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In vitro dissolution of some commercially available sustained-release theophylline preparations

G. Buckton, D. Ganderton and R. Shah

Chelsea Department of Pharmacy, King's College London, University of London, London (U.K.)

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Summary

The in vitro dissolution profiles of 5 controlled-release commercially available theophylline preparations were studied using the USP paddle method. The pH of the medium was adjusted from 2.6 to 6.0 after 3 h. Apparent first-order rate constants were calculated to quantify drug release profiles. Two products showed significant change in in vitro release rate when the pH was changed, and one product showed two consecutive apparent first-order processes, due to different regions of formulation, but was not affected by change in pH. The other two products approximated to one release rate throughout the experiment. Theoretical blood levels have been calculated from the data to demonstrate how formulation differences and gastric emptying may considerably alter the therapeutic response obtained.

Introduction

Xanthine bronchodilators have been used therapeutically for over 60 years. During this time serious toxicity problems have occurred which had to be balanced against therapeutic benefits. This narrow therapeutic index has made such products ideal candidates for administration as sustained- or controlled-release preparations. The ideals of controlled-release preparations are twofold: (1) to increase patient compliance — a once or twice daily dosage being preferable to 3 or 4 times a day; (2) to provide a better control of therapeutic drug level — this will have two benefits; the first is fewer side effects, giving greater likelihood of compliance, and the second is improved disease management.

The therapeutic effects observed after administration of sustained release products in vivo have been reported extensively for studies on xanthine bronchodilators (see Weinberger et al., 1981; Summers et al., 1986; and the study and literature review of Hannaway and Hopper, 1986). A large but fragmented literature also exists concerning in vitro studies on such systems. However, most of these studies consider only one product, or a comparison of only a few products with limited experimental methodology, e.g. in vivo - in vitro correlation of Theograd (Lagas and Jonkman, 1986). It appears that there are no reports in the literature where numerous products have been compared in vitro under differing pH conditions.

Clearly in vitro comparisons can be used to attempt to explain the release processes, and give

Correspondence: G. Buckton, Chelsea Department of Pharmacy, King's College London (KQC), University of London, Manresa Road, London SW3 6LX, U.K.

indications of the reasons for therapeutic differences that are noted in vivo. The aim of this work was to compare 5 controlled release theophylline preparations and to gain an understanding of the release processes involved by use of in vitro methodology.

Materials and Methods

The products and the techniques used were:
Nuelin (Riker, theophylline 250 mg) which consists of a waxy non-disintegrating bed, the surface of which is coated with cellulose acetate. The tablet undergoes surface erosion.
Theo-Dur (Fisons, theophylline 200 mg) which is a tablet of coated pellets, containing much of the drug content, embedded in a matrix which also contains the drug.
Pro-Vent (Wellcome, theophylline 300 mg) which is a capsule containing a mixture of pellets coated to various extents, release rate being inversely proportional to coat thickness.
Theo-grad (Abbott, theophylline 350 mg) which is a non-erodable acrylic polymer matrix containing the drug.
Uniphyllin continus (Napp, theophylline 400 mg) which is manufactured by adsorbing the drug onto hydroxyalkyl cellulose which is then incorporated within an aliphatic melt, cooled, granulated and tabletted.

The dissolution rate was measured using Apparatus 2 of USP XX1, the paddle rotating at 100 rpm. The pH of the fluid was controlled using Universal Buffer (Vogel, 1979). Experiments were carried out at pH 2.6 and then pH 6.0 after the first 3 h of the experiment. In the latter case, pH was altered by replacing a prescribed quantity of the dissolution media with 1 N sodium hydroxide solution. In order to ensure that the results were not altered as a result of change in concentration experiments were repeated at pH 6.0 throughout, and at pH 2.6 with a removal of medium and replacement with more pH 2.6 buffer. The results of these controls demonstrated that any changes in release following changes in pH were not the result of concentration changes in the medium.

Samples (1 ml) were removed at prescribed times, filtered, diluted and assayed spectrophotometrically. The concentration of the samples was related to a calibration curve which was constructed using the pure drug (Sigma, analytical grade). Standard sampling procedures were adopted.

Results and Discussion

The results for the products, which are the average of 6 replicate determinations, are presented in Figs. 1 and 2 as % released as a function of time (mean ± S.E.M.).

Release characteristics

Very different release characteristics are observed with the different formulations studied. This is to be expected when the diversity of formulation technique is considered. The factors affecting the release from each product are discussed below.

Nuelin. This tablet consists of a non-disintegrating matrix which shows only minimal surface erosion, at either pH studied, throughout the experiment. From Fig. 1 it is clear that the release profile is pH-dependent. The release into pH 6.0 media produces a far more rapid release. The apparent first-order rate constant, derived from a semilogarithmic plot of the data for release at pH 6.0 at 100 rpm is some 20 × that of the value obtained for release into acid pH.

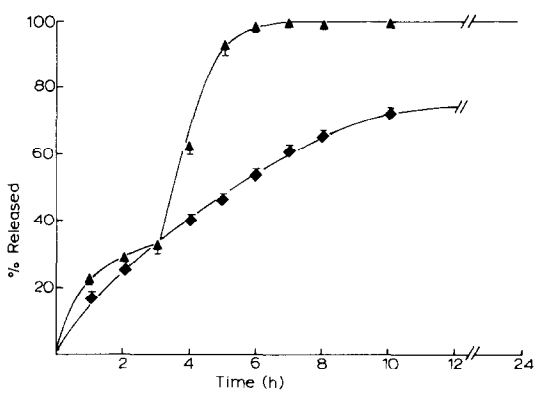

Fig. 1. % Drug release as a function of time for Nuelin (▲) and Provent (◆).

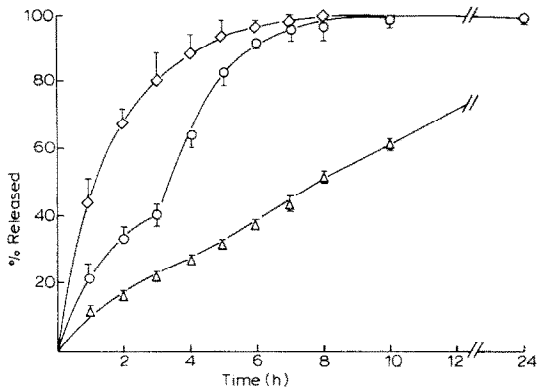

Fig. 2. % Drug release as a function of time for Theo-grad (◇), Theo-Dur (○) and Uniphyllin (△).

Theo-Dur. This is a product that consists of two different regions of drug release, a matrix in which some drug is dispersed, and a pellet formulation which is embedded in the matrix. The data in Fig. 2 clearly show that the release is pH-dependent, with the product showing more rapid release in the intestinal pH than in that of the stomach. However, there is no indication that the unusual structure of the tablet confers special dissolution characteristics.

Pro-Vent. Fig. 1 shows that dissolution is largely, but not entirely, independent of change in pH from 2.4 to 6.0. The many release processes from the individual pellets sum to an approximate first-order process. Apparent first order rate constants have been calculated and are presented in Table 1, these show the release rate constant at pH 6.0 to be less than twice that at pH 2.0.

Theo-grad. The dissolution curves for the two experimental profiles are perfectly coincident showing that change of pH has no effect on dissolution rate.

Uniphyllin. The release of drug is dependent upon two factors: dissolution of the higher aliphatic alcohol and diffusion of the drug through hydration of the hydroxyalkylcellulose. The release, which is independent of pH, is for a reasonable period of time (1–4 h), approximately zero order. However, the profile can be represented as two apparent first order processes (before and after 4 h).

TABLE 1

Apparent first-order rate constants for release of theophylline at the pH of the stomach and the small intestine

Product	Apparent first order rate constant (h^{-1})	
	pH 2.4	pH 6.0
Nuelin	0.015 (0.982)	0.539 (0.959)
Theo-Dur	0.059 (0.934)	0.340 (0.999)
Theograd	0.160 (0.947)	0.160 (0.947)
Pro-Vent	0.020 (0.982)	0.060 (0.994)
Uniphyllin		
first stage	0.030 (0.998)	independent
second stage	0.040 (0.997)	of pH

Correlation coefficient in parentheses.

Kinetics of drug release

If the pattern of drug release from Uniphyllin is analysed as two stages before and after 4 h, all products closely follow first-order kinetics. The values of the rate constants for the different experimental conditions are given in Table 1.

Projected in vivo data

The results show wide variation in the pattern of in vitro release, both in absolute terms and in the influence of pH. Variation of this magnitude would be expected to have significant influence in vivo. If it is assumed that (1) dissolution is the rate-limiting process for absorption, (2) all drug released will be absorbed, whether in the stomach or intestine, i.e. no absorption window problems; (3) the elimination rate remains constant, the amount of drug in the body (A) can be calculated in the manner described by Welling (1983):

$$A = \frac{Ds\ kr}{kr - kel}\left[e^{-kel\ t} - e^{-kr\ t}\right] \quad (1)$$

where Ds = dose of drug available

kr = release rate constant

kel = elimination rate constant

t = time after taking dose.

Calculated value of $kel = 0.077$ assuming a plasma half-life of 9 h (Goodman-Gilman et al. 1980). If

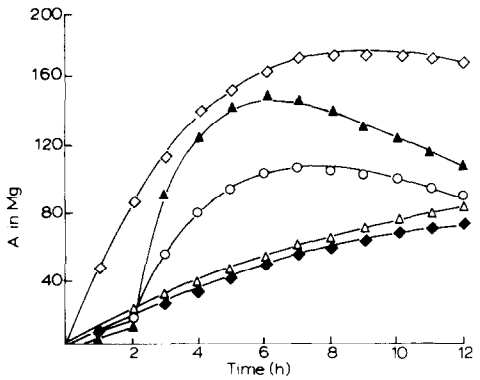

Fig. 3. Theoretical amount of drug in the body as a function of time with gastric emptying after 2 h. Key: ▲, Nuelin; ○, Theo-Dur; ◆, Provent; △, Uniphyllin; ◇, Theo-grad.

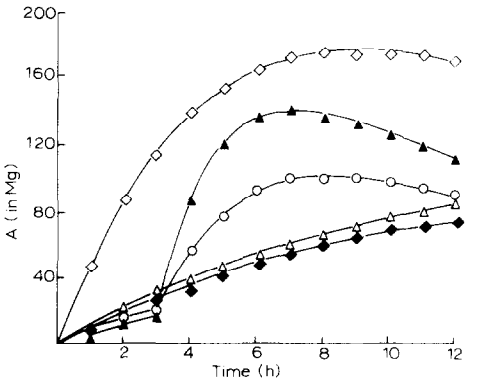

Fig. 4. Theoretical amount of drug in the body as a function of time with gastric emptying after 3 h. Key: ▲, Nuelin; ○, Theo-Dur; ◆, Provent; △, Uniphyllin; ◇, Theo-grad.

the dosage form releases at constant rate, the values of A are simply calculated from Eqn. 1. If, however, the dosage form exhibits two release rates, then values of A are calculated up until the change occurs and an exponential decline calculated from that point. This quantity is added to the levels expected from the second phase with Ds calculated as remaining payload and blood levels calculated at the new release rate.

By this method, the amount of drug in the body can be calculated for each product, assuming different lengths of time in the stomach. It is clear that rapid emptying from the stomach will present the intestine with a dosage form with high drug load which (depending on the product) will then release very rapidly, whilst long duration in the stomach will present a depleted dosage form to the intestine giving less chance of high blood levels occurring. Fig. 3 shows the theoretical amounts of drug in the body for 2 h residence in the stomach, Fig. 4 for 3 h and Fig. 5 for 4 h.

The theoretical data presented in Figs. 3–5 demonstrate the enormous potential for variation in blood level, both between products, and within the same product, depending on the gastric transit time. For example, the maximum amount of drug in the body for Nuelin after 2 h gastric transit is 147 mg at 6 h compared to 136 mg after 8 h with 4 h transit. Both of these values are significantly different from Uniphyllin, for example, which does not reach a maximum within 12 h, but by this time has 85 mg in the body. Furthermore, the gastric release section for each product shows zero order rise in the theoretical amount of drug in the body, despite first-order in vitro release.

Uniphyllin and Pro-vent have release profiles which predict a zero order increase in the amount of drug in the body; with these products, a maximum blood level is not achieved within the transit time of one dosage unit and residence time in the stomach does not influence drug release; this situation is clearly different from that predicted for Nuelin and Theo-Dur, which result in higher blood levels than either Uniphyllin or Pro-vent with the maximum level and time taken to achieve the maximum level being dependent upon the time in the stomach. The blood levels predicted for Nuelin and Theo-Dur drop after reaching the

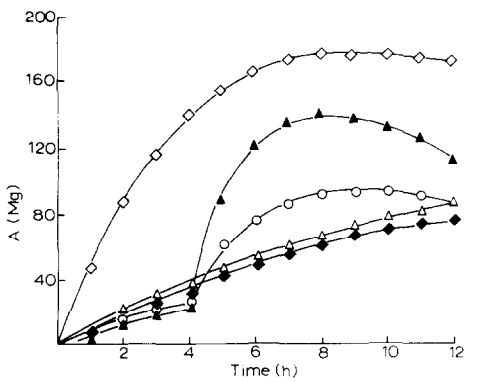

Fig. 5. Theoretical amount of drug in the body as a function of time with gastric emptying after 4 h. Key: ▲, Nuelin; ○, Theo-Dur; ◆, Provent; △, Uniphyllin; ◇, Theo-grad.

maxima, until after 12 h they return to a similar level to that of the other products. Theo-grad showed a higher predicted blood level than any of the other products, the profile being independent of time in the stomach.

Conclusion

An extensive literature describes significant clinical differences between theophylline products. We have shown that the diverse manufacturing techniques employed give very different release patterns and, using certain assumptions, we translated in vitro performance to show how they might behave in vivo. From these results, the conclusion must be drawn that sustained-release preparations, particularly of drugs with a narrow therapeutic index, should not be generically prescribed. Patients should be stabilised and maintained on one product only. If the trend towards generic substitution is to continue it is essential that sustained/controlled release products come under compendial control, and this will not be an easy process.

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References

Goodman-Gilman, A., Goodman, L.S. and Gilman, A., *The Pharmacological Basis of Therapeutics*, 6th edn., Macmillan, New York, 1980, pp. 592–605.

Hannaway, P.J. and Hopper, G.D.K., Comparison study of sustained-release theophylline products: slo-bid capsules versus theo-dur tablets in 20 children and young adults with asthma. *J. Allergy Clin. Immunol.*, 77 (1986) 456–464.

Lagas, M. and Jonkman, J.H.G., Studies on the delivery mechanisms of theophylline from a sustained release tablet. *Drug. Dev. Ind. Pharm.* 12 (1986) 489–506.

Summers, R.S., Summers, B. and Rawnsley, S., The bioavailability, absorption characteristics and formulation of 4 commercially available controlled release theophylline products. *Int. J. Pharm.*, 30 (1986) 83–88.

Vogel, A.I. *Textbook of Macro and Semi-Macro Qualitative Inorganic Analysis*, 5th edn., Longman, London, 1972, p. 52.

Weinberger, M., Hendeles, L., Wong, L. and Vaughan, L., Relationship of formulation and dosing interval to fluctuation of serum theophylline concentration in children with chronic asthma. *J. Paediatr.*, 99 (1981) 145–152.

Welling, P.G., Oral controlled drug administration. *Drug Dev. Ind. Pharm.*, 9 (1983) 1185–1225.