J. Pharm. Pharmacol. 1989, 41: 369–372
Received November 10, 1988

Dissolution of Theophylline from Film-coated Slow Release Mini-tablets in Various Dissolution Media

A. R. FASSIHI AND D. L. MUNDAY*

*Department of Pharmacy, University of the Witwatersrand, Medical School, York Road, Parktown, Johannesburg, 2192, South Africa, *School of Pharmacy, Cape Technikon, Cape Town 8000, South Africa*

Abstract—The dissolution of an experimental formulation of film-coated slow release theophylline mini-tablets has been investigated using the USP paddle apparatus in test media at pH 1·2 (hydrochloric acid), pH 5·4 and 7·4 (phosphate buffers) at 37°C. Monitoring of in-vitro theophylline release over 12 h, under identical hydrodynamic conditions, showed that the dissolution rate at pH 1·2 is substantially greater (95% of total drug content released in < 10 h) than that in phosphate buffers. The maximum release after 12 h was approximately 20 and 30% of total drug content of the tablet at pH 5·4 and 7·4, respectively. However, in-vivo bioavailability after oral administration of tablets to rabbits corresponded to over 95% of total drug, compared with the same dose administered intravenously. The retarded drug release during in-vitro dissolution in phosphate buffer was attributed to a possible interaction of phosphate ions with theophylline molecules at the tablet core-coat interface. These findings indicate that both rate and extent of theophylline release from the slow release coated mini-tablets are highly sensitive to phosphate buffers. The data also emphasize the usefulness of an animal model for assessment of in-vivo drug release and subsequent absorption, during the development of modified release dosage forms.

Modern pharmaceutical technology allows the design of oral dosage forms that modify the bioavailability of a drug by retarding the rate of dissolution so that this becomes the rate-limiting step. pH is a major variable affecting this but dissolution test data are also influenced by mechanical, chemical and physical factors associated with either the apparatus itself or its environment (Prasad et al 1982; Mazuel et al 1983). Although dissolution testing has not replaced in-vivo bio-availability assessment it can be a valuable tool to predict in-vivo performance of a dosage form. If bioavailability problems exist with a drug, this commonly reflects continued absorption for only a limited time after ingestion. This places an upper time limit on the dissolution process in the gut, if the total amount of drug absorbed is to be maximised. Attempts to correlate in-vivo/in-vitro performance for tablets commonly involve either the time for a specified fraction (usually 50%) of drug content to dissolve, or the amount of the total dose content which dissolves in a specified time. During a dosage form design programme in our laboratories (Munday & Fassihi 1987) for the development of a multiple unit mini-tablet controlled release system we initiated an investigation of the effect of various recommended dissolution media (USP XX) on the release profiles of those tablets. An animal model was also employed together with the in-vitro studies, to assess the in-vivo performance of the dosage forms.

Materials and Methods

Theophylline (anhydrous) BP quality was used. Ethylcellulose was obtained from the Hercules Company, UK, and PEG 1540 and magnesium stearate were from BDH Chemicals Ltd. Isopropanol and acetone were reagent grade, and sodium carboxymethylcellulose (Holpro Chemical Corporation) was used as a binder. A series of B.S. sieves and a mechanical sieve shaker were used for particle size selection. A Manesty Type F3 tableting machine with 3 mm diameter concave punches was used for compression. Breaking strength was measured on an Erweka testing machine. An Aeromatic fluidized bed (Size 1, laboratory unit, capacity 1–2 kg) was used for coating. The USP XX dissolution apparatus (paddle method) used was from Hanson Research Corp., Northridge, CA. Male, white New Zealand rabbits, 2·8–3·5 kg, were used for in-vivo studies.

Correspondence to: A. R. Fassihi, Department of Pharmacy, University of the Witwatersrand, Medical School, York Road, Parktown, Johannesburg 2192, South Africa.

Solution properties

The solubility of theophylline in various solvents was determined by adding excess drug to the solvent. The solutions were mixed overnight at 25±0·5°C to achieve saturation, then filtered through a 0·22 μm filter and measured spectrophotometrically at 273 nm. Solubilities were (mol L^{-1}): 0·0458 (water, pH 5·8), 0·0469 (HCl, pH 6), 0·0455 (HCl, pH 1·2), 0·0462 and 0·0468 (phosphate buffers pH 5·4 and 7·4, respectively). Kinematic viscosities of the dissolution media were measured at 25±0·2°C by the standard capillary-tube Ostwald viscometer. Values were ($\times 10^{-6}$ m^2 s^{-1}): 0·892 (HCl, pH 1·2), 0·889 and 0·888 (phosphate buffers pH 5·4 and 7·4). Density was determined by weighing a known volume of the solution at 25±0·2°C.

Preparation of tablets

Sodium carboxymethylcellulose (4% w/v) in water was added to the theophylline powder in a Turbula mixer, and blended for 7 min; the wet mass was then passed through a 16 mesh (1·0 mm) screen sieve in an oscillating granulator and dried. The granules were sieved and the fraction finer than 200 μm was lubricated in the cube mixer with 0·5% w/w magnesium stearate for 5 min. Concave mini-tablets weighing 22±1 mg (3 mm diameter × 2 mm thick) having an average breaking strength of 26 N, and containing approximately 20 mg of drug, were produced by compressing the

Table 1. The process conditions for optimum film coating.

Bed weight	60 g
*Coating solution	Film former in isopropanol acetone 1:1
Solution delivery rate	8–10 mL min^{-1}
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^{-1}

* The film former used in this study was 5% w/v ethylcellulose and 2% w/v PEG 1540 in the given solvent system.

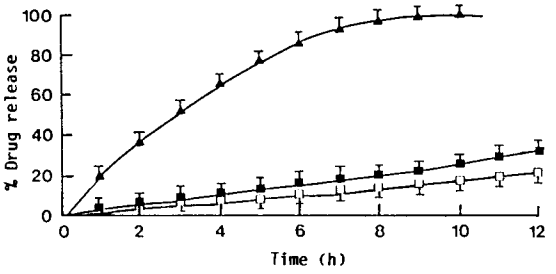


FIG. 1. Release profiles of slow-release theophylline tablets coated with ethylcellulose-PEG in hydrochloric acid pH 1·2 (▲), phosphate buffers pH 7·4 (■) and pH 5·4 (□), respectively. Each value represents the mean ± s.e.m. (n = 5).

granules. Tablets were coated by fluid bed technology using an ethylcellulose-PEG mixture in equal parts of acetone and isopropanol as a coating solution. The conditions for optimum film coating and thickness are given in Table 1.

Preparation of solvent-cast membranes

The solution of ethylcellulose (5% w/v) and PEG 1540 (2% w/v) in equal proportions of isopropanol–acetone was prepared and the required amounts were cast on clean glass plates and allowed to dry. The hardened membranes were removed and cut into round (20 mm) disks. The thickness were recorded and selected samples exposed to the various dissolution media.

Dissolution studies

The dissolution tests were conducted using the USP paddle method (apparatus II) at 50 rev min^{-1}, and 900 mL of dissolution fluid at 37 ± 0·2°C. Five coated tablets were tested individually in dissolution media at pH 1·2 (HCl). Further dissolution studies were made in phosphate buffers at pH 5·4 and 7·4. Dissolution rate measurements were carried out by passing filtered dissolution medium through a spectrophotometer cell and monitoring absorbance at 273 nm. Samples of the medium (5 mL) were removed at 1 h intervals for 12 h, and filtered through a 0·22 μm Millipore filter. The volume was restored by adding fresh dissolution medium at 37°C. The pH of the dissolution medium was checked at the end of each hour during the dissolution run. No significant change in the pH of the test medium occurred when phosphate buffers were used. The hydrochloric acid medium increased from an initial pH 1·2 to a final pH 2·1.

Administration and blood sampling

Rabbits were fasted overnight with water freely available. One theophylline coated tablet was administered to the rabbit via a plastic catheter sufficiently far into the oropharynx to avoid ejection (Venho & Eriksson 1986). Blood samples (2·0 to 3·0 mL) were drawn from the marginal ear vein at suitable time intervals. The serum was separated and stored at −18°C before theophylline concentrations were measured by fluorescence polarization immunoassay (TDX-analyser system, Abbott Laboratories).

Results and Discussion

For drugs formulated as modified-release dosage forms, it is appropriate to assess the extent to which pH of the dissolution medium affects release, and whether such effects are significant.

Drug release profiles from the coated mini-tablets in various dissolution media over a period of 12 h, under identical hydrodynamic conditions, are shown in Fig. 1. The rate of dissolution of theophylline at pH 1·2 is substantially greater than the rate of dissolution in phosphate buffers. Theophylline solubility is pH-independent and its pk_a is 8·7 (Merck Index 1983) so pH-dependent release of the drug was not expected in the pH range studied. Although a lag period of 15 to 25 min to commencement of dissolution was observed in all the dissolution media, drug release into media containing phosphate ions (pH 5·4 and 7·4) was slow over the entire range of sampling times (Fig. 1). The maximum amount of drug released after 12 h was approximately 20 and 30% of total drug content of the tablet in pH 5·4 and 7·4, respectively. When quality control limits are defined for a finished product specification, these should normally ensure that at least 80% of the active content is released within a narrow "release window" (Cartwright 1987). The results of the present investigation with film coated mini-tablets provide further evidence of the substantial effect that different dissolution media may have on both the rate and the extent of dissolution (Fig. 1).

While retarded drug dissolution is intended for the controlled release tablets, too slow a release process may result in poor bioavailability. Fig. 2 shows the results of an

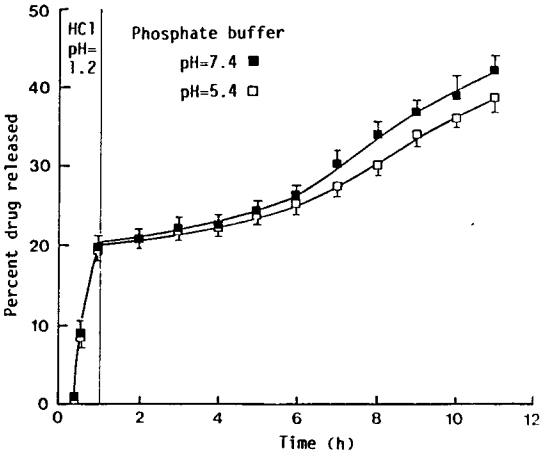


FIG. 2. Dissolution profile of film coated slow-release theophylline tablet in hydrochloric acid dissolution medium (first hour) and in phosphate buffers (second hour and thereafter). Data are expressed as mean ± s.e.m. (n = 5).

attempt to simulate an initial 1 h exposure of the tablet to gastric fluid (pH 1·2), followed by exposure to intestinal fluid of pH 5·4 and pH 7·4. Both buffers inhibited the release process in comparison with media containing hydrochloric acid. Dissolution studies were also performed using water and dilute hydrochloric acid (pH 6) to evaluate the influence of pH on the dissolution rate in the absence of phosphate ions. The release profiles obtained were within < 5% of data obtained for dissolution rates at pH 1·2 (hydrochloric acid), with no change being observed in the pH of the dissolution medium during the test. In an attempt to establish that the cause of inhibition in the release process was not a lack of channel formation, solvent-cast films of the coating solution were prepared. Scanning electron micrographs confirmed that pores were formed in the coating film on exposure to the various dissolution media investigated and that pore formation was not affected by phosphate ions. The size and size distribution of channels formed in the membranes exposed to both dilute hydrochloric acid (pH 1·2) and phosphate buffers (pH 5·4 and 7·4) were similar. Thus retardation of dissolution in phosphate buffer apparently cannot be ascribed to an effect of phosphate ions on the coating film.

An investigation was initiated to establish the in-vivo bioavailability and the influence of gastrointestinal fluid on drug delivery and absorption, using the rabbit as an animal model. Fig. 3 shows the serum concentration-time profile of theophylline administered as a slow-release, coated mini-tablet. Comparison of the area under this curve with data following intravenous infusion demonstrated that the orally administered dose was 95% bioavailable. This clearly indicates that phosphate buffered media are not suitable dissolution fluids for the in-vitro screening of release profiles of coated theophylline tablets. It appears that the rate-determining step for theophylline release is a transport step, since water channels were formed in the film by each of the various dissolution media and the solubility of theophylline was not significantly affected by the medium used (see solution properties). This may involve an interaction of phosphate ions with theophylline molecules at the core-coat interface resulting in an insoluble complex or large molecular structure in comparison with that arising in the presence of chloride ion. This is depicted in Fig. 4, showing that the dissolution rate may be controlled by a surface reaction. The classical theory describing dissolution rate in relation to pH and pk_a, based on the Noyes-Whitney equation, suggests that the dissolution rate per unit area of a weak acid is

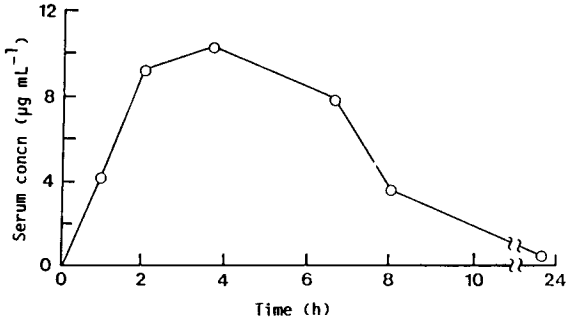


FIG. 3. Theophylline serum concentration versus time profile following oral administration of 20 mg slow release coated mini-tablet to a rabbit.

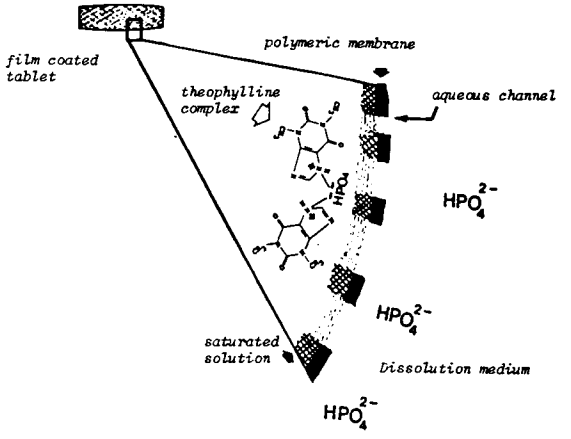
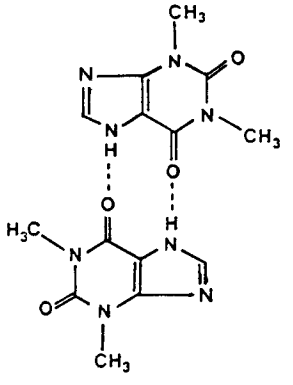


FIG. 4. Schematic representation of proposed interaction of phosphate ions with theophylline at the core-coat interface influencing the mass transport phenomenon.

controlled by its solubility, diffusion coefficient and Nernst diffusion layer thickness. On this basis, Higuchi et al (1958, 1964) developed a theory describing the dissolution rate as a combined process of simultaneous chemical reaction and diffusion. When the concentration of drug in the film pores approaches saturation the reverse process should also be taken into account, that is the simultaneous deposition of solid drug (Kallay & Senjkovic 1987). Conversion of anhydrous theophylline into the less soluble hydrated form, and crystallization on the surface of the undissolved anhydrous theophylline as a direct surface reaction, may also occur (Shefter & Higuchi 1963; De Smidt et al 1986). These processes, as well as decreased fluid shear rate over the dissolving surface within the pores, may influence mass transport causing less efficient removal of dissolved solute from the vicinity of the dissolving surface. This would result in a concentration build-up at the core-coat interface within the pores, conducive to self-association of theophylline molecules (I), (Thakker et al 1971). Consequently partial



supersaturation within the diffusion boundary layer, and changes in kinematic viscosity, pH gradient, and hydrodynamic conditions with respect to pore size and diameter, may alter the rate of dissolution and diffusivity of drug molecules in the system investigated. The rate limiting step may alternatively be attributable to an activated complexation, the stoichiometry of which would depend to a large extent on the physicochemical properties of the drug and tablet

constituents at the core-coat interface. These results emphasize the importance of screening and selection of dissolution media in dissolution testing. In-vitro dissolution tests do not necessarily give reliable information about the absorption properties of drugs, and an animal model therefore is useful for the evaluation of in-vivo drug release and subsequent bioabsorption during the development of modified-release dosage forms.

References

Cartwright, A. C. (1987) Controlled release: A regulatory dilemma. Manuf. Chem., March, pp. 33, 36, 42

De Smidt, J. H., Offringa, J. C. A., Crommelin, D. J. A. (1987) Dissolution kinetics of griseofulvin in sodium dodecylsulphate solutions. J. Pharm. Sci. 76: 71–715

Higuchi, W. I., Parrot, E., Wurster, D., Higuchi, T. (1958) Investigation of drug release from solids II. J. Am. Pharm. Ass. Sci. Ed. 47: 376–383

Higuchi, W. I., Nelson, E., Wagner, J. G. (1964) Solubility and dissolution rate in reactive media. J. Pharm. Sci. 53: 333–335

Kallay, N., Senjkovic, R. (1987) Kinetics of drug dissolution from tablets and capsules at high saturation. Pharm. Acta Helv. 62: 337–340

Mazuel, G., Cohen, E. M., Bastide, M. (1983) Standardization of in vitro dissolution assays. Int. J. Pharm. 16: 97–103

Munday, D. L., Fassihi, A. R. (1987) Oral controlled release system: The use of multiple unit microporous polymeric coated mini-tablets. J. Pharm. Pharmacol. Suppl. 39: 129 p

Prasad, V. K., Rapaka, R. S., Knight, P. W., Cabana, B. E. (1982) Dissolution medium a critical parameter to identify bioavailability problem of frusemide tablets. Int. J. Pharm. 11: 81–90

Shefter, E., Higuchi, T. (1963) Dissolution behaviour of crystalline solvated and non-solvated form of some pharmaceuticals. J. Pharm. Sci. 52: 781–791

Thakkar, A. L., Tensmeyer, L. G., Wilham, W. L. (1971) NMR evidence for self-association of theophylline in aqueous solution. Ibid. 60: 1267–1269

The United States Pharmacopeia XXth Revision, Mack Easton, Pa. 1980, p 959

"The Merck Index" 10th edn (1983) Windholy, M. (Ed.) Merck: Rahway N.J., p 1328

Venho, V. M. K., Eriksson, H. (1986) The rabbit: an animal model for comparative bioavailability studies of drug. Int. J. Pharm. 30: 91–94