Use of Hydroxypropyl Methylcellulose Acetate Succinate in an Enteric Polymer Matrix To Design Controlled-Release Tablets of Amoxicillin Trihydrate

ALAN K. HILTON AND PATRICK B. DEASY[x]

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Abstract ☐ A controlled-release tablet of amoxicillin trihydrate was developed by use of a matrix formulation based on the enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS). Sustained drug release was shown by in vitro dissolution testing; the polymer could suppress drug release in the presence of gastric pH but could enhance drug release in the presence of small intestinal pH, compared with compacts of pure drug. Grinding or physical mixing of the drug with the polymer, an alteration in normal compaction pressure, or a substitution of other enteric polymers did not markedly affect drug release from compacts. Physicochemical testing of samples confirmed that the method of mixing did not alter powder morphology. An ethanolic granulation procedure was used in the production of final tablets (21 × 10 mm) containing amoxicillin (750 mg), HPMCAS, anhydrous directly compressible lactose, and lubricants. These large tablets showed a promising sustained-release effect in vitro when a variable-pH-shift dissolution procedure was used. However, single-dose studies with a panel of fasting subjects showed that the tablets had a relative bioavailability of only 64.4%. Other pharmacokinetic parameters confirmed a lack of therapeutic advantage of these tablets over an equivalent dose of conventional capsules.

Much research has been carried out to elucidate the impact of dosage regimens on the efficacy of antibiotic treatment. There is evidence from in vitro research and in vivo animal experiments that the efficacy of β-lactam antibiotics depends mainly on the length of time that bacteria are exposed to antibiotic concentrations above the minimum inhibitory concentration. There is also direct and indirect evidence from human trials to support this claim.[1,2] Consequently, a controlled-release dosage form of a β-lactam antibiotic might be therapeutically more efficacious than the existing conventional products, which are rapidly absorbed to produce transient peaks in serum drug levels. Amoxicillin was chosen as the candidate drug, because it is currently the most widely prescribed oral semisynthetic penicillin worldwide.[3]

Several attempts have been made by others to develop a sustained-release amoxicillin product, with little success. Studies on amoxicillin-containing fatty-matrix tablets have been carried out, but the products obtained were not compared with unretarded drug.[4] This situation is unfortunate, because the incorporation of passage-delaying food excipients, principally fatty acids, to delay gastric emptying might be a useful approach to the development of a sustained-release version of the drug.[5] Amoxicillin-containing gelatin microcapsules have been prepared by a coacervation procedure and subjected to dissolution studies at various pHs.[6] The dissolution profile for the microcapsules coincided with that for the pure drug and, as expected, the microcapsules did not provide effective sustained release of the drug when administered to gastric-emptying-controlled rabbits. The development of a controlled-release amoxicillin formulation has been reported, but details of the composition of the formulation were not given.[7] However, no drug was detectable more than 8 h after the administration of either the conventional or the controlled-release formulation. Others have produced amoxicillin-containing microcapsules coated with ethylcellulose; these microcapsules showed a sustained-release effect when administered to dogs.[8] However, it is not surprising that this effect was observed, because beagle dogs have been reported[9] to have a resting gastric pH of ~6, at which the drug is least soluble.[10] In contrast, humans have a reported lower fasting gastric pH of ~2, and release from the microcapsules under these acidic conditions would be almost as quick as that from the pure drug.[11] It was recently shown[12] that a multiparticulate dosage form of amoxicillin prepared by coating drug-containing granules with Gelucire 64/02 (Gattefossé) had adequate sustained-release properties in vitro. However, the amount of unaltered amoxicillin excreted in the urine of humans decreased progressively as the sustained-release effect was increased by the application of larger amounts of coating. This in vivo effect was attributed without confirmation to the presence of an absorption window, rather than to the inadequate release of drug at the pH of the small intestine.

A novel approach to the design of a suitable controlled-release product would involve the incorporation of an enteric polymer that retards drug release at a low pH but that either does not affect or enhances dissolution at intestinal pH. Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is a new enteric polymer that is claimed[13] to dissolve more readily at the pH of the upper small intestine, and thereby to prevent release further down the small intestine, which might lead to a reduction in bioavailability or unwanted large bowel complications. This material is reported to be more resistant than other enteric polymers to moisture accumulation, a property that would be an advantage in the formulation of penicillin-containing products. Also, HPMCAS contains no phthalate groups, which pose possible health hazards and interfere with the UV analysis of a drug. Amoxicillin trihydrate and structurally related penicillins exhibit poor solubility in most common organic solvents. Therefore, large quantities of these solvents would be required to prepare relatively small yields of products by the solvent method of forming solid dispersions. For example, coprecipitates of ampicillin trihydrate with an acrylic resin were produced by dissolving appropriate quantities of drug and polymer together in methanol.[14] However, the yield was low, because ampicillin was only soluble to a level of 6.6 g/L in the solvent. A more efficient way of producing solid dispersions is the melt method.[15] However, amoxicillin trihydrate exhibits poor stability at elevated temperatures.[16] A more novel technique of effecting enhanced rates of drug dissolution is mixing by grinding.[17,18] In those studies, a vibratory ball mill was used to mix phenytoin with microcrystalline cellulose or polyvinylpyrrolidone. X-ray diffraction patterns indicated that

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there was a transition of phenytoin from the crystalline to the amorphous form after 2 h of grinding, a result consistent with reported higher dissolution rates and bioavailability.

This investigation describes the use of HPMCAS in the design of a matrix tablet for the controlled release of amoxicillin after oral administration. The new product developed is compared with conventional capsules (Amoxil; Bencard) in humans at an equivalent dose.

Experimental Section

Materials—Amoxicillin trihydrate (micronized; Roferm), HPMCAS (LF grade; Shin-Etsu), carboxymethyl ethylcellulose (Freund), Eudragit polymethacrylate (L100 5.5 grade; Rohm Pharma), anhydrous directly compressible lactose (DCL21; DMV), tetrabutylammonium hydrogen sulfate (TBA; Sigma), benzoic acid, citric acid, hydrochloric acid, magnesium stearate, paraffin wax, sodium dihydrogen phosphate, sodium hydroxide, talc (British Drug Houses), ethanol, methanol (HPLC grade; Rathburn Chemicals), and distilled water were used. All materials were reagent grade unless otherwise stated.

Preparation of Compacts—Powdered materials were physically mixed with a mortar and pestle. Mixing by grinding was performed for 200-g batches with various drug:HPMCAS ratios by use of a ball mill (type KM10; Copley) run at maximum speed for 3 h and an Erweka KU 1 motor. Disks (tablets) were compressed at 1–5 ton (1 ton = 10^3 kg) for 10 min in an IR press by use of a 13-mm flat-faced punch and die set or on pillow-shaped tooling (21 × 10 mm). The final tablet formulation, containing a ground mixture of drug and HPMCAS, DCL as a filler, and both magnesium stearate and talc as lubricants, was granulated with ethanol before compression on pillow-shaped tooling at a dose equivalent to 750 mg of amoxicillin.

Dissolution Studies—Dissolution testing was carried out with 1000 mL of aqueous citric acid–phosphate buffer at pH 2, 3.2, 4.4, 5.6, 6.8, or 8 and 37 °C by use of an Erweka DT6 dissolution tester fitted with paddles rotating at 100 rpm. In certain experiments, the pH of the dissolution medium was shifted from 2 to 5.6 or 2 to 6.8 after 2 h. For intrinsic dissolution studies, disks were mounted in stainless steel dies, sealed underneath with molten paraffin wax so as to expose only the upper face.

Powder Morphology—Samples of powdered drug, mounted on aluminum stubs with 3-M glue (3M) and vacuum coated with gold film by use of an Emscope SC 500 sputter unit, were examined with a Hitachi S-520 scanning electron microscope fitted for energy-dispersive analysis (EDA) and connected to the Link system (Link Analytical). X-ray diffraction patterns were obtained over the range 2θ = 5–35 ° for 30-mm-diameter compressed disks (2 g) of drug and HPMCAS. Samples formed by both physical mixing and grinding of the two components were studied, and diffraction patterns were obtained with a Philips PW 1049/01 goniometer equipped with a Philips PW 1010 generator and linked to a Vitatron pen recorder. Differential scanning calorimetry (DSC) was performed for samples with a Mettler TC 10A TA processor and an Epson FX-800 printer.

In Vivo Studies—Serum drug levels produced after administration of tablets containing the equivalent of 750 mg of amoxicillin were compared with those produced by the same dose of conventional capsules [one of 500 mg (lot 34382D) plus one of 250 mg (lot 33234B)]. Six male subjects who had fasted for at least 8 h before and for 4 h after the administration of the dosage forms participated in the single-dose crossover study, whose protocol was approved by the National Drugs Advisory Board, as legally required in Ireland. Demographic details for the subjects are shown in Table I. A standard light meal, low in fat and carbohydrate, was provided at both 4 and 7 h after dose administration, and consumption of normal meals was permitted after a further 4 h. A 2-week wash-out period was allowed between consecutive doses. To limit degradation, we stored plasma samples at −70 °C before analysis as recommended elsewhere.[19] A modification of the published reversed-phase HPLC method was used to determine serum drug levels.[20] Disposable columns used for the ion pair extraction with TBA of plasma samples were 1-mL Bond Elut columns (Analytichem International) filled with 100 mg of octadecyl sorbent. The internal standard used was benzoic acid. Eluant samples of 25 μL were injected onto a main column (25 × 0.46 cm) protected by a guard column (1 × 0.3 cm); both columns were packed with Ultratech 5-μm octadecyl silica. The filtered and degassed mobile phase consisted of 31 parts of methanol:69 parts of 0.005 M TBA with 0.05 M sodium dihydrogen phosphate (pH 6.0, adjusted with sodium hydroxide solution) and was pumped at a flow rate of 1.5 mL/min. A Shimadzu LC-6A liquid chromatograph equipped with a Shimadzu SPD-2A variable-wavelength UV detector set at 229 nm was used. Output from the detector was plotted and analyzed for peak area by use of a Shimadzu C-R3A Chromatopac integrator. The assay was validated by evaluation of its precision, linearity, recovery, and specificity for amoxicillin.

Table I—Demographic Details for the Subjects Participating in the In Vivo Studies

Subject	Age, years	Height, m	Weight, kg
1	27	1.89	80
2	24	1.88	73
3	25	1.70	71
4	22	1.90	78
5	22	1.71	70
6	23	1.73	72

Results and Discussion

Preliminary Grinding and Physical Mixing Studies—Intrinsic dissolution studies at pH 6.8 (Figure 1) showed that there was no significant difference in the release profile between the samples prepared by physical mixing and grinding at a 1:1 drug:HPMCAS ratio. However, both mixture types showed a significant increase in the rate of release over that from disks of the pure drug. The shearing forces necessary to achieve crystal dislocation[18] may not have been achieved in the conventional ball mill used, whereas the energy used for grinding was derived solely from the acceleration of the balls in a gravitational field. Rapid dissolution and leaching of HPMCAS from the eroding matrix surface at pH 6.8 may have resulted in a highly porous surface network of exposed drug particles. Thus, the effective surface area of amoxicillin trihydrate in contact with the dissolution medium would have increased substantially with respect to that of the pure-drug disks, a result leading to an increase in the release rate.

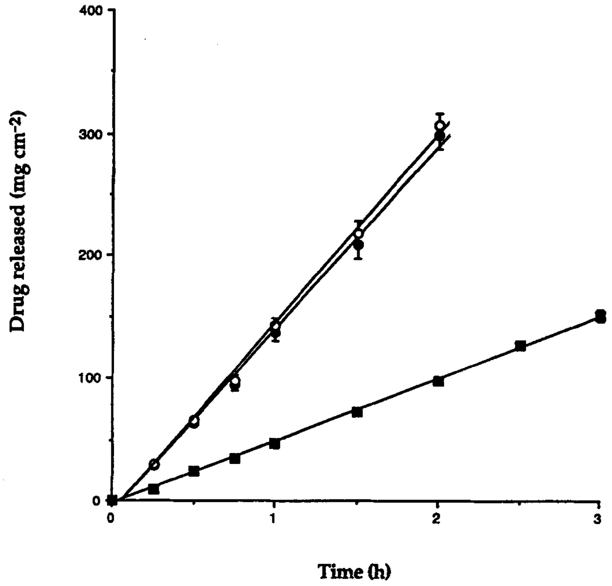

Figure 1—Intrinsic dissolution testing at 37 °C and pH 6.8 of 1:1 amoxicillin trihydrate:HPMCAS mixtures prepared by either physical mixing (●) or grinding (○) in comparison with compacts of 100% drug (■). Bars represent ±1 SEM.

Table II—Drug Release Determined from Zero-Order Plots of Release at pH 6.8 or from $t^{0.5}$ Plots of Release at pH 2 for Disks Containing Various Amoxicillin Trihydrate:HPMCAS Ratios

Drug:HPMCAS Ratio	Drug Release, (r) at:	
	pH 6.8, mg/cm^2/h^a	pH 2, mg/cm^2/h$^{0.5\ b}$
1:1	154.1 (0.998)	28.4 (0.999)
2:1	149.7 (0.999)	29.8 (0.998)
4:1	158.8 (1.000)	28.5 (0.996)
6:1	159.5 (1.000)	37.9 (0.995)
10:1	129.0 (0.998)	55.8 (0.994)
15:1	109.7 (0.998)	
100% Drug	51.0 (0.999)	

[a] At 1 h. [b] At 0.5 h.

Table II shows the effect of progressively lower proportions of the polymer on drug release from the disks at pH 6.8. In all cases, the release was linear with time, consistent with surface detachment control.[21] After surface area correction, there was little difference in drug release from disks containing drug:HPMCAS at ratios of 1:1–6:1. This result indicated that within this range of drug loading, there was a proportionate increase in the surface area of the drug presented to the dissolution medium. However, the equivalent results for disks containing drug:HPMCAS at ratios of 10:1 and 15:1 indicated a progressive decrease in drug release. Although the corrected drug release from these two systems was higher than that from pure-drug disks, there appeared to be progressively less matrix erosion on the basis of release data and hence less enhancement of drug release associated with the reduction in HPMCAS content. Linear release profiles for square-root-of-time plots for 1:1 drug:HPMCAS disks were also obtained at pHs 5.6 and 8; they showed a progressive increase in drug release as the pH was increased.

Figure 2 shows the intrinsic dissolution plots at pH 2 for disks containing variable drug:HPMCAS ratios, at which release is characteristic of a nondisintegrating matrix.[22] The release rates calculated from $t^{0.5}$ plots are listed in Table II. The fit was significant at the 5% level in all cases and became progressively better as the proportion of HPMCAS in the mixture was increased. This trend was consistent with a better correlation with the diffusion model of Higuchi[22]; the higher polymer content improved matrix integrity. After correction for surface area, rates of drug release from disks containing drug:HPMCAS ratios of 1:1–4:1 were similar. However, at higher drug loadings, the retardant effect of the enteric polymer became less pronounced and release from disks containing a 10:1 ratio was linear with time. At the low pH of the dissolution medium, the amount of polymer in the 10:1 ratio system did not appear to be adequate to prevent disintegration of the matrix, so erosion seemed to control drug release. Linear release profiles with time for 1:1 drug:HPMCAS disks were also obtained at pHs 3.2 and 4.4; they showed a progressive decrease in drug release as the pH was increased from 2 to 4.4.

Figure 3 shows that the release from disks of 1:1 drug:HPMCAS at pHs 2 and 6.8 was not significantly affected by compaction pressures in the range of 1–5 ton. Also, polymethacrylate and carboxymethyl ethylcellulose were examined as examples of other enteric polymers; they provided results similar to those obtained with HPMCAS on intrinsic dissolution testing at pHs 2 and 6.8. However, in comparison with HPMCAS, their effect was not so marked in causing the retardation of drug release at a low pH and enhancement at a higher pH; consequently, they were not studied further.

Powder Morphology—Scanning electron microscopy, X-ray diffraction, and DSC studies have shown that grinding can reduce the crystallinity of some β-lactam antibiotics.[23–25]

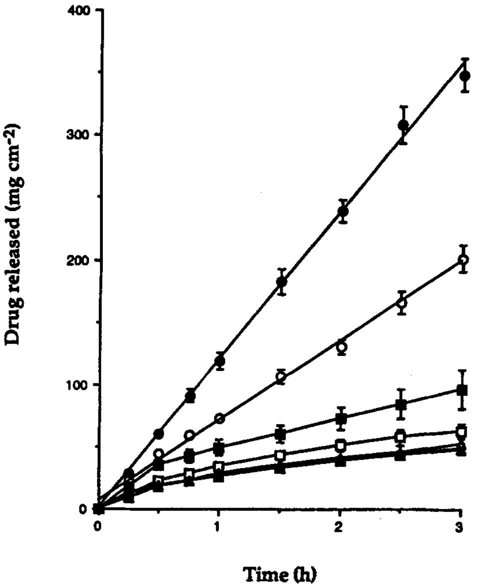

Figure 2—Intrinsic dissolution testing at 37 °C and pH 2 of 1:1 (×), 2:1 (△), 4:1 (▲), 6:1 (□), 10:1 (■), and 15:1 (○) ground amoxicillin trihydrate:HPMCAS mixtures in comparison with compacts of 100% drug (●). Bars represent ±1 SEM.

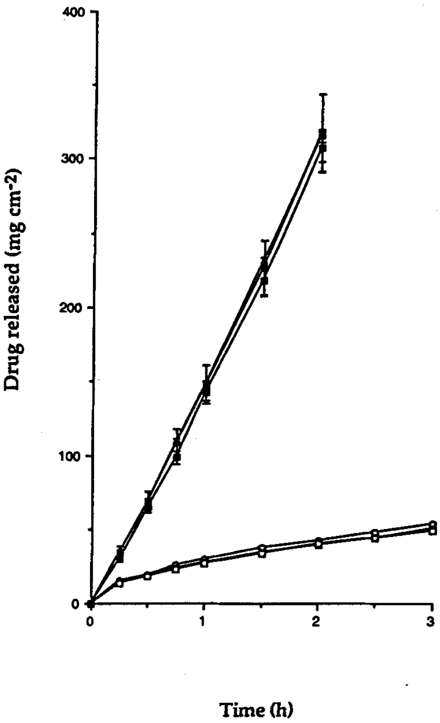

Figure 3—Intrinsic dissolution testing at 37 °C and pH 6.8 (●, ▲, and ■) or pH 2 (○, △, and □) of compacts prepared from ground 1:1 amoxicillin trihydrate:HPMCAS mixtures compressed at 1 (● and ○), 3 (▲ and △), or 5 (■ and □) tons. Bars represent ±1 SEM.

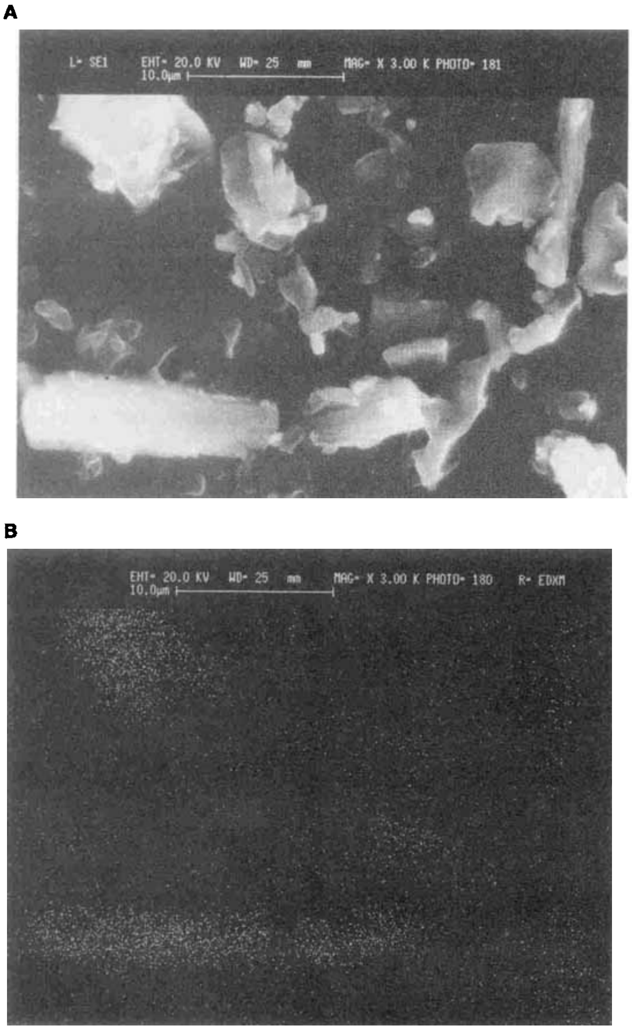

Figure 4—Scanning electron micrographs of a physically mixed 1:1 amoxicillin trihydrate:HPMCAS sample. Magnifications: A, ×3000; B, ×3000 but with EDA.

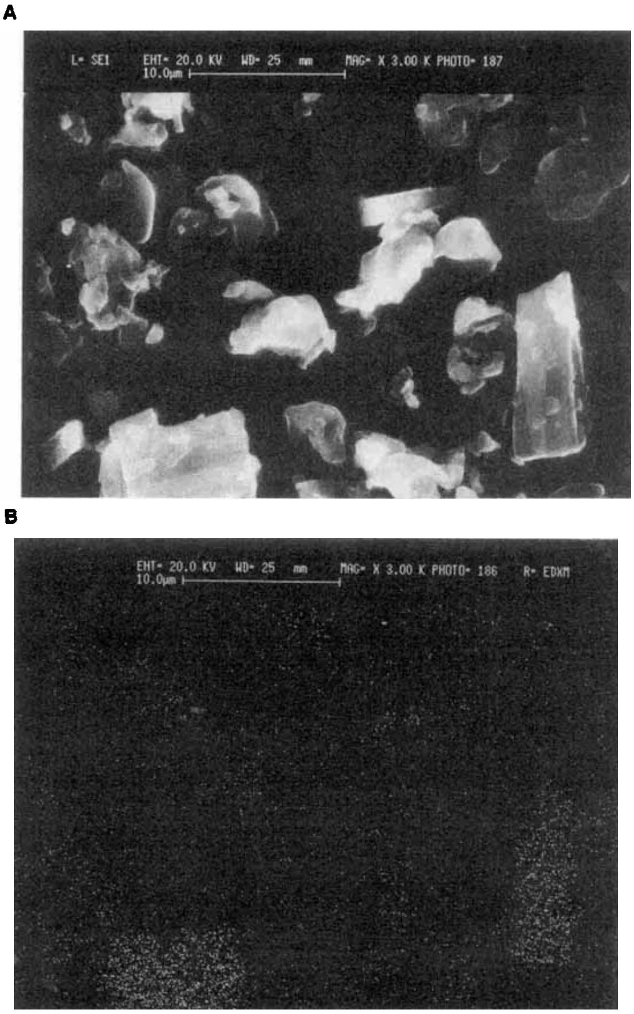

Figure 5—Scanning electron micrographs of a ground 1:1 amoxicillin trihydrate:HPMCAS sample. Magnifications are as in Figure 4.

Figures 4 and 5 show micrographs of 1:1 drug:HPMCAS mixtures prepared by physical mixing and grinding, respectively. Because of the presence of a sulfur atom only in amoxicillin trihydrate, EDA aids in the identification of drug particles in a mixture with the enteric polymer, as shown in Figures 4 and 5. The size, shape, and crystalline form of the antibiotic appeared to remain unchanged after physical mixing and grinding. These results are consistent with the results of dissolution testing not being attributable to an alteration in drug form. X-ray diffraction studies run at the highest drug peak ($2\theta = 15.1°$) confirmed by similar peak heights that there was no significant difference in the crystallinity of the drug after either physical mixing or grinding. Likewise, examination of the relevant transitional parameters obtained by DSC, after correction for the relative drug content, indicated that there was no loss of drug crystallinity with physical mixing or grinding.

Development of Dosage Forms Containing HPMCAS—HPMCAS was chosen as the enteric polymer for designing the controlled-release amoxicillin product because preliminary studies had shown its ability to retard drug release at the pH of the stomach after a fast while permitting progressively faster rates of dissolution under pH conditions simulating those of the small intestine. Pillow-shaped tablets containing 750 mg of amoxicillin as its equivalent trihydrate form in a 2:1 drug:HPMCAS ratio with 3% talc as a lubricant by weight of the ground mixture were prepared. Figure 6 shows the results of pH dissolution testing of the tablets. Although the gastric retention time of single nondisintegrating dosage units appeared to be erratic both after a meal and after a fast, it was reported that the average time was ~2 h.[26] However, by the time of the pH shift in the dissolution test (2 h), only 10% of the drug had been released from the tablets. After the shift in pH to 6.8, the rate of drug dissolution increased significantly. About 60% of the drug was released within 1 h from the time at which this pH change occurred. It was considered that this level of retardation at the pH of the resting stomach would produce an excessive lag period in vivo before effective serum drug levels would be attained. Accordingly, in an attempt to speed up the initial release, tablets containing 10:1 and 15:1 drug:HPMCAS ratios were also prepared; the results of dissolution testing of these tablets are also shown in Figure 6. As the proportion of HPMCAS in the formulation was decreased, the initial release at pH 2 in-

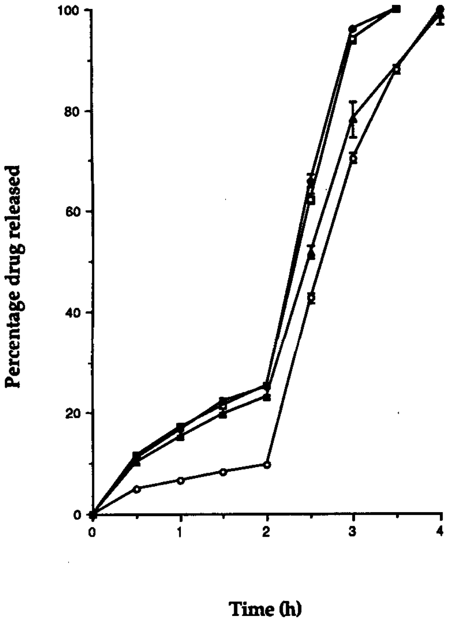

Figure 6—Percent drug release at 37 °C from tablets (21 × 10 mm) containing 750 mg of amoxicillin as its equivalent trihydrate form and 3% talc (by weight of the ground mixtures) for 2:1 (○), 10:1 (△), or 15:1 (□ and ◇) drug:HPMCAS mixtures without (□) or with (◇) the addition of 400 mg of DCL, determined by use of a pH shift from 2 to 6.8 at 2 h. Bars represent ±1 SEM.

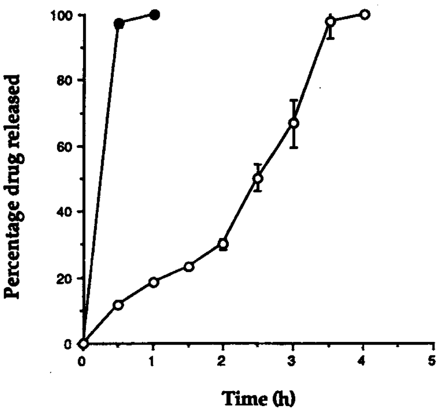

Figure 7—Percent drug release at 37 °C from conventional capsules (●) and the final tablet formulation (○), both containing 750 mg of amoxicillin as its equivalent trihydrate form, determined by use of a pH shift from 2 to 5.6 and 2 to 6.8 at 2 and 3 h, respectively. Bars represent ±1 SEM.

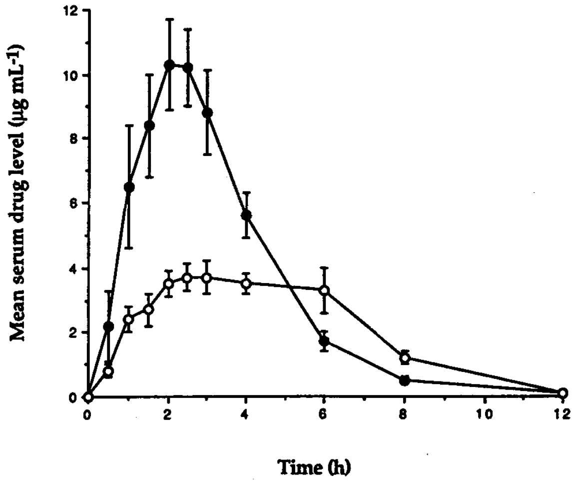

Figure 8—Mean serum amoxicillin levels in six subjects administered a single dose of conventional capsules (●) and the final tablet formulation (○), both containing 750 mg of amoxicillin as its equivalent trihydrate form. Bars represent ±1 SEM.

creased, but capping of the tablets became more evident, a result suggesting that the enteric polymer acted as a binder.[27] Capping was eliminated in tablets containing the 15:1 ratio by inclusion of 400 mg of DCL as a soluble filler. By improving hydration and reducing the tortuosity of the matrix, this inclusion further increased the initial release at pH 2 (Figure 6).

To further improve the formulation and reduce the bulk of the final tablets, we developed the following formulation: amoxicillin trihydrate, 861 mg; HPMCAS, 43 mg; DCL, 254 mg; talc, 35 mg; and magnesium stearate, 6 mg. The formulation had a 20:1 drug:HPMCAS ratio, was a ground mixture, and was prepared by an ethanolic granulation technique. In an attempt to better simulate dosage form passage along the gastrointestinal tract, we used a more elaborate pH shift dissolution technique that involved an initial 2 h at pH 2, 1 h at pH 5.6, and finally dissolution to 100% release at pH 6.8. Figure 7 shows the results obtained in comparison with those for an equivalent dose of conventional capsules. Obviously, the new product has an attractive controlled-release profile in vitro when compared with the quick-release conventional product.

In Vivo Studies—The mean serum drug profiles obtained after the administration of 750 mg of amoxicillin as either conventional capsules or the new controlled-release tablet formulation to a panel of six fasting subjects are shown in Figure 8. Pharmacokinetic parameters derived from the data are shown in Table III. No adverse reaction to either product was reported by any of the subjects. Five of the individual serum plots for the new product showed a biphasic profile, with double peaks occurring at variable times because of the enteric nature of the dosage form. Much intersubject variation in serum drug levels was observed, a result consistent with the conclusions of others, on the basis of a literature review of the technology.[28] The mean conventional capsule profile exhibited a maximum concentration in serum (C_{max}) of 10.3 μg/mL at 2 h; the profile for the new enteric product was smoother, with a plateau from 2–6 h and a C_{max} of 3.7 μg/mL at both 2.5 and 3 h. However, the mean relative bioavailability of the new product was only 64.4%, in comparison with the conventional product.

Also shown in Table III is a statistical evaluation of the pharmacokinetic parameters after parametric and nonparametric testing, for which significance was assessed at the 5% level. Using the paired t test and the Wilcoxon signed-ranks test, we found a significant difference between the conventional capsules and the enteric-matrix tablets for C_{max} and T_5 (see Table III). Values for $T_{0.1}$, $T_{2.5}$, and T_5 were derived, because susceptible gram-positive organisms are susceptible to very low concentrations of the antibiotic (0.1 μg/mL), whereas moderately susceptible gram-negative bacteria are susceptible to ~2.5–5 μg/mL. The paired t test alone showed the AUC_{0-24} and C_{max}/C_8 (see Table III) to be significantly different. Collectively, these results favor the conventional product.

Table III—Pharmacokinetic Parameters and Statistical Analysis of Data from a Human Trial[a]

Subject	C_{max}, µg/ml		T_{max}, h		AUC_{0-24}, µg · h/mL		C_{max}/C_8		$T_{0.1}$, h		$T_{2.5}$, h		T_5, h	
	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP	CP	NP
1	10.1	4.6	2.5	2.0	31.2	26.4	33.7	3.1	10.3	17.8	4.4	4.7	2.4	0.0
2	9.5	5.5	2.5	3.0	26.4	27.9	—	3.9	6.9	11.1	3.9	6.4	2.3	0.7
3	12.2	5.1	2.0	6.0	41.9	27.1	15.1	2.8	16.0	11.5	5.0	5.5	3.5	0.3
4	15.2	4.5	2.5	6.0	62.7	30.5	25.3	2.6	12.0	11.9	5.8	6.9	4.7	0.0
5	12.4	5.0	2.0	3.0	46.5	20.0	24.8	16.7	12.0	11.0	5.3	3.6	4.0	0.2
6	6.8	2.8	1.0	6.0	26.9	20.1	13.6	4.0	8.7	12.0	4.7	4.0	2.0	0.0
Mean	11.0	4.6	2.1	4.3	39.3	25.3	22.5	5.5	11.0	12.6	4.9	5.2	3.2	0.2
SEM	1.2	0.4	0.2	0.8	5.8	1.8	3.7	2.2	1.3	1.1	0.3	0.5	0.4	0.1
n	6	6	6	6	6	6	5	6	6	6	6	6	6	6
Paired *t* test ($p < 0.05$)	6.22 (Yes)		2.49 (No)		2.60 (Yes)		4.07 (Yes)		0.90 (No)		0.56 (No)		6.18 (Yes)	
Wilcoxon signed-ranks test ($p < 0.05$)	0 (Yes)		19.5 (No)		1 (No)		NA (NA)		13 (No)		13 (No)		0 (Yes)	

[a] T_{max}, time to maximum concentration in serum; AUC_{0-24}, area under the serum concentration–time curve from 0–24 h; C_8, concentration in serum at 8 h; $T_{0.1}$, $T_{2.5}$, and T_5, time at or above a concentration in serum of 0.1, 2.5, and 5 µg/mL, respectively; CP, conventional product (Amoxil 750-mg capsules); NP, new product (enteric-matrix 750-mg tablets); NA, nonapplicable statistical test because of inadequate sample size[32].

The pharmacokinetics of amoxicillin have been interpreted by a one-compartment model for oral administration,[29] and it has been claimed[30] that the slow absorption of drugs from controlled-release formulations generally precludes the description of resulting drug profiles by more complex models. Figure 9 shows the predicted mean levels in serum for both dosage forms after four doses given at 8-h intervals; these quickly reached a steady state because of the short half-life of amoxicillin.[31] From the data, it was calculated that the mean relative bioavailability of the new formulation would increase to 69.3% in the steady state, with increases in other pharmacokinetic parameters being likewise small.

Conclusions

Overall, the results of the in vivo studies of the new product compared with the conventional product were disappointing, despite promising in vitro data. Some potential reasons, particularly for the poorer bioavailability of the new product, may include (i) incomplete drug release within the time of small intestinal transit of the dosage form, (ii) inherently poorer absorption of amoxicillin from the distal jejunum and ileum than from the duodenum and proximal jejunum, (iii) drug inactivation before drug absorption by β-lactamases, and (iv) degradation of the drug after release by alkaline hydrolysis.

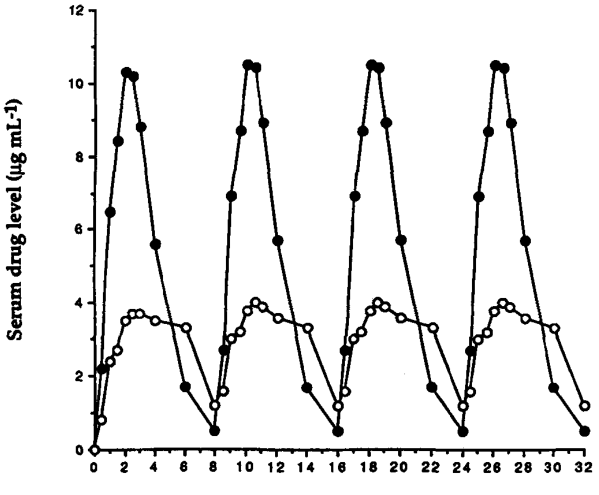

Figure 9—Superposition plot showing the predicted mean steady-state serum drug levels after administration of conventional capsules (●) and the final tablet formulation (○), both containing 750 mg of amoxicillin as its equivalent trihydrate form, at 8-h intervals.

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