribution of paracetamol granules on some tablet mechanical properties of paracetamol tablets. Granules were formed by wet massing paracetamol powder (200 g) with 20% (w/w) of maize starch mucilage as binder. Resulting granules were classified into different size fractions (212 - 1700 µm) by sieve analysis and samples of granules from the various size fractions were compressed into tablets of weight 500 ± 4.3 mg, diameter 12.3 ± 2.3 mm and thickness 3.6 ± 1.2 mm, using a single punch tablet machine at a compression pressure load of 7 arbitrary units on the load scale. The tablets were equilibrated for 24 h before evaluation. Tablet mechanical parameters evaluated were packing fraction (P_f), tensile strength (T), particle density, porosity and friability. The results showed that T values and friability index decreased slightly from 1.48 MNm^{-2} to 1.35 MNm^{-2} and 1.77 to 0.93%, respectively, following an increase in the granule sizes from 212 to 1700 µm. These differences were, however, not statistically significant. The packing fraction (P_f) of the tablets increased from 0.853 to 0.960 significantly following an increase in granule size from 212 to 1700 µm. The indication is that there is a higher degree of consolidation of the compacts formed from larger granules as a result of plastic deformation and fragmentation than those from smaller granules. The study showed that varying the granule size distribution in a powdered bed affects some tablet mechanical characteristics. The implication of this is that the granule sizes should be controlled during tableting and/or filling into capsule in order to avoid weight and content variation while ensuring that only tablets with desirable mechanical characteristics are formed.

Key words: Particle size, paracetamol granule, tensile strength, friability, tablet characteristics.

INTRODUCTION

The formulation of solid dosage forms involves processing of multiparticulate powders which are heterogenous in shape, size and size distributions. Individual drug particles in a powder bed vary widely in shape, size and size distribution. Particle size and its distribution are important parameters of a powder bed to be considered during compaction into tablets and/or filling into capsules (Stanifort, 2002; Eichie et al., 2005; Mullarney and Leyva, 2009; Duberg and Nystrom, 1986). Practically, every solid dosage form used in pharmacy must be handled as a powder at some stage and this handling is greatly influenced if the powder is free flowing (Travers, 1972). An essential desire of some pharmaceutical preparations such as dusting powder is the need to flow easily (Gunn and Carter, 1965). The importance of regular flow properties of powder or granules from the hopper to the die of the machine can not be over emphasized. The need to ensure the free flow properties of powders poses a lot of challenges to the pharmaceutical formulator and hence there is a desire for pre-granulation procedure prior to further processing.

Granulation is the process by which powdered particles are made to possess cohesive qualities, aggregate or adhere to form regular larger sized multiparticulate entities called granules by the addition of a granulating (binding) fluid. Granulation of drug particles is usually carried out to impart cohesiveness to the tablet formulation and to improve on the flow characteristic properties of the individual particles in order to improve the inherent poor compression properties and to prevent segregation of the constituents which may arise primarily from differences in size or density (Rudnic and Schwartz, 2000;

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Norman, 2002). Poor flow characteristics often results in a wide variation in tablet/capsule weight and this result primarily from variable fill of tablet dies or capsule body. An important consideration which is often ignored during tablet processing is the size of the particles before compaction (Malcom and Aulton, 2002). It is not certain whether an increase or a decrease in particle size will influence tablet mechanical characteristics. Tablet bond strength and capping/lamination tendency as measured by tensile strength (T) and the brittle fracture index (BFI) are important parameters that determine the mechanical properties of compressed compacts (Itiola and Pilpel, 1982; Esezobo and Pilpel, 1987). Hence this study therefore aimed at investigating the effect of particle size of granules on some mechanical characteristics of paracetamol tablets. The influence of particle size distribution on packing fraction, tensile strength, porosity and the friability properties of the tablets were also investigated.

MATERIALS AND METHODS

Materials

Paracetamol powder was obtained from May and Baker, Poole England and was used in this study as a drug model. The choice was based on its poor compaction properties. Maize starch and magnesium stearate were obtained from British Drug House (BDH) Chemicals Ltd, Poole, England.

Preparation of paracetamol granules

20% (w/v) starch mucilage was used to wet mass 200 g sample of paracetamol powder in a planetary mixer (Kenwood Electrus, UK) to form a crumbly cohesive mass. The wet mass was passed through a laboratory sieve of aperture size 1.7 mm and dried at 60°C for 1 hour on a tray in the hot air oven. The mass was passed through another sieve of aperture size 710 µm and finally dried at 60°C for 5 hour to a moisture content of 2.9 ± 0.3%w/w. Moisture content was determined by a balance fitted with a sample heater (Denward Instuments Ltd, model 33H). After drying, the granules were stored in an air tight dessicator activated with dry silica gel before further evaluation.

Size classification of the granules

The granules obtained were fractionated into five different sizes by shaking for 10 min with a nest of sieves mounted on a sieve shaker (Endecotts Ltd, London). The following sieve sizes were employed as follows: 1700, 850, 710, 500 and 212 µm, respectively. The weight of granules retained on each sieve was determined.

Preparation of the tablets

The single punch tableting machine (Kilian and Co Frankfurt, Germany) was used for the preparation of the tablets from the various size fractions. A 1% dispersion of magnesium stearate in chloroform was used to lubricate the die and punch surfaces prior to the compression of the tablets. A sample (500 mg) of the granules was filled into the die and compressed into tablets of dimension: 3.6 mm thickness and 12.3 mm diameter at an arbitrary pressure load of 7 on the load scale. The resulting tablets were stored overnight in a dessicator to allow for complete equilibration before their evaluation.

Determination of tablets packing fraction

The packing fraction of the tablets from each size fractions was calculated from the particle densities of the tablet compositions (that is, paracetamol and maize starch) previously determined by the liquid paraffin displacement method because liquid paraffin does not wet paracetamol. The packing fraction P_f was computed using the following equation (Itiola and Pilpel, 1986):

$$P_f = \frac{W}{\pi r^2 t \ell} \quad (1)$$

where W is mean weight of the tablets, r is the radius, t is the tablet thickness and ℓ is the particle density using fluid displacement method.

Evaluation of the tablet tensile strength (T)

The load (P) required to cause diametral fracture in a tablet was determined using the Monsanto hardness tester (Brook and Marshall, 1986). Ten tablets randomly selected from a given size fractions were used for the determination. The mean fracture load was used to calculate the tensile strength (T) using the expression below (Fell and Newton, 1970):

$$T = \frac{2P}{\pi D t} \quad (2)$$

Where t and D represent the thickness and diameter of the tablet respectively. Triplicate determinations were carried out for the various size fractions and mean determinations are reported.

Values of tablet friability

This determination was carried out using the Erweka friabilator (GMBH Heusenstamin, Germany). Ten tablets randomly selected each from a given size fraction were weighed and placed in the friabilator. These were rotated for 10 min at 20 rev.min^{1}. The tablets were dusted of adherent particles and then reweighed and the percentage friability which was taken as the friability index was calculated (Eichie et al., 2008). Triplicate determinations were carried out for the various size fractions and mean values are reported.

RESULTS AND DISCUSSION

Effect of granule size distribution on the compression properties of paracetamol

The results of the effect of granule size distribution of paracetamol granules on the packing fraction (P_f) of tablets are shown in Table 1. The packing fraction of the tablets compressed from the various size fractions were generally dependent on the granule sizes. It can be seen that an increase in particle size led to a corresponding increase in the packing fraction of the tablets. For

Table 1. Effect of granule size distribution on the compression properties of paracetamol tablets.

Granule size (µm)	Packing fraction (P_f)	Tensile strength (T) MNm^{-2}	Particle density ($g.cm^{-3}$)	Porosity (%)	Friability Index (%)
212	0.853	1.48	1.253	9.57	1.77
500	0.877	1.44	1.249	12.95	1.15
710	0.893	1.42	1.160	14.77	0.98
850	0.958	1.37	1.159	16.75	0.97
1700	0.960	1.35	1.082	17.57	0.93

in-stance, an increase in granule size from 212 to 1700 µm brought about an increase in the P_f values from 0.853-0.960. The differences in the P_f values of tablets derived from larger granules and those from smaller granules were statistically significant (at a probability level: $P \geq 0.05\%$). A high packing fraction is an indication of a high degree of consolidation of the particles in the tablet. This may be ascribed to the series of events that follows the compression processes such as repacking, deformation, fragmentation and bonding. There is a greater tendency for the larger granules to deform and fragment readily thereby creating a larger number of bonding points during compression compared to the smaller granules. Such plastic and elastic deformation and/or fragmentation of the larger granules is expected to bring about an increase in the surface area of the fragments which is also necessary for greater particle-particle contact and bonding and hence a greater tendency for closer packing. In contrast to the smaller particles, there is a limited tendency to deform (that is, highly elastic) and fragment and hence they form less consolidated compact. It has also been reported previously that a reduction in particle size may be related to a decrease tendency to fragment (Alderborn and Nystrom, 1985).

Effect of granule size on the tablet tensile strength (T)

The results of the effect of granules size on the tensile strength are presented in Table 1. Generally, an increase in granule size brought a slight decrease in T values. However, the changes were not significant when the data were subjected to student t – test statistical analysis. The decrease in T values as the particle size increases is related to the decrease in particle surface area for contact and cohesion. This was probably due to greater strength of inter-particulate bonding (cohesion) as a result of the larger surface area to volume ratio of the smaller granules (Mullarney and Leyva, 2009). This eventually resulted in a decrease in the tensile strength of the tablets with increase in granule sizes. The larger granules with smaller surface area and higher void spaces formed compacts with weak inter-particulate bonding thus requiring a lower crushing strength for diametral fracture (Itiola and Pilpel, 1986; Okor et al., 1998). Tablets prepared from smaller granules exhibited greater compactibility compared to tablets made from larger granules and hence a higher tensile strength.

The influence of granule size on particle density and porosity

The results of the effect of granule size on the particle density and porosity as shown in Table 1 revealed that a general increase in the granule sizes brought about a decrease in the particle density and an increase in the percentage porosity of the tablets. The increase in percentage porosity displayed by the larger granules may be attributed to the presence of larger void spaces, a feature characteristic of larger particles and a limited surface area available for inter-particulate bonding. This is probably the reason why the porosity of the resulting compacts was relatively high compared to the smaller granules. For instance, the porosity of tablets formed from 850–1700 µm granule sizes was two times that of tablets formed from 212 µm. Previous authors have reported similar findings (Vachon and Chulia, 1999; Alebiowu and Itiola, 2003). When porosity decreases, more solid bridges are formed and this makes the annihilation of inter-particle forces more difficult.

The effect of granule size on the friability of the tablets

As shown in Table 1, generally, all tablets except those made from size fractions of 212 and 500 µm had friability index greater than 1% values which is in conformity with the official standard in USP 2003. Again, an increase in the granule sizes brought about a corresponding decrease in the friability of the tablets. This may be attributed to insufficient quantities of binder in the smaller sized range granules (fines). Binder content deficiency in the smaller granules accounted for the friable tablets resulting from the smaller granules (fines). The production of strong but friable tablets at low binder concentrations had been reported earlier by Itiola and Pilpel (1986) and Okor et al. (1998) in previous studies. Binders are known to impart plasticity on the granules thereby promoting particle-particle bond strength with

resultant compacts that are capable of withstanding handling and transportation shocks (Eichie et al., 2008).

Conclusion

The study has shown that varying the granule size distribution in a powdered bed affects some tablet characteristics. An increase in the granule sizes brought about an increase in the packing fraction of tablets indicating that there is a higher degree of plastic deformation and fragmentation of the larger granules during compaction with a resultant increase in the surface area of the fragmented particles necessary for particle-particle bonding; while the smaller sized granules have limited sizes and were not prone to further deformation and fragmentation. The implication of this is that the granule sizes should be controlled during tableting and/or filling into capsules in order to avoid weight and content variation while ensuring that only tablets with desirable mechanical characteristics are formed.

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