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Characterisation of commercially available theophylline sustained- or controlled-release systems: in-vitro drug release profiles

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Summary

Release of theophylline, either in the form of the free xanthine or complexed with choline or ethylene diamine, from commercially available dosage forms is modelled using a series of standard drug-release models. Those included the first order and the cube root models. Equations which take into account the geometries of the products were also assessed and compared with the more generic square root of time model. It is shown that in practice discrimination between the competing models is difficult even with use of mean square errors. All the products on the U.K. market showed pH-dependency although to variable extents. Sabidal®, for example, gave good consistency within the pH range 2.1–6.9 but much slower release rates at pH 1.2. Such a profile may be desirable given the known irritant effects of theophylline in the stomach. Lasma® showed a similar pH effect but the rates of release were extremely fast at pH 2.1 and above. This suggests a potential dose-dumping effect in vivo. Phyllocontin® showed relatively little pH variability in its release profiles. Ionic strength had a dramatic effect on drug release from Lasma® tablets. Sabidal® was also markedly affected as was Pro-Vent®. These results certainly show that theophylline sustained-release products are not interchangeable without re-adjustment to steady-state blood levels.

Introduction

There is a wide array of sustained-release formulations available in the U.K. and worldwide. It is not possible to define the release profiles of theophylline from those products by simple macroscopical or microscopical examination and in-vitro drug-release tests are necessary. This study reports on the drug release profiles of theophylline from sustained-release theophylline products on the U.K. market. Emphasis is placed on modelling of the drug release profiles using established mathematical equations for reservoir and matrix systems (Hixson and Crowell, 1931; Higuchi, 1963; Roseman and Higuchi, 1970; Baker and Lonsdale, 1974; Cobby et al., 1974a,b). The effects of various dissolution variables on theophylline-release from the sustained-release formulations are also studied with a view to evaluating whether potential problems should be anticipated in vivo.

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Materials and Methods

All the proprietary theophylline products were commercial lots purchased on the open market. Anhydrous theophylline was purchased from Sigma (U.K.).

Drug-release studies

An automated dissolution assembly (Caleva Model 5ST) consisting of a thermostated water bath (37°C) fitted with six flat-bottomed cylindrical flasks and BP dissolution baskets rotated at 100 rpm was used. The dissolution medium consisted of 1 l of pH 6.9 McIlvaine's buffer adjusted to an ionic strength of 1 M. Solutions from the dissolution vessels were pumped with a Watson Marlow peristaltic pump (502S/170/AA) through an ultraviolet spectrophotometer (LKB 4052 Ultrospec) set at 293 nm. The baskets were set at 20 mm from the bottom of the flask and rotated at 100 rpm. Absorbance was monitored continuously and readings stored in a computer for subsequent analysis (TDS Software). Calibrations were carried out using standard solutions of theophylline. The highest strength available of each product was used in the release studies.

In the investigations of pH effects, McIlvaine's buffer adjusted to an ionic strength of 1 M was used except at pH 1.2 when hydrochloric acid was employed. The effect of ionic strength was investigated at pH 1.2 by using potassium chloride to make the necessary adjustments over the range 0.1–1 M.

The behaviour of the same product but of different strengths was also evaluated when those strengths were commercially available.

Solubility of theophylline

This was determined by shaking buffer solutions in the presence of excess theophylline at 37°C until equilibrium was achieved. Typically 48 h were sufficient. The suspensions were then filtered and diluted before analysis by ultraviolet spectrophotometry. The buffers used were again McIlvaine's adjusted to 1 M ionic strength.

Intrinsic dissolution rate

The intrinsic dissolution rate of theophylline was measured using disks of theophylline compressed to 3 ton, maintained over a period of 10 s, in an infrared disk die and hydraulic press. The disks were mounted onto rotating shafts using hard paraffin wax so that only one surface was exposed. The disks measured 13 mm in diameter. Dissolution rate was measured at 100 rpm in 1 l of McIlvaine buffer solution of varying pH but fixed ionic strength. Theophylline concentration was again measured by ultraviolet spectrophotometry.

Results and Discussion

Drug delivery systems can theoretically be tailored to release drug according to specific profiles depending on the drug release mechanisms built into the system. However, in practice, difficulties in manufacturing processes often lead to deviation from the anticipated behaviour. Despite being non-ideal, such systems are still widely used because, provided the release profile is consistent and reproducible, blood level profiles can still be controlled to be within clinically safe and therapeutically effective limits. One problem however relates to non-interchangeability of sustained-release products, a problem well appreciated by many users of theophylline sustained-release formulations. Despite the wide acceptance of sustained-release theophylline products with non-ideal release behaviour, it is still worthwhile to investigate whether such behaviour can be mathematically modelled with a view to assessing potential problems in their use. Theoretically a number of drug release profiles can be anticipated and those of particular relevance to the present study are briefly discussed below.

Zero-order profile

For a system which maintains constant drug release surface area and activity gradient, zero-order release is predicted. During the initial stages of drug release, a number of sustained-release systems often release drug by an apparent zero-order profile. Typically, zero-order drug release systems consist of a drug reservoir, containing suspended drug, enclosed within a rate-limiting barrier.

First-order profile

In this case, drug activity within the reservoir declines exponentially and the rate of drug release is proportional to the residual activity. Typically the reservoir contains only dissolved drug. A plot of logarithm of residual drug against time is therefore linear with the slope being equal to the rate constant as shown in Eqn 1.

$$\ln(1-M_t/M_\infty) = -kt \tag{1}$$

Hixson and Crowell cube-root equation

The Hixson and Crowell model was developed (Hixson and Crowell, 1931) to describe drug release from systems which showed dissolution-rate limitation. The model applies to any such system which in addition does not dramatically change in shape as release proceeds. According to this model drug release may be expressed by the following equation.

$$(1-M_t/M_\infty)^{1/3} = -kt \tag{2}$$

Higuchi square-root of time model

Starting with Fick's first law of diffusion, Higuchi (1963) was able to show that drug release into a sink from a system consisting of drug dispersed within a diffusion rate-limiting planar matrix could be adequately modelled by Eqn 3, at steady state.

$$(M_t/M_\infty)^2 = kt \tag{3}$$

$$M_t/M_\infty = \frac{A}{M_\infty}[DtC_s(2C_0 - C_s)]^{1/2} \tag{3a}$$

Baker and Lonsdale equation for a spherical matrix

For a system consisting of drug dispersed within a spherical diffusion rate-limiting matrix, Baker and Lonsdale (1974) have shown that drug release may be satisfactorily modelled by Eqn 4.

$$\frac{3}{2}[1-(1-M_t/M_\infty)^{2/3}]-M_t/M_\infty = \frac{3DC_s}{r_0^2C_0}t = kt \tag{4}$$

Roseman and Higuchi equation for cylindrical matrices

For a cylindrical matrix with suspended drug, Roseman and Higuchi (1970) have shown that the drug release profile may be modelled by Eqn 5 assuming the same constraints as those used in deriving the Higuchi square root of time model.

$$M_t/M_\infty + [1 - M_t/M_\infty]\ln[1 - M_t/M_\infty] = \frac{4DC_s}{r_0^2C_0}t = kt \tag{5}$$

To facilitate comparisons, all the equations for the different models were transformed to straight line equations (Eqns 1–5) so that the response variable is a function of time. In the literature, some of the above models have been used to describe drug release from sustained-release systems. Buckton et al. (1988), for example, used a first-order model to describe theophylline release from a series of products on the British market. Boraie and Naggar (1984), on the other hand, used the square root of time model to describe theophylline release from hydrophilic matrices as did Said and Al-Shora (1980). Parab et al. (1986) went further and compared the square root of time, the cube root and the first-order models for describing theophylline release from experimental matrix tablets based on comparisons of goodness-of-fit and appropriate F tests. Such goodness-of-fit tests of hypothesis have previously been proposed by Bamba et al. (1979a). This approach seems to be the most objective in choosing the most appropriate model and is preferable to the use of correlation coefficients (r) or their squared (r^2) values. While the r^2 value measures the fraction of the total sum of squares variation assignable to the straight line model, the inadequacy of using it as the sole criterion for judging the appropriateness of a proposed model for predicting drug release has been discussed by Sheiner and Beal (1981). Those authors proposed the use of mean square error and mean prediction error instead. In the present study, the goodness-of-fit approach, necessarily involving the calculation of mean square error, was used.

Figs 1 and 2 illustrate the release profiles of the theophylline products investigated. It is clear that not only do the systems show wide inter-product variability but also that some systems, notably Theograd®, released drug with much more variability than others. Such variability in theophylline release has previously been reported by Upton et al. (1980) and Spangler et al. (1978) in their in vivo pharmacokinetic studies. Simons et al. (1984, 1985) showed wide variability in dissolution profiles of nine sustained-release theophylline products available on the North American market. Even products with the same formulation but of different strengths showed marked variability.

Phyllocontin® and Uniphyllin® showed highly reproducible in-vitro release profiles under our in-vitro conditions. Lasma® tablets on the other hand give cause for concern since although the in-vitro release profiles were reasonably consistent, the rapidity of release indicates that if the in-vitro profiles were a reasonable reflection of in-vivo behaviour, then those tablets would give poor prolongation of release relative to immediate release formulations. Under the conditions of the present study, theophylline release from the Lasma® tablets was essentially complete within 1 h and its release profiles were not further modelled.

The profiles for theophylline release were fitted to different mathematical models and models which were clearly inappropriate for any given

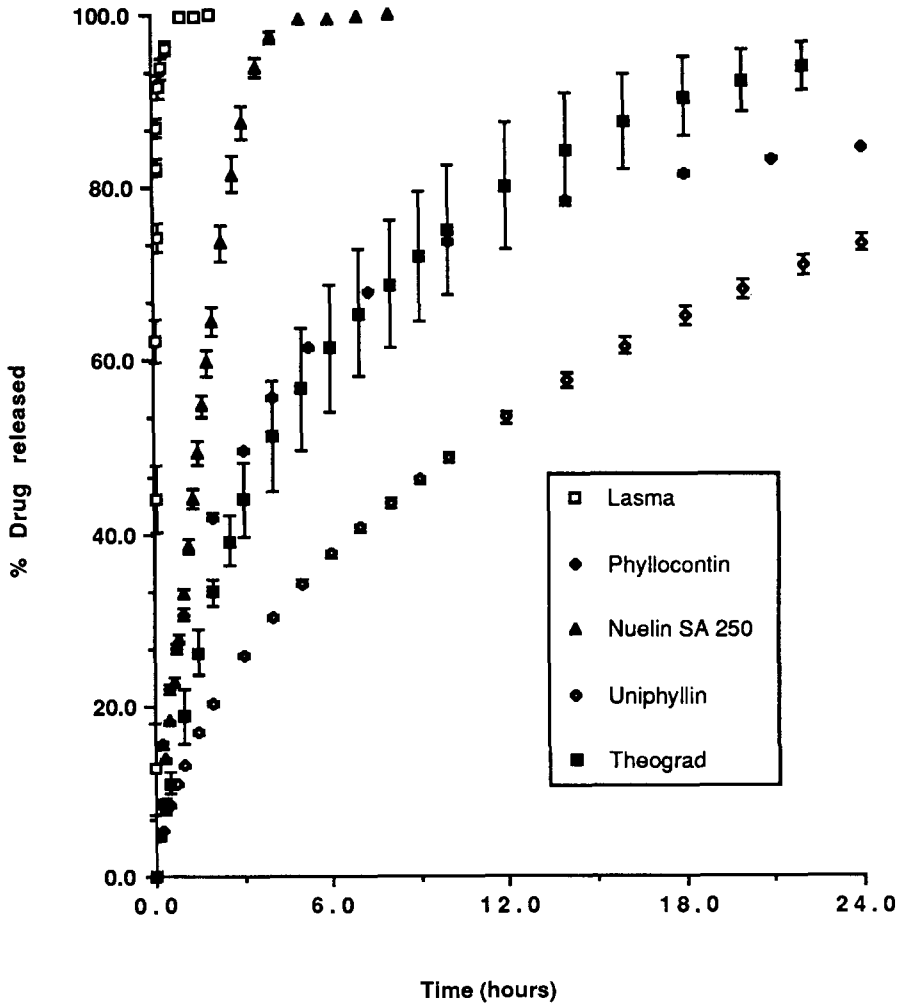

Fig. 1. In vitro release profiles of matrix theophylline products in pH 6.9 McIlvaine buffer (mean ± SD).

product were left out. For example, the Baker and Lonsdale model for spherical matrices is clearly inappropriate for formulations with cylindrical geometries. In calculating the parameters of the linear fits, drug release in the region 10–80% released only is considered in order to account for non-steady state regions and terminal decays. Simple visual inspection enables rapid elimination of some inappropriate models. Theo-Dur®, for example, shows a release profile which is poorly modelled by first-order kinetics and similar poor fits are observed for the Hixson-Crowell cube root model. Examination of the correlation coefficient squared values and the mean square errors (Table 1) improves the sensitivity with which the competing model can be dissociated and the F tests enable the choice of the most appropriate model.

In evaluating the most appropriate model for the observed theophylline release data, in addition to the numerical goodness-of-fit data, it is essential to have an appreciation of the physical make-up of the formulations being investigated.

Difficulties arise when comparing different products using the same basic models. Pro-Vent® capsules, for example, seem to include 25% (25.8 + 1.0%) of their theophylline content in the form of an immediate-release loading dose. Therefore, censoring of early data is required before fitting to

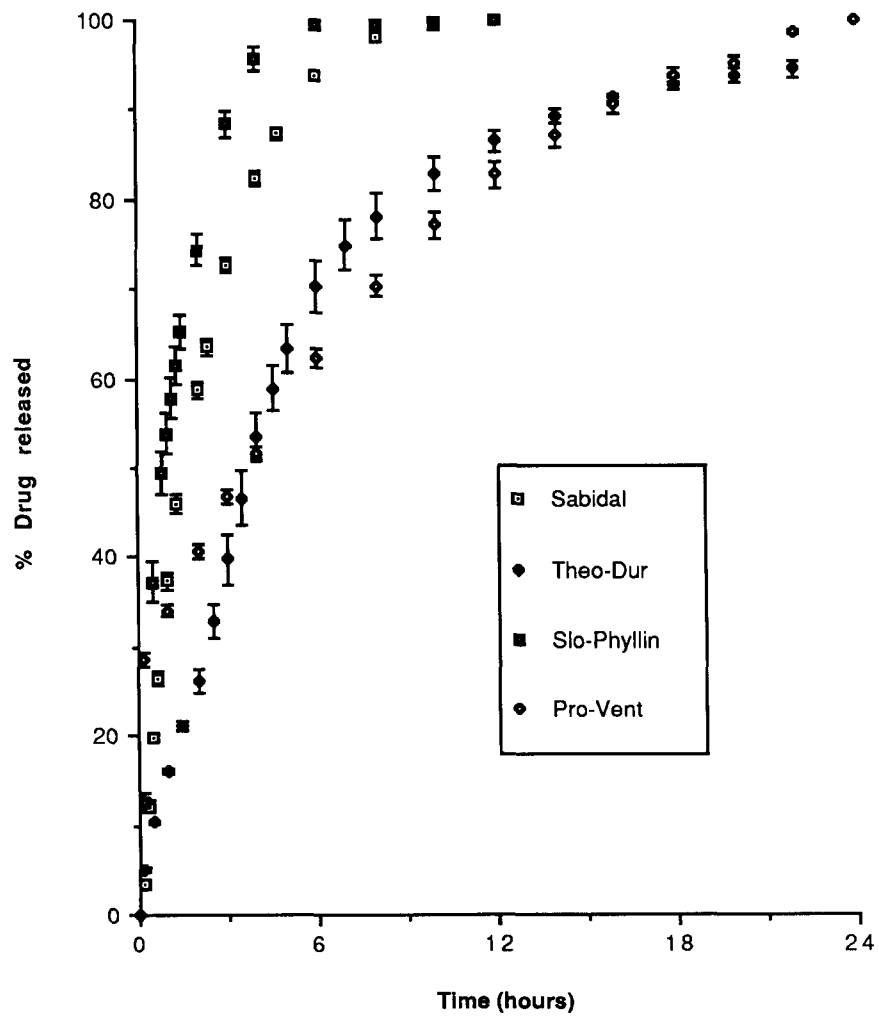

Fig. 2. In vitro release profiles of theophylline from pseudo-reservoir systems in pH 6.9 McIlvaine buffer (mean ± SD).

TABLE 1

Goodness of fit data for the various models used

Product	Model	Intercept (SD)	Slope (SD)	r^2 (%)	Mean square error
Nuelin SA 250® tablets	First order	0.135 (0.041)	−0.578 (0.030)	97.5	0.0038
	Cube root	1.02 (0.007)	−0.155 (0.005)	98.9	0.00011
	Square root of time	−0.288 (0.031)	0.648 (0.028)	98.2	0.00074
	Square root of time transformed	−0.125 (0.023)	0.263 (0.016)	96.4	0.0011
	Roseman and Higuchi cylindrical matrices	−0.0976 (0.021)	0.182 (0.015)	93.7	0.0010
Phyllocontin® 350 mg	First order	−0.327 (0.047)	−0.094 (0.006)	94.4	0.0147
	Cube root	0.892 (0.014)	−0.023 (0.002)	91.3	0.0014
	Square root of time	0.124 (0.025)	0.190 (0.011)	95.9	0.0021
	Square root of time transformed				
	Roseman and Higuchi cylindrical matrices	0.042 (0.014)	0.032 (0.002)	95.7	0.0013
Provent®	First order	−0.293 (0.017)	−0.122 (0.003)	99.4	0.001
	Cube root	0.898 (0.002)	−0.030 (0.0005)	99.8	0.00002
	Square root of time	0.173 (0.018)	0.187 (0.009)	98.2	0.0006
	Square root of time transformed				
	Baker and Lonsdale spherical matrices	0.005 (0.004)	0.016 (0.0008)	98.3	0.00006
Sabidal®	First order	−0.018 (0.014)	−0.439 (0.008)	99.8	0.0005
	Cube root	0.976 (0.008)	−0.113 (0.005)	98.8	0.0002
	Square root of time	−0.159 (0.021)	0.524 (0.017)	99.3	0.0004
	Square root of time transformed				
	Roseman and Higuchi cylindrical matrices	−0.0526 (0.004)	0.143 (0.002)	99.8	0.00005
Slo-Phyllin® 250 mg	First order	−0.128 (0.030)	−0.668 (0.028)	98.6	0.002
	Cube root	0.944 (0.012)	−0.172 (0.011)	96.8	0.0004
	Square root of time	−0.060 (0.031)	0.605 (0.032)	97.9	0.0009
	Square root of time transformed				
	Baker and Lonsdale spherical matrices	−0.012 (0.001)	0.085 (0.001)	99.9	0.000003
Theo-Dur® 300 mg	First order	0.054 (0.024)	−0.203 (0.005)	99.2	0.0019
	Cube root	0.995 (0.007)	−0.052 (0.002)	98.9	0.0002
	Square root of time	−0.200 (0.028)	0.358 (0.014)	98.3	0.001
	Square root of time transformed	0.080 (0.016)	0.090 (0.004)	98.2	0.0009
	Roseman and Higuchi cylindrical matrices	−0.074 (0.013)	0.066 (0.003)	97.7	0.0006
Theograd®	First order	−0.132 (0.025)	−0.131 (0.0045)	98.7	0.0025
	Cube root	0.946 (0.010)	−0.034 (0.0018)	97.1	0.0004
	Square root of time	−0.048 (0.020)	0.264 (0.009)	98.6	0.00067
	Square root of time transformed	−0.0021 (0.010)	0.060 (0.002)	98.9	0.00043
	Roseman and Higuchi cylindrical matrices	−0.018 (0.0033)	0.0429 (0.0006)	99.8	0.00004

(continued)

TABLE 1 (continued)

Product	Model	Intercept (SD)	Slope (SD)	r^2 (%)	Mean square error
Uniphyllin®	First order	−0.142 (0.011)	−0.050 (0.0008)	99.6	0.0009
	Cube root	0.944 (0.005)	−0.013 (0.0004)	98.4	0.0002
	Square root of time	−0.0103 (0.006)	0.154 (0.002)	99.7	0.00013
	Square root of time transformed	0.0038 (0.004)	0.0226 (0.0003)	99.7	0.00012
	Roseman and Higuchi cylindrical matrices	−0.014 (0.001)	0.0164 (0.0001)	99.9	0.00002

the basic models. Theo-Dur® tablets, on the other hand, possess features of a planar matrix and of spherical or non-constant activity reservoirs as they are made up of sustained-release pellets embedded within a second matrix which disintegrates during drug release. With such a system, biphasic release is observed. Such a biphasic release pattern is observed irrespective of which model is used to fit the Theo-Dur® data.

Nuelin SA250® tablets are essentially non-erodible matrices and one would therefore expect better fits to the matrix diffusional models rather than to the first-order or cube root models. Examination of the profiles and of the numerical fits, however, indicates that this was not the case (Table 1). The cube root and the square root of time models gave comparable fits.

Both the Phyllocontin® and Uniphyllin® systems can be described as swellable erodible systems. Bamba et al. (1979b), in their study of such systems, have suggested the following processes as being potentially rate-limiting: permeation of water, gelation rate, dissolution rate and diffusion rate of drug in the permeating fluid. In their study of gel-forming systems, they found the rate of water permeation and drug diffusion out of the gel to be rate-limiting. Korsmeyer et al. (1983) similarly studied the influence of molecular size of diffusant, diffusant/excipient ratio and swelling and dissolution rates of polymer matrix on release mechanisms using a simple power function of time as the independent variable and the fraction of drug released as the dependent variable. In their study, a time exponent ranging from about 0.47 to 0.70 was observed for drug release from planar systems releasing drug from one surface. This illustrates the complexity in modelling drug release data. An exponent of 0.5 is of course consistent with the Higuchi square root of time model for suspension matrices. In the present study, drug release from Uniphyllin® was adequately modelled by most of the models used (Table 1). Phyllocontin®, presumably using the same matrix as Uniphyllin®, but with aminophylline (ethylenediamine-theophylline) as the diffusant instead of theophylline, gave poor fits to all the models tested possibly due to markedly different solubility characteristics and equilibrium of the free xanthine with the complex (Table 1).

Theograd® is formulated as a non-erodible matrix. In the present study, the tablets were observed to erode partially and electron-micrographs revealed the presence of a porous matrix after dissolution. In the absence of erosion, matrix diffusional models can be expected to describe the data well and indeed the Higuchi and Roseman equation gave the best fit.

Sabidal® consists of drug and excipients surrounded by a rate-controlling membrane. Contact with dissolution medium leads to the formation of a porous membrane which allows choline theophyllinate to diffuse through. The system seems to function as a non-constant activity reservoir and therefore first-order kinetics can be expected to model the data well. This was in fact the case but the Roseman and Higuchi model for drug release from a cylindrical matrix also gave an equally good fit for most of the release profile (Table 1).

The Pro-Vent® capsules contain a mixture of pellets coated to different thicknesses and thus behave as non-constant activity reservoirs. First-order kinetics are expected to give a good fit although, as already indicated, a loading dose presumably in the form of uncoated pellets is also included. A good fit is indeed obtained although the cube root model was superior indicating that dissolution rather than diffusion was rate limiting

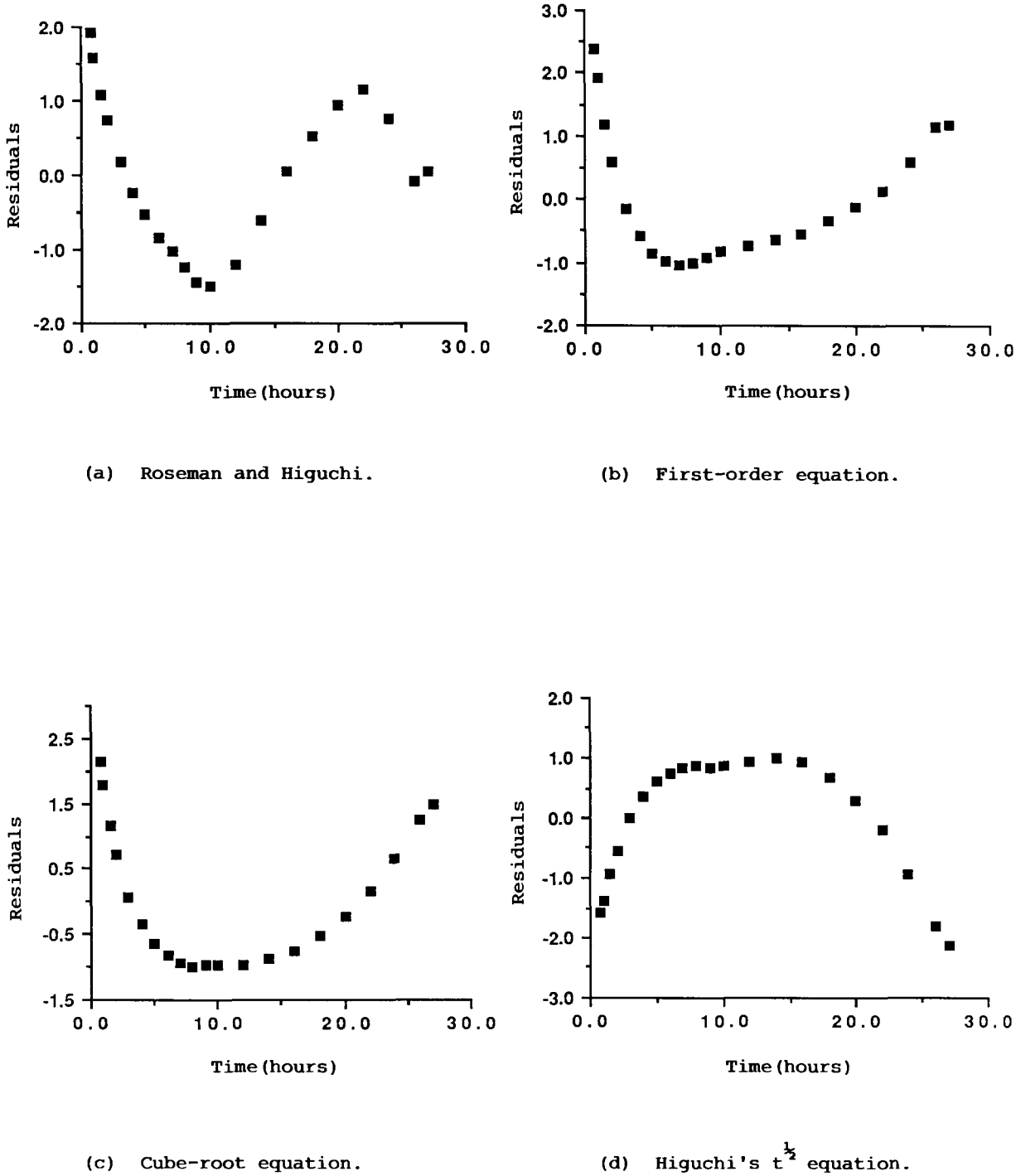

Fig. 3. Plot of residuals for theophylline release from Uniphyllin 400 mg fitted to different models. (a) Roseman and Higuchi, (b) first-order equation, (c) cube-root equation, (d) Higuchi's $t^{1/2}$ equation.

(Table 1).

It is clear from Table 1 that use of appropriate statistics enables distinction between adequacy of competing mathematical models. However, that in itself is not sufficient to enable comment about the most likely mechanism of release. For this, visual, including microscopical, examination of the systems is required. For the drug formulator, the actual formulation excipients used and the manufacturing methods will provide further insight. However, even where numerical fits appear satisf?actory based on how closely the data fit the predicted profile, examination of the residuals may indicate that all is not well. For example, although the Uniphyllin® data were closely modelled by a number of the proposed models (Table 1), a graphical analysis of the residuals shows very clear trends indicating departure of experimental from theoretical values. The Roseman and Higuchi model, for example, gave an r^2 value of 99.9% and a mean square error of 2×10^{-5}. Yet the non-random pattern in the residuals is quite evident (Fig. 3). This is indeed seen in all the fits attempted in this study.

If the residual plots show such marked deviations of the observed data from those predicted by the models, is modelling at all worthwhile? The mean residual errors indicate that in many cases, only small errors, probably of little practical significance, are observed. Therefore,for use as indi-

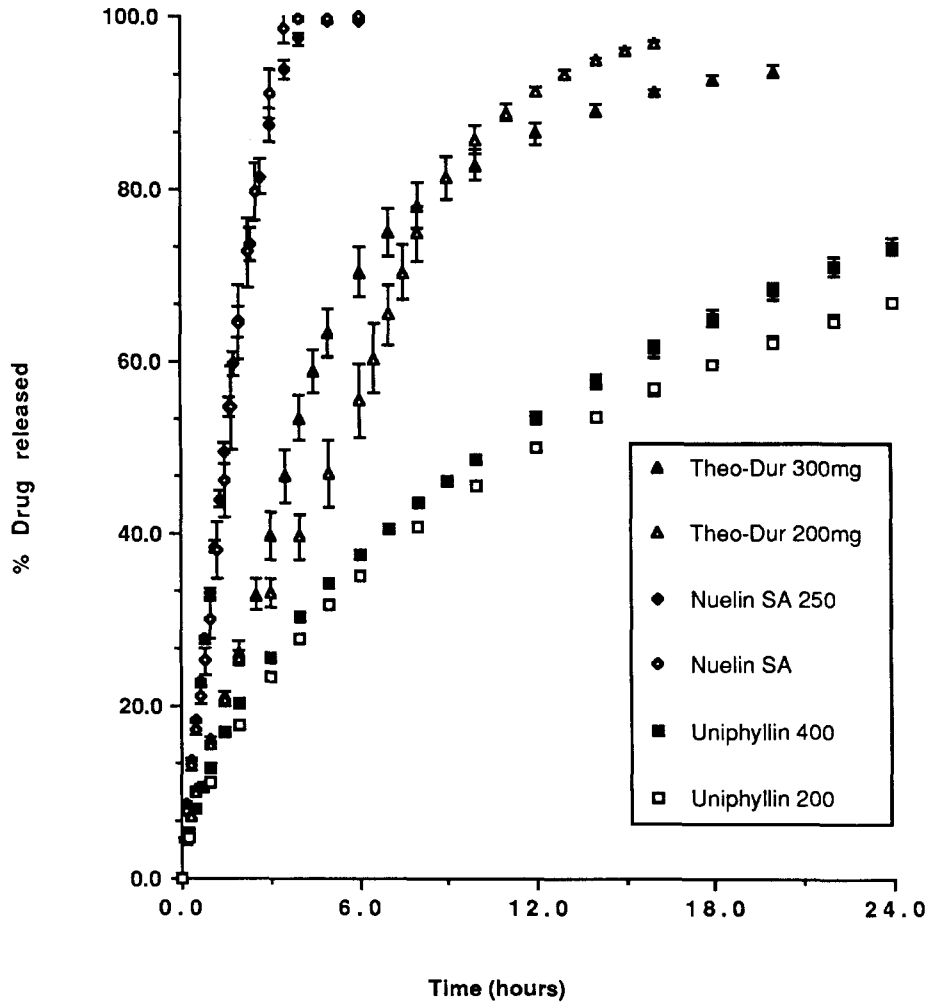

Fig. 4. Effect of drug strength on theophylline release from Theo-Dur, Nuelin SA and Uniphyllin tablets.

cators during quality control of sustained-release pharmaceutical products or for predicting variability in in-vivo performance, the parameters of the models give very adequate predictions which will of course need subsequent validation. The present study shows Lasma® and Theograd® to be products with potential in-use problems: Lasma® because of too rapid release and Theograd® because of erratic drug release. Theograd® tablets have recently been withdrawn from sale.

To investigate these potential problems further the effects of product strength, pH of dissolution medium and ionic strength on the release profiles were studied.

The need for close theophylline dose titration has led to products of different strengths. Those products may however have different release profiles and therefore lead to potential clinical problems. Simons et al. (1984), for example, showed differences in release profiles with Slo-Phyllin® 125 and 250 and with Aerolate 65 and 130. The results of the present study (Figs 4 and 5) show that some of the products investigated did in fact produce different release profiles with different strengths. Slo-Phyllin® 125 mg released drug significantly faster than the 250 mg and 60 mg products. For Phyllocontin®, the 100 mg formulation released drug substantially faster than the 225 mg and the 350 mg strengths. Uniphyllin® tablets

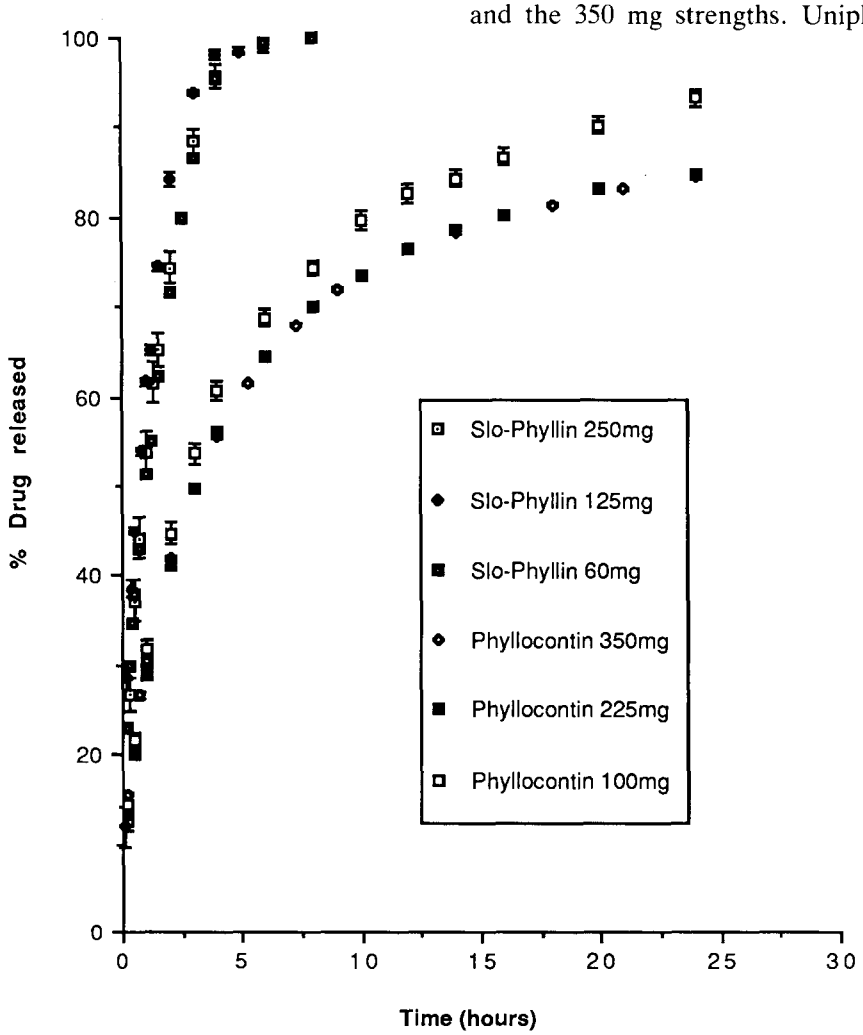

Fig. 5. Effect of drug strength on theophylline release from Slo-Phyllin capsules and Phyllocontin tablets.

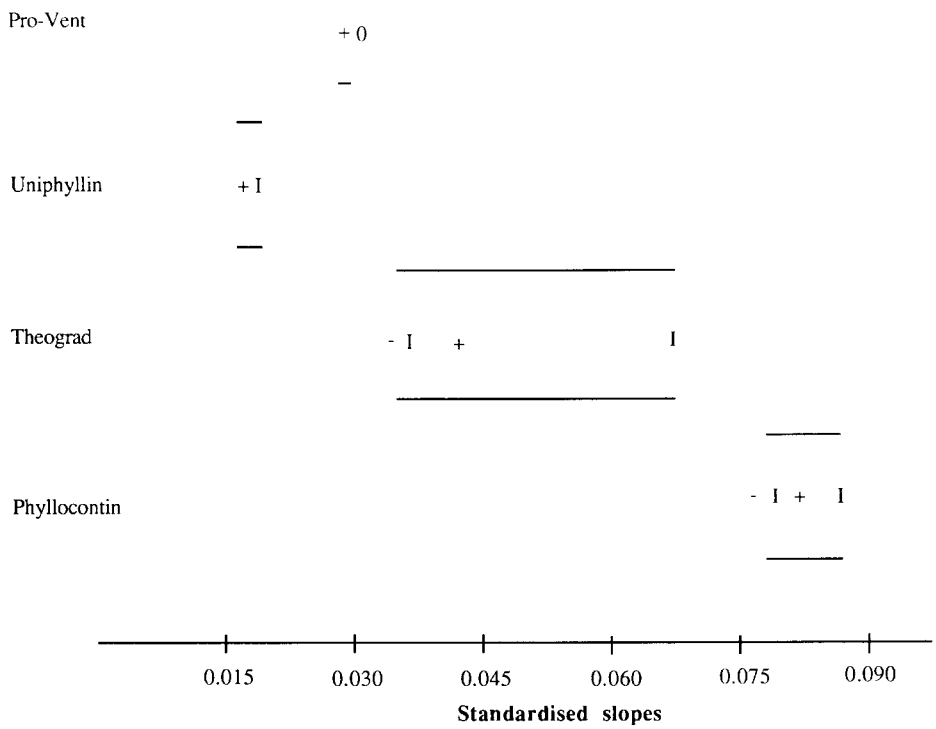

Fig. 6. Box plot of standardised slopes to show the wide variability in release of theophylline from sustained-release products on the U.K. market.

also showed product-strength dependent release. Despite the profiles shown in Fig. 4, there was no statistical difference in the release profiles of the two Theo-Dur® products. This result must however be interpreted with caution. The release profiles of the same strength show much wider variability for Theo-Dur® than with most of the other products. Therefore the *within* single strength product variability is more likely to mask small differences in *between* product strengths variability with Theo-Dur® than with most of the other products. Fig. 6 shows the wide differences in release profiles of different theophylline products standardised using slopes of the best fit model for each product. To obtain slopes within the same order of magnitude, the individual values were adjusted by subtracting appropriate constants.

The effect of pH on the release of theophylline from the commercial sustained-release products has been investigated and the results of the statistical multiple range tests are shown in Table 2. Dramatic effects are seen with a number of the products and these have been shown graphically. With Lasma® tablets release was reasonably sustained at pH 1.2 (Fig. 7). However, once the pH rose to pH 2.1, release of theophylline was essentially complete well within 1 h. Higher pH values gave equally rapid drug release. Those in-vitro data would strongly indicate possible in-vivo problems. Dose dumping, as reported by Hendeles et al. (1984), appears to be a distinct possibility. Possible problems are also indicated by the Nuelin SA® data in that theophylline release at pH 6.9 was substantially faster than at other pH values (Fig. 8). Release was, however, much more sustained than with Lasma® tablets. The pH variability seen with Nuelin SA® tablets confirms earlier reports that, generally, pH has most marked effects in the near neutral and alkaline pH ranges (Jonkman et al. 1981; Jonkman 1984; Buckton et al., 1988). Mild agitation may not reveal the pH effects seen at higher agitations. This has been explained on the basis of faster hydroxyl ions induced erosion of the cellulose acetate phthalate ma-

TABLE 2

Multiple range test for effect of pH on rates of release of theophylline from sustained release products

Lasma®
Response variable: Slope of initial zero-order plot

	pH			
	1.2	2.1	4.9	6.9
Population 1	———	———	———	
Population 2				———

increasing slope →

Nuelin SA®
Response variable: Slope of cube root plot

	pH			
	4.9	1.2	2.1	6.9
Population 1	———	———	———	
Population 2				———

Phyllocontin®
Response variable: Slope of square root of time model

	pH			
	1.2	2.1	6.9	4.9
Population 1		———	———	
Population 2	———			
Population 3				———

Pro-Vent®
Response variable: Slope of cube root model

	pH			
	2.1	4.9	1.2	6.9
Population 1	———			
Population 2		———		
Population 3				
Population 4				———

Sabidal®
Response variable: Slope of cylindrical matrix model

	pH			
	1.2	2.1	6.9	4.9
Population 1	———			
Population 2		———		
Population 3			———	
Population 4				———

Slo-Phyllin®
Response variable: Slope of spherical matrix model

	pH			
	2.1	4.9	1.2	6.9
Population 1	———	———		
Population 2			———	
Population 3				———

Theo-Dur®
Response variable: Slope of first-order model

	pH			
	4.9	1.2	6.9	2.1
Population 1	———	———		
Population 2			———	
Population 3				———

Theograd®
Response variable: Slope of cylindrical matrix model

	pH			
	2.1	1.2	6.9	4.9
Population 1	———	———	———	

(continued)

TABLE 2 *(continued)*

Uniphyllin®
Response variable: Slope of cylindrical matrix model

	pH			
	6.9	4.9	2.1	1.2
Population 1		———		
Population 2	———			
Population 3				———

trix (Crombeen and Blaey, 1983). Phyllocontin® showed some pH variability in its aminophylline release profiles as shown by ANOVA of the areas under the percentage drug release-time curves ($F_{3, 12} = 4.92$). However, the differences were small and very unlikely to lead to any bioavailability problems. Pro-Vent® also showed significant pH variability in release profile although even

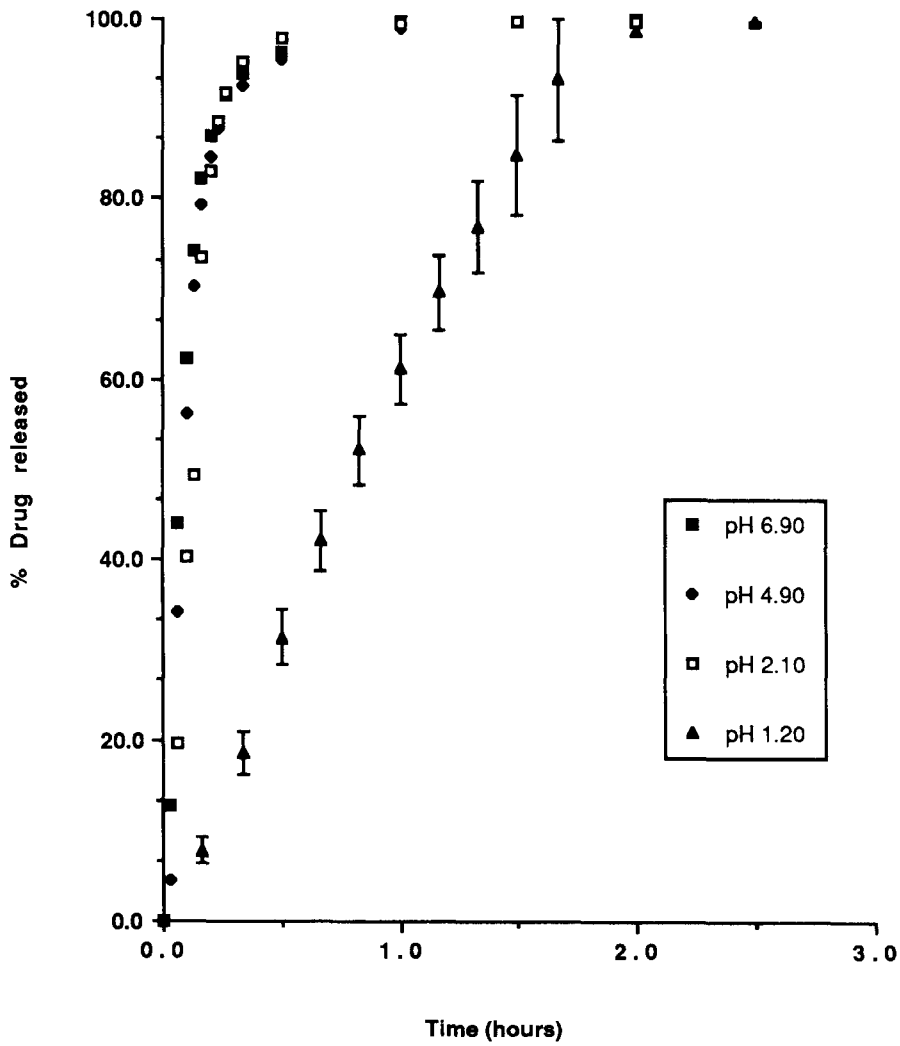

Fig. 7. Effect of pH on theophylline release from Lasma tablets.

at pH 6.9 there was reasonable sustaining of drug release (Fig. 9). The higher release rates found at the higher pH values were consistent with results reported by Florence (1987). With Slo-Phyllin® only small albeit statistically significant (F3, 12 = 58.3) differences in release profiles were observed as the pH of the dissolution medium was increased from pH 1.2 to pH 6.9.

Theo-Dur® showed a biphasic type of release profile (Fig. 10) reflecting the design of the product. It would appear that the first stage rate of release was not significantly affected by pH variation, being equally rapid at all the pH values investigated. Once the outer matrix of the product had disintegrated the entrapped spherical matrices can then release drug at a slower rate. Theophylline release from the spheres was pH dependent as the rate was substantially higher at pH 6.9 than at the other pH values. This is consistent with the results reported by Buckton et al. (1988) and by Simons et al. (1984), although McGinity et al. (1983) have claimed super-imposable profiles for theophylline release from Theo-Dur® in simulated intestinal fluid (pH 7.5) and in 0.1 M hydrochloric acid containing 0.02% Tween 80. The surfactant may explain the faster theophylline release

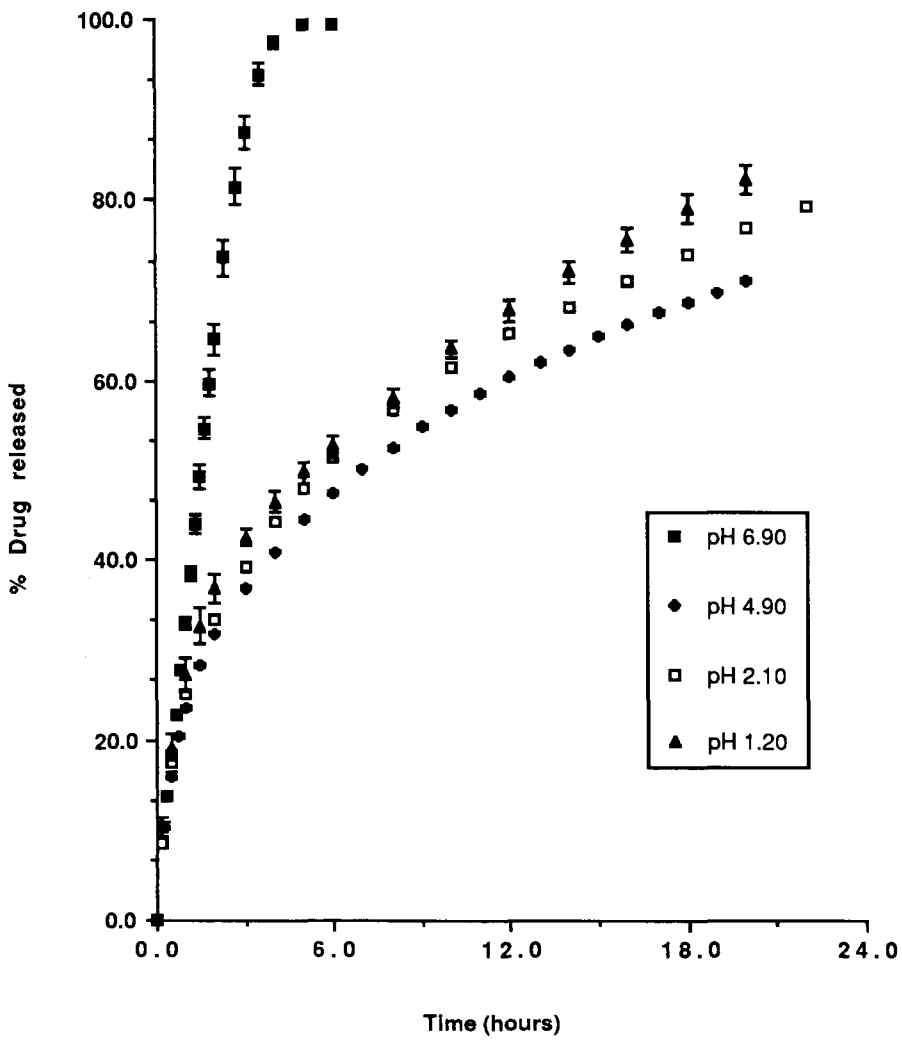

Fig. 8. Effect of pH on theophylline release from Nuelin SA tablets.

at pH 1 relative to those seen in the present study and in the other reports. With Theograd® tablets, pH-induced changes in release profiles were of less concern than the intrinsic variability in the product's performance under controlled conditions. Indeed, Theograd® tablets have now been withdrawn from the U.K. market.

In the present study, theophylline was released in a pH-dependent manner from Uniphyllin® tablets. The release rate decreased with increasing pH, an observation which is consistent with the known decreased intrinsic dissolution rate of the drug with increasing pH (Table 3). Buckton et al. (1988) indicated that the initial release profiles of theophylline from Uniphyllin® were pH dependent while Florence (1987) reported a pH effect when studying the same product in the pH 1.6 and 6.5 range. It would therefore appear that when investigating drug release rates from sustained-release profiles, complete release should be investigated to avoid misleading conclusions.

With Sabidal® tablets, the release of choline

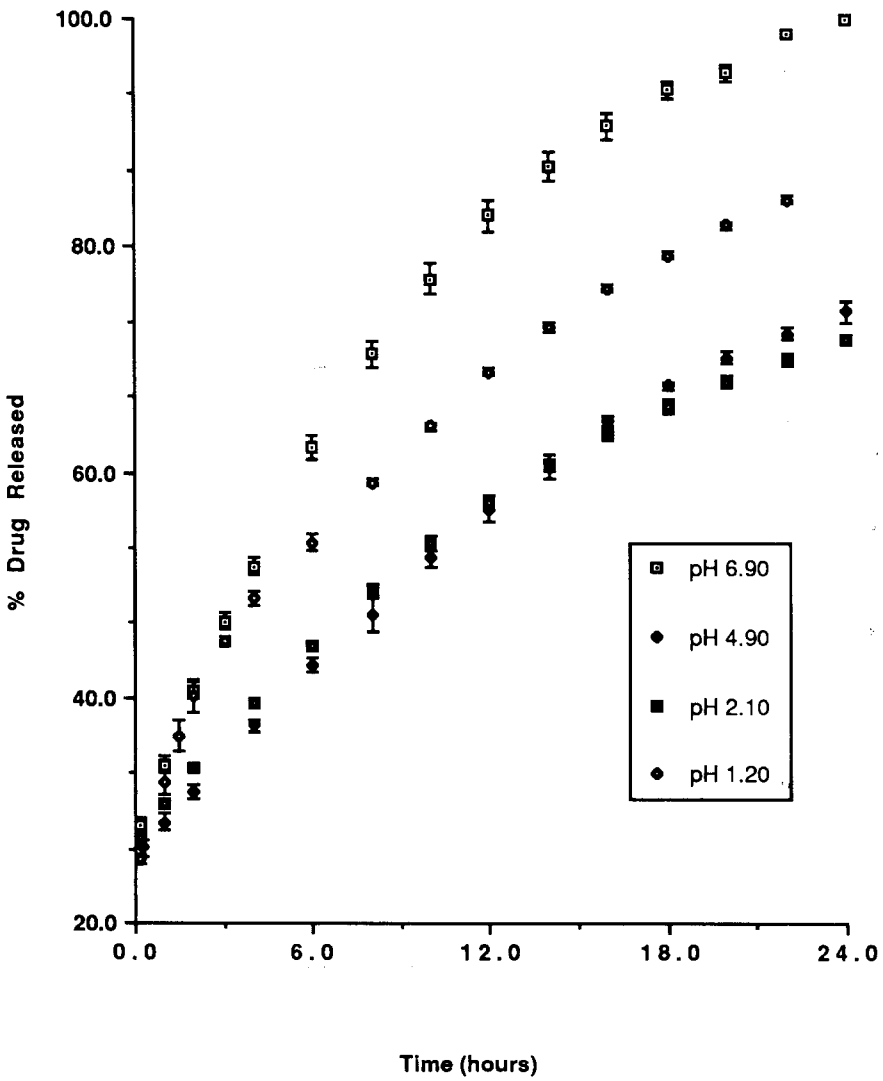

Fig. 9. Effect of pH on theophylline release from Pro-Vent capsules.

theophyllinate was essentially pH-independent within the pH 2.1 to pH 6.9 range. At pH 1.2 the release was substantially lower, a feature which may not be undesirable given the known gastric-irritant properties of theophylline.

While pH-solubility and pH-intrinsic dissolution dependencies (Table 3) give some indication of how theophylline release may be affected by changes in pH, the data are of limited usefulness in the present study. It would appear that the polymers making up the rate-controlling membrane or the matrix are the determinants. Membranes or polymers such as cellulose acetate phthalate which are enteric in nature tend to release drug faster at higher pH values than at the lower pH values stud-

TABLE 3

Effect of pH on the solubility and intrinsic dissolution rate of theophylline

pH of dissolution medium	Intrinsic dissolution rate (mg min^{-1} cm^{-2})	Solubility (± SD) (mg ml^{-1})
1.2	1.44 ± 0.02	12.76 ± 0.32
2.1	1.25 ± 0.01	8.91 ± 0.22
4.9	1.17 ± 0.06	8.91 ± 0.22
6.9	1.14 ± 0.03	9.03 ± 0.22

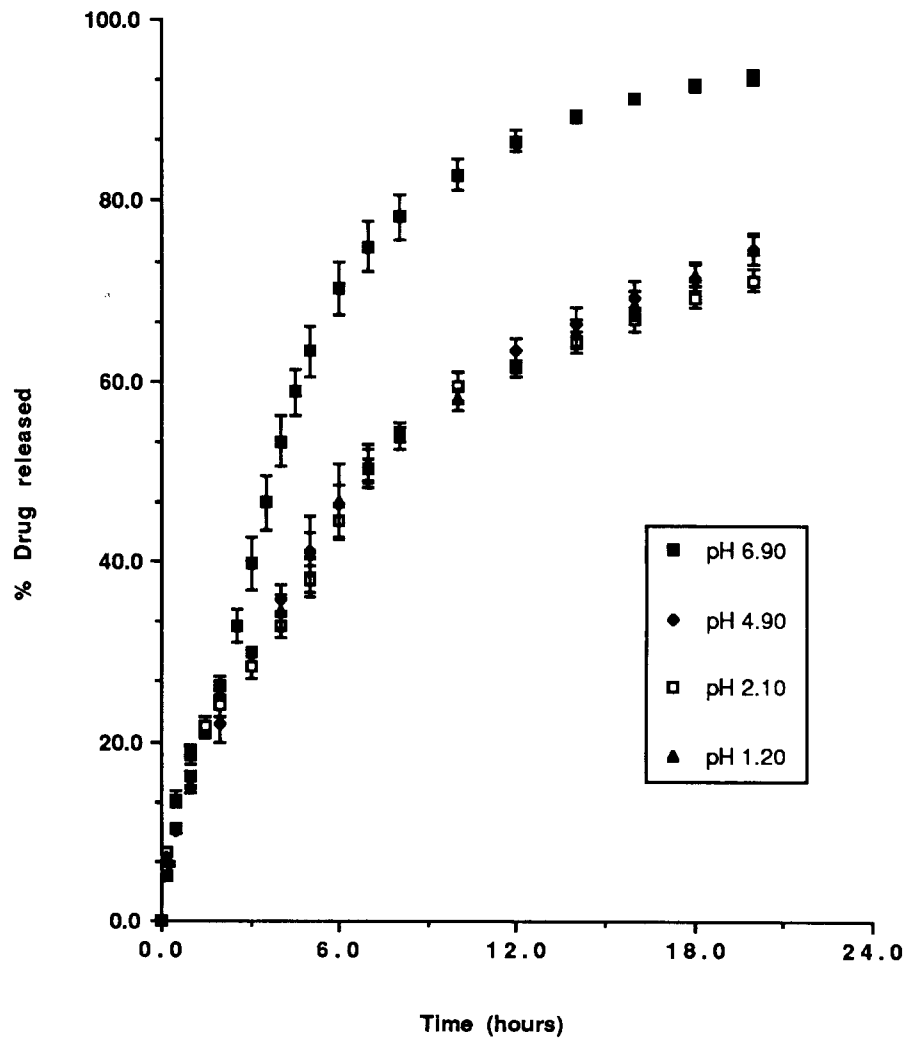

Fig. 10. Effect of pH on theophylline release from Theo-Dur tablets.

ied. The increase in intrinsic dissolution rate and solubility of theophylline at pH 1.2 had no apparent over-riding influence in theophylline release. When aminophylline (Phyllocontin®) or choline theophyllinate (Sabidal®) is used instead of theophylline, the increased solubility may yield more consistent release profiles.

For systems with porous membranes (Sabidal® and Pro-Vent®), one would expect ionic strength to affect the rate of release of theophylline. This was indeed observed with those two products as shown in Figs 11 and 12. The more dramatic effects were seen with Sabidal® tablets. Surprisingly, the effect of ionic strength on release rate appeared to be parabolic with Lasma® tablets (Fig. 13), a matrix system. This observation may be rationalised on the basis of the increased ionic strength initially providing increased resistance to outward flow of solute out of the system. Gradually, however, the ionic strength starts to cause disruption of the system leading to increased drug release. Sustained activity at pH 6.9 is seen when the ionic strength is low. However, at 1 M ionic strength, release is virtually complete within 1 h.

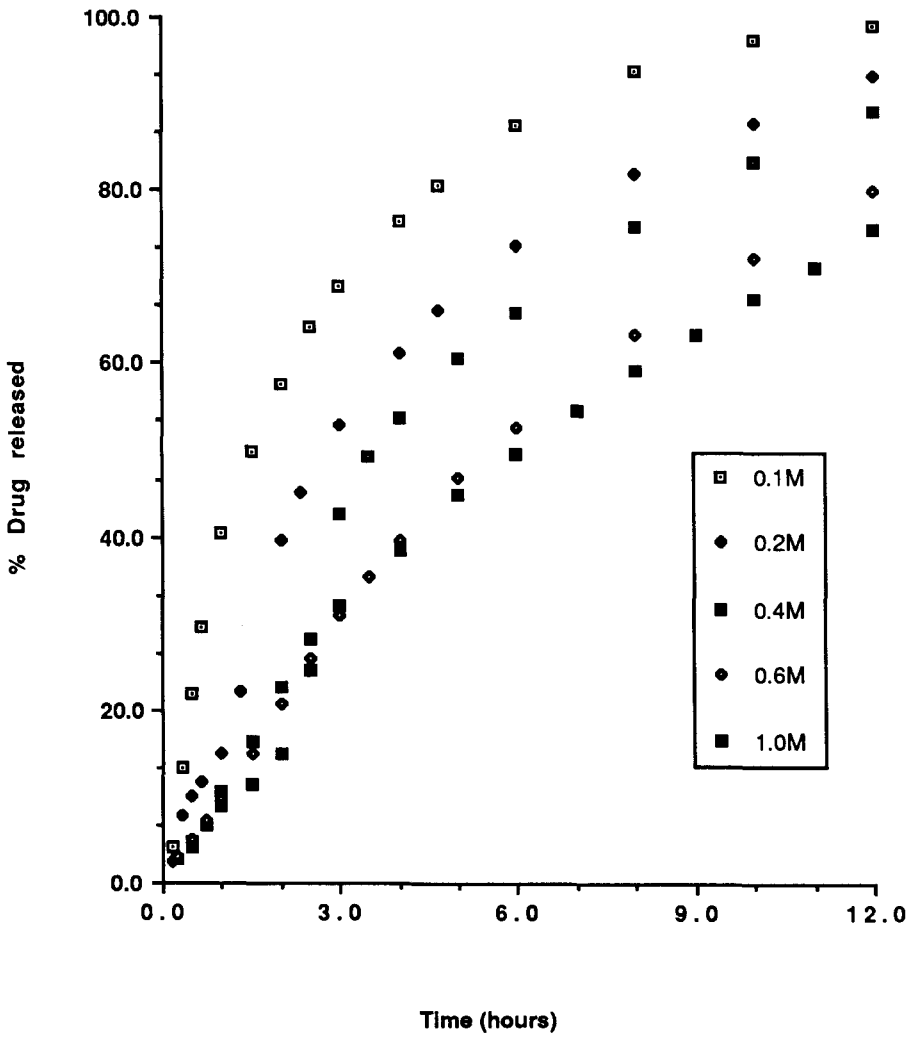

Fig. 11. Effect of ionic strength on the release of theophylline from Sabidal tablets.

Conclusion

The drug release data were fitted to appropriate models. It is shown that although high r^2 values and small mean square errors are obtained with a number of the systems, plots of residuals indicate clear cyclic patterns. Changes in mechanisms of release at various stages may partly account for this. It is obvious from the available data that discrimination between the models is not easy and therefore inference with respect to the most appropriate model should take into account physicochemical make-up, microscopical appearance and design features, in addition to numerical goodness of fit to the models. For comparative purposes, however, a numerically adequate model may be useful. Using such a model, the behaviour of various sustained-release theophylline products was shown to be affected by the dissolution test variables and by the product strength.

Thus, the results discussed in this paper confirm the previously reported high variability in release profiles between different sustained-release theophylline products (Upton et al., 1980; Simons et al., 1984, 1985; Buckton et al., 1988: Jalal et al., 1989). Clearly, therefore, those products are not clinically interchangeable without a significant change-over period with a high risk of unaccept-

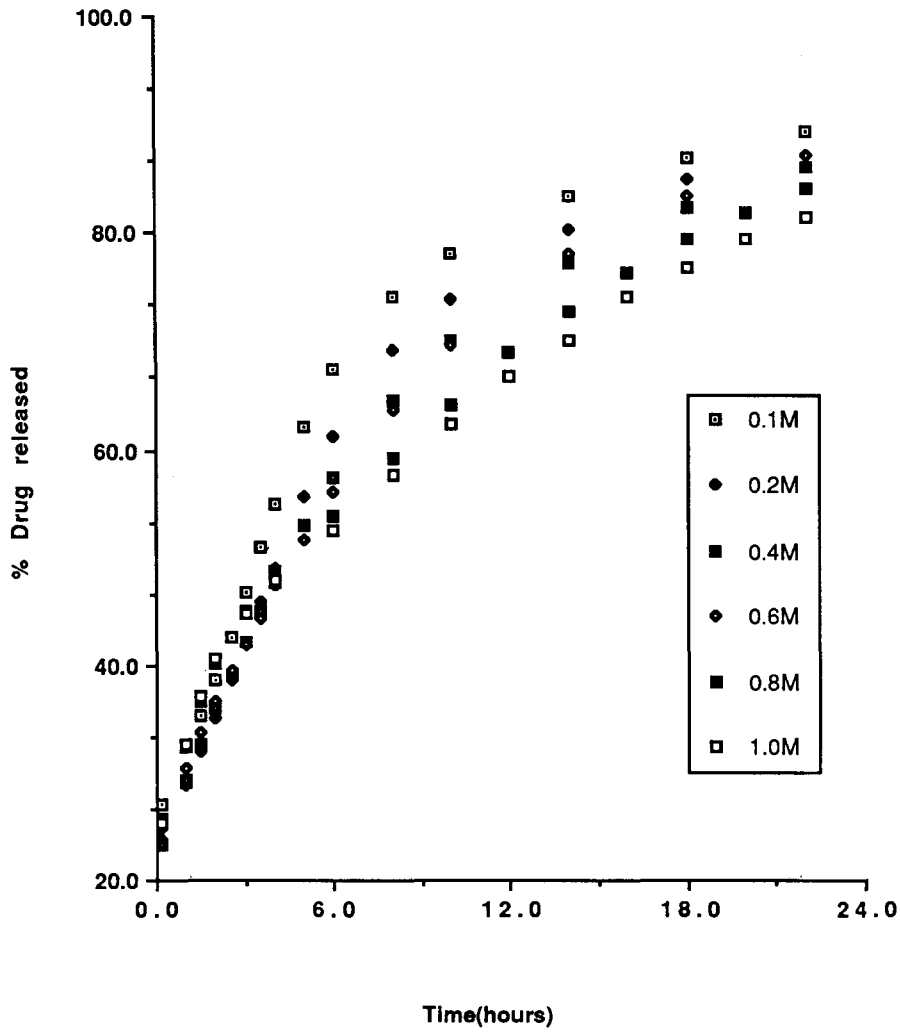

Fig. 12. Effect of ionic strength on the release of theophylline from Pro-Vent capsules.

able fluctuations in blood levels of theophylline. Of even greater concern, however, is the wide variability seen in the release profiles within the same product. Lasma® tablets seem particularly poor in this respect. Theo-Dur® also shows wide intra-variability when compared with products such as Uniphyllin®. Despite the absence of in-vivo in-vitro correlations, the variability observed would suggest that with Lasma®, dose-dumping is a real possibility and that the manufacturers may well be wise to examine their formulations closely both in the laboratory and in the clinic.

Glossary

Symbol	Meaning
M_t	amount of drug released from time 0 to time t
M_∞	amount of drug released from time 0 to time ∞
k	constant depending on model
D	diffusion coefficient
C_s	solubility of drug in matrix
C_0	initial drug concentration
A	surface area
t	time
r_0	radius

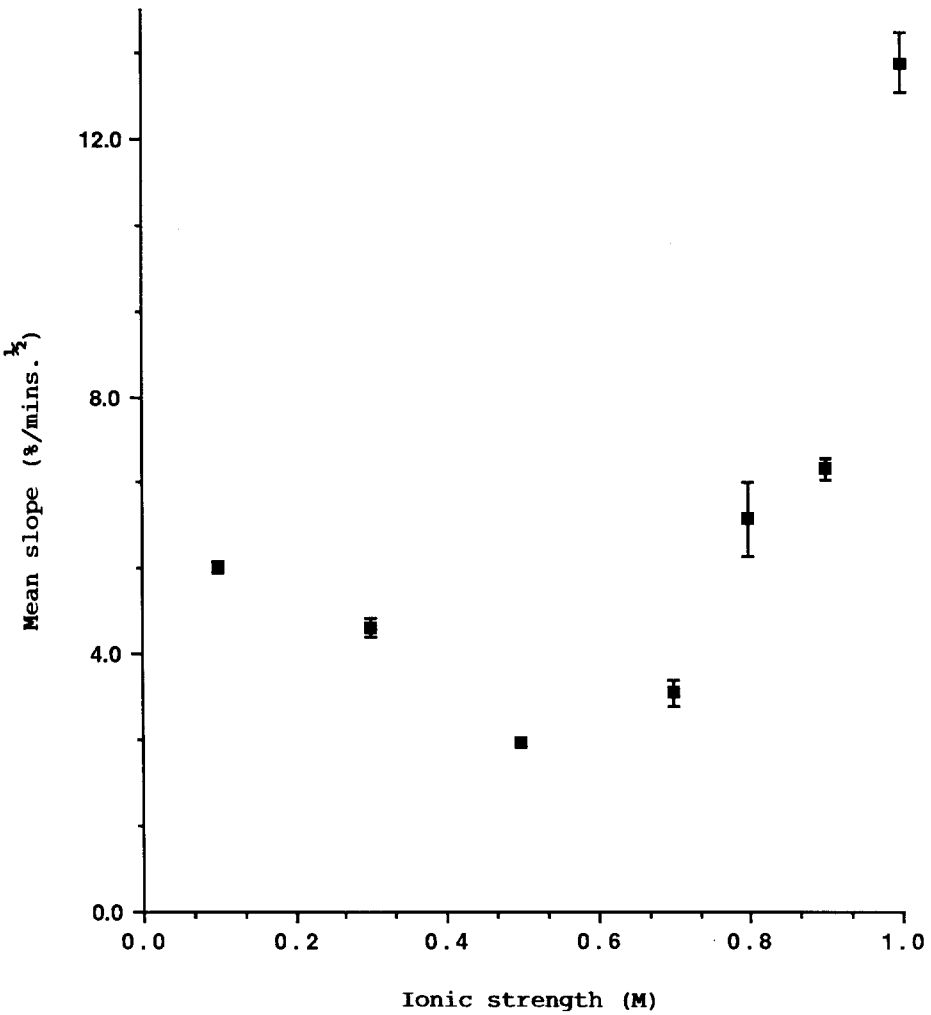

Fig. 13. Effect of ionic strength on the release of theophylline from Lasma tablets – Plot of slope of square root of time versus ionic strength.

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