African Journal of Biotechnology Vol. 5 (9), pp. 766-769, 2 May 2006
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2006 Academic Journals

Full Length Research Paper

Effect of matrix granulation and wax coating on the dissolution rates of paracetamol granules

M .U. Uhumwangho* and R. S. Okor

Department of Pharmaceutics, University of Benin, Benin City, Nigeria

Accepted 3 March, 2006

The study was carried out to investigate the release profile of matrix (non-disintegrating) granules consisting of paracetamol (drug) and acrylatemethacrylate copolymer, a matrix forming material. The effect of coating the matrix granules with wax on the drug release profiles was also investigated. The objective was to produce drug particles of different release profiles for application as multi-unit dosage forms. The matrix granules were formed by massing paracetamol powder with a concentrated ethanolic solution of the acrylatemethacrylate copolymer (40%, w/v) followed by drying and screening. Wax coating was achieved by mixing the matrix granules with a melt of carnuba wax. Conventional granules of paracetamol were made by granulation with starch mucilage (20%, w/v); this served as reference samples for comparison. The granules were subjected to size analysis, packing/flow property, friability and dissolution tests. All the granules (i.e. conventional, matrix as well as the coated matrix granules) flowed readily and were also compressible upon tapping. The compressibility index values were conventional granules (39±2.2%), matrix granules (27±1.8%) and coated matrix granules (24±1.9%). The friability values were conventional granules (1.96±0.02), matrix granules (0.78±0.01) and coated matrix granules (0.63±0.03), indicating that matrix granulation increased the cohesive strength of the granules. The dissolution rates were conventional granules (16% h^{-1}), matrix granules (9.4% h^{-1}) and coated matrix granules (4.4% h^{-1}). Thus, matrix granulation and wax coating of the matrix granules are approaches for retarding drug release and hence prolonging the biologic action of drugs with short biologic half live.

Key words: Matrix granules, melt granulation, carnuba wax, acrylatemethacrylate copolymer, retard release.

INTRODUCTION

In the past few decades, different types of oral controlled release (CR) formulations have been developed to improve the clinical efficacy of drugs and patient compliance (Dehaan and Lerk, 1984; Li and Lee, 1987). These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and durations of therapeutic treatment. Matrix-based systems in which the drug is dispersed as a fine powder in a matrix of polymeric and/or non-polymeric material are choices for CR applications, mainly because they are easy to manufacture (Cardinal, 1984).

Modifications in the release profiles are aimed at altering the onset, the rate of release from the dosage form or the site of release of the drug. Modifications can be performed on oral as well as non-oral dosage forms to control the drug release. For an oral dosage form, modification of drug release can be achieved via control of mechanisms that include diffusion, erosion, osmosis, etc. Matrix and coated systems represent a major portion of the oral modified release dosage forms. CR systems are therefore invariably multi-unit dosage forms consisting of particles of different release profiles. The term matrix granulation refers here to the formation of non-disintegrating granules by wet massing the drug powder with concentrated gels of water-insoluble polymers. The resulting matrix granules do not disintegrate to their primary particles when agitated in aqueous fluids. Hence, matrix granulation is an approach for retarding drug release from the granules. Melt granulation of the matrix granules is achieved by mixing a drug powder/or granule with a melt of a wax material (e.g. carnuba wax or glyceryl monosterate) with the objective of coating the granules and further retarding drug release

*Corresponding authors E-mail: mike2003u@yahoo.com.

from the granules (Anurag et al., 2004). Dissolution of drug particles can also be similarly modified by film coating, but the operation is complex and expensive requiring initial spheronization and use of large volumes of expensive organic solvents during coating (Nastruzzi et al., 2000).

In the present study therefore we have examined the effect of matrix granulation followed by melt granulation (i.e. wax coating) on the dissolution rates of paracetamol granules.

MATERIALS AND METHODS

Materials

Carnuba wax (Halewood chemicals Ltd, England) is a fine waxy solid with melting point of 80 - 88°C, yellowish in colour. An acrylatemethacrylate copolymer was received under the trade name Eudragit RS_{100} as a gift from Rohm Gmbh (Darmstadt, Germany). It is water insoluble but dissolves slowly in ethanol. The polymer (in the form of gel) and maize starch BP (BDH, Poole, UK) were used as binders in the granulation of the drug powder. The test drug, paracetamol was a product of BDH (Poole, UK). Although sustained release formulations are usually applied to potent drugs with short biologic half-lives, paracetamol was selected because of its availability and ease of assay by spectrophotometric methods.

Granulation technique

Paracetamol granules were formed by the convectional granulation technique using starch mucilage (20%, w/w) as binder and these were designated conventional granules. Matrix (i.e. non-disintegrating) granules were formed by wet massing the drug powder with a concentrated (40%, w/v) ethanolic solution of the polymer. The ethanolic solution was of gel consistency. The cohesive mass was pressed through a mesh (1 mm pore size) and drying in a hot air oven (Kottermann, Germany) at 50°C for 1 h to a moisture content, 1.3±0.2% (w/w). Lower concentrations (<40%) of the polymer solution in ethanol formed granules that disintegrated to their primary particles in aqueous fluids which informed the use of 40% (w/v) polymer gel in the matrix granulation. The granules were stored in an airtight container for 24 h before their evaluation.

Wax coating of the matrix granules

The matrix granules were wax coated by mixing a sample of the matrix granules (40 g) with 10 g of the wax previously melted in a water bath at 90°C. During mixing the granules would acquire film coating of the wax. The mass was screened through a sieve of pore size (1 mm), allowed to cool, and stored in a dessicator, 24 h before use.

Physical characterization of the granules

Particle size distribution: This was carried out by sieve analysis using test sieves ranging in pore size from 1.7 mm to 212 µm and shaking samples of the granules for 5 min with the Endicott sieve shaker (Endicott's Ltd, UK). Fractions retained on each sieve were weighed to determine the size distribution.

The Packing properties: These were determined by measuring the bulk density (BD) and tapped density (TB) using standard procedures (Richards, 1972). From the data compressibility index (CI) values of the granules were calculated as CI = {(TB-BD)/TB} × 100% (Carr, 1965).

Flowability: The flowability of the granules was determined by measuring the angle of repose formed when a sample of the granules (40 g) was allowed to fall freely from the stem of a funnel to a horizontal surface (Richards, 1972).

Friability: Fines in the granules samples were first removed by shaking the samples (5 min) on a sieve of pore size 212 µm. A sample of the residual coarse granules (20 g) was placed in the drum of an Erweka friabulator (Heusenstamm, Germany) rotating at 20 rev per min for 10 min. The % dust formed due to the impact was determined and taken as index of friability. The test was carried out for the conventional, matrix and coated matrix granules, each in triplicate.

Dissolution test

A sample of the granules (500 mg) was filled into a capsule shell and 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 ± 2°C). The fluid was stirred at 100 rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A. Cat No: SS530). Samples (5 ml) were withdrawn from the leaching fluid at selected time intervals with a pipette fitted with a cotton wool plug, 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 paracetamol spectrophotometrically at λ max, 245 nm (Model Spectronic 21D, Bausch and Lomb, USA). For coated matrix granules, the samples were kept in the fridge overnight to allow solidification of the wax which may have leached during the dissolution test. The samples were filtered before assay. The amounts released were expressed as a percentage of the initial amount of drug in the granule samples. The determination was carried out in triplicate and the mean results reported.

RESULTS AND DISCUSSION

Packing and flow properties

The results (Table 1) showed the packing and flow properties of conventional, matrix and the coated matrix granules. All the granules exhibited satisfactory flowability as reflected by the low angles of repose (<20°). The results also showed that the granules were fairly compressible by tapping. CI values ranged from 24% (coated matrix) to 39% (conventional granules) attributable to the higher proportion of fines in the conventional granules. The fines will fill into intragranular spaces during tapping.

Friability of the granules

Matrix granulation imparted greater interparticulate cohesiveness to the granules compared with the

Table 1. Physical properties of the granules.

Parameters assessed	Conventional	Matrix	Coated matrix
Angle of repose (0°)	12.3±1.2	15.2±1.1	17.2±1.1
Bulk density (g/cm^3)	0.35±0.02	0.45±0.03	0.51±0.01
Tapped density (g/cm^3)	0.58±0.03	0.62±0.02	0.67±0.02
Compressibility (Carr's index)	39 ± 2.2	27±1.8	24±1.9
Friability (%)	1.96±0.02	0.78±0.01	0.63±0.03

conventional granulation. As can be seen in Table 1, the friability index values of the conventional granules was significantly higher than that of the matrix granules or the coated matrix granules ($p<0.05$).

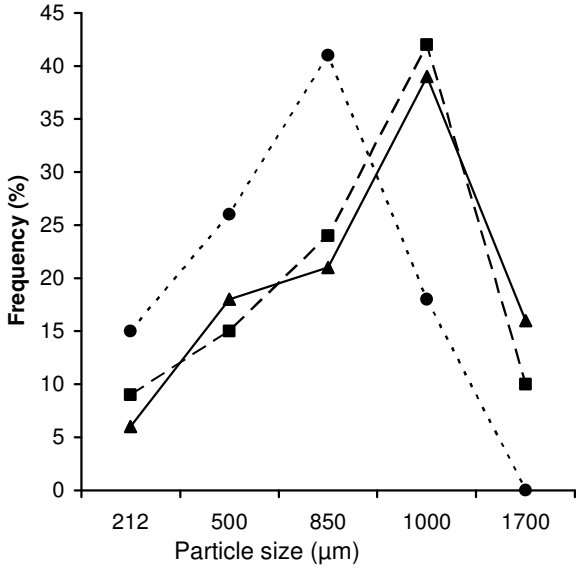

Figure 1. Particle size distribution in the conventional (… • ….), matrix (----■----) and coated matrix granules.

Particle size distribution

The data are plotted in Figure 1 (frequency/size curves). The particle size ranged from 212 to 1000 µm(conventional granules) and 212 to 1700 µm (matrix granules). The most frequent size in the granules increased to 1000 µm (matrix granules) compared with conventional granules (850 µm). On the other hand the proportion of fines of size ≤ 212 µm was higher in the conventional (15%) compared with the matrix granules (5%). This observation is attributable to the stronger binder effect of the polymer gel used in the matrix granulation, producing larger and more cohesive granules. Wax coating did not modify the size distribution of the matrix granules (Figure 1).

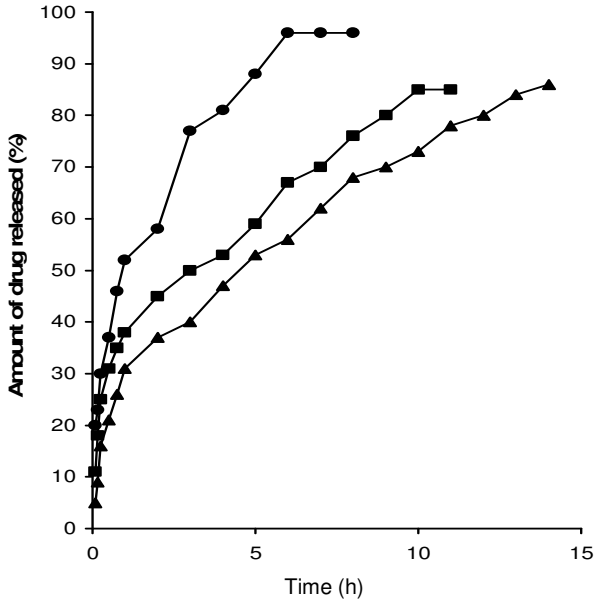

Figure 2. Drug release profiles of the ensembles of the different granules; (•) conventional granules, (■) matrix, (▲) coated matrix granules.

Release profiles of the conventional, matrix and the coated matrix granules

The release profiles from conventional, matrix and coated matrix granules are shown in Figure 2. The matrix granules compared with the conventional granules displayed a slower drug release; the coated matrix granules in turn displayed a slightly slower release than the matrix (Table 2). Thus, matrix granulation imparted a retard release property to the granules. Wax coating of the granules will further retard the release. Whereas drug release from the conventional granules would be by rapid dissolution (i.e. surface erosion) the release from the matrix systems will be by slow diffusion via aqueous channels (Sandip et al., 2003). The wax coat in the coated matrix granules will only introduce another diffusion layer for drug transfer but will also hinder influx of the aqueous leaching fluid into the core of the granules, thus accounting for the greater retarded release from the system.

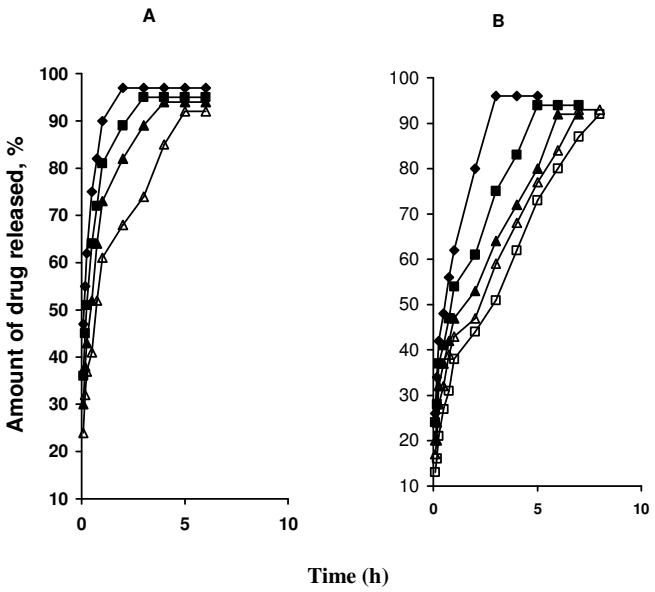

Figure 3. Release profiles of paracetamol from different fractions of the conventional (A) and the matrix granules (B), size fractions 212µm (•), 500µm (■) , 850µm (▲), 1.0mm (□), 1.7mm (□)., Note conventional granules does not have 1.7mm size fractions.

Table 2. Dissolution rates of the conventional, matrix and coated matrix granules of paracetamol.

Type of granules	Dissolution rate (% h^{-1})
Conventional	16
Matrix	9.4
Coated matrix	4.4

Table 3. Dissolution rates of the different size fractions of the conventional and matrix granules.

Particle size (µm)	Dissolution rates (% h^{-1}) of the granules	
	Conventional	Matrix
212	48.5	32
500	31.7	19
850	23.5	15.3
1000	13.4	13.3
1700	-	11.5

Effect of particle size on drug release rate of the granules

The % frequency of the different size fraction of the granule is presented in Figure 1. The release profile of the different size fractions for the conventional and the matrix granules are shown in Figure 3. It can be seen that the granule fraction with the smallest size displayed the highest release rate compared with the fraction with bigger size (Table 3). This finding relates to the larger specific surface area associated with the smaller size particles. The application of this finding is that the particle size distribution can be predetermined to optimize drug release profiles.

CONCLUSION

The study has shown that matrix granulation of drug powders with concentrated gels of a hydrophilic polymer and wax coating of such granules are approaches for retarding drug release, and hence a means of prolonging the action of drugs with short biologic half life. Also, the study showed that the particle size distribution of the granules can be predetermined to optimize the drug release profiles. These findings have applications in the design of multi-unit dosage forms.

REFERENCES

Anurag S, Yasvanth A, Ramesh P (2004). Use of extrusion-spheronization to develop controlled-release dogage forms for Diltrazem Hydrochloride. Pharm Tech 62-85.

Cardinal JR (1984) Matrix systems In : Langer RS and Wise DL (eds) Medical applications of controlled release, Classes of systems, CRC Press, Boca Raton, FL pp. 41-67.

Carr RL (1965) Classifying flow properties of solids. Chem Eng. 72:69-72.

DeHaan P, Lerk CP (1984) Oral Controlled Released Dosage Forms A review Pharm weekbl. Sci Ed, 6:57 – 67.

Li VHK, Lee VHL (1987). Influence of Drug Properties and Route of Drug Administration on the Designed of Sustained and Controlled Release Sytems In: Robinson JR and Lee VHL. (eds) Controlled drug delivery: Fundamentals and Applications. Marcel, Dekker Inc, New York, NY pp. 3-94.

Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C, Menegatti E (2000) Influence of formulation and process parameters on pellet production by powder layering techquue AAPS PharmSciTech 1: (2) article 9.

Richards JH (1972) Powder flow and compaction In: Carter SJ. (ed) Tutorial Pharmacy. Pitman Medical Publishing Ltd, London, 6th ed., pp. 211-233.

Sandip BT, Murthy KT, Pai MR, Mehta PR, Chowdary PB (2003) Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS Pharm. Sci. Tech. 4: (3) 31.