International Journal of Pharmaceutics, 86 (1992) 79–88

IJP 02896

In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate

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(Received 27 March 1992)
(Accepted 7 May 1992)

Key words: Amoxycillin; Sustained-release tablets; Intragastric buoyancy; Dissolution testing; Bioavailability studies

Summary

Various hydrophilic polymers were investigated for the preparation of amoxycillin trihydrate sustained-release (SR) tablets. The most suitable system contained a 1 : 2 ratio of hydroxypropylcellulose (HPC) to drug, which compressed easily and was not affected by alteration in normal compaction pressure. Intrinsic dissolution studies at pH 2 showed that reduction in drug loading decreased drug release, which being linear with time was characteristic of an eroding matrix with a hydrated layer. Examination of compacts over a wider range of pH showed the slowest rate of drug release at pH 6, corresponding to minimum solubility of the drug. Further formulation to enhance gastric retention time (GRT), by incorporation of a gas-generating system, yielded either bilayer tablets which prematurely failed or large single-layer tablets which remained buoyant for 6 h and had satisfactory in vitro SR. However, when the latter tablets were compared against conventional capsules in fasted humans at 500 mg equivalent dose of amoxycillin, their relative bioavailability was reduced to 80.5% and other pharmacokinetic parameters indicated lack of improved efficacy.

Introduction

Amoxycillin trihydrate is a widely prescribed broad-spectrum antibiotic, available only in conventional dosage forms for peroral delivery. Such capsules and tablets produce a large plasma peak of drug about 2 h after administration, which rapidly declines to below the minimum inhibitory concentration (MIC) of most pathogenic microorganisms, before subsequent doses of 250–500 mg are administered at 8 h intervals. It has often been claimed without clinical substantiation (Schneider et al., 1978; LeBel and Spino, 1988) that this pulsed pattern of administration is more effective than sustained delivery of therapeutic concentrations of active, as it may encourage outgrowth of resistant organisms when antibiotic levels become sub-therapeutic. However this suggestion is at variance with the practice of giving the antibiotic as its sodium salt by slow intravenous infusion when treating severe infections and by the increasing use of orally active cephalasporin and tetracycline antibiotics with a once- or twice-a-day dosage regimen. Experiments in immunocompromised animal models (Mordenti

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et al., 1985; Zhi et al., 1988) confirm the greater efficacy of multiple small doses of penicillins compared to administration of the same dose as a single bolus. Also, Vogelman and Craig (1986) showed in vitro that β-lactam antibiotics differ from the aminoglycosides in that their antibacterial effect was less concentration-dependent, but was more related to the duration of active antibiotic levels.

Attempts to develop a sustained release dosage form of amoxycillin have been hindered by the bulk of the conventional dose (250 or 500 mg as trihydrate equivalent), short biological half-life of 1–2 h (Adam et al., 1982; Lovering et al., 1990), possible dose-dependent pharmacokinetics (Dalhoff et al., 1981; Sjovall et al., 1985) and the dangers of causing unwanted large bowel complications such as overgrowth of non-susceptible organisms and diarrhoea if drug absorption is not confined to the upper gastrointestinal tract (GIT).

Cognizant of the difficulties involved, this investigation describes the development and in vivo evaluation in humans of a SR dosage form of amoxycillin based on a matrix tablet with a buoyancy effect to prolong GRT. As the drug is more soluble at the low pH of the fasting stomach compared to pH 5–6 of the upper small intestine, greater retention in the stomach of a retard release dosage form should aid the achievement of a SR product without loss of bioavailability or large bowel complications. The drug should be slowly released in the stomach by diffusion from the floating matrix tablet and then trickle towards the proximal intestine where absorption largely occurs. The achievement of an effective product was considered to be a desirable goal for the improved delivery of this antibiotic resulting in more uniform levels of antibiotic following less frequent oral dosing. Improved compliance has been associated with less antibiotic resistance (Goto et al., 1984; Lauwo et al., 1990).

Peroral intragastric floating dosage forms have a bulk density lower than gastric fluids and remain buoyant on the stomach contents without affecting the gastric emptying rate. One approach is to intimately mix the drug with a gel-forming hydrocolloid which swells after oral ingestion in contact with gastric fluid and maintains within the outer gelatinous barrier a relative integrity of shape and a bulk density of less than one. The gel structure should act as a reservoir for sustained drug release. An alternative approach is to incorporate a carbon dioxide generating mechanism into the gel containing matrix. The carbon dioxide, liberated by the acidity of the gastric content, is entrapped in the gellified hydrocolloid, producing an upward motion of the tablet and maintaining its buoyancy. The carbon dioxide generating mechanism may be intimately mixed within the tablet matrix, in which case a single-layered tablet is produced (Hashim and Li Wan Po, 1987), or a bilayered tablet may be compressed which contains the gas mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a SR effect (Ingani et al., 1987).

Materials and Methods

Materials

Amoxycillin trihydrate was obtained from Antbioticos S.A. and was micronized prior to use by a Micron Mills 4 inch fluid energy mill incorporating a vibratory feeder. Sodium alginate (NaA; Manucol LHR, Alginate Industries), methylcellulose (MC; Methocel A15C (i), A4M (ii), Dow Chemicals), hydroxypropylmethylcellulose (HPMC; Methocel E5 (i), K15M (ii), K4M (iii), E4M CR (iv), E10M CR (v), Dow Chemicals), sodium carboxymethylcellulose (NaCMC; Courlose F75P (i), F350P (ii), F1000P (iii), Courtaulds), poly(methyl vinyl ether/maleic anhydride) (PMVE/MA; Gantrex AN 169 (i), AN 119 (ii), GAF Chemicals), methylhydroxyethylcellulose (MHEC; Tylose MH300 (i), MH10000 (ii), Hoechst), hydroxypropylcellulose (HPC; Klucel LF (i), MF (ii), Hercules) and ethylcellulose (EC; Ethocel 10 cp, Dow Chemicals) were the polymers used. Benzoic acid, calcium carbonate, citric acid, diethylphthalate, hydrochloric acid, magnesium stearate, paraffin wax, sodium bicarbonate, sodium dihydrogen phosphate, sodium hydroxide, talc (British Drug Houses), ethanol (HPLC grade), methanol (GPR and HPLC grades), methylene chloride (Rathburn Chemicals), colloidal silicon

dioxide (Aerosil 200 (i), R972 (ii), Degussa), dibasic calcium phosphate (EmcomPress, Mendell), lactose (Merck), microcrystalline cellulose (Avicel PH101; FMC), Opaspray Yellow (Colorcon), polyethylene glycol 4000 (ICI), sodium stearyl fumarate (PRUV; Forum Chemicals), tetrabutylammonium hydrogen sulphate (TBA; Sigma) and glass-distilled water were the other chemicals used. All reagents were GPR unless otherwise stated.

Methods

Preparation of floating matrix tablets

A wide variety of potential SR tablets were produced in pilot-scale batches. After mixing the required powders in a mortar and pestle, aliquots were compressed using 12.5 mm diameter flat-faced tooling fitted in a Manesty hand-operated tablet press or on 21 × 10 mm pillow-shaped concave tooling with an IR press at defined pressures from 1 to 5 ton. Following completion of preliminary studies, a moist granulation procedure involving ethanol and Erweka equipment was used for the manufacture of larger batches of the most promising formulations followed by compression as described above or by use of a Manesty D3B 16 station rotary tablet press fitted with the same pillow-shaped tooling. Some batches of tablets were film-coated for taste-masking purposes to 2% weight gain by a pan coating procedure with HPMC (i) and EC as film-formers, diethylphthalate as plasticizer, Opaspray Yellow as pigment and methanol/methylene chloride as mixed solvent.

Dissolution testing

An Erweka DT6 dissolution tester fitted with paddles was used. The dissolution medium employed at 37°C was 500–1000 ml (adequate to ensure sink conditions) of citrate/phosphate buffer of variable pH or solutions of hydrochloric acid with pH values of 1–2. The absorbance of the dissolution medium was measured at 272 nm using a Shimadzu UV160 spectrophotometer and the concentration of drug calculated by reference

TABLE 1

Matrix integrity, floating and release characteristics of compressed tablets of amoxycillin trihydrate and hydrophilic polymer physical mixtures

Mixture	Polymer	Ratio of polymer to drug	Matrix integrity at pH 2	Floating capacity at pH 2	% drug released at pH 2
A	NaA	1:2	good	none	26% at 6 h
B	NaA	2:5	good	no	31% at 6 h
C	NaA	3:10	good	no	30% at 6 h
D	NaA	1:5	good	no	32% at 6 h
E	NaA	3:20	good	no	35% at 6 h
F	NaA	1:10	good	no	40% at 6 h
G	NaA	1:20	good	no	43% at 6 h
H	MC (i)	1:2	eroded quickly	no	100% at 1.5 h
I	HPMC (ii)	1:2	good	no	17% at 6 h
J	HPMC (iii)	1:2	good	no	19% at 6 h
K	NaCMC (i)	1:2	poor, gels	gel floats	57% at 6 h
L	NaCMC (ii)	1:2	poor, gels	gel floats	32% at 6 h
M	NaCMC (iii)	1:2	poor, gels	gel floats	26% at 6 h
N	PMVE/MA (i)	1:2	good	no	27% at 6 h
O	PMVE/MA (ii)	1:2	eroded slowly	no	100% at 5 h
P	MHEC (i)	1:2	poor, gels	gel floats	100% at 6 h
Q	MHEC (ii)	1:2	good	no	20% at 4 h
R	HPC (i)	1:2	eroded slowly	no	46% at 6 h
S	HPC (i)	1:5	eroded slowly	no	70% at 6 h
T	HPC (ii)	1:2	good	no	20% at 6 h

to a linear calibration curve constructed at the same pH. Intrinsic dissolution studies were also carried out at various pH values on 13 mm discs compressed from drug or granulate and mounted in stainless-steel dies sealed underneath with molten paraffin wax so as to expose only the upper face.

In vivo studies

As legally required in Ireland, the protocol for the human studies was approved by the National Drugs Advisory Board, Dublin. A panel of six healthy fasted male subjects was used, whose serum drug levels were compared in a single-dose cross-over study following administration of tablets of the final formulation and Amoxil® 500 mg capsules. A 2 week 'wash-out' period was allowed between doses. To limit degradation, serum samples were stored at −70°C as recommended by Schaad et al. (1986) prior to analysis. Drug levels were determined using a modification of the reversed-phase high-performance liquid chromatography method of Jonkman et al. (1985). The internal standard used was benzoic acid and the mobile phase was 31 parts of methanol to 69 parts of 0.005 M TBA with 0.05 M sodium dihydrogen phosphate (pH 6.0 adjusted with sodium hydroxide solution).

Results and Discussion

Preliminary studies

Tablets containing 500 mg amoxycillin trihydrate with various hydrophilic polymers were compressed on the hand operated tablet press in order to make a preliminary assessment of suitability in terms of matrix integrity, floating tendency, and percentage drug release after up to 6 h dissolution testing at pH 2.0 for the design of the final product. Table 1 shows the results obtained. Tablets containing NaA (mixtures A–G) and HPMC (mixtures I and J) swelled to form an intact hydrated gel layer through which only an inadequate proportion of the entrapped drug could diffuse over the 6 h of the dissolution study. In contrast, tablets produced with MC (mixture H) eroded quickly with excessively rapid release of drug. NaCMC-containing tablets (mixtures K–M) quickly gelled to lose shape and floated on the surface of the dissolution medium, but had inadequate drug release. Other hydrophilic polymers examined gave similar results with a tendency for increasing both viscosity grade of the polymer and polymer : drug ratio to reduce drug release.

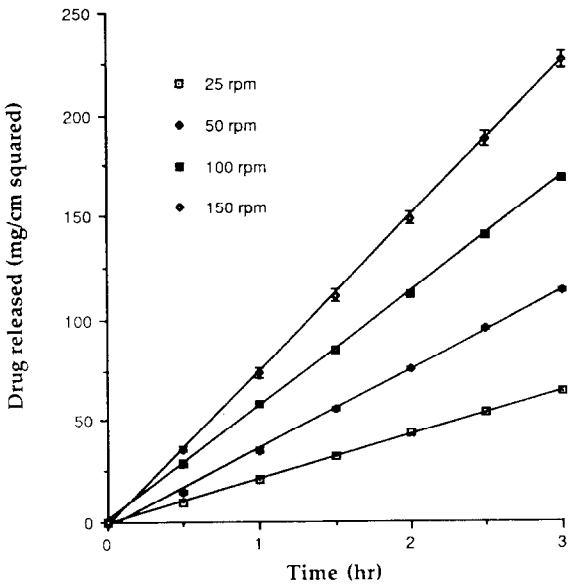

Fig. 1. Plot showing the effect of stirrer speed on drug release at pH 2 from HPC (i)/amoxycillin trihydrate (1:2) matrix. Bar: ± 1 SE.

Of all the systems examined, mixture R containing HPC (i) was the most easily compressed using the single punch press to tablets of excessive hardness (over 15 Monsanto units). This was reduced to 9–13 units using the IR press with 73% drug release in 5 h, which was not significantly affected by compaction pressure over the range 1–5 ton. Fig. 1 shows the results of intrinsic dissolution tests at paddle agitation speeds of 25, 50, 100 and 150 rpm on tablets of mixture R compressed at 1 ton, showing that as agitation increased so did the amount of drug released. The release was linear with time indicating that drug release was controlled by a combination of surface erosion, diffusion through the gel layer of constant thickness (measured as about 200 μm using a travelling microscope) and diffusion

through the laminar layer at the interface between the dissolving drug and the dissolution medium. Studies by Levich (1962) have shown that the thickness of this laminar layer decreases approximately as the square-root of the velocity of stirrer speed. Consequently, plotting the reciprocal of the total diffusional resistance using the method of Senjkovic and Jalsenak (1982) vs $1/\text{speed}^{0.5}$ gave a linear relationship ($r = 0.966$, $p < 0.05$). Extrapolation to a stirrer speed of infinity, where the diffusional resistance posed by the laminar layer was zero, yielded a diffusional resistance value of 1.3×10^3 s cm^{-1}. In the case of the amoxycillin trihydrate/HPC matrix, this value represents the overall resistance to drug release from the matrix, taking into consideration diffusion through the gel layer as well as erosion of this layer.

The results of intrinsic dissolution tests at pH 2 on discs containing pure drug and HPC (i):amoxycillin trihydrate in the ratio 1:5, 1:2, 1:1 and 2:1 are shown in Fig. 2. In all cases the plots of the amount of drug released vs time are linear. Even at lower drug loadings, the release is as expected from a system of constant surface

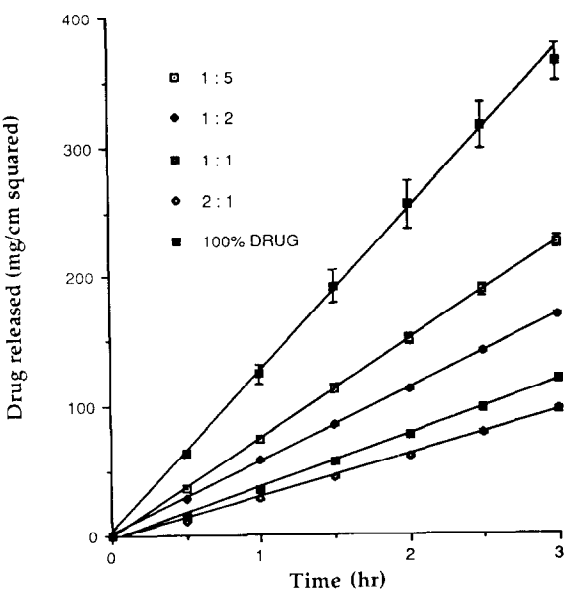

Fig. 2. Plot showing the effect of drug loading on drug release at pH 2 from matrices containing HPC (i)/amoxycillin trihydrate in the ratios shown. Bar: ±1 SE.

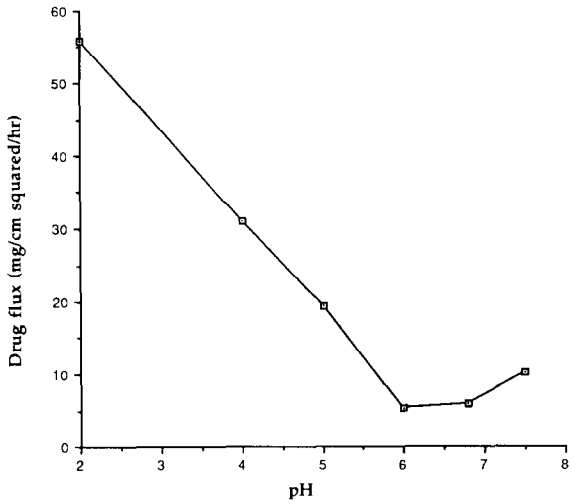

Fig. 3. Plot showing the effect of pH on the drug flux (mg/cm^2 per h) from HPC (i)/amoxycillin trihydrate (1:2) matrix.

area subject to dissolution in a perfect sink and characteristic of a matrix with an eroding hydrated layer (Lapidus and Lordi, 1968). With a decrease in drug loading, it would be expected that the hydrated layer would eventually remain intact, leading to $t^{0.5}$ release from a planar surface.

The results of drug flux as a function of pH, derived from intrinsic dissolution testing on discs of mixture R, show the characteristic U-shaped profile similar to that of the pure drug, indicating that the slowest rate of drug release from the matrix occurs around pH 6 (Fig. 3). HPC is non-ionic and is reported in the manufacturer's literature to have a stable viscosity over the physiological pH range.

In order to increase the release rate of tablets compressed from mixture R and improve its lubrication properties, 15% lactose or 0.5 and 2% magnesium stearate was added. As shown in Fig. 4, addition of the water-soluble lactose increased the flux from 56.0 to 61.4 mg/cm^2 per h, whereas the hydrophobic lubricant reduced the flux to 53.2 and 38.8 mg/cm^2 per h for the lower and higher concentrations used, respectively.

Bilayer floating tablets

The results of the preliminary studies showed that it was possible to retard the release of

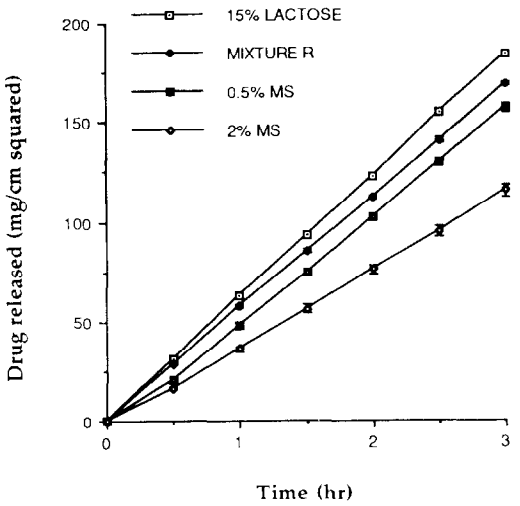

Fig. 4. Plot showing the effect of lactose and magnesium stearate (MS) on drug release at pH 2 from HPC (i)/amoxycillin trihydrate (1 : 2) matrices. Bar: ± 1 SE.

amoxycillin trihydrate at pH 2 to obtain an adequate SR effect under fasting stomach pH conditions. However, such HPC containing matrix tablets would probably have low bioavailability if allowed to travel too rapidly along the GIT, because the drug has minimum aqueous solubility under intestinal pH conditions. In an attempt to get the matrix to float so as to prolong its GRT, bilayered floating tablets were formed initially, wherein the SR drug layer composed of drug 500 mg and HPC (i) 100 mg was bonded to an in situ gas generating layer. Table 2 shows the formulation of the gas-generating layer based on the general formulation, F_{gen}, where sodium bicarbonate and calcium carbonate were used as the gas-generating mechanism and the hydrophilic polymer to trap the carbon dioxide liberated. Such compacts were placed into 500 ml of pH 2 medium at 37°C, agitated at 25 rpm and assessed for their floating characteristics which were considered satisfactory or lacking in adequate integrity as recorded in Table 2. After further extensive studies, the best gas-generating layer developed contained HPMC (ii) 20%, sodium bicarbonate 30%, calcium carbonate 20% and microcrystalline cellulose 30%, which floated after 5 min for 4 h, with reasonable integrity. However, when this layer was bonded onto the drug matrix layer, the composite tablet failed to float due to the weight of the latter and prematurely split along the joining of the two layers. Consequently, it was decided to abandon this approach in favour of a single-layer floating tablet.

TABLE 2

Hydrophilic polymers used in the general formulation, F_{gen}, for the gas-generating layer with results of floating studies at pH 2 on bilayer tablets

F_{gen}	
Hydrophilic polymer	210 mg
Sodium bicarbonate	12 mg
Calcium carbonate	168 mg
Citric acid	24 mg
Microcrystalline cellulose	120 mg
Dibasic calcium phosphate	64.2 mg
Colloidal silicon dioxide (i)	1.8 mg

Formulation	Hydrophilic polymer used	Result of floating and integrity studies
F1	HPMC (ii)	floated after 40 min, sank after further 20 min
F2	HPMC(iii)	floated after 35 min, sank after further 25 min
F3	MC (ii)	floated after 0.5 min, fully eroded within 3 min
F4	HPMC (ii)/MC (ii) 1 : 1	floating system eroded prematurely
F5	NaA	gas-generating layer possessed poor integrity
F6	HPMC (iv)	gas-generating layer possessed poor integrity
F7	HPMC (v)	gas-generating layer possessed poor integrity

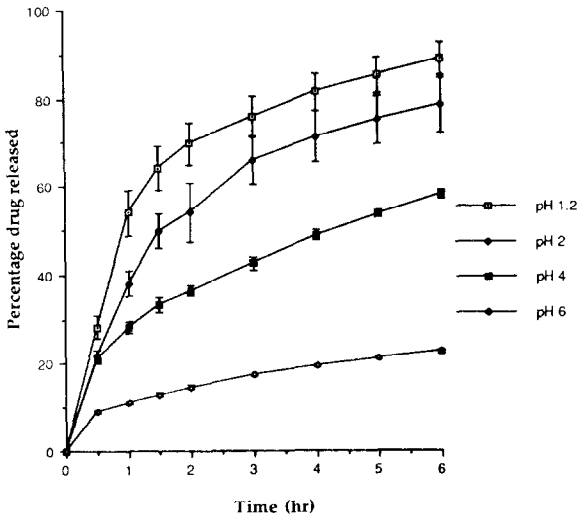

Fig. 5. Plot showing the effect of pH on the % amoxycillin trihydrate released vs time from matrices containing formulation F11. Bar: ±1 SE.

Single-layer floating tablets

Single-layer floating tablets were also tested, examples of whose composition with results of floating and integrity studies are listed in Table 3. Unlike F8 and F9, F11 was typical of a formulation which had reasonable drug loading, yet floated within a few seconds of agitation at 100 rpm in pH 2 medium and remained buoyant for 6 h due to the presence of adequate quantities of both gas-generating materials, whose carbon dioxide evolution was entrapped in the gel formed by the hydrophilic polymer.

The results of dissolution tests carried out on formulation F11 are shown in Fig. 5. Hashim and Li Wan Po (1987) used low concentrations of effervescent materials in an attempt not to disrupt the matrix during the release phase. However, in the case of formulation F11, an initial vigorous liberation of gas occurred due to the large amount of sodium bicarbonate and calcium carbonate required to induce buoyancy of the macro dosage unit. Across the range of pH values studied, no consistent kinetic pattern was noted in the initial stages of release except that there appeared to be a burst effect. This was more pronounced at low pH and consistent with the greater level of matrix disruption and drug solubility observed.

A wide variety of lubricants was incorporated into formulation F11, including magnesium stearate 0.5%, sodium stearyl fumarate 2%, talc 2%, colloidal silicon dioxide (i) 0.3% or (ii) 0.5%. The final formulation chosen, which was film-coated, contained the last of these lubricants, none of which affected the dissolution profile of the floating tablets after granulation using ethanol and compression on the pillow-shaped tooling at 1, 2 and 5 ton using the IR press and also on the rotary press. There was no significant difference in tablet hardness (about 30 kg measured on a Holland C40 tablet hardness tester) or release profile of pillow-shaped tablets produced by alteration in the compression force or the means of compaction.

In vivo studies

Fig. 6 shows the mean serum levels of six fasted subjects following a single dose of amoxycillin 500 mg as either the Amoxil® capsules or as the new product. Pharmacokinetic parameters are

TABLE 3

Some potential single-layer floating tablets and their assessment

Formulation (weights in mg)	D	HPMC (ii)	SB	CC	PEG	Result of floating and integrity studies
F8	500	100	5	45	–	did not float
F9	500	100	50	200	–	did not float
F10	500	100	200	300	–	floated within 1 min, buoyant for 6 h
F11	500	100	200	200	–	floated within 1 min, buoyant for 6 h
F12	500	100	200	–	–	floated within 1 min, sank after 3 h
F13	500	100	200	200	100	floated within 1 min, buoyant for 6 h

D, drug; HPMC (ii), Methocel K15M; SB, sodium bicarbonate; CC, calcium carbonate; PEG, polyethylene glycol 4000.

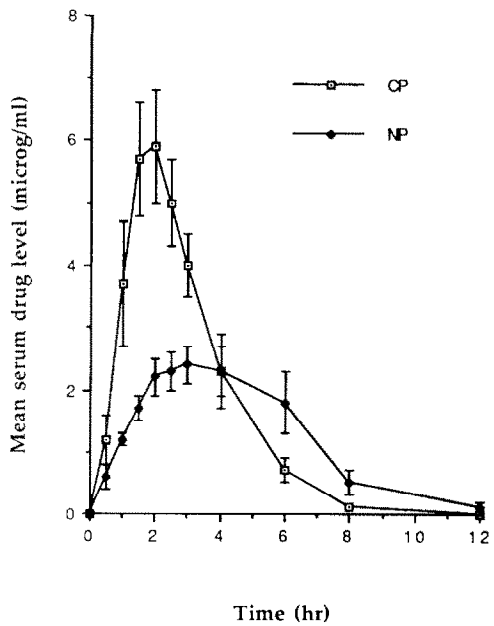

Fig. 6. Plot comparing mean serum drug levels in six subjects, where CP is the conventional product, Amoxil® 500 mg capsules and NP denotes the new product, SR floating 500 mg tablets. Bar: +1 SE.

listed in Table 4. No adverse reactions were reported by any of the subjects taking either product.

The MIC of amoxycillin varies according to the type of microorganism. Sensitive Gram-positive organisms are susceptible to very low concentrations, in the order of less than 0.1 μg/ml, while moderately sensitive Gram-negative bacteria are susceptible to about 2.5–5 μg/ml. Therefore, it would seem reasonable to define the pharmacokinetic parameters $T_{(0.1\,\mu g/ml)}$, $T_{(2.5\,\mu g/ml)}$ and $T_{(5\,\mu g/ml)}$, corresponding to the length of time (h) the serum levels remained greater than or equal to 0.1, 0.5 and 5 μg/ml, respectively. Despite reservations in relation to the usefulness of MICs, there is considerable evidence that the therapeutic response to β-lactam therapy depends on the time spent above the MIC (Bakker-Woudenberg and Roosendaal, 1988; Drusano, 1988). Hence, these pharmacokinetic parameters shown in Table 4 may prove to be an indicator of the relative efficacies of the conventional and SR dosage forms.

The mean Amoxil® profile was similar to that reported in the literature for conventional capsules containing 500 mg amoxycillin, whereas the new product profile was smoother and exhibited a plateau. The proprietary product resulted in a C_{max} of 5.9 μg/ml at a T_{max} of 2 h, compared to the new product where the values were 2.4 μg/ml and 3 h, respectively. These values for C_{max} and T_{max} are the maximum concentration and time to maximum serum concentration seen when the results for the six subjects are averaged out, i.e.,

TABLE 4

Pharmacokinetic parameters from human trial

Subject no.	C_{max} (μg/ml)		T_{max} (h)		AUC_{0-12h} (μg ml^{-1} h)		C_{max}/C_{6h}		$T_{(0.1\,\mu g/ml)}$ (h)		$T_{(2.5\,\mu g/ml)}$ (h)		$T_{(5\,\mu g/ml)}$ (h)	
	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP
1	7.8	3.3	1.5	3.0	19.6	17.9	-	1.8	5.7	12.0	3.2	3.3	2.1	0
2	4.4	3.8	4.0	6.0	18.6	22.2	2.6	1.0	11.7	11.4	3.6	3.8	0	0
3	8.7	3.0	2.0	2.0	21.4	12.9	12.4	3.0	6.8	7.7	3.2	1.8	1.6	0
4	7.9	2.4	1.5	6.0	23.4	17.5	8.8	1.0	10.0	12.0	3.9	0.	1.7	0
5	4.2	1.7	1.5	2.0	11.2	7.6	8.4	3.4	7.9	11.0	1.6	0	0	0
6	8.0	3.4	1.0	3.0	19.6	13.6	16.0	2.0	7.8	7.4	2.9	1.5	1.6	0
Mean	6.8	2.9	1.9	4.3	19.0	15.3	9.6	2.0	8.3	10.3	3.1	1.7	1.2	0
SE	0.8	0.3	0.4	0.7	1.7	2.0	2.2	0.4	0.9	0.9	0.3	0.7	0.4	0
n	6	6	6	6	6	6	5	6	6	6	6	6	6	6

C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; AUC_{0-12h}, area under serum curve from 0 to 12 h; C_{6h}, serum concentration at 6 h; $T_{(0.1\,\mu g/ml)}$, time at or above serum level of 0.1 μg/ml; CP, conventional product – Amoxil® 500 mg capsules; NP, new product – SR floating 500 mg tablets.

they are the C_{max} and T_{max} of the mean profile. These values are different from the mean of the C_{max} and T_{max} values shown in Table 4, which are the means obtained by averaging out the individual C_{max} and T_{max} from each subject and for each product. The latter two measurements give an indication of the 'usual' C_{max} and T_{max} which may be expected on administration of these products to a 'typical' subject.

The results of a statistical analysis of the pharmacokinetic parameters are shown in Table 5 following parametric and non-parametric testing, where significance was recorded at the 5% level. Using both the paired *t*-test and the Wilcoxon signed ranks test, there was a significant difference between the conventional and new SR product in terms of the C_{max}, while the same conclusion was drawn for the T_{max} on the basis of the parametric test. Although the mean relative bioavailability of the SR product was only 80.5%, the null hypothesis could not be rejected at the 5% significance level using both statistical techniques. The paired *t*-test showed that the C_{max}/C_{6h}, lower values being an indication of effective retard property, was different for the conventional and SR products. Both of the statistical tests employed showed that the $T_{(0.1\,\mu g/ml)}$ and $T_{(2.5\,\mu g/ml)}$ values were not significantly different, while the parametric test indicated that the $T_{(5\,\mu g/ml)}$ value was. In terms of these pharmacokinetic parameters, the SR product possessed no advantages and might be less effective in the treatment of moderately sensitive Gram-positive and sensitive Gram-negative microorganisms.

In the absence of in vivo scintigraphy, the gastric retentivity of the floating dosage form was unknown. However, the results from the six subjects suggest variable and in many cases, premature gastric clearance leading to decreased bioavailability. Evidence is mounting that floating dosage forms do not possess enhanced GRT when administered to fasting subjects, and in the presence of food, matrices similar in formulation to that in the SR floating tablets would not be expected to release drug at a rate sufficient to maintain in vivo levels above the MIC of many common pathogens. There is also evidence (Kuna, 1964) that the resting gastric pH is variable between 3 and 5 in humans and this would disproportionately reduce the drug release profile of the SR product. In addition, the conventional dosage form was at least as effective at maintaining in vivo levels above the MIC of many Gram-positive pathogens, while the SR dosage form did not produce levels high enough for in vivo activity against many important Gram-negative organisms. Following premature gastric clearance of the SR tablet form, it was felt that repeated administration of the slow release form of the drug might lead to superinfection further down the GIT.

A tablet of the final formulation containing 750 mg amoxycillin as the trihydrate was also compared with Amoxil® (500 mg plus 250 mg capsule) in one subject, whose relative bioavail-

TABLE 5

Statistical analysis of the pharmacokinetic parameters calculated for Amoxil® capsules and SR floating tablets equivalent to 500 mg amoxycillin as the trihydrate

Variable	Paired *t*-test values	$p < 0.05$	Wilcoxon *S* value	$p < 0.05$
C_{max} ($\mu g/ml$)	4.78	yes	0	yes
T_{max} (h)	2.76	yes	NA	NA
AUC_{0-12h} ($\mu g\ ml^{-1}\ h$)	2.11	no	2.5	no
C_{max}/C_{6h}	3.68	yes	NA	NA
$T_{(0.1\,\mu g/ml)}$ (h)	1.86	no	18	no
$T_{(2.5\,\mu g/ml)}$ (h)	2.12	no	3	no
$T_{(5\,\mu g/ml)}$ (h)	3.27	yes	NA	NA

NA, non-applicable statistical test because of inadequate sample size (Eason et al., 1980).

ability on the floating matrix was 78.8% compared to the conventional product. Also, there was no improvement in the $T_{(2.5\,\mu g/ml)}$ or $T_{(5\,\mu g/ml)}$ values, levels which concur with typical MICs of amoxycillin against moderately sensitive Gram-positive and sensitive Gram-negative bacteria, for the new compared to the conventional product.

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