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A COMPARISON OF THE DISSOLUTION CHARACTERISTICS OF THEOPHYLLINE FROM FILM COATED GRANULES AND MINI-TABLETS

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ABSTRACT

Granules and mini-tablets containing theophylline were film coated by fluidised bed technology with various amounts of ethylcellulose and Eudragit RL. Scanning electron micrographs of both whole and fractured film coated granules and mini-tablets were taken. In vitro dissolution studies were carried out on encapsulated samples of film coated material equivalent to about 150mg of theophylline. Dissolution studies were also carried out on individual granules and mini-tablets and the time for 10% release (t10% values) of drug were determined. A comparison of the dissolution profiles showed that granules required about 2.5 to 3 times more coating material than mini-tablets to achieve the same release rate. It is also shown from the t10% values that drug release from mini-tablets is more consistent than from granules. Since the mini-tablets contain uniform weights of theophylline, their use allows precise adjustment of the number of encapsulated mini-tablets for individual dosage titration.

INTRODUCTION

Much work has been carried out to develop multiple-unit sustained release dosage forms for various drug compounds (1-5). The multiple-unit dosage form (MUDF) products, consisting of pellets, particles, granules or mini-tablets enclosed in hard gelatin capsules, have definite advantages over the single-unit dosage forms (SUDF) such as tablets (6,7). The chief advantage being that once ingested the particles will be distributed over an ever increasing area as they pass down the gastrointestinal tract, thereby compensating for the local variations in milieu conditions and individual unit imperfections. As a result, toxic side effects will be minimised.

The use of a fluidised bed technique is a popular method for film coating the units prior to encapsulation. Irregularly shaped particles such as granules or crystals can be relatively well coated even if they are extensively fissured. However, more uniform units such as mini-tablets have been produced (8) for enclosure in hard gelatin capsules. These mini-tablets are uniform in size, geometrical shape and drug content.

The aim of this work was to compare the *in vitro* release of a model drug, theophylline, from irregular granules and uniform mini-tablets film coated by fluidised bed technology with popular water-insoluble polymers namely, ethylcellulose and Eudragit RL.

EXPERIMENTAL

Materials

Theophylline anhydrous and sodium carboxymethylcellulose (the binding agent) were both received from Holpro Chemical Corporation. Ethylcellulose 10 cps (Hercules Inc., Wilmington) and Eudragit RL 100 (Röhm Pharma, Darmstadt) were selected as the water-insoluble polymers used for film coating. Isopropanol and acetone (AR) were used as solvents. Magnesium stearate was the lubricant used during tablet production.

Preparation of Granules

A sufficient quantity of a 5% w/v aqueous solution of sodium carboxymethylcellulose was mixed with a 100 g batch of theophylline anhydrous in fine powder form to produce a wet mass. The soft mass was passed through a sieve (2.5 mm) and dried in a warm oven (55° C) for 12 hours. After drying the granules were passed through a 2.5 mm sieve with a 1.7 mm sieve underneath. The granules used for coating were in this range of >1700 μm to <2500 μm. The average hardness of twenty granules, randomly selected, tested using a ERWEKA TBH 28 Tablet Hardness Tester, (F.R.G), was 20.8 ±7.0 N and the average weight was 10.9 ±3.23 mg.

Preparation of Mini-tablets

The theophylline anhydrous powder was granulated using sodium carboxymethylcellulose as binder as described above in the preparation of granules. However, after drying the granules were passed through a 355 μm sieve, lubricated with 0.5% w/w magnesium stearate, and compressed to form 3 mm diameter mini-tablets using a MANESTY F3 Single Punch Tablet Machine (Manesty Machines Ltd., Liverpool). The mini-tablets had an average hardness of 25 ±3.2 N and average weight of 15.4 ±0.697 mg, determined by randomly selecting twenty mini-tablets.

Film Coating

Batches of granules and mini-tablets were film coated by the fluidised bed (upward spray) technique using an AEROMATIC AG Film Coating Dryer (Muttenz, Switzerland) under optimally controlled coating conditions shown in TABLE 1.

Batches of granules and mini-tablets were film coated with gradually increasing amounts of ethylcellulose and Eudragit RL. The coating solutions were applied in layers until the weight of the batch being coated increased by the percentage amount shown in TABLE 2. At each stage samples of material were removed from the fluidised bed chamber before coating was continued,so that increasing amounts of polymers were applied in layers.

In vitro Dissolution Studies

The USP rotating basket method was used to monitor the *in vitro* dissolution rate of theophylline from test samples consisting of 10 film coated mini-tablets or about 150 mg (accurately weighed) of film coated granules enclosed in hard gelatin capsules (size 1). The apparatus used was a ERWEKA Dissolution Tester (Type DT6) (Germany) connected to a continuous flow LKB Biochrom Ultrospec II spectrophotometer and LKB Tablet Dissolution Software programme (Cambridge, England).The dissolution medium was deionised water

TABLE 1

Coating Conditions Controlled during Film Coating of Granules and Mini-tablets by Fluidised Bed Technology

Bed weight	50 g
Coating solution	5% w/v of polymer in isopropanol:acetone 1:1
Solution delivery rate	6 - 8 mL/min
Atomizing air pressure to spray	1.8 - 2.0 kg/cm^2
Rated value drying temperature	55° C
Drying temperature	60° C
Outlet air temperature	45° C
Fluidising air flow rate	100 - 120 m^3/h

TABLE 2

Polymer Coating Materials Used and the Amount of Coating expressed as % w/w.

Coating Polymer	Amount of Coating (% w/w)*
Ethylcellulose	2,3,4,5 and 6
Eudragit RL	2,3,4,5 and 6

* ± SD of amount of polymer coating was always less than 0.15.

(900 mL) at 37 ±0.5° C. The baskets were rotated in all determinations at 50 ±1 rpm. The encapsulated samples were placed in the mesh stainless steel baskets. At suitable time intervals the absorbance was measured at 271 nm. Samples consisting of single mini-tablets and granules were also monitored, but these were not encapsulated.

Scanning Electron Microscopy

Photomicrographs of whole and fractured film coated granules and mini-tablets were taken using a JEOL JSM 840 Scanning Electron Microscope. Samples were sputter-coated with gold prior to microscopic examination.

RESULTS AND DISCUSSION

Scanning electron micrographs of a typical granule of theophylline using sodium carboxymethylcellulose as the binding agent and film coated with ethylcellulose to the extent that the granule weight increased by 6% w/w is shown in FIGURE 1. The granules used for film coating were in the size range of 1700μm to 2500μm. The approximate average diameter of the granules were 2200μm and the average weight of 20 granules randomly selected and weighed was 10.9 ±3.23 mg. The SEM (FIGURE 1A) shows the granule in surface view to be very irregular. As the granules are covered with coating solution in the initial stages of the fluidised bed film coating process, the solution will flow around the granules and fill the irregularities tending to make the granules smoother and more even. The thickness of the film coating will therefore vary significantly over the surface area of the granules. It is expected that this uneven thickness will produce significant intergranule variability in drug release rate between granules coated with the same amount of polymer.

On the other hand, the mini-tablets (3mm in diameter) fabricated on a tablet machine have a smooth surface (see FIGURE 2). Each mini-tablet is more uniform in weight (average weight of 20 mini-tablets was 15.4 ±0.697 mg) and, provided the compression force remains consistent, will have a uniform height. The mini-tablet surface will therefore be coated more evenly with polymeric film. Unlike granules therefore the intermini-tablet drug release rate is expected to be more regular and consistent.

Using the average estimated diameter of the granules (2.2 mm) and the known exact diameter of the mini-tablets (3 mm), the surface area of an "average" granule and the surface area of a mini-tablet was calculated. The calculated surface areas of a granule and a mini-tablet were 15.2 mm^2 and 18.8 mm^2 respectively. However, the surface area of a granule was calculated assuming that the granule was perfectly spherical. Considering that the surface of a granule is in fact uneven, the surface area would be somewhat greater than the calculated value and would perhaps be approximately equivalent to that of a mini-tablet.

FIGURES 3 and 4 are graphs comparing time for 10% release (t10%) from individual mini-tablets and granules film coated with two commonly used polymers, ethylcellulose and Eudragit RL respectively, which

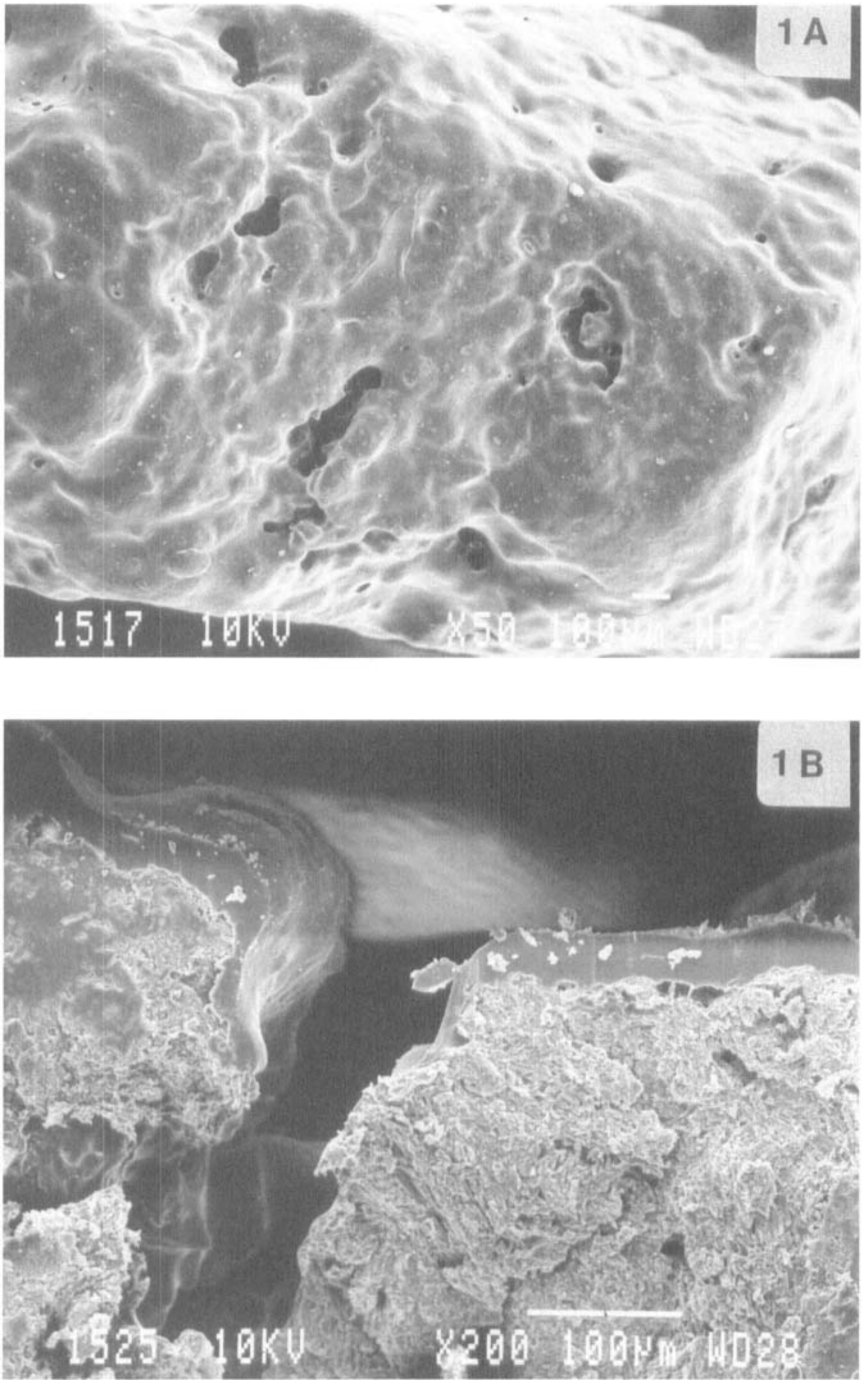
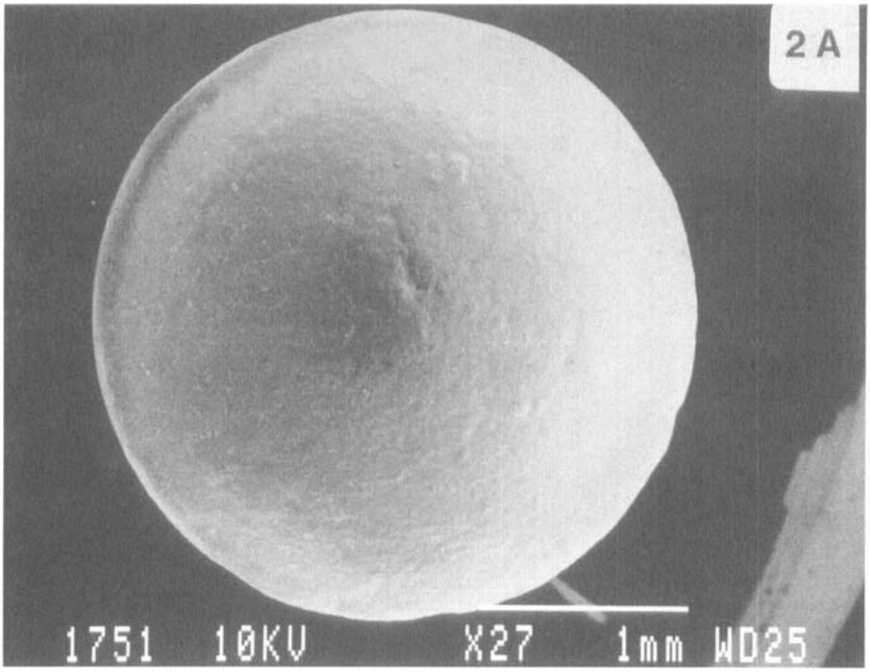


FIGURE 1
Scanning electron micrographs of a typical granule film coated with ethylcellulose 6% w/w in surface view (A) and in cross section view (B)



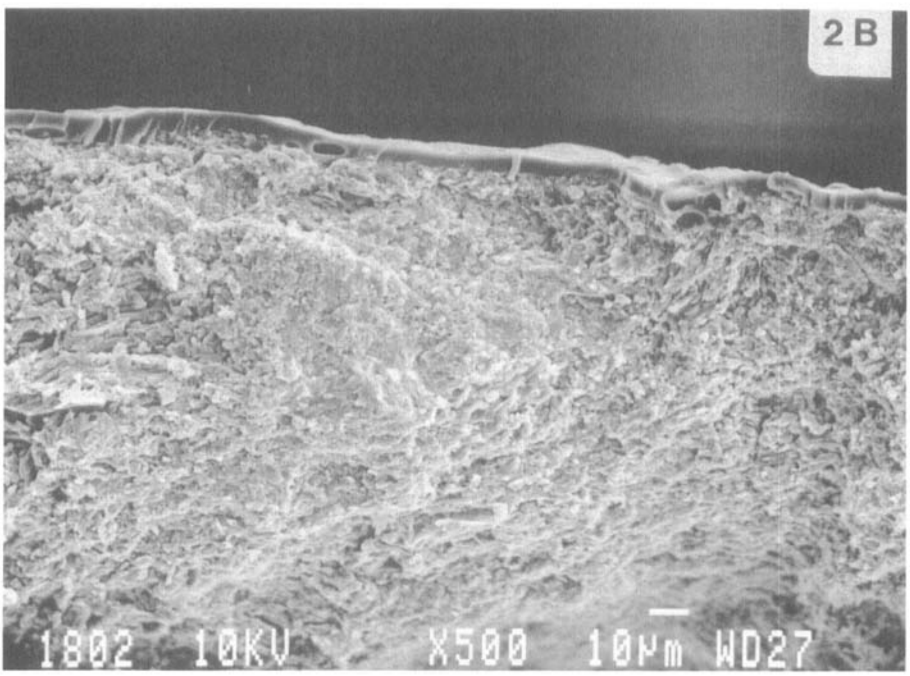


FIGURE 2
Scanning electron micrographs of a mini-tablet film coated with ethylcellulose 2% w/w in surface view (A) and in cross section view (B)

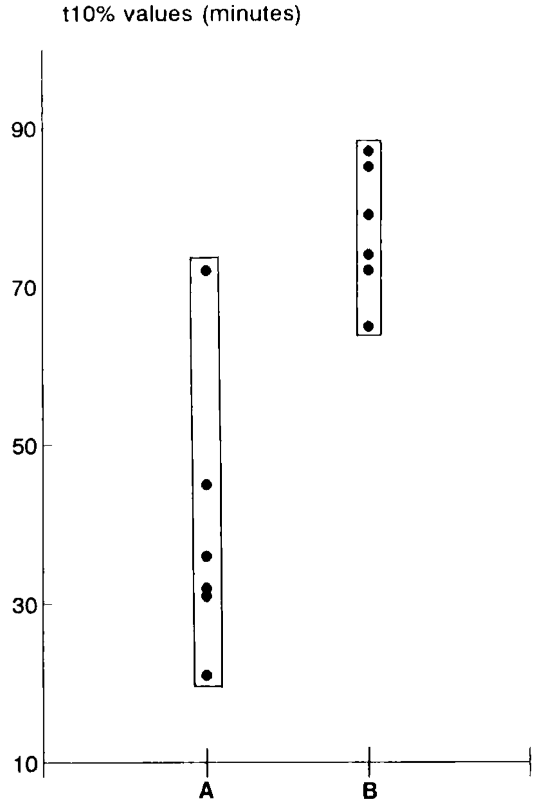


FIGURE 3
Time for 10% release (t10%) in minutes from individual granules coated with ethylcellulose 2% w/w (A) and from individual mini-tablets coated with ethylcellulose 3% w/w (B). (n=6).

confirm these expectations where it is seen that the t10% values of the individual granules show greater variability compared with the t10% values of the mini-tablets.

These results provide further evidence for the point of view that encapsulated multiple unit dosage forms containing regular units such as mini-tablets within the capsule will produce more reliable sustained release dosage forms than those containing irregular units such as pellets, granules or particles. Moreover, since the mini-tablets contain uniform weights of theophylline, the exact number of

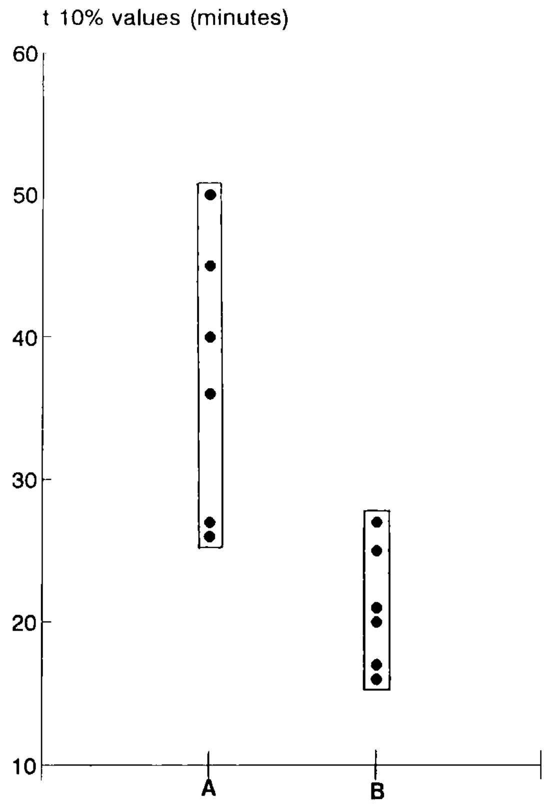


FIGURE 4
Time for 10% release (t10%) in minutes from individual granules coated with Eudragit RL 6% w/w (A) and from individual mini-tablets coated with Eudragit RL 2% w/w (B). (n=6).

mini-tablets can be more easily adjusted to facilitate individual dose titration.

The in vitro dissolution of theophylline from granules and mini-tablets film coated with varying amounts of ethylcellulose is shown in FIGURE 5. As seen in FIGURE 5 there is a close similarity between the dissolution curves for granules coated with 6% w/w ethylcellulose, and mini-tablets coated with 2% w/w of the same polymer. It is necessary therefore to coat the granules with about 3 times more of the ethylcellulose to achieve the same drug release rate as that from the coated mini-tablets. The use of mini-

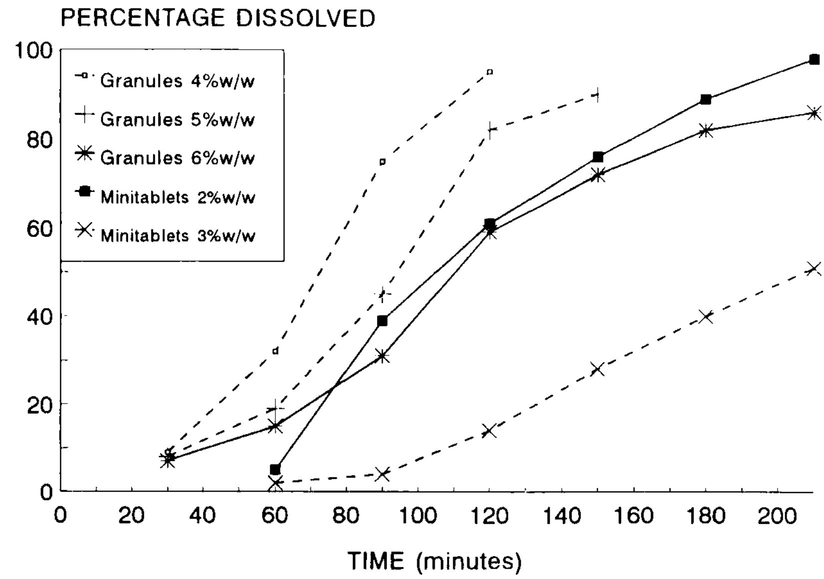


FIGURE 5
Comparison of the in vitro dissolution of theophylline from granules and mini-tablets film coated with varying amounts of ethylcellulose

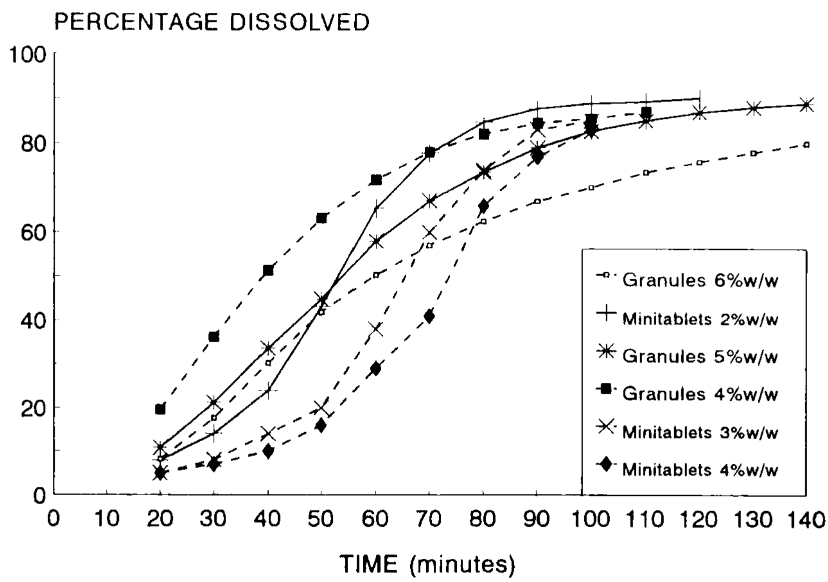


FIGURE 6
Comparison of the in vitro dissolution of theophylline from granules and mini-tablets film coated with varying amounts of Eudragit RL

tablets would therefore constitute a potential economic saving by a reduction in the amount of coating polymer required. Similar results can be achieved for granules and mini-tablets film coated with Eudragit RL (FIGURE 6). In this case the greatest similarity in dissolution profiles is with granules film coated with 5% w/w Eudragit RL and mini-tablets coated with 2% w/w of this same polymer. This represents about a 2.5 times reduction in the amount of polymer required.

CONCLUSIONS

The use of uniform film coated mini-tablets has advantages over the use of irregularly-shaped units such as granules, pellets and particles enclosed in hard gelatin capsules in the manufacture of multiple unit sustained release dosage forms. The drug release rate from mini-tablets is more consistent than from granules, and the amount of coating required for mini-tablets is from 2.5 to 3 times less than for granules of approximately the same surface area. The exact number of mini-tablets, each containing 15 mg of theophylline, included in the hard gelatin capsule can be carefully adjusted according to patient requirements, whereas this is not convenient for irregular granules which contain variable weights of the drug.

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