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Controlled release delivery: effect of coating composition on release characteristics of mini-tablets

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Summary

A means of providing constant drug delivery of theophylline in vitro from a multiple-unit oral capsule dosage form over a 12-h period and up to 95% release of the total drug content is described. Uniform concave mini-tablets (0.3 cm in diameter \times 0.2 cm thick) of theophylline, weighing 20 ± 1 mg, were produced, and evenly film-coated with polymers. Coating was carried out by fluidized-bed technology, using organic solvents and a bottom spray coating method. The fluidization dynamics were optimised for reproducibility and film uniformity. The coating composition consisted of insoluble polymers such as Eudragit RS, Eudragit RL and ethylcellulose-containing soluble channelizing agents such as PEG, Eudragit L, CAP and polysorbate 20. Scanning electron micrographs displayed a smooth continuous film of polymer. The dissolution characteristics of 20 mini-tablets with different coating thicknesses enclosed in hard gelatin capsules were evaluated and a slow-release profile corresponding to 95% of total drug content was achieved. The significance of slight variation in coating composition on drug release has been demonstrated.

Introduction

The development of an ideal orally administered drug delivery system providing constant release of drug has been the focus of recent research activity (e.g. Källstrand and Ekman, 1983; Suryakusuma and Jun, 1984; Baveja et al., 1987). The objective is to provide constant drug delivery during passage through the gastrointestinal tract (GIT) irrespective of variations in pH, surface tension and viscosity within the GIT. In certain

cases like theophylline, which has a narrow therapeutic range, constant plasma levels should be strictly maintained during the intervals between doses. Various attempts have been made to produce slow-release preparations of theophylline. Some of these have been single-unit dosage forms (SUDF) such as tablets where the drug is incorporated in a polymeric matrix (McGinity et al., 1983; Nakano et al., 1983; Parab et al., 1986), while others are multiple-unit dosage form (MUDF) products consisting of pellets, granules or particles which can be enclosed in gelatin capsules (Lippold and Förster, 1982; Kawashima et al., 1985; Motycka et al., 1985). The MUDF products have definite advantages over the SUDF (Bechgaard 1982; Beckett 1981).

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Previous attempts have not achieved the ideal characteristics of zero-order release between dosage intervals over almost the entire drug content of the dosage form, as demonstrated by numerous *in vitro* dissolution tests (Simons et al., 1984; Chung and Shim, 1987; Summers et al., 1986; Buckton et al., 1988). A possible reason for non-uniform release rates of the medicament may be due to the irregularity in shape of the pellets or granules. Every film-coated pellet or granule is different in size, shape and coating thickness, which could produce erratic release rates.

In order to regularise the coated unit in respect of size, shape and coating thickness and to determine the resulting effect on theophylline release, mini-tablets (0.3 mm diameter, 20 ± 1 mg) were produced and film-coated with a variety of polymers (insoluble and soluble). The *in vitro* dissolution rate of theophylline from 20 tablets enclosed in a hard gelatin capsule was monitored at regular intervals over a 12-h period. Differences in release profiles depending on the composition and the thickness of the polymer film are demonstrated.

Materials and Methods

Chemicals

Theophylline anhydrous was received from Holpro Chemical Corporation. Sodium carboxymethylcellulose (Holpro Chemical Corporation) was the binder and magnesium stearate was the lubricant during tablet production. Ethylcellulose 10 cps (Hercules Inc., Wilmington), Eudragit RS 100 and Eudragit RL 100 (Röhm Pharma, Darmstadt) were chosen as the water-insoluble polymers while the water-soluble polymers included PEG 1540 (Riedel-De Haen AG, Seelze-Hannover), Eudragit L (Röhm Pharma), cellulose acetate phthalate (CAP; Eastman Chemical International, U.K.) and Polysorbate 20 (Honeywell-Atlas, U.K.). Isopropanol and acetone (AR) were used as solvents.

Preparation of the mini-tablets

The theophylline anhydrous powder was granulated using sodium carboxymethylcellulose

TABLE 1

Coating conditions controlled during film coating of mini-tablets by fluidized bed technology

Bed weight	60 g
Coating solution	5–8% w/v total polymer in isopropanol : acetone 1 : 1
Solution delivery rate	8–10 ml/min
Atomizing air pressure to spray	2 kg/cm ²
Rated value drying temperature	55 °C
Drying temperature	60 °C
Outlet air temperature	45 °C
Fluidizing air flow rate	100–120 m ³ /h

in the form of a 5% w/v aqueous paste. After drying the granules were 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) having an average hardness of 25 N and weighing 20 ± 1 mg. The tablet hardness was measured using a Erweka TBH 28 Tablet Hardness Tester, F.R.G.

Film coating of mini-tablets

Film coating using an Aeromatic AG Film Coating Dryer (bottom spray) was carried out under optimum carefully controlled conditions (See Table 1). Various batches of mini-tablets were coated, each differing in the composition and thickness of the polymeric coating mixture.

Assay for theophylline content

The theophylline released into the dissolution medium was, after suitable dilution, assayed by UV spectrophotometric determinations of absorbance measured at 275 nm using a Beckman Model 25 Spectrophotometer (Beckman Instruments Co., Irvine).

Drug dissolution studies

The USP XX paddle method was utilised for *in vitro* dissolution studies of theophylline from 20 coated mini-tablets enclosed in a hard gelatin capsule (size 0). Apparatus used was a Hanson Dissolution Drive Control and Multiple Spindle Drive (Northridge, CA) with a constant tempera-

ture water bath at $37 \pm 0.5^\circ\text{C}$. Both deionized water and Simulated Intestinal Fluid USP XX, without pancreatin (pH 7.5) at volumes of 900 ml were used as dissolution media. The paddles' rotational speed was 50 ± 1 rpm. The encapsulated mini-tablet samples were contained in mesh stainless-steel baskets.

Suitable volumes of dissolution medium were removed at appropriate intervals, diluted and the absorbance measured at 275 nm. An equal volume of dissolution medium at 37°C was added to maintain constant volume.

Scanning electron microscopy

Photomicrographs of fractured mini-tablets of different coating thickness were taken using a Jeol JSM 840 Scanning Electron Microscope at magnification, $25\times$ and $500\times$, as well as a surface view at $25\times$. Samples were sputter-coated with gold prior to microscopic examination.

Results and Discussion

The release in vitro of theophylline from samples of encapsulated film coated mini-tablets from batches differing in composition and thickness of the polymeric coating mixture was investigated and percent drug released vs time was calculated. All batches coated with ethylcellulose contained a water-soluble polymer (e.g. PEG 1540, Eudragit L, CAP and polysorbate 20) as a channelizing agent in the ratio of ethylcellulose:water-soluble polymer 2:1. Batches were also coated with the insoluble but permeable polymethacrylate materials Eudragit RL 100 and Eudragit RS 100. No channelizing agents were incorporated in these polymethacrylate materials.

The dissolution profiles for mini-tablets coated with ethylcellulose and PEG 1540 at different thicknesses using deionized water as dissolution medium are shown in Fig. 1 where the effect of thickness on the initial lag period (time for water to pass through the membrane to the drug core) is clearly demonstrated.

By the selection of a definite number of mini-tablets from each coating thickness making a total of 20 mini-tablets enclosed in a hard gelatin caps-

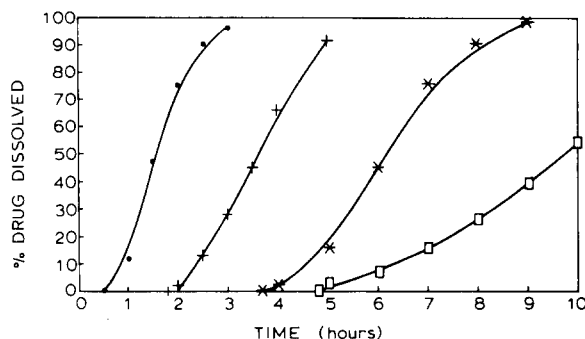


Fig. 1. % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose (Eth. cell.) and PEG 1540 (2:1) at thicknesses expressed as % w/w. Dissolution medium: water. (■), Eth. cell. 1.7% + PEG 0.85%; (+), Eth. cell. 3.3% + PEG 1.7%; (*), Eth. cell. 5.0% + PEG 2.5%; (□), Eth. cell. 5.0% (no PEG).

ule, a constant release profile could be obtained (Fig. 2). Theophylline dissolution profiles are shown for mini-tablets coated with ethylcellulose containing Eudragit L, CAP and polysorbate 20 (Figs. 3, 4 and 5 respectively). It appears in each instance that after an initial lag period (during which time pores are formed as a result of the leaching of the water-soluble component), there is a gradual release of drug into the dissolution medium. In certain instances, the amount of drug released was up to 95% of the total drug content. This is considerably higher than total release for some of the commercially available sustained-release preparations of theophylline (e.g. Simons et al., 1984). It was noted, however, that the rate of

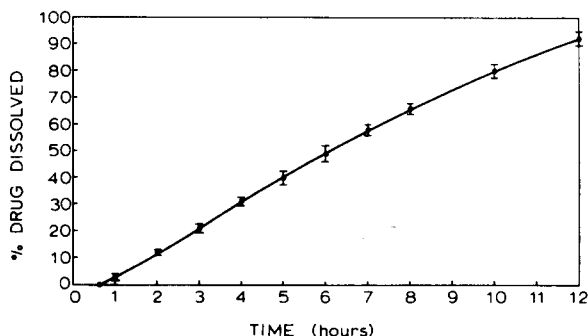


Fig. 2. % Theophylline dissolved as a function of time from a mixture of 20 mini-tablets coated with different thicknesses (% w/w) of an ethylcellulose:PEG 1540 (2:1) mixture. Dissolution medium: water.

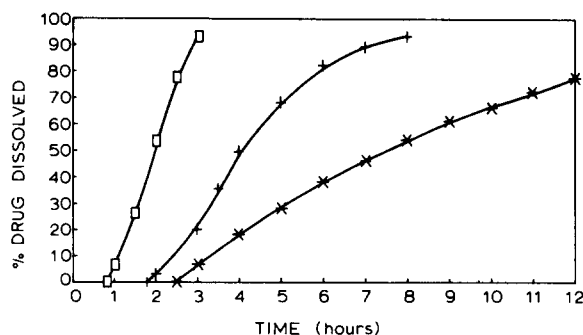


Fig. 3. % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and Eudragit L (2:1) at thicknesses expressed as % w/w. Dissolution medium in parentheses. (□), Eth. cell. 2% + Eudragit L 1% (water); (+), Eth. cell. 3%; (+), Eudragit L 1.5% (water); (*), Eth. cell. 3% + Eudragit L 1.5% (Simulated Intestinal Fluid (abbreviated Sim. Int. FL.) pH 7.5).

drug dissolution into simulated intestinal fluid was significantly reduced under identical hydrodynamic conditions. This reduction in dissolution rate may be due to molecular interaction at the core-coat interface between theophylline and the phosphate ions leading to the inhibition of transport process. It is noteworthy also that for equivalent coating thicknesses the mini-tablets coated with Eudragit RL and Eudragit RS produced dissolution curves with a shorter lag period and generally a more constant rate of release (Fig. 6).

Electronmicrographs of Eudragit RL-coated mini-tablets show the uniformity of the polymer

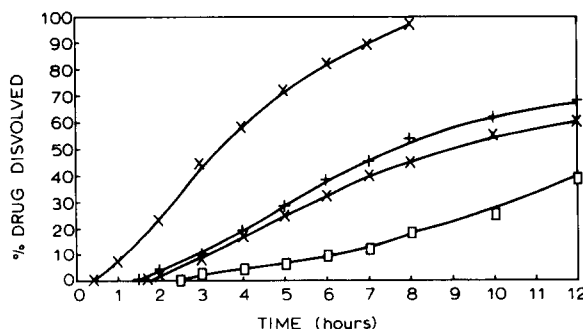


Fig. 4. % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and C.A.P. (2:1) at thicknesses expressed as % w/w. Dissolution medium in parentheses. (x), Eth. cell. 2% + C.A.P. 1% (water); (+), Eth. cell. 3% + C.A.P. 1.5% (water); (*), Eth. cell. 2% + C.A.P. 1% (Sim. Int. FL.); (□), Eth. cell. 3% + C.A.P. 1.5% (Sim. Int. FL.).

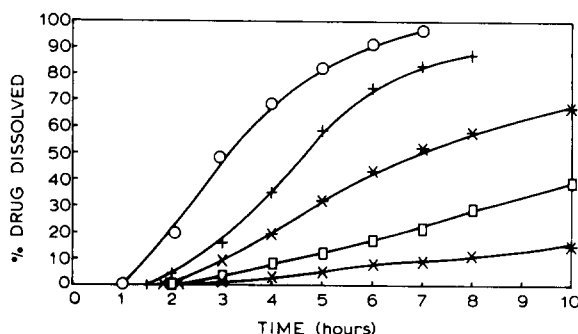


Fig. 5. % Theophylline dissolved as a function of time from mini-tablets coated with ethylcellulose and Polysorbate 20 (2:1) at thicknesses expressed as % w/w. Dissolution medium in parentheses. (◇), Eth. cell. 2% + Polysorbate 20 1% (water); (+), Eth. cell. 3% + Polysorbate 20 1.5% (water); (*), Eth. cell. 4% + Polysorbate 20 2% (water); (□), Eth. cell. 2% + Polysorbate 20 1% (Sim. Int. FL.); (x), Eth. cell. 3% + Polysorbate 20 1.5% (Sim. Int. FL.).

film coatings around the tablets (Fig. 7) illustrating the reproducibility and efficiency of this coating method.

This work has demonstrated the importance of slight variation in coating composition on drug release from film-coated tablets.

However, it is important to note that release of up to 95% of total drug content is achievable by the selection of a suitable polymeric mixture to film coat mini-tablets of uniform size and shape. By selecting definite numbers of mini-tablets with varying coating thicknesses and enclosing them in a hard gelatin capsule, the desired modified-release characteristics may be consistently achieved.

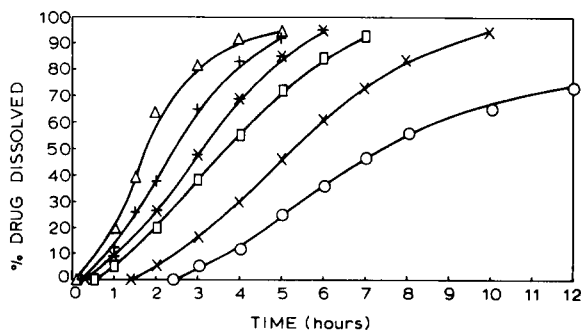


Fig. 6. % Theophylline dissolved as a function of time from mini-tablets coated with Eudragit RL and RS at thicknesses expressed as % w/w. Dissolution medium: water. (Δ), Eudragit RL 2%; (+), Eudragit RL 4%; (*), Eudragit RL 6%; (□), Eudragit RS 2%; (x), Eudragit RS 4%; (◇), Eudragit RS 6%.

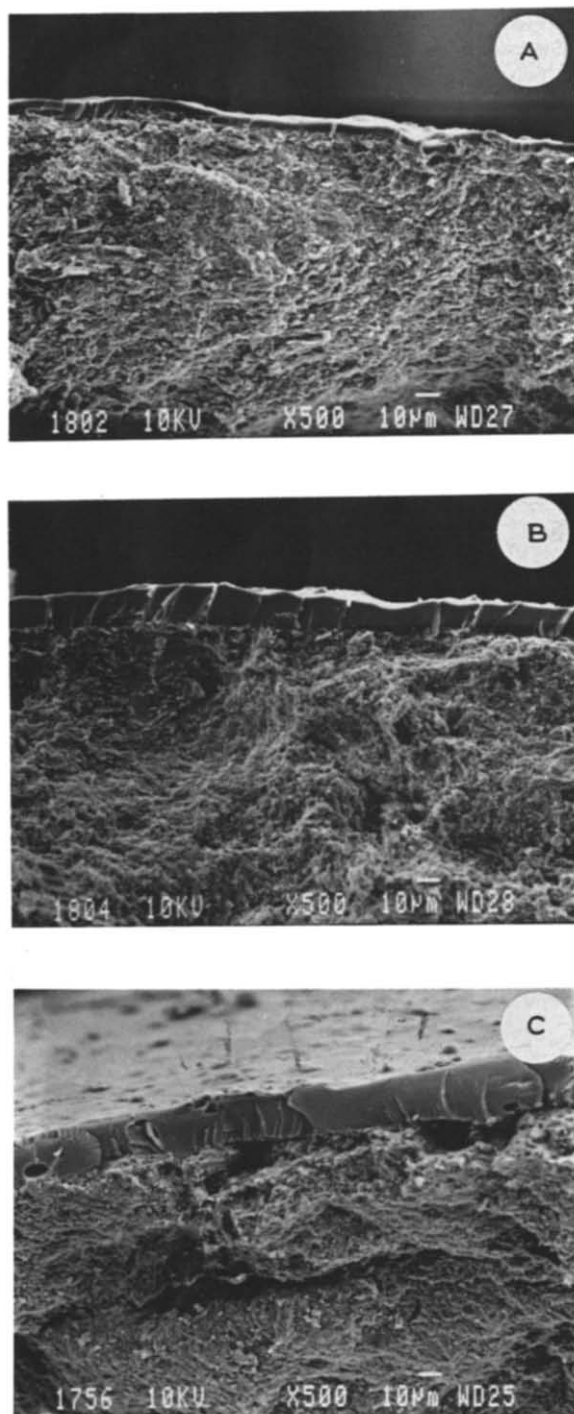


Fig. 7. Scanning electron micrographs of mini-tablets coated with Eudragit RS. A: 2% w/w coating. B: 4% w/w coating. C: 6% w/w coating. Mini-tablets fractured and coating in cross-sectional view. $\times 500$.

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