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In vivo and in vitro evaluation of four different aqueous polymeric dispersions for producing an enteric coated tablet

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Abstract

The human in vivo single dose pharmacokinetics of a model tablet coated with four different aqueous enteric coat polymeric dispersions were assessed, using an uncoated tablet core as a control. In vitro release properties were also investigated. The four aqueous polymeric dispersions were cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), 50:50 CAP/CAT, and methacrylic acid copolymer. Naproxen sodium was the model drug. Polymer pH dissolution profiles showed that CAT dissolved at the most acidic pH, followed by 50:50 CAP/CAT, and then by CAP and methacrylic acid copolymer. It was found that all of the enteric coat formulations performed satisfactorily during initial in vitro disintegration and dissolution testing. Human in vivo testing showed that all of the enteric coat formulations were bioequivalent to the standard (uncoated) tablet with respect to AUC, half-life, and C_{max}. However, the CAP, 50:50 CAP/CAT, and methacrylic acid copolymer formulations had T_{max} values that were significantly longer than the uncoated tablet ($p < 0.001$), while the CAT formulation was statistically similar to the standard tablet ($p = 0.130$). Therefore, the CAT formulation may not have adequately protected the tablet in the upper gastrointestinal tract. After being stored for 9 months at room temperature, none of the enteric coat formulations studied passed USP disintegration testing.

Keywords: Enteric coat; Tablet; Aqueous dispersion; Dissolution; In vivo release; Oral administration; Pharmacokinetics

1. Introduction

Aqueous polymeric dispersions have recently come into use for enteric coating pharmaceutical solid dosage forms. These systems have numerous advantages over organic solvent solutions with respect to ecological, toxicological, and manufacturing safety concerns. However, a literature search did not reveal any clinical studies that examined aqueous enteric coat polymeric dispersions. Therefore, this study was designed to demonstrate clinically whether aqueous polymeric dispersions could confer satisfactory enteric coat properties upon tablets.

The objective of this study was to assess the human in vivo single dose pharmacokinetics of a

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model tablet coated with four different aqueous enteric coat polymeric dispersions, using a standard (uncoated) tablet core as a control. In vitro polymer film pH dissolution profiles were determined and compared to in vivo performance. In vitro tablet release properties were also investigated. The four aqueous polymeric dispersions were cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), 50:50 CAP/CAT, and methacrylic acid copolymer. Naproxen sodium was chosen as a model drug due to its rapid and complete absorption throughout the gastrointestinal tract.

The different release qualities of various enteric coatings can impact pharmacokinetic parameters (Lee et al., 1979; McLean et al., 1979; Kaniwa et al., 1985) by the coating either dissolving in the stomach (in which case the coating is not performing its intended task), or by it dissolving very late or not at all in the gastrointestinal tract (which can adversely impact plasma drug concentrations). Differences in pharmacokinetic parameters can affect a drug's efficacy and safety (Canada and Little, 1975; Brune, 1987; Tuominen et al., 1988). Therefore, it is important to understand the human in vivo release characteristics of the different aqueous polymeric dispersions.

2. Materials and methods

2.1. Materials

The 550 mg naproxen sodium tablet cores (Syntex) complied with the USP monograph. The same lot of tablet cores was used for all of the batches. The cellulose acetate phthalate (Eastman Chemical), methacrylic acid copolymer (Eudragit L™, Rhom Pharma), triethyl citrate (Morflex Chemical), poloxamer 407 (BASF Wyandotte), polyvinyl alcohol (Air Products), dibutyl phthalate (Eastman Chemical), diethyl phthalate (Eastman Chemical), strong ammonia solution (Mallinckrodt), and purified water (Syntex) were all USP/NF grade. The cellulose acetate trimellitate (Eastman Chemical) was noncompendial.

2.2. Coating

The CAP dispersion solution was manufactured by dispersing 8.71% w/w CAP in 56.65% w/w water and then adding 1.59% w/w strong ammonia solution, dispersing 2.44% w/w diethyl phthalate and 0.11% w/w polyvinyl alcohol in 30.5% w/w water, and mixing the two dispersions together. The CAT coating dispersion was produced by dispersing 8.69% w/w CAT in 55.85% w/w water and then adding 1.95% w/w strong ammonia solution, dispersing 2.43% w/w triethyl citrate and 1.00% w/w poloxamer 407 in 30.08% w/w water, and mixing the two dispersions together. The 50:50 CAP/CAT coating dispersion was made by dispersing 4.35% w/w CAP and 4.35% w/w CAT in 56.49% w/w water and then adding 1.81% w/w strong ammonia solution, dispersing 2.43% w/w triethyl citrate and 0.15% w/w polyvinyl alcohol in 30.42% w/w water, and mixing the two dispersions together. The methacrylic acid copolymer coating dispersion was manufactured by dispersing 14.62% w/w methacrylic acid copolymer in 52.27% w/w water and then adding 0.87% w/w strong ammonia solution, dispersing 2.93% w/w triethyl citrate and 1.17% w/w dibutyl phthalate in 28.14% w/w water, and mixing the two dispersions together. The tablets were coated using a Vector/Freund HCT 30 coating pan equipped with a HCA-1033-X spray system with a 1.5 mm liquid nozzle and a 3.0 mm air nozzle. Exhaust air temperature was maintained at 40–44°C. The tablets were coated to a $12.5 \pm 0.3\%$ weight gain.

2.3. Study subjects

20 healthy male and female volunteers between 22 and 51 years of age were enrolled and completed the study. No drugs, including over-the-counter medications, vitamins, and alcohol, were allowed 24 h prior to and throughout the study.

2.4. Study design and drug schedule

An open label, randomized, single dose, five-way crossover study design was employed. After

an overnight fast (10 h), each subject received a single oral dose of their assigned formulation with 200 ml of water. Subjects fasted until the 4 h blood sample had been collected. Serial blood samples were collected immediately prior to dosing and at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h post-dose for determination of naproxen plasma concentrations by HPLC. The plasma was separated immediately from each blood sample and frozen for subsequent assay of naproxen. There was a washout period of 1 week following each treatment.

2.5. Pharmacokinetic parameters

The parameters for naproxen that were analyzed using analysis of variance procedures were: (1) time to maximum plasma concentration (t_{max}); (2) plasma half-life ($t_{1/2}$) computed over the 24–72 h interval by log linear regression analysis of the plasma concentration vs time data; (3) peak plasma concentration (C_{max}); (4) area under the plasma concentration-time curve from 0 to 24 h (24 h AUC) computed using the linear trapezoidal rule; and (5) area under the plasma concentration-time curve from 0 to infinity (total AUC) computed using the linear trapezoidal rule to the last measurable concentration ($C_{p,last}$), then adding the term C_{last}/β, where β is the terminal decay rate constant.

The pharmacokinetic parameters were analyzed according to an analysis of variance model appropriate for a randomized block design (Winer, 1971). Statistical analyses were performed using the GLM procedure of the Statistical Analysis System, Version 5.16 (SAS) (Barr, 1979). The ANOVA model included terms for formulation and subject.

2.6. Polymer pH dissolution profiles

15% w/w solutions of the polymers were prepared in 95:5 acetone/water. Films were cast with a thickness of 40 mils and dried at room temperature for 16 h (which was to a constant weight). The films were then cut into pieces (3/4 × 1–1/4 inches) that would precisely fit into the USP dissolution basket apparatus, and weighed. Dissolution of the films was determined using USP XXI Apparatus 1, at a rate of rotation of 100 rpm for 1 h. 500 ml of a 37 ± 0.5°C citrate-phosphate buffer system was used as the dissolution medium. After dissolution testing at different pH values ranging from 4 to 7, the films were dried in a vacuum oven at 50°C and 27 kPa for 16 h (which was to constant weight), weighed, and the amount of film dissolved was calculated.

2.7. In vitro disintegration

Tablet disintegration was tested using the method detailed for enteric coated tablets in USP XXI.

2.8. In vitro dissolution

Dissolution of the enteric coated tablets was determined using USP XXI Apparatus 2, agitated at 50 rpm. 12 tablets were tested for each batch. Two dissolution media were used – 1000 ml of 0.1 N HCl for the first 2 h and 900 ml of 0.1 M phosphate buffer (pH 7.4) for a third hour. The replacement of the 0.1 N HCl medium with the phosphate buffer medium was carried out within 10 min of the 0.1 N HCl solution being sampled at 2 h. The amount of drug dissolved in each medium was determined, after filtering the sample through a 8.0 μm filter, by ultraviolet spectrophotometry at 272 nm. The same parameters were used for the dissolution test for the uncoated tablet, except that the 0.1 N HCl portion of the test was deleted.

3. Results and discussion

After manufacture, all of the aqueous dispersion enteric coated tablets readily passed the USP enteric coated tablet disintegration test. The initial in vitro dissolution profiles for the uncoated tablets and the CAP, CAT, 50:50 CAP/CAT, and methacrylic acid copolymer coated tablets are shown in Table 1. All of the aqueous dispersion enteric coats demonstrated excellent physical resistance to the acid medium, with the tablets being 0% dissolved after 2 h.

Table 1
Initial in vitro dissolution profiles [a] for the uncoated tablets and the CAP, CAT, 50:50 CAP/CAT, and methacrylic acid copolymer aqueous dispersion enteric coated tablets

	% dissolved ±S.D.		
	15 min	30 min	45 min
Uncoated tablets	76±4	100±4	102±1
CAP coated tablets	93±4	98±2	99±2
CAT coated tablets	64±7	98±4	99±4
50:50 CAP/CAT coated tablets	78±8	100±3	101±2
Methacrylic acid copolymer coated tablets	39±7	93±7	99±3

[a] Since all of the enteric coated tablets were 0% dissolved after 2 h in 0.1 N HCl, the data shown refer to tablet to dissolution after the tablets were transferred to the buffered dissolution medium.

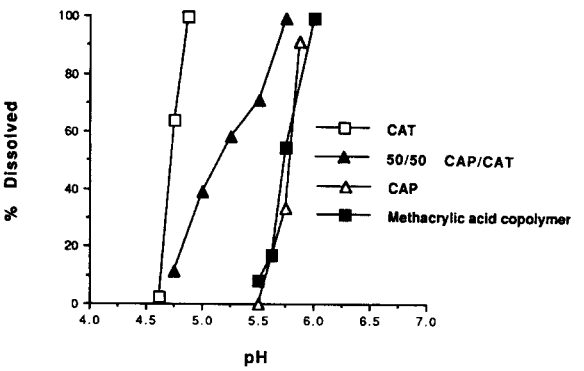

Fig. 1. Graph of the polymer pH dissolution profiles of CAT, 50:50 CAP/CAT, CAP, and methacrylic acid copolymer.

When the tablets were placed in the pH 7.4 phosphate buffer, the CAP coated tablets dissolved the fastest, being 93% dissolved after 15 min, while the methacrylic acid copolymer coated tablets dissolved the slowest, with 39% dissolved after 15 min. All of the tablets were completely dissolved at the 45 min time point, which is in compliance with the USP monograph for naproxen sodium tablets with respect to dissolution, since the monograph specifies a Q of 70% dissolved in 45 min. Therefore, the in vitro testing indicated that all of the enteric coat formulations were effective.

The dissolution of the enteric coat polymers at various pH values are shown in Fig. 1. The material that dissolved in the most acidic media is CAT. CAT dissolved at about pH 4.75. 50:50 CAP/CAT dissolved at about pH 5.25, whereas CAP and methacrylic acid copolymer dissolved around pH 5.75. Fig. 2 shows a time vs concentration plot for the mean plasma profiles of naproxen for the first 6 h following oral administration of

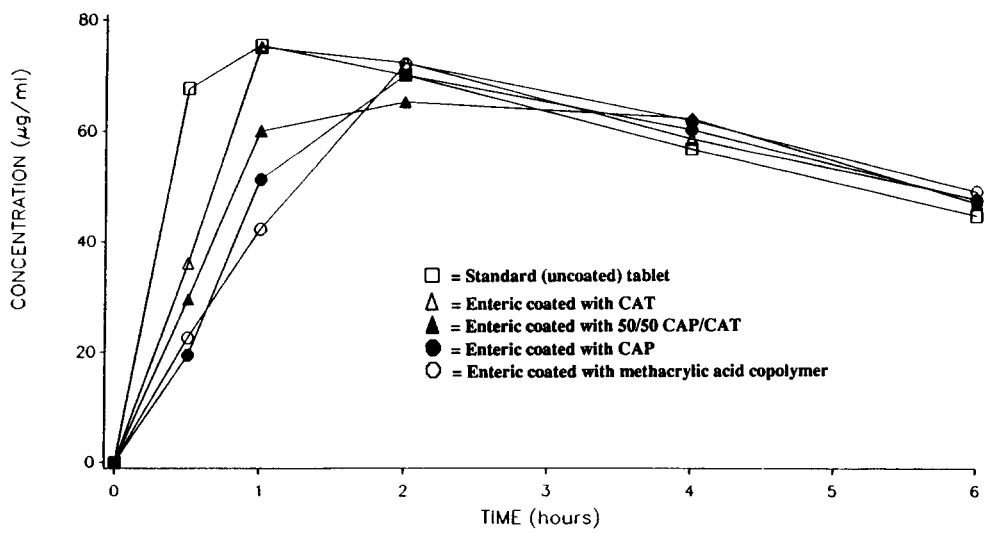

Fig. 2. Plot of mean drug plasma concentrations following dosing with tablets that have been enteric coated with aqueous dispersions of CAT, CAP, 50:50 CAP/CAT, or methacrylic acid copolymer, and a standard (uncoated) tablet.

Table 2
Computed mean human pharmacokinetic parameters (±S.D.) [a] for CAP, CAT, 50:50 CAP/CAT, and methacrylic acid copolymer aqueous dispersion enteric coated tablets

	CAP formula	CAT formula	50:50 CAP/CAT formula	Methacrylic acid copolymer formula	Uncoated tablet	P value [b] formulation
Half-life (h)	16.74 ± 2.76	16.59 ± 2.17	16.69 ± 2.31	16.73 ± 1.73	17.08 ± 2.05	0.772
T_{max} (h)	2.25 ± 1.12	1.52 ± 1.16	2.20 ± 1.28	2.60 ± 1.27	1.05 ± 0.46	< 0.001
C_{max} (μg/ml)	79.10 ± 13.47	83.47 ± 11.25	80.57 ± 11.41	76.43 ± 11.69	79.18 ± 11.80	0.155
24 h AUC (μg h ml^{-1})	832.3 ± 118.8	859.1 ± 100.6	836.9 ± 118.0	826.5 ± 120.8	846.5 ± 117.6	0.060
Total hour AUC (μg h ml^{-1})	1260.3 ± 213.5	1281.5 ± 199.9	1263.2 ± 221.0	1276.5 ± 241.5	1265.7 ± 228.3	0.890

[a] $n = 20$.
[b] The model included terms for formulation and subject.

the four enteric coated formulations and the uncoated tablet. When Fig. 1 is compared to Fig. 2, it can be seen that there is a correlation between the polymer pH dissolution profiles and the absorption profiles of the tablets that have been coated with the polymers. Specifically, the polymers that dissolved at the most acidic pH values exhibited faster drug absorption. This indicates that coating material that dissolves at a more acidic pH in vitro (such as CAT) will also dissolve at a more acidic pH in vivo, i.e., the coating will dissolve higher up in the gastrointestinal tract (CAT probably dissolves in the proximal small intestine). This correlation is in contrast to the in vitro disintegration and dissolution testing, where the CAT coating performed similarly to the other enteric coat formulations. Table 2 contains the computed human pharmacokinetic parameters. The plasma half-life of naproxen ranged between 16.6 and 17.1 h for all of the formulations, which were statistically similar ($p = 0.772$). The C_{max} and AUC values of the enteric coated tablet formulations were also bioequivalent to the uncoated tablet. The T_{max} was significantly ($p < 0.001$) longer for the CAP, 50:50 CAP/CAT, and methacrylic acid copolymer formulations (T_{max} was 2.3, 2.2, and 2.6 h, respectively) compared to the uncoated tablet (which had a T_{max} of 1.1 h). However, the T_{max} of the CAT formulation (1.5 h) was significantly faster ($p < 0.03$) than the other three enteric formulations, and was statistically similar ($p = 0.130$) to the uncoated tablet formulation. This suggests that the CAT formulation may not have effectively protected the tablet's

Table 3
In vitro dissolution profiles [a] for the uncoated tablets and the CAP, CAT, 50:50 CAP/CAT, and methacrylic acid copolymer aqueous dispersion enteric coated tablets, after storage at room temperature for 9 months

	% dissolved ±S.D.		
	15 min	30 min	45 min
Uncoated tablets [b]	76 ± 3	100 ± 1	100 ± 1
CAP coated tablets	all tablets disintegrated after 2 h in 0.1 N HCl		
CAT coated tablets	50 ± 10	91 ± 9	98 ± 4
50:50 CAP/CAT coated tablets	27 ± 20	87 ± 11	101 ± 1
Methacrylic acid copolymer coated tablets	50 ± 7	95 ± 6	100 ± 3

[a] Since all of the CAT, 50:50 CAP/CAT, and methacrylic acid copolymer enteric coated tablets were 0% dissolved after 2 h in 0.1 N HCl, the data shown refer to tablet dissolution after the tablets were transferred to the buffered dissolution medium.
[b] Tested after 14 months of storage.

integrity in the upper gastrointestinal tract. Therefore, in this case in vitro disintegration and dissolution testing did not discriminate between which aqueous enteric coat dispersions would perform satisfactorily in vivo, although the polymer pH dissolution profiles correctly indicated which polymer (CAT) would be most prone to failure.

The tablets were also stored for 9 months at room temperature in high-density polyethylene bottles with polypropylene caps. The aged tablets were then tested for disintegration and dissolution. The uncoated tablets exhibited similar behavior at the initial time point and the 9 month time point in terms of USP disintegration test results (they always disintegrated within 6–8 min) and dissolution test results (they were 76% dissolved at the 15 min time point), demonstrating the good physical stability of the tablet core. It was found that when the tablets underwent disintegration testing all four of the aqueous enteric coat dispersion formulations failed specifications, with all of the test tablets being bloated after 2 h in gastric fluid, although the integrity of the film coats remained intact. Table 3 shows that, when the aged tablets were tested for dissolution, the CAP coated tablets did not maintain their integrity in the 0.1 N HCl medium. Since naproxen sodium is a weak base, the inability of the CAP coated tablets to maintain their integrity during dissolution testing may be due to an interaction between the enteric coat and the drug, resulting in the premature dissolution of the coating. Upon aging, the 50:50 CAP/CAT coated tablets demonstrated a significant decrease in dissolution at the 15 min time point, but the later time points were largely unaffected. Aging did not markedly affect the dissolution characteristics of the CAT or methacrylic acid copolymer coated tablets. Therefore, when the in vivo data and the after storage in vitro dissolution data are considered together, the 50:50 CAP/CAT and the methacrylic acid copolymer coated tablets performed better than the CAT or CAP formulations. However, the 50:50 CAP/CAT and the methacrylic acid copolymer formulations require additional optimization in order to obtain satisfactory in vitro stability characteristics. This instability is probably due to an interaction between the drug (which is a weak base) and the enteric coat; future work will examine whether a nonenteric film subcoat (to physically separate the drug from the enteric coating) will produce a stable aqueous dispersion enteric coated product.

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