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DESIGN AND EVALUATION OF A SUSTAINED-RELEASE AMINOPHYLLINE TABLET

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ABSTRACT

An ethanolic granulation procedure was used to produce sustained -release tablets containing 225 mg aminophylline with ethylcellulose and paraffin wax or hydrogenated castor oil as retardant matrix. The former waxy material gave undesirable sticking problems during compression. Acceptable tablets were formed using the latter material, which after fusion at 95 °C for 30 min, had an in-vitro release profile similar to the commercial product, "Phyllocontin" (Napp). Increasing the ratio of hydrogenated castor oil to ethylcellulose in the matrix or increasing its drug loading tended to give faster drug release. Application of up to 1% of a pH-independent polymethacrylate coating to the tablets for reduction of the burst-effect and for taste/odour masking, was associated with progressive reduction in drug release and was replaced by a non-controlled release coating not significantly affected by the level applied. The annealing treatment of tablet cores

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caused <2% volatilization of ethylenediamine and their drug content remained within compendial specification.

Three of the fused and film-coated tablet batches with variable drug loading were examined in a panel of human volunteers, compared to "Phyllocontin" on acute dosing with 450 mg aminophylline. The product with 82.5% drug loading was bioequivalent to the commercial product, when a range of pharmacokinetic parameters were compared.

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INTRODUCTION

Aminophylline is an incorporation of about 85% theophylline and 15% ethylenediamine as a dihydrate form, used mainly as a bronchodilating drug in the prophylactic management of asthma. The major sustained-release dosage form available in Europe and elsewhere is "Phyllocontin" (Napp), which is a controlled release tablet containing 225 mg active intended for twice daily administration, film-coated for taste/odour masking and based on 'Continus' technology (1). Plasma theophylline levels of 5-15 $\mu g\ ml^{-1}$ are generally considered to be in the therapeutic range, although values below 10 $\mu g\ ml^{-1}$ may not provide adequate therapy, especially during exposure to allergens or periods of respiratory tract infections. Plasma levels above 15 $\mu g\ ml^{-1}$ may result in toxic symptoms, although these do not normally appear until plasma levels of 25 $\mu g\ ml^{-1}$ are reached. Because of the narrow therapeutic index, variable plasma binding and the high inter- and intra-patient variability affected by age, exercise, diurnal rhythms, coadministration of dietary methylxanthines or drugs and smoking, frequent toxicity has been reported when the dose has been determined empirically and when conventional dosage forms which produce high plasma spikes are used (2).

Aminophylline presents difficulties for formulation as a sustained-release product due to its large aqueous solubility, the high pH of its solution and incompatibilities with many widely used pharmaceutical excipients. Also a commercial obstacle to developing a new sustained-

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release product is that once stabilized on a particular product, a patient should not be changed to another without due care, because of the reported differences in bioavailability between theophylline containing products (3). An attempt at developing a competitor sustained-release product to "Phyllocontin" has been described in the literature with variable success and without adequate detail of formulation to permit replication of the work (4). This project describes the detailed formulation development of a new sustained-release product and its assessment in comparison to the leading commercial product.

EXPERIMENTAL

Materials

Aminophylline BP (Knoll), disodium-hydrogenorthophosphate dodecahydrate, formic acid (Riedel-de-Haen), ammonium sulphate (analar), citric acid monohydrate, diethylphthalate, hydrochloric acid, paraffin wax (British Drug Houses), castor oil (Whewell), ethanol (Cooley Distillery), chloroform, dichloromethane, dioxane, isopropanol, methanol (GPR and HPLC grades, Lab-Scan), ethylcellulose (Ethocel 7 cp, 10 cp, 22 cp, Dow), hydrogenated castor oil (Cutina HR, Henkel), hydroxypropylmethylcellulose (Methocel E5, Dow), 3-isobutyl-1-methylxanthine (Sigma), magnesium stearate, talc (Organon), oxygen-free nitrogen (Irish Industrial Gases), Opaspray Yellow K-I-6133 (Colorcon), "Phyllocontin" (Lot 1322 and 1930), polymethacrylate (Eudragit, RL 12.5% solution, RS 12.5% solution, Rohm Pharma) and deionized water were used. All reagents were GPR unless otherwise indicated.

Tablet production

A wet granulation procedure involving moistening mixed powders with hot ethanol was used to prepared tabletting feed material. Tablets containing 225 mg aminophylline were compressed using circular 9 mm shallow concave tooling on an IR press at 5 ton or for larger

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TABLE 1

Composition of Some Tablets Produced.

Batch No	A %	HCO %	PW %	EC %	T %	MS %
1	64.7	-	23.2	8.7	3.4	-
2	65.6	23.6	-	8.6	2.2	-
3	65.6	25.5	-	6.9	2.0	-
4	65.6	21.6	-	10.8	2.0	-
5	66.0	23.3	-	8.7	2.0	-
6	65.6	16.2	-	15.2	2.0	1.0
7	72.8	15.5	-	8.7	2.0	1.0
8	77.6	12.6	-	6.8	2.0	1.0
9	82.5	9.3	-	5.2	2.0	1.0
10	87.3	6.2	-	3.5	2.0	1.0

A = Aminophylline, EC = Ethylcellulose 7 cp, HCO = Hydrogenated Castor Oil, MS = Magnesium Stearate, PW = Paraffin Wax, T = Talc.

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batches a 16 station rotary tablet press (Manesty B3B) was used. The composition of the various tablets produced is shown in Table 1.

Tablets obtained were subject to annealing at variable temperature and duration, prior to coating. The theophylline and ethylenediamine content of the aminophylline powder and its tablets was assayed using the methods described in the British Pharmacopoeia.

Coating procedure

Tablet cores were coated using a spherical-shaped 50 cm pan (Apex) driven at 30 rpm. The pan was preroughened and sealed using talc and the same coating system applied to the cores as described (5). A gravity feed spray gun (DeVilbiss) was used to apply coatings. Coated product was dried in a fan-driven oven at 40 °C for 16 h to remove residual solvent and thermoset the coating. Table 2 shows the composition of the two coatings examined.

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TABLE 2

Composition (% w/w) of the Coatings Used.

Coating No	Film Formers	Plasticizer	Antitack agent	Pigment	Solvent
1	PMA (i) 14.4 PMA (ii) 28.8	CO 0.5	T 4.8	OY 3.9	IP 47.6
2	HPMC 3.25 EC 0.75	DEP 0.5		OY 3.25	M 34.5 DCM 57.75

CO = Castor Oil, DCM + Dichloromethane, DEP = Diethylphthalate, EC = Ethylcellulose 10 cp, HPMC = Hydroxypropylmethylcellulose, IP = Isopropanol, M = Methanol, OY = Opaspray Yellow, PMA (i) = Polymethacrylate (Eudragit RL 12.5% solution), PMA (ii) = Polymethacrylate (Eudragit RS 12.5% solution), T = Talc (<90 μm).

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Dissolution testing

An Erweka DT6 dissolution tester fitted with paddles rotated at 50 rpm was used, unless otherwise stated. The dissolution medium employed at 37 °C was 500 ml (adequate to assure sink conditions) of citrate/phosphate (McIlvaine's) buffer of pH 4.0, 7.0 and 8.0 or a solution of hydrochloric acid 0.01 M with a pH of 1.6. Where dosage forms were tested using a pH-shift method, the dissolution medium was changed from pH 1.6 to 7.0 after 1.5 h. The absorbance of the filtered dissolution medium was measured at 273 nm using a Shimadzu UV160 spectrophotometer and the concentration of drug calculated by reference to a linear calibration curve constructed at the same pH.

In-vivo studies

The protocol for the human studies was approved by the National Drugs Advisory Board, Dublin, as required by Irish law. A panel of 8 healthy fasted male subjects was used, whose plasma theophylline levels were compared in single dose cross-over studies following administration of two sustained-release 225 mg aminophylline tablets of various formulations or two "Phyllocontin" 225 mg tablets. A two

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week 'wash-out' period was allowed between doses. Heparinized plasma samples, withdrawn periodically from each volunteer fitted with an in-dwelling cannula, were stored at -20 °C prior to assay. Drug levels were determined using a modification of the normal-phase high-performance liquid chromatography method (6), which unlike other assays is capable of determining theophylline even in the presence of caffeine metabolites arising from unauthorized consumption of certain beverages. Samples were deproteinized with saturated ammonium sulphate solution, 3-isobutyl-1-methylxanthine was added as internal standard and theophylline was extracted with chloroform:isopropanol 95:5. After evaporation to dryness under a stream of oxygen-free nitrogen, the residue was reconstituted in degassed mobile phase composed of chloroform:dioxane:formic acid 95.5:4.5:0.01. Aliquots of 50 µl were injected onto a 10 x 0.20 cm main column protected by a 1 x 0.3 cm guard column, both packed with "Techsil" 5 µm silica (HPLC Technology), and the mobile phase was pumped at a flow rate of 1.4 ml min^{-1}. A Shimadzu LC-6A liquid chromatograph, equipped with a Shimadzu SPD-6A variable length UV detector set at 273 nm was used. Output from the detector was plotted and analysed for peak area using a Shimadzu C-R3A chromatopac integrator. The assay was validated for precision, linearity, recovery and specificity. As further verification of the assay, the theophylline content of plasma samples from one volunteer was also determined independently using an enzyme immunoassay procedure, EMIT (Syva Corporation), performed using a Roche Cobas-Bio centrifugal analyser.

RESULTS AND DISCUSSION

Dissolution studies

The dissolution profile of batch 1 tablets containing ethylcellulose and paraffin wax as the retardant matrix material is shown in Figure 1, in comparison to that of "Phyllocontin" tablets. Before fusion at 70 °C for 30 min, batch 1 tablets ruptured after about 1 h of dissolution

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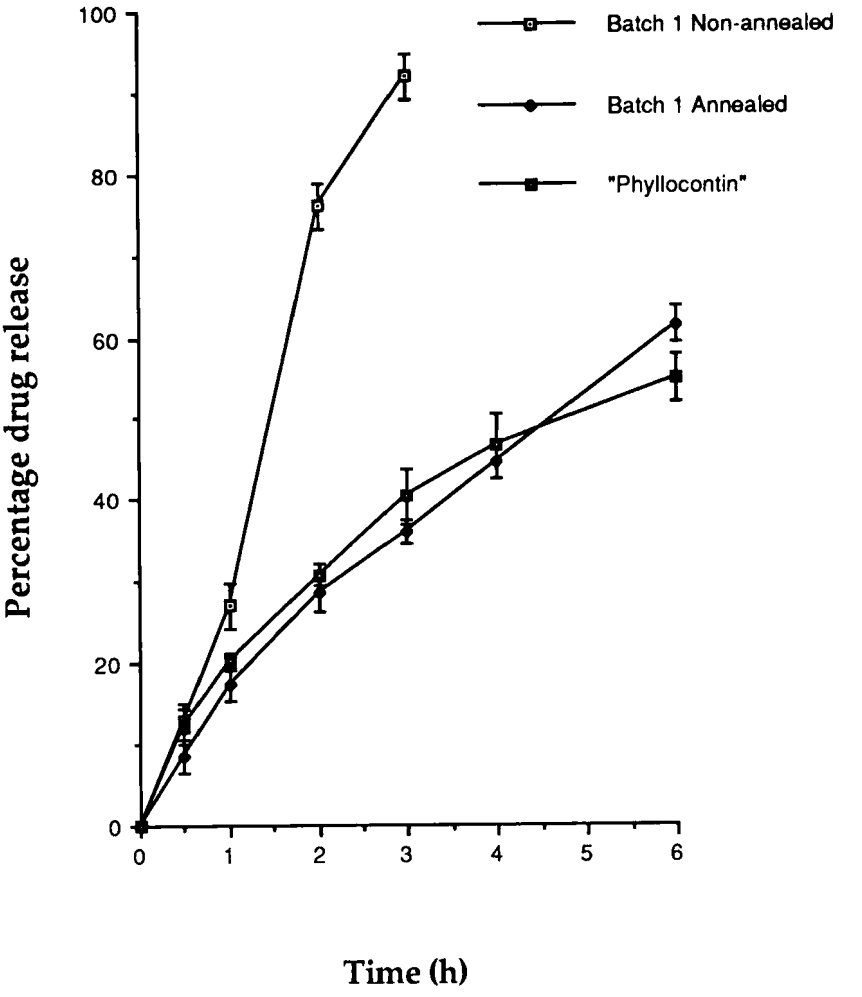

FIGURE 1
Effect of annealing of batch 1 tablets on drug release into McIlvaine buffer pH 7.0 at 37 °C, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

treatment to cause loss of controlled release property, but this effect was eliminated by the heat treatment to produce a product with an almost identical release profile to the commercial product. However because the paraffin wax used had a low congealing temperature of about 60 °C and was difficult to uniformly disperse in the tablet mix because of its granular form, unsightly picking of the sufaces of the

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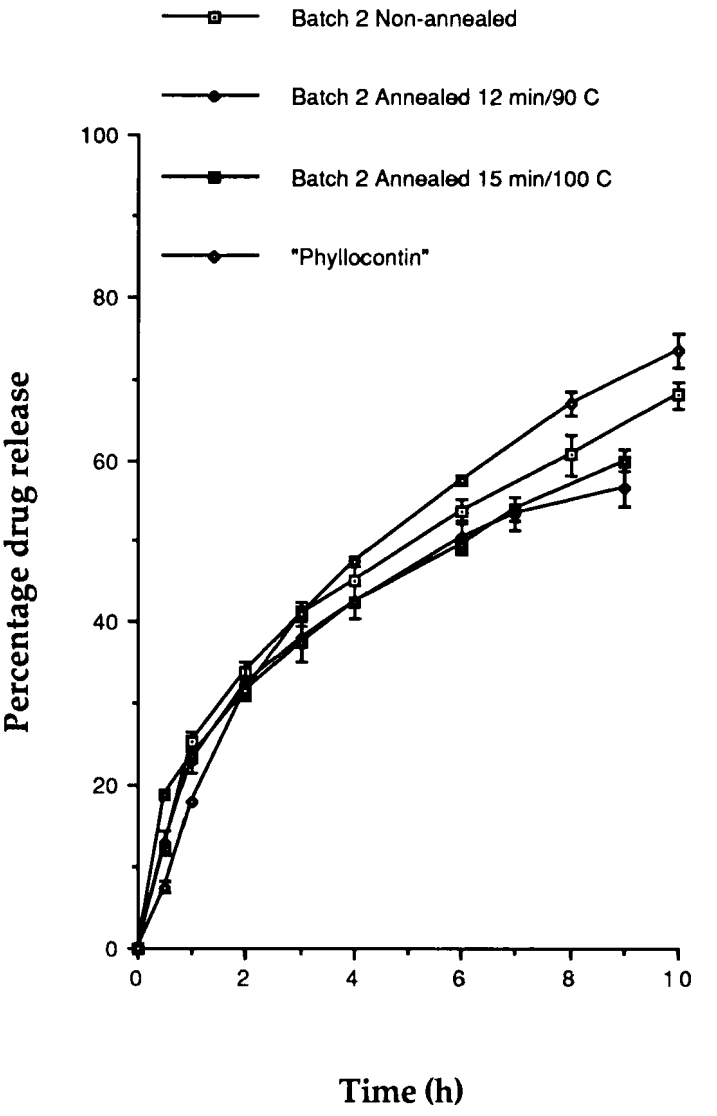

FIGURE 2
Effect of annealing of batch 2 tablets on drug release into McIlvaine buffer pH 7.0 at 37 °C, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

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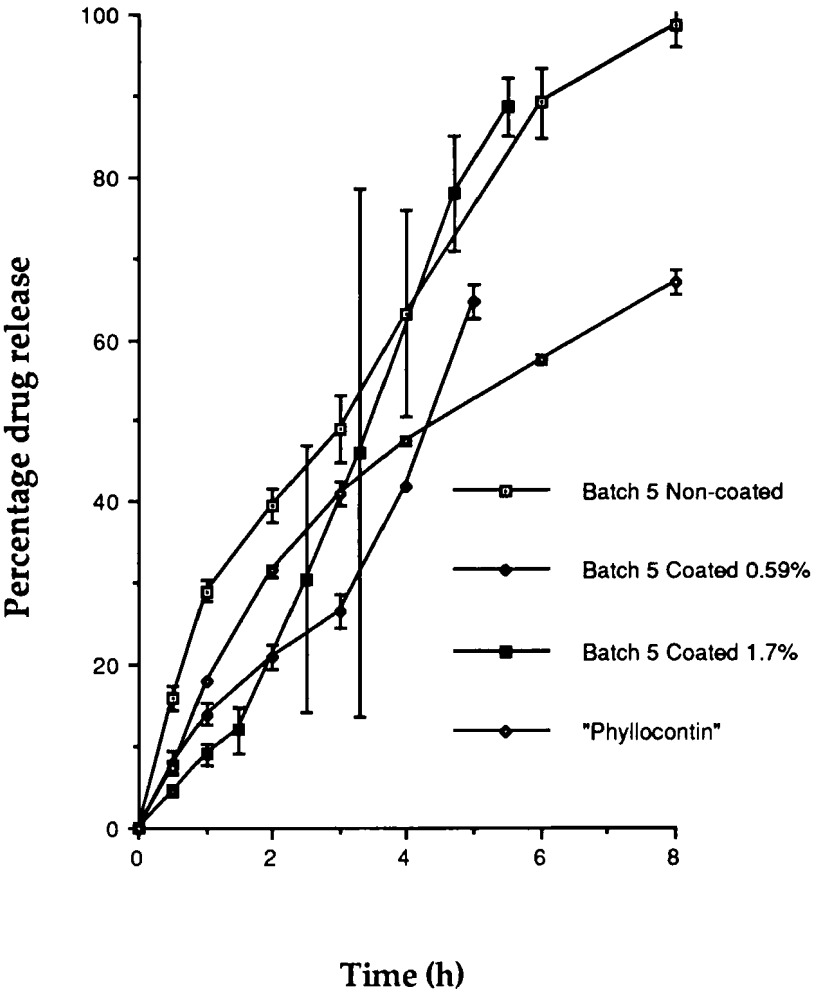

FIGURE 3
Effect of application of coating 1 to batch 5 tablets on drug release into McIlvaine buffer pH 7.0 at 37 °C, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

tablets tended to occur as the tooling heated during multiple compressions. Consequently the tablets of batch 2 were prepared by substituting the waxy component with powdered hydrogenated castor oil, which was more easily dispersed and has a higher melting point range (80-85 °C). Figure 2 shows the release profile of the tablets before and after fusion under conditions adequate to liquefy the waxy

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component. All release profiles were similar to the commercial product, indicating that increasing heat treatment caused progressive sintering of the matrix. Batch 3 and 4 were examined to study the effect of variation in the ratio of hydrogenated castor oil to ethylcellulose, higher wax content tending to yield a slightly faster drug release profile, but being undesirable as it tended to give rise to greater picking and sticking problems during compression. Peters et al 1970 (7) noted a similar effect with waxy matrix tablets and stated that highly water soluble drugs like aminophylline require a low ratio of waxy component to ethylcellulose to effectively retard their release. When the grade of ethylcellulose used (7 cp) was altered to one with a higher average molecular weight (22 cp), there was no significant alteration in release profile.

All the remaining batches of tablets were compressed on a rotary tablet press whose mechanism of compression differs from that of the IR press used to produce the initial batches. Figure 3 shows the release profile from tablets of batch 5, which is almost identical in composition to batch 2. Whereas the initial release profile was similar to that of the commercial product, drug release increased rapidly after about 2 h of dissolution treatment due to premature splitting of the unfused matrix, which could be only partially prevented by application of increasing percentage of the sustained-release coating 1, which was also considered desirable for taste/odour masking of the drug.

Batch 6 was prepared with a 1:1 ratio approximately of hydrogenated castor oil:ethylcellulose, with magnesium stearate to reduce picking and fused progressively by heating up to 1 h at 95 °C, in an attempt to overcome the premature splitting of tablets during dissolution testing observed in the previous batch. Provided heating exceeded 10 min, the splitting problem was overcome, the tablets lost their lustrous outer surface and when broken mechanically, they yielded smooth fracture surfaces indicating good matrix continuity. Figure 4 illustrates the release profiles obtained, which showed similar in vitro release to the commercial product when adequately fused. The large standard deviation associated with some of the poorly fused product points was

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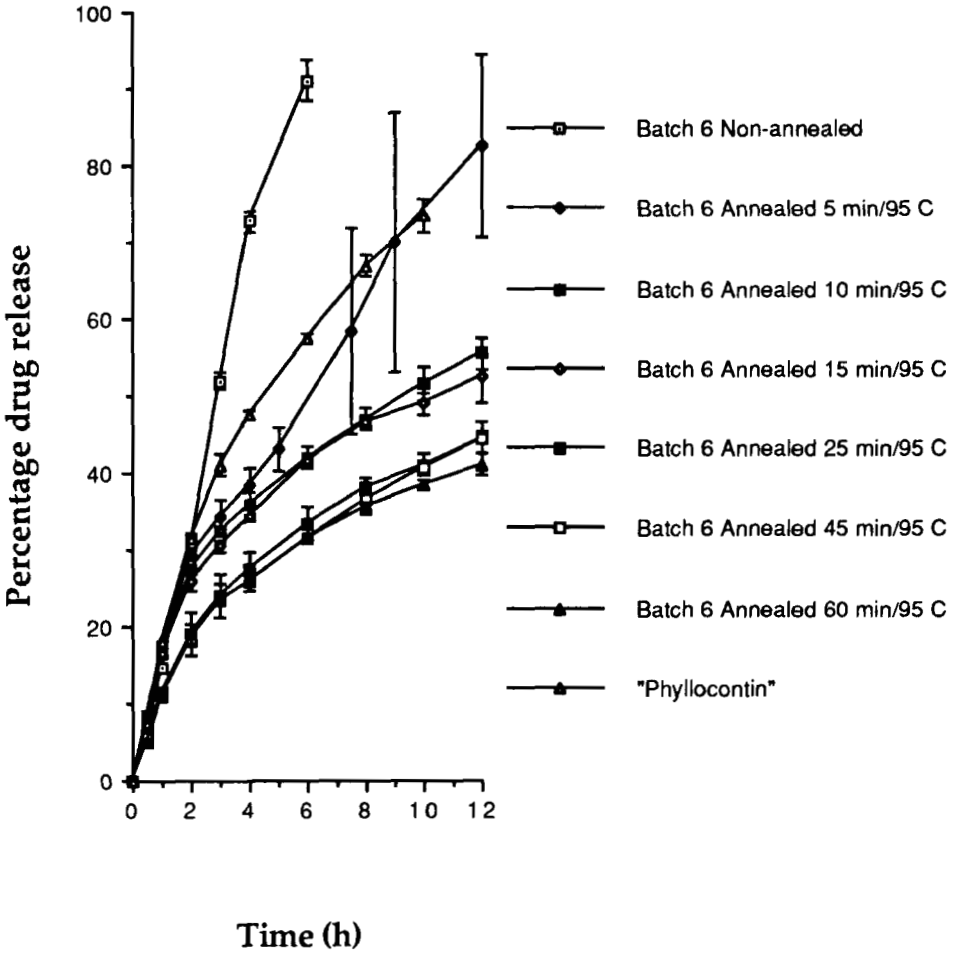

FIGURE 4
Effect of increasing annealing time at 95 °C of batch 6 tablets on drug release into McIlvaine buffer pH 7.0 at 37 °C, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

due to variable time of splitting of the tablets, which resulted in irregular drug release.

Tablets of batch 7 were prepared with a higher drug loading and increased ratio of hydrogenated castor oil:ethylcellulose to compensate for the retardant effect of application of 0.5% of coating 1 considered desirable to reduce the burst-effect and for taste/odour masking. The

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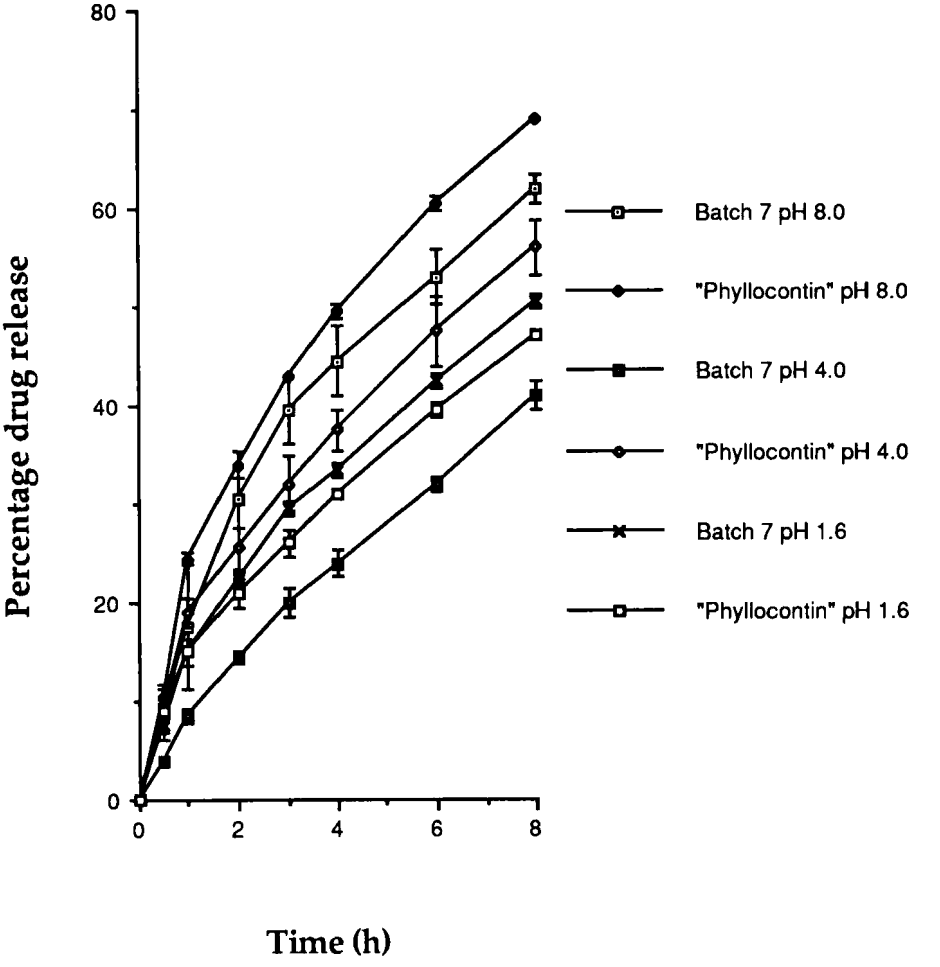

FIGURE 5
Effect of variation in pH of the dissolution medium at 37 °C on drug release from batch 7 tablets, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

results of dissolution testing on the product formed in comparison to the commercial product at a range of pH values is shown in Figure 5. The release profile of the new product at pH 1.6 is intermediary between those at pH 4.0 and 8.0, whereas for "Phyllocontin" the release profile decrease progressively with reduction in pH of the dissolution medium as expected for the pH-solublity profile of the drug (8). The

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anomalous behaviour of the the new product, which was also demonstrated in uncoated tablets, confirms that the waxy matrix, rather than the influence of the applied coating, behaves differently in response to changes in physiological pH than the matrix used in "Phyllocontin" tablets, which are also film-coated for taste/odour masking. However when the effect of variation in amount of applied coating was examined, small increments up to 1% produced progressive reduction in drug release. Because of the difficulties anticipated in applying consistent amounts of coating during production, it was decided to apply the non-controlled release coating 2 to batch 7 tablets, which even when applied up to 2% or greater level, did not significantly affect drug release as shown in Figure 6, where the release profile is seen to be similar to the commercial product when examined using a pH-shift procedure.

Further tablet batches were prepared and after fusing at 95 °C for 30 min were coated with 2% of coating 2, to study the influence of increasing the drug loading in the tablets (72.8%, 77.6%, 82.5% and 87.3% for batches 7, 8, 9 and 10 respectively), while maintaining the same ratio of hydrogenated castor oil:ethylcellulose. As expected higher drug loading gave greater drug release as shown in Figure 6, indicating that it was possible to readily influence drug release over a wide range by altering this parameter. The product with the highest drug loading had a tendency to cap during compression, often splitting prematurely during dissolution testing to give irregular drug release as indicated by the large standard deviations associated with the plotted points and was not considered suitable for further study. Consequently coated batches 7, 8 and 9 were examined in-vivo in comparison to the commercial product at equivalent dosage.

The coated "Phyllocontin" product exhibited a greater tendency to bind to the base of the dissolution vessel when agitated at 50 rpm with a paddle in comparison to the coated tablet batches produced in-house. Apart from the effect on diffusion layer thickness, when the effective surface area was increased by employing a paddle speed of 100 rpm or by use of baskets rotatated at 50 rpm, both product types showed a small increase in drug release (<12% at 6 h), which however was more

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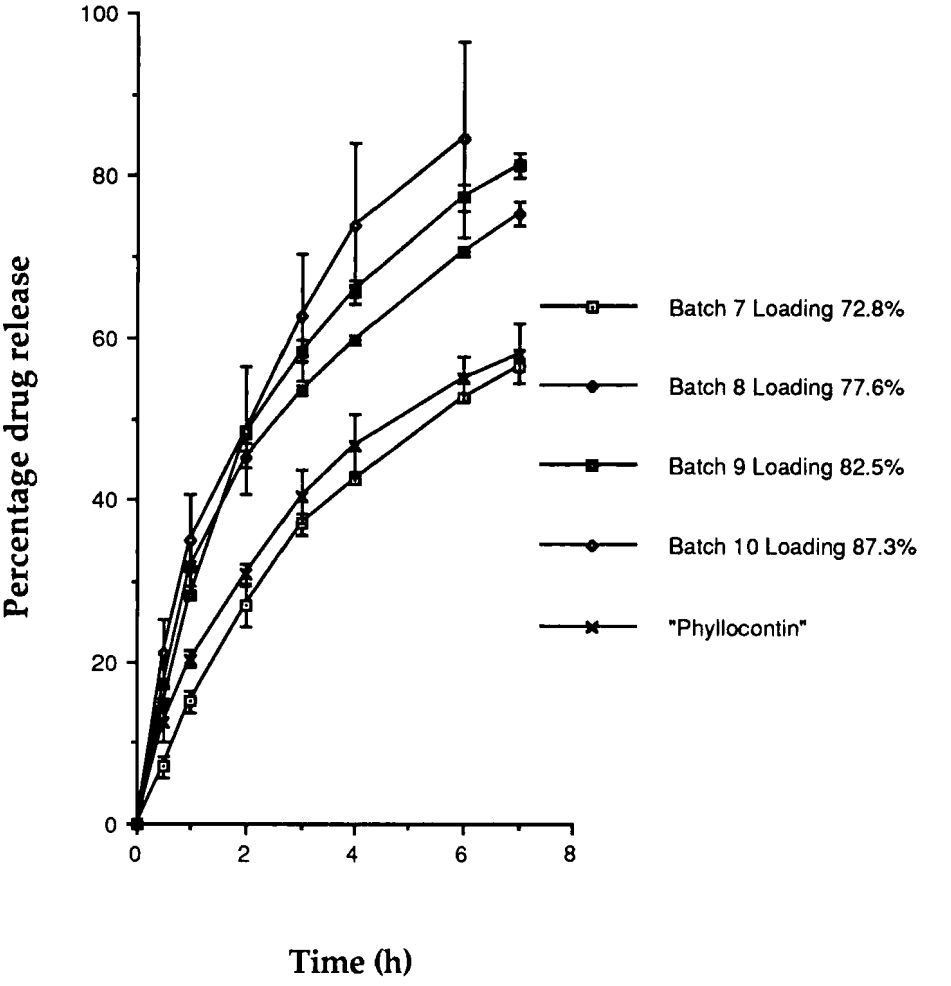

FIGURE 6
Effect of increasing drug loading in batch 7-10 tablets on drug release using a pH-shift procedure at 37 °C, compared to "Phyllocontin" tablets. The bar represents ±1 standard deviation.

pronounced for the commercial product. This finding illustrates one of the difficulties of using in vitro dissolution testing to effectively model comparative plasma profiles likely to be produced by both products in humans.

The results of assay of the drug alone, coated tablets of batches 7, 8 and 9 and "Phyllocontin" tablets for anhydrous theophylline and

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TABLE 3

Mean Percentage Anhydrous Theophylline and Ethylenediamine in the Drug Used and in Other Products Tested In-vivo.

	Aminophylline	Batch 7	Batch 8	Batch 9	"Phyllocontin"
Anhydrous Theophylline	81.3	79.2	82.1	81.1	80.7
Ethylenediamine	13.8	12.8	12.2	12.5	12.9

ethylenediamine content are shown in Table 3. All are within the limits specified in the British Pharmacopoeia. However the content of ethylenediamine in the tablets annealed by heating at 95 °C for 30 min is reduced slightly (<2%) due to volatilization during the heating process.

DSC studies confirmed that the composition of the tablet cores for batches 7-9 following fusion at 95 °C for 30 min was a simple physical mix. This observation was supported by plotting % drug release versus square root of time, which plots were linear well beyond 60% drug release, indicating that the matrix system is one where the drug is dispersed rather than dissolved in the continuum (9).

In-vivo studies

Figure 7 shows the plasma profile of subject 1 determined by both assay procedures, confirming that the two are in good agreement and that the modified HPLC assay developed was reliable when used in the assay of all other plasma profiles presented. Batch 7 tablets were compared to "Phyllocontin" tablets in two subjects only, whose mean plasma profiles after identical acute dosage with 450 mg of aminophylline (two tablets) are shown in Figure 8. Table 4 shows the pharmacokinetic parameters estimated from the data.

Batch 7 tablets produced a lower and more uniform plasma profile than "Phyllocontin", but with a mean relative bioavailability of only

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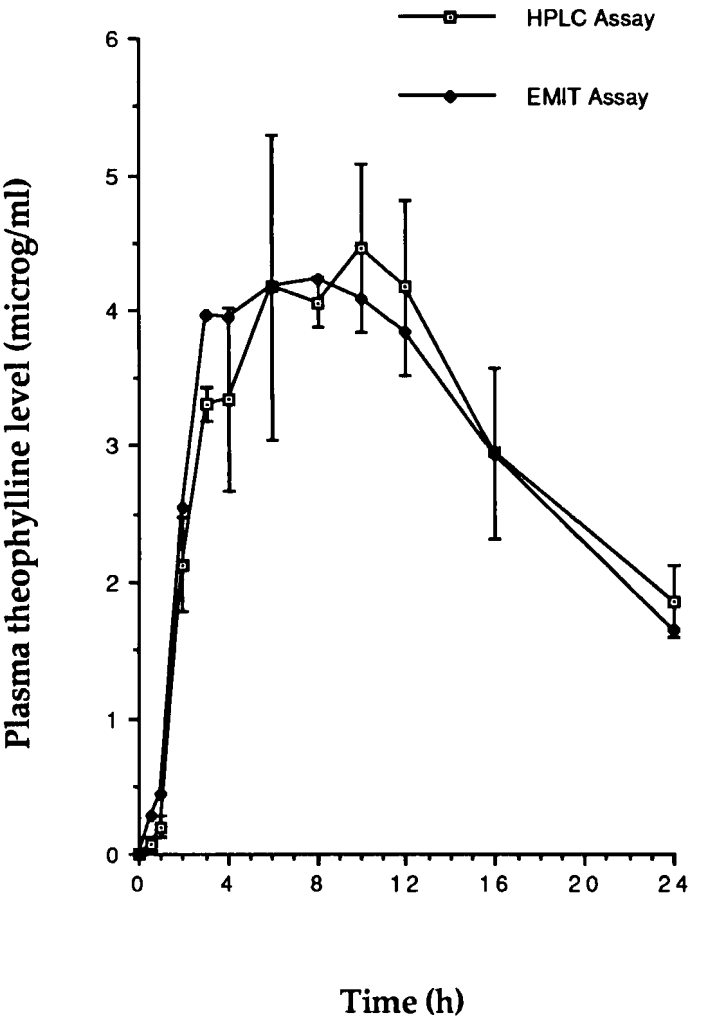

FIGURE 7
Plot comparing the plasma theophylline level in a subject following administration of 450 mg aminophylline as "Phyllocontin" tablets, determined by HPLC and EMIT assays. The bar represents ±1 standard error for HPLC samples.

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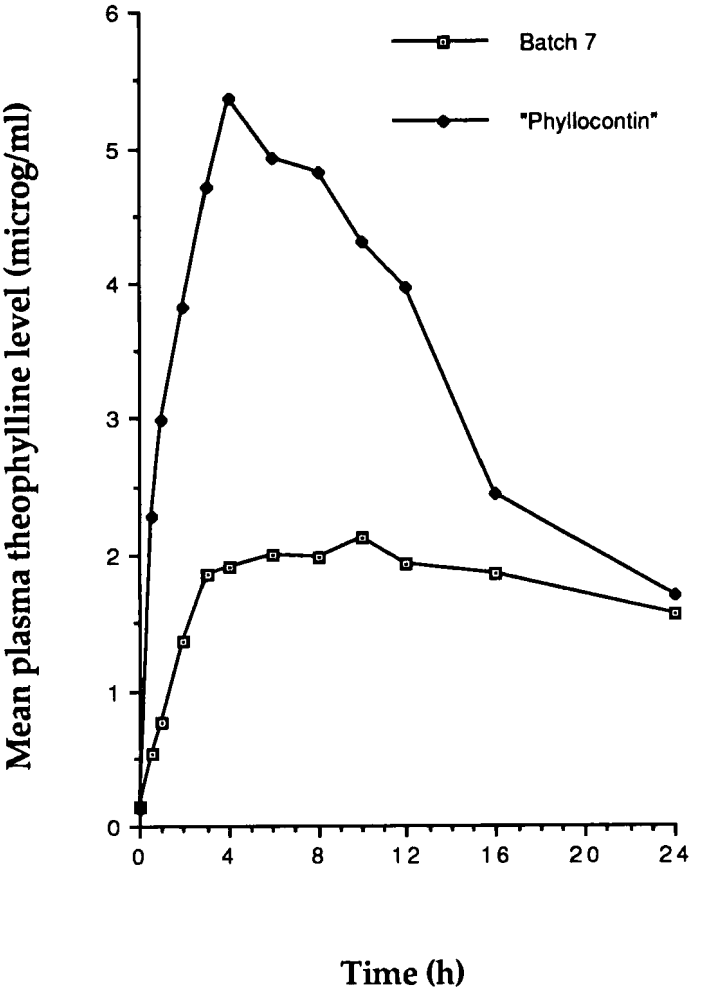

FIGURE 8
Plot comparing mean plasma theophylline levels in two subjects following administration of 450 mg aminophylline as batch 7 tablets or "Phyllocontin" tablets.

58.4% compared to the proprietary product. These observed differences are probably mainly due to the previously reported slower dissolution of the drug from batch 7 tablets compared to to "Phyllocontin", particularly noticeable if maximum surface area is exposed. A contributory factor to the delayed absorption of drug from the batch 7 and the other tablet batches examined in vivo may be that

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TABLE 4

Pharmacokinetic Parameters Estimated from Human Trials.

Subject No	C_{max} (μg/ml) Product				T_{max} (h) Product				AUC (μg/ml.h) Product				$C_{max}/C_{12\,h}$ Product			
	7	8	9	P	7	8	9	P	7	8	9	P	7	8	9	P
1	2.01	4.09	6.15	4.76	3	8	4	3	36.06	71.55	90.48	75.53	1.32	1.11	1.51	1.39
2	2.49	4.14	4.66	6.55	10	6	8	4	48.71	49.49	70.29	87.36	1.06	2.08	1.38	1.45
3	-	2.74	3.14	5.22	-	6	8	6	-	48.97	53.05	65.18	-	1.42	1.18	1.83
4	-	3.33	6.39	5.34	-	8	6	6	-	55.66	94.77	78.83	-	1.32	1.49	1.43
5	-	3.18	4.23	6.14	-	6	10	4	-	45.72	81.11	80.97	-	1.61	1.14	2.01
6	-	3.39	3.06	3.51	-	4	3	4	-	53.11	45.67	41.67	-	1.65	1.84	2.34
7	-	3.57	5.55	4.58	-	4	6	10	-	49.96	87.54	89.07	-	1.92	1.45	1.07
8	-	3.82	4.66	3.91	-	10	6	4	-	64.90	76.73	61.84	-	1.18	1.12	1.32
Mean	2.25	3.53	4.73	5.00	6.50	6.50	6.38	5.38	42.39	54.92	74.96	72.56	1.19	1.54	1.39	1.61
SE	0.24	0.17	0.44	0.37	3.50	0.73	0.80	0.79	6.33	3.15	6.26	5.56	0.13	0.12	0.09	0.15
n	2	8	8	8	2	8	8	8	2	8	8	8	2	8	8	8

C_{max}= maximum serum concentration, T_{max} = time to maximum plasma concentration, AUC = area under plasma curve from 0 to 24 h, $C_{12\,h}$ = plasma concentration at 12 h, Product 7, 8, 9 and P = batch 7, 8, 9 and "Phyllocontin" tablets respectively.

these products contained hydrogenated castor oil, which consists mainly of the triglyceride of 12-hydroxystearic acid. Similar fatty acids arising from the hydrolysis of fatty material in the stomach and upper small intestine have been shown to decrease gastric emptying rate (10). Cook et al 1990 (11) have shown that the bioavailability of a theophylline sustained-release tablet formulation is increased on coadministration of a high-fat breakfast, compared to under fasting conditions. Jonkman et al 1985 (12) have reported that the absorption of theophylline from the stomach is approximately 4 times slower than from the small intestine. This delayed gastric clearance would be further enhanced by the fact that the subjects were fed a standard continental breakfast 1 h after administration of the dosage forms (13). Davis et al 1989 (14) have investigated the gastrointestinal transit time of radiolabelled "Phyllocontin" tablets by gamma scintigraphy, showing it to be quite variable between lightly fed individuals with

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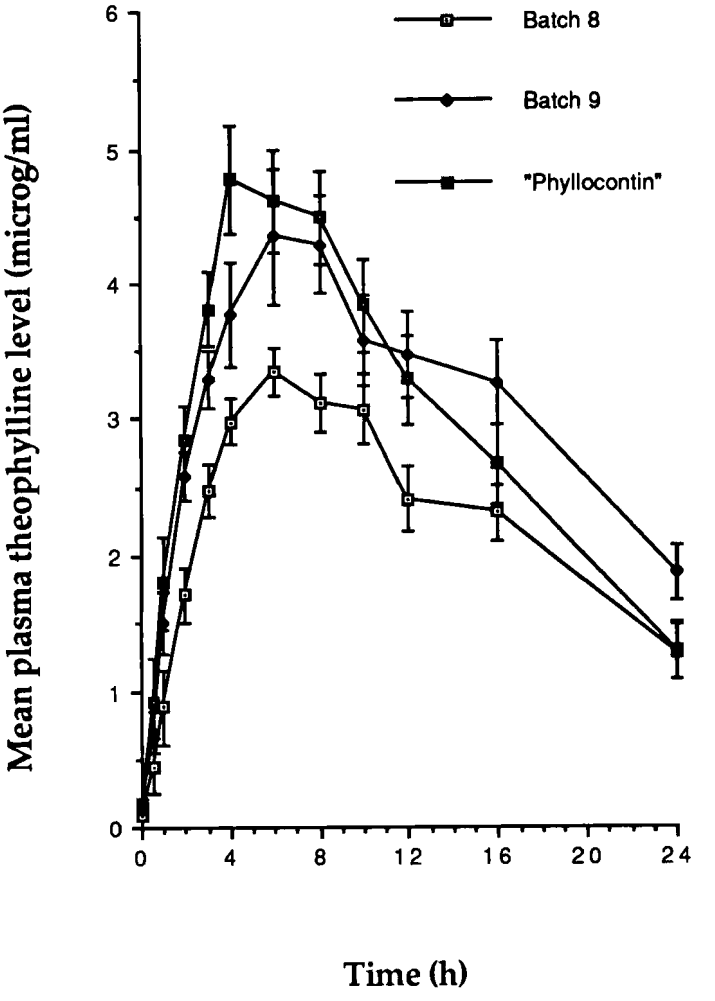

FIGURE 9
Plot comparing mean plasma theophylline levels in eight subjects following administration of 450 mg aminophylline as batch 8, batch 9 or "Phyllocontin" tablets. The bar represents ±1 standard error.

four of the volunteers demonstrating gastric emptying within 2.5 h and two others retaining the tablets in the stomach for greater than 8 h.

Batch 8 and 9 tablets are progressively faster releasing in-vitro due to increased drug loading and were compared to "Phyllocontin" in 8 subjects, whose mean plasma profiles following acute dosing with 450

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mg aminophylline is shown in Figure 9. Batch 8 tablets produced a similar shaped profile to the commercial product with reduced mean C_{max} and delayed T_{max} values, but with only a mean relative bioavailability of 75.7% (see Table 4). Also this new formulation shows a secondary absorption phase after about 12 h, characterized by the biphasic profile with broad peaks at 6 and 16 h. The second peak may be associated with the delayed gastrointestinal transit time previously discussed and may be contributed to by the fact that the subjects were then sleeping, as Jonkman et al 1983 (15) have reported that the plasma half-life of theophylline increases at night during rest due to reduced biotransformation. All the individual profiles show evidence of a similar biphasic profile only for the new product, whereas the "Phyllocontin" profile resembles that reported by Warren et al 1985 (16) in the supine position, who administered two tablets to six subjects also in the standing position. The subjects used in the study reported herein were largely supine for the duration of the study period.

Batch 9 tablets produced an almost identical AUC of 103.3% compared to the commercial product, indicating that the two products are bioequivalent. The batch 9 tablets show a smooth and steady increase to a mean C_{max} value of 4.73 $\mu g\ ml^{-1}$ at 6 h, followed by a short plateau to 8 h. This is followed by a sharp decline to the 10 h point, a secondary peak also seen with the batch 8 tablets and then a slower decline to the 24 h point. Possible superiority of batch 9 tablets in producing more uniform plasma profiles than "Phyllocontin", is confirmed by the its lower $C_{max}/C_{12\ h}$ value, which may be due to its longer absorption phase. However none of the mean pharmacokinetic parameters listed in Table 4 for comparison of batch 9 tablets with "Phyllocontin" were significantly different at $P = 0.05$.

Neither "Phyllocontin", nor batch 8 or 9 tablets achieved the mean minimum therapeutic concentration of 5 $\mu g\ ml^{-1}$. None of the individual subjects achieved therapeutic levels with batch 8 tablets, while 3 and 4 did with batch 9 tablets and "Phyllocontin" respectively. These findings indicate the need for multiple dose studies with these products, which are intended for twice daily administration. Semi-

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logarithmic transformation of individual and mean plots failed to produce a linear profile for the terminal points, indicating that the elimination half-life could not be determined reliably from the available data. However the anticipated build-up of plasma levels at steady-state has been reported by Caldwell and Cotgreave 1984 (17), who showed following identical dosage with "Phyllocontin" that the mean C_{max} of 4.2 μg ml^{-1} after single dosage, increased to 7.1 μg ml^{-1} following 5 consecutive doses at 12 h intervals.

CONCLUSIONS

This study reports the successful development of a new sustained-release aminophylline formulation which shows evidence of bioequivalence to the brand leader, "Phyllocontin", at identical dosage. Further evaluation of this product would be necessary utilizing multiple dosage regimens in a larger panel of both fasting and non-fasting subjects, as the single dose studies performed did not produce therapeutic theophylline plasma levels. Stability of the new batch 9 tablets would need to be tested in the final container at ambient and elevated storage temperature under a range of humidity conditions, in order to assign an expiry date to the product. Detailed specifications for the production and testing methods would need to be developed, and any problems associated with the scale-up of the formulation to larger commercial size batches would need to be investigated and resolved.

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