A COMPARATIVE STUDY OF DISSOLUTION CHARACTERISTICS OF POLYMERIC AND WAX GRANULATIONS OF THEOPHYLLINE AND THEIR TABLETS

MICHAEL U UHUMWANGHO* AND ROLAND S OKOR
Department of Pharmaceutics, University of Benin, Benin City, Nigeria

ABSTRACT
Matrix (non disintegrating) granules of theophylline have been formed and their dissolution characteristics investigated for sustained release application. The polymeric granulations were formed by massing the drug powder with a concentrated (40%w/w) ethanolic solution of an acrylatemethacrylate copolymer (ERS_{100}^{R}). Wax granulations were also formed by massing the drug powder with previously melted carnuba wax followed by screening and drying. The content of polymer or wax in the resulting granules was 16.7%w/w. Conventional granules of theophylline were formed by massing the drug powder with starch mucilage (20%w/v). Resulting granules were subjected to particle size analysis and *in vitro* dissolution tests. The granules were further compressed to tablets (weight 500±4.2mg each) at a constant load (30 arbitrary units on the load scale). The tablets were subjected to hardness, disintegration and dissolution tests. The dissolution kinetics were also considered. The mean granule size was 646.5±4.3µm (conventional), 821.4±4.8µm (polymeric granulations) and 892.7±5.4µm (wax granulations), the matrix granules were therefore larger than the conventional granules. Dissolution of the granules generally followed a first order rate kinetic. The rate constant (k_1) for the conventional, polymeric and wax granulations were (h^{-1}): 0.53, 0.31 and 0.27 respectively. Thus, the wax granulations appeared to be more effective than the polymeric granulations in retarding drug release from the granules but the difference was not statistically significant ($p>0.05$). The tensile strength of tablets derived from the conventional, polymeric and wax granulations were (MNm^{-2}) 0.85, 1.68 and 1.96 respectively, indicating that the matrix granules (compared with the conventional granules) produced harder tablets at the same compression load. The corresponding first order dissolution rate constants were (h^{-1}): 0.46, 0.28 and 0.21. Thus, tableting of the matrix granules produced a slight but significant decrease in dissolution rates, attributable to the disintegration of the tablets to more compact particles.

Keywords: Theophylline, granulation, matrices, dissolution rates.

INTRODUCTION

Theopylline is a methylxanthine derivative which is often indicated for the treatment of chronic asthma. It has a short biologic half life (4.5h), hence a prolonged action formulation of the drug is desirable.

Various approaches have been used to modify dissolution rates of drug particles. Perhaps the oldest technique is spheronisation of the drug particles to form pellets for subsequent film coating with water insoluble polymeric substances (Dyer *et al*., 1995, Nastruzzi *et al*., 2000, Sood *et al.,* 2004). This method is complicated and expensive requiring the use of organic solvents as coating fluid. Besides, the organic solvents are potentially hazardous to the environment. The acrylatemethacrylate copolymers and ethylcellulose have been frequently employed in the film coating of drug particles for controlled release applications (Plaizier-Vercammen *et al*., 1997, Jovanovic *et al.,* 1997, Eichie and Okor, 2002).

Matrix granulation to form granules which will not disintegrate to their primary particles in an aqueous environment has also been exploited for modifying the dissolution profiles of drug particles for controlled release applications. In the so called melt granulation technique, the drug powder is triturated with a melted wax such as bees wax, carnuba wax, glyceryl monostearate and monooleate (Adeyeye and Price, 1991, 1994, Kumar *et al*., 2004). A recent work (Uhumwangho and Okor 2006[a]) showed that goat fat has a potential in this area of application. Of the various waxes cited above, carnauba wax is considered superior to the others in producing less sticky and free flowing granules (Uhumwangho and Okor 2006[b]). Hence, carnuba wax was selected for the present study as the wax matrix former. Polymeric granulation using viscous gels of polymeric substances (e.g. the acrylatemethacrylates) as the massing fluid can also be used to form matrix granules (Uhumwangho and Okor 2006[c]). The matrix granulation technique is considered simpler, safer and less expensive compared with the film coating technique. Hence, in the present study the matrix granulation technique was exploited to develop sustained release formulations of the theophylline.

The objectives of the study are twofold. Firstly, to

**Corresponding author:* Tel: +234-8052057767, +234-8066446552, e-mail: mike2003u@yahoo.com, uhumwangho@uniben.edu

investigate which of the two matrix granulation/ procedures (polymeric or melt) will be more effective in retarding dissolution of the drug from the matrix granules. Secondly, to investigate any differences in the dissolution profiles of the matrix granules and those of their tablets. This second aspect of the study is relevant because the granules could be encapsulated (in which case the individual release characteristics of the particles will be intact) or tableted (in which case the individual release characteristics of the particles may be altered due to compaction). If, so to what extent? The tablet formulation included a disintegrant (dried maize starch, 5%w/w) and hence the tablets will be expected to disintegrate to their primary particles (i.e. the matrix granules) during dissolution test. The present study is a preliminary step in the development of multi-unit dose tablets of the drug (i.e. tablets containing both the prompt and prolonged release components in a unit dose) and are expected to yield the primary particles intact as much as possible upon disintegration.

MATERIALS AND METHODS

Materials

The test drug (theophylline) was received as a gift from Vitaboitics Nigeria Ltd. Carnuba wax (Halewood chemicals Ltd, England) was used as the wax matrix former. It is a fine waxy solid with melting point of 80-88^{0}C, yellowish in colour. An acrylatemethacrylate was the polymeric matrix former and was received under the trade name Eudragit RS_{100}^Ras a gift from Rohm Pharma Gmbh (Darmstadt, Germany). It is water insoluble but dissolves slowly in ethanol. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20%w/v) and as disintegrant (5%w/w) as dried powder, while magnesium stearate (Sakai Chem Co, Japan) was used as lubricant at a concentration of 0.5%w/w in the tablet formulations.

Methods

Wet granulation to produce the conventional granules

A sample of the theophylline powder (100g) was wet-massed with 50ml of starch mucilage (20%w/v). Hence, the content of starch binder in the resulting granules was 9.1%w/w. The wet mass was pressed through a sieve of aperture size 1.7mm, spread thinly on trays and then dried at 50^{0}C for 1h in a hot air oven (Kottermann, Germany). The half dried mass was pressed through a sieve of aperture size 710µm and dried finally at 50^{0}C for 2h to a moisture content of 2.1±0.5%w/w. The granules were stored in an airtight container for 24h before they were filled into hard gelatin capsules or compressed to tablets.

Matrix granulation

Polymeric matrix (i.e. non disintegrating) granules were formed by wet-massing the drug powder (100g) with 50ml of concentrated (40%w/v) ethanolic solution of the polymer, this being the least concentration of the polymer that formed matrix granules. The cohesive mass was screened and dried as described above. Content of polymer in the resulting granules was 16.7%w/w.

To form the wax matrix granules, 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^{o}C). The theophylline powder (100g) was then added to the melted wax and mixed well, then allowed to cool to room temperature (28^{o}C). The resulting cohesive mass was pressed through a sieve of mesh 10 (aperture size; 710µm). The content of wax in the resulting granules was 16.7%w/w. Higher concentrations produced a sticky mass which was difficult to screen to granules while lesser concentrations did not form matrix granules. The granules were stored in air tight containers before use.

Particle size analysis

This was carried out by sieve analysis using a nest of sieves decreasing in pore size from 1.7mm to 212µm. A sample of the granules (100g) was placed on the top-most sieve and shaken for 5min with a sieve shaker (Endecott Ltd, UK). Fractions retained on each sieve were weighed to determine the size distribution. The mean particle size (χ) was calculated using the formula:

$$\bar{x} = \frac{\sum fx}{\sum f} \qquad (1)$$

where f is the frequency of each size χ. The determination was carried out in triplicate.

Tableting

The granules were compressed using a single punch tableting machine (Manesty Type F_3, Poole, England) at a constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5mm, thickness, 3.38mm, and weight 500mg. Immediately prior to compression of the granules, magnesium stearate (0.5%w/w) and dried maize starch powder (5%w/w) were added as lubricant and disintegrant respectively.

Determination of tablet tensile strength (T)

This is the stress needed to fracture a tablet by diametral compression. It is given by (Fell and Newton 1970) as:

$$T = 2P/\pi Dt \qquad (2)$$

while P is the fracture load that causes tensile failure of a tablet of diameter, D and thickness, t. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester, following Brook and Marshal (1968). The mean values of the fracture loads were used to calculate the T values for the various tablets.

Table 1: Particle Size distribution of the theophylline granules

Type of granulation	Mean size (μm)	Range (μm)	Median size (μm)
Conventional	646.5±4.3	212 – 1000	875
Polymer matrix	821.4±4.8	212-1700	925
Wax matrix	892.7±5.4	212-1700	1000

Table 2: Dissolution parameters m_∞ and t_∞ of the granules and tablets of theophylline .

Parameters	Type of granulations		
	Conventional	Polymeric matrix	Wax matrix
Granules			
m_∞ (%)	96	96	96
t_∞ (h)	5	8	9
M_∞ / t_∞ (%h^{-1})	19	12	11
Tablets			
m_∞ (%)	94	95	95
t_∞ (h)	7	14	15
M_∞ / t_∞ (%h^{-1})	13	7	6

Table 3: Values of linear regression coefficient (R^2) for the dissolution data based on zero order, first order and Higuchi analysis.

Models considered	Conventional	Polymeric matrix	Wax matrix
Granules			
Zero order	0.7359	0.8535	0.8855
First order	0.9613	0.9870	0.9851
Higuchi	0.8604	0.9594	0.9482
Tablets			
Zero order	0.8963	0.9021	0.9123
First order	0.9613	0.9677	0.9978
Higuchi	0.9746	0.9771	0.9684

Table 4: Dissolution rate constants of the granules and their tablets based on first order and Higuchi analysis.

Models	Conventional	Polymeric matrix	Wax matrix
Granules			
First order (h^{-1})	0.53± 0.04	0.31± 0.02	0.27± 0.03
Higuchi (%$h^{-1/2}$)	42.8±1.4	36.8±1.8	32.2±1.6
Tablets			
First order (h^{-1})	0.46± 0.08	0.28± 0.05	0.21± 0.03
Higuchi (%$h^{-1/2}$)	32.3± 1.9	23.6± 2.1	22.1.2± 1.7

Disintegration test (DT)

The method described in the British Pharmacopoeia BP (2003) was followed using 0.1N hydrochloric acid maintained at 37^0C as the disintegration fluid. Six each of the tablets or empty capsule shells or capsules filled with the matrix granules (500mg each) were used in the determination. The time (DT) taken for all the disintegrated particles to pass through the mesh was recorded. The determination was carried out in triplicate and mean results reported.

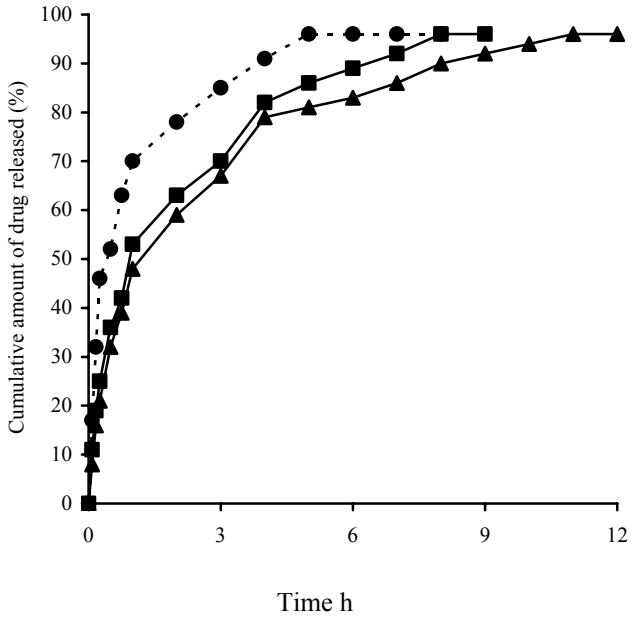

Fig. 1: Cumulative percentage of theophylline released from different granules: conventional (… • …), polymeric matrix (■) and wax matrix (▲).

Dissolution test

A stirred beaker method described previously by Okor *et al* (1991) was followed. In the procedure, a sample of the matrix granules (500mg) was filled into a rapidly disintegrating hard gelatin capsule shell (DT≤ 2min). The filled capsule was placed in a cylindrical basket (aperture size 425µm, diameter 20mm; height 30mm), which was immersed in 800ml of leaching fluid (0.1N hydrochloric acid maintained at 37 ± 2°C). The fluid was stirred at 100rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A. Cat No: SS530). 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 the blank dissolution fluid and were analysed for content of theophylline spectrophotometrically at λ max, 272nm (Model Spectronic 21D, Bausch and Lomb, USA). The amount of drug dissolved was expressed as a percentage of the initial amount of drug in the granules. In each case the test was carried out in quadruplicate and the mean results reported. Individual results were reproducible to ±10% of the mean. The test was carried out similarly for the tablets. The parameters measured were the maximal release (m_∞) and the time to attain it (t_∞). The ratio m_∞/t_∞ was taken as the overall dissolution rate.

Investigation of the dissolution kinetics

To establish the drug release kinetics and mechanism, the drug release data were fitted into various drug-release kinetic models, including zero order, (cumulative percentage of drug released vs time), first order (log residual amount of drug vs time), and the Higuchi model (cumulative percentage of drug released vs square root of time). Thus the mathematical models tested were (Richards 1972, Higuchi 1963):

$$\text{Zero order equation: } m = k_0 t \quad (3)$$

$$\text{First order equation: } \log m_1 = \log m_0 - 0.43 k_1 t \quad (4)$$

$$\text{Higuchi equation: } m = k_2 t^{1/2} \quad (5)$$

where m is the amount of drug (%) released in time, t; m_0 is the initial amount of drug (100%) at the beginning of the first order release, m_1 is the residual amount (%) of drug in time, t, and k_0, k_1 and k_2 are the release rate constants for the zero order, first order and the Higuchi release model, respectively.

RESULTS AND DISCUSSION

Particle size distribution of the granules

The data are presented in table 1 where it can be seen that the matrix granules were generally larger than the conventional granules. Perhaps, the matrices were more cohesive and hence less prone to crumbling during screening and drying of the granules.

Disintegration times

The capsule shells disintegrated rapidly (within 2 mins) but the granule content did not pass through the 410µm mesh of the basket, indicating matrix property. Capsules filled with the conventional granules disintegrated within 3min. The disintegration times for the tablets of the conventional, polymeric and wax matrix granules were 4,

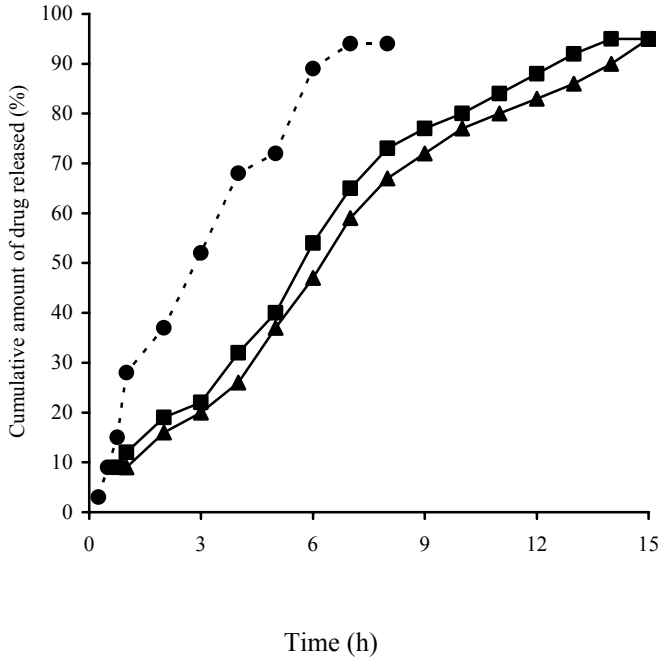

Fig. 2: Cumulative percentage of theophylline released from different tablets: conventional (… • …), polymeric matrix (■) and wax matrix (▲).

9 and 11mins respectively. Matrix granulation thus slowed the disintegration rates of resulting tablets.

Tensile strength of resulting tablets

The tensile strength of tablets derived from the conventional, polymeric and wax granulations were (MNm^{-2}) 0.85, 1.68 and 1.96 respectively, indicating that the matrix granules (compared with the conventional granules) produced harder tablets. In turn, carnuba wax produced a strong binder effect compared with polymeric binder.

Dissolution profiles of the granules and tablets

The data are plotted in fig. 1 showing curves of decreasing slope. The matrix granules displayed slower dissolution compared with the conventional granules as manifested by the considerable longer time to attain maximal release from the matrix granules (table 2). Also, the overall dissolution rates (m_∞/t_∞) were less with the matrix granules. The polymeric and wax granules displayed comparable dissolution profiles (fig. 1).

There was no measurable dissolution from the tablets in the first 15mins of the dissolution test (fig. 2), which was not the case with the granules (fig. 1), perhaps as a result of the need for the tablets to disintegrate first before a measurable dissolution can take place. Compared with the granules, the tablets displayed a greater retardation of the dissolution rates (tables 2 and 4). This difference in the dissolution profiles of the granules and tablets is more marked in the matrix systems (table 2). As a result of compression to form the tablets, the matrix granules resulting from disintegration of the tablets will be more compact than the original particles prior to tableting, which explains the slower dissolution of the tablets. Thus, the dissolution retardant effect of matrix granulation can be further increased by their formulation to disintegrating tablets.

Drug release mechanisms

Knowledge of the drug release kinetics will provide understanding of the drug release mechanism, as well as provide a basis for predicting release profiles from the systems studied. Three mathematical models for drug release were considered, namely: zero order, first order and the Higuchi square root of time plots. Values of the linear regression coefficients (R^2) are presented in table 3. The R^2 values indicated that drug dissolution from the matrix granules and tablets followed both the first order and the Higuchi model ($R^2 \geq 0.95$), whereas the conventional granules did not follow the Higuchi release model ($R^2 < 0.90$) but was more consistent with a first order release profile ($R^2 = 0.96$). This finding suggests that drug release from the matrix granules was by diffusion while that from the conventional granules was by dissolution/surface erosion following the disintegration of the granules to their primary (powder) particles. The Higuchi compliant systems are usually characterized by a

receding zone of depletion which constitutes the diffusion layer (Higuchi, 1963). Upon compression of the granules, the resulting tablets gave both the first order and the Higuchi profiles (R^2>0.95), similar to the release kinetic of the matrix granules. This similarity is attributable to the disintegration of the tablets to their primary particles (i.e. matrix granules). However, it should be noted that the particles resulting from disintegration of the tablets were more compact than the original particles prior to compression as reflected by the slower release from the tablets (table 2). Whereas the release profile of the conventional granules was not consistent with the Higuchi release, data for tablets derived from the conventional granules displayed a Higuchi release (R^2=0.97), which is a matrix behavoiur. Apparently, the particles resulting from the disintegration of the tablets during the dissolution test were too hard to disintegrate further to their primary (powder) particles, hence the matrix behavoiur.

Dissolution rate constants of the granules and the tablets

The first order and the Higuchi rate constants for drug dissolution from the granules and the tablets were obtained from equations 4 and 5 respectively, and are presented in table 4. The rates are conspicuously higher in the conventional compared with the matrix granules, indicating that matrix granulation is an effective means of retarding release from drug particles. The dissolution rate constants appeared to be more retarded in the wax compared with the polymeric granulations but the difference was not statistically significant (p>0.05).

The dissolution rate constants of the tablets were in turn lower than those of the granules. Although the tablets disintegrated during the dissolution test, the particles resulting from disintegration would be more compact than the original particles prior to compression. The difference in the rate constants (tablets compared with the granules) was slight but significant (p<0.05).

CONCLUSIONS

The study has shown that polymeric or wax granulation (to obtain matrix granules) is an effective means of retarding the dissolution of drug particles. The rates can be further retarded by compression of the granules to tablets which upon disintegration will yield the primary but now more compact particles. This finding can be exploited in the design of controlled release tablets of the theophylline. Such a system will comprise of the prompt release component (i.e. the conventional granules) and the retard release component (i.e. the matrix granules) in a unit dose.

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