Pharmaceutical Research, Vol. 8, No. 6, 1991

Research Article

A Polymer Carrier System for Taste Masking of Macrolide Antibiotics

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Received September 7, 1990; accepted December 18, 1990

A polymer carrier system was developed to reduce the bitterness of erythromycin and its 6-*O*-methyl derivative, clarithromycin, by absorption to Carbopol. The mechanism involves ionic bonding of the amine macrolide to the high molecular weight polyacrylic acid, thereby removing the drug from the solution phase in an ion-free suspension. After ingestion, endogenous cations displace the drug from the polymer in the gastrointestinal tract to achieve bioavailability. The macrolide–Carbopol complexes were prepared by dissolving or slurrying predetermined ratios of drug and polymer in water or hydroalcoholic mixtures. A series of *in vitro* equilibrium studies, taste screening, and bioavailability studies in dogs established the characteristics for the various drug–polymer ratios. Taste protection was further improved by encapsulating the adsorbate particles with polymer coatings. Hydroxypropyl methylcellulose phthalate (HP-55) provided the best combination of suspension stability, taste protection and bioavailability. Human bioavailability studies demonstrated that the microencapsulated Carbopol absorbates of erythromycin and clarithromycin gave blood levels comparable to those obtained from conventional solid formulations.

KEY WORDS: macrolides; erythromycin; clarithromycin; taste coverage; Carbopol; hydroxypropyl methylcellulose phthalate.

INTRODUCTION

Erythromycin and its 6-*O*-methyl derivative, clarithromycin, are potent macrolide antibiotics (1,2) with clinical use predominantly in pediatrics, where liquid products are generally the preferred dosage form. Both erythromycin and clarithromycin have a very bitter taste, making the formulation of a palatable product difficult. Taste masking with sweeteners or established flavoring systems is inadequate. Insoluble prodrugs, such as the ethylsuccinate and proprionate esters, have been successfully used for erythromycin (3). However, prodrugs frequently possess pharmacokinetics different from those of the parent drug and, as new chemical entities, would require extensive independent evaluation. Conventional microencapsulation techniques, very useful in solid products, would not be as applicable for liquids, because of the need to limit dissolution in the formulation over 10–14 days while still achieving rapid dissolution once the drug is ingested.

The use of ion-exchange resin systems presents a useful alternative for palatable suspensions. Resin adsorbates have been used as drug carriers for controlled release liquid products (4). Further, such polymers were found useful in taste protection of bitter drugs (5). The resins form insoluble adsorbates or resinates through weak ionic bonding with oppositely charged drugs. The adsorbates thus maintain a low solution concentration of drug in a suspension free of soluble counterions. After ingestion and exposure to ions in the body, the resinate dissociates and drug is eluted to be absorbed.

A recent patent (6) described the properties of complexes or adsorbates formed between erythromycin or clarithromycin and Carbopol 934, a polyacrylic acid polymer, as a means to obtain taste protection. As with conventional ion-exchange resins, the Carbopol ionically binds the macrolide antibiotic, keeping almost all drug out of solution in an ion-free suspension:

$$CLAR^+ + R-COO^- \text{——} R\text{-}COO^-CLAR^+$$

Immediately after ingestion, ions in the body cause rapid dissolution and bioavailability:

$$R\text{-}COO^-CLAR^+ + H^+ \text{ or } Na^+ \text{——} CLAR^+ + R\text{-}COOH \text{ or } R\text{-}COO^-Na^+$$

Carbopol has advantages over conventional ion-exchange resins for this application. It readily swells, allowing rapid cation exchange; it dissolves in neutral buffers; and it has been reported to have bioadhesive properties (7). The taste protection provided by the absorption process was shown to be further improved with the use of polymer coatings. Hydroxypropyl methylcellulose phthalate (HP-55) appeared particularly suited for the system.

This paper describes our studies on the properties of the

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0724-8741/91/0600-0706$06.50/0

macrolide–Carbopol system. It includes studies related to formation of the polymer adsorbates, various polymer coating systems, *in vitro* dissolution testing, and results of several animal and human bioavailability studies.

MATERIALS AND METHODS

Materials

Erythromycin was USP grade. Clarithromycin, the 6-*O*-methyl derivative of erythromycin, was assayed as greater than 99% pure by HPLC. Carbopol 934 is a high molecular weight acrylic acid polymer with an equivalent weight of 76. Hydroxypropyl methylcellulose phthalate (HP-55) is insoluble in acid solutions but dissolves at pH levels above pH 5.5. All other chemicals were USP or reagent grade.

Preparation of Erythromycin/Carbopol (5:1)

One hundred grams of erythromycin was dissolved in 500 ml of ethanol and a slurry of 20 g of Carbopol 934 in 600 ml of ethanol was added slowly at room temperature. After stirring for 1 hr, the mixture was slowly added to 6 liters of water to crystallize the complex formed. The solids were separated by filtration, washed with 8 liters of water, and dried in an oven at 50°C. Percentage potency, defined as weight of erythromycin divided by weight of complex, was determined by dissolving a weighed amount of complex in pH 7.5 buffer and assaying the drug concentration by HPLC. Complexes based on different ratios were prepared by adjusting the weight of Carbopol used in the preparation.

Preparation of Clarithromycin/Carbopol (5:3)

Twelve grams each of clarithromycin and Carbopol 934 were mixed dry in a Hobart mixer. A solution of 8 g clarithromycin in 200 ml acetone was added slowly with stirring. The acetone was removed by air evaporation in a hood followed by vacuum drying at 50°C. The percentage potency, defined as weight of clarithromycin divided by weight of complex times 100, was determined by dissolving a weighed amount of complex in a pH 7.5 buffer and assaying the drug concentration by HPLC. Complexes based on different ratios were prepared by adjusting the weight of Carbopol used in the preparation.

Particle Coating

A laboratory-scale Glatt fluid-bed air-suspension coater was used for all coating applications. Initial particle loadings of approximately 300 g were used. When substantially less complex was available, the complex was mixed with 35 to 40-mesh nonpareil beads which could be easily separated from the coated complex by screening. A 10% solution of HP-55 or alternate coatings in ethanol or acetone–alcohol was applied by atomization. Castor oil (approximately 10%) was used as a plasticizer in the polymer coating.

Assay

An HPLC assay was used for all erythromycin and clarithromycin assays. Typical conditions used a Waters autosampler, Spectra-Physics 8800 ternary pump, Kratos 783 detector at 214 nm, Spectra-Physics 4270 integrator, and Regis "Little Champ" C18 column. The mobile phase was 0.05 *M* potassium phosphate buffer at pH 4.0:acetonitrile (60:40). The flow rate was 0.9 ml/min with an injection volume of 25 μl.

Dialysis Studies

Two milliliters of a solution containing 3.7 mg/ml erythromycin was placed in each of five test tubes. To two tubes 1.5 mg carbopol was slowly added to give a drug:carbopol weight ratio of approximately 5:1 (amine:carboxylic acid equivalent ratio of about 1:2). Three milligrams of carbopol was added to two of the other tubes to give a weight ratio of 5:2 and an equivalent ratio of 1:4. The fifth tube served as a control with no carbopol addition. The five solutions were transferred to dialysis tubing with a molecular weight cutoff of 3000, and the sealed tubing was placed in a flask with 2 ml deionized water. After overnight shaking at 25°C the erythromycin concentrations in the external solution were determined using HPLC.

UV Determination of HP-55 Coating Levels

A HP-8452 diode array spectrophotometer equipped with software for multiple component determinations was used for all spectra and computations. The coated particles were stirred in a beaker with pH 7.0 buffer. Samples were filtered at prescribed intervals, and the concentration of HP-55 was determined at 282 nm after subtracting the Carbopol absorption (the Carbopol concentration was determined at 320 nm, where HP-55 had no absorption).

In Vitro Dissolution Screening

Dissolution-Versus-pH Study (Fig. 3). Two hundred milligrams of complex was added to a series of test tubes containing 10 ml of preheated buffer (0.05 *M* in phosphate). The mixtures were rotated in a 37°C bath for 5 to 120 min using a different tube for each time. The mixture was filtered immediately after the prescribed time and the solution assayed by HPLC.

Dissolution of Drug at pH 7.0, 37°C. Weighed amounts of complex containing approximately 15 mg of erythromycin or clarithromycin were added to 15 ml of preheated pH 7.0 (0.05 *M*) phosphate buffer in a test tube. The mixture was rotated in a 37°C bath for 5 to 120 min and filtered immediately after the prescribed time and assayed by HPLC. Varying amounts (10–50 mg) of uncoated complex were tested to establish requirements for complete release. Similar procedures using different pH buffers (pH 3.0 to 8.0, all 0.05 *M* phosphate) were used to test the integrity of polymer coating and effect of pH on the coating.

Dissolution of HP-55 Coating and Drug at pH 7.0, Ambient. This method was designed to monitor early release as a simulated taste test. A weighed amount of coated particles containing approximately 15 mg drug was added to a test tube containing pH 7.0 (0.05 *M*) phosphate buffer. The mixture was agitated vigorously for 0.5 to 10 min using a vortex stirrer, and the solution was immediately filtered. The drug concentration was determined by HPLC. The HP-55 concentration was determined from the UV spectrum at 282 nm

after subtracting the concentration due to carbopol by comparison to a standard solution.

Preparation of Suspensions

Suspensions prepared for taste evaluation, stability, and bioavailability contained approximately 20–25 mg/ml drug (as complex), 600 mg/ml sucrose, and 3 mg/ml xanthan gum in an aqueous system with or without flavors.

Taste Testing

Bitterness was quantitated by consensus of a trained taste panel. Five milliliters of suspension containing coated or uncoated complex was held in the mouth for 5–10 sec, then spat out, and the bitterness level recorded. A numerical scale was used with the following values: 0 = tasteless, 0.5 = very slight, 1 = slight, 1.5 = slight to moderate, 2 = moderate, 2.5 = moderate to strong, 3 = strong, and 3+ = very strong.

Bioavailability of Clarithromycin in Dogs

The effect of drug:Carbopol ratio was determined by a parallel bioavailability study, using groups of three beagle dogs (9–11 kg) for each formulation. All dogs were fasted overnight, and histamine was administered 1 hr prior to dosing to stimulate gastric acid secretion and low stomach pH. A quantity of the test formulation containing 250 mg of clarithromycin was administered to each dog. Blood samples were withdrawn at prescribed intervals, and serum assays were performed by standard microbiological methods. All dogs were fed 12 hr after dosing.

A three-way complete crossover study using nine dogs was run to assess bioavailability from suspensions made using coated and uncoated clarithromycin–Carbopol complex. A 100-mg capsule containing unformulated drug was used as a control. All dogs were fasted overnight, and histamine was administered 1 hr prior to dosing to stimulate gastric acid secretion and low stomach pH. A 100-mg dose of the test formulation (100 mg/ml of clarithromycin) or capsule control was administered to each dog. Blood samples were obtained periodically for 8 hr, and serum assays were performed by standard microbiological methods. All dogs were fed 12 hr after dosing. Each study was separated by a 1-week washout period.

Bioavailability of Erythromycin in Humans

A three-way complete-crossover single-dose study was run to compare the bioavailability of both coated and uncoated erythromycin/Carbopol in suspensions to a marketed erythromycin base formulation. The study involved 24 healthy volunteers who were fasted overnight before dosing with 250 mg erythromycin. The formulations used were (i) a suspension containing 250 mg erythromycin/5 ml as the uncoated complex, (ii) a suspension containing 250 mg/5 ml as a HP-55-coated (20%) complex, and (iii) a commercial particle-coated erythromycin base capsule (Eryc) containing 250 mg in two capsules. Blood samples were collected periodically for 10 hr after the dose was administered and the serum was assayed for erythromycin using a standard microbiological assay.

Bioavailability of Clarithromycin in Humans

A suspension containing coated clarithromycin–Carbopol (41% HP-55) was evaluated as part of two four-way complete-crossover single-dose studies using healthy human volunteers. A thoroughly tested ovaloid, film-coated 250-mg clarithromycin tablet (mean dissolution, 98.2% after 20 min; SD, 2.8%; using pH 5.0, 50 RPM, USP method 2) was used as the control. In addition to the tablet, two other experimental clarithromycin suspensions were included. The study was conducted using two separate regimens. One utilized a fasting regimen (16 subjects) and the other a nonfasting regimen (13 subjects). The coated clarithromycin–Carbopol was given as a suspension containing 250 mg/10 ml. Blood samples were collected periodically for 14 hr after the dose was administered, and the serum was assayed for clarithromycin using a standard microbiological assay.

RESULTS AND DISCUSSION

Erythromycin/Carbopol Complex Formation

Since erythromycin degradation is acid catalyzed, the complex formation involved adding the Carbopol to the basic erythromycin in ethanol solution. This prevented formation of an acid environment. Large volumes of water were required to recover the insoluble Carbopol complex. Distillation was used to reduce the ethanol after water dilution to maximize recovery. An alternative procedure was also used to prepare the erythromycin–Carbopol complex without ethanol, through slow addition of Carbopol to a water slurry of erythromycin. The latter procedure is more suitable in a production setting.

Based on stoichiometry, 1 g of carbopol can theoretically bind approximately 10 g of macrolide. Therefore a series of mixtures varying from equal weights to a 10:1 ratio of erythromycin:carbopol was prepared and evaluated. At the 10:1 ratio, where all the carboxylic acid sites on the Carbopol are required for ionic bonding, taste was still quite bitter. Apparently physical restraints may limit the extent of binding. At the 5:1 ratio, using about half the anionic sites, substantial bitterness reduction was obtained (slight to moderate on the taste panel scale). With decreasing percentage of erythromycin, the pH of the water slurry decreased, so that below 60% the pH was too low to sustain erythromycin stability.

The binding of erythromycin to carbopol was demonstrated through both dialysis studies and solubility effects. The following concentrations in the external water phase were obtained in a comparable dialysis test using a donor

Table I. Solubility of Erythromycin (Ery) from Carbopol (Carb) Complex

Composition	Ery:Carb ratio	Assayed potency	pH	Solubility (mg/ml)
Erythromycin	5:0	100%	8.24	2.12
Erythromycin	5:0	100%	7.72	12.22
Complex	5:1	82.3	7.94	0.66
Complex	5:2	69.7	7.00	0.11
Complex	5:3	61.3	6.75	0.08

Table II. Solubility of Clarithromycin (Clari) from Carbopol (Carb) Complex

Composition	Clari:Carb ratio	Assayed potency	pH	Solubility (mg/ml)
Clarithromycin	5:0	100%	7.98	0.134
Clarithromycin	5:0	100%	7.00	1.65
Clarithromycin	5:0	100%	6.20	7.00
Complex	5:1	78.1	6.69	0.051
Complex	5:2	69.8	6.94	0.022
Complex	5:3	61.5	6.56	0.010

Table III. Erythromycin Elution from Carbopol Complex by Na^+ and H^+

Erythromycin (mEq)	HCl (mEq)	NaCl (mEq)	pH	% drug dissolved	Complexed/sol ratio
0.76	0	0	6.84	7.72	12.0
0.76	0.40		5.93	43.5	1.30
0.76	0.80		4.88	89.3	0.12
0.76	1.20		3.63	99.1	0.01
0.76		0.40	6.84	10.2	8.8
0.76		0.80	6.69	15.2	5.6
0.76		1.2	6.58	21.4	3.7

concentration of 3.7 mg/ml and a 3000 molecular weight cutoff: erythromycin solution, 1.56 mg/ml; 5:1 ratio of erythromycin:carbopol, 0.51 and 0.42 mg/ml; and 5:2 ratio, 0.11 and 0.08 mg/ml. Table I shows the equilibrium solubility of erythromycin as a function of drug:Carbopol ratio in the complex. Since erythromycin solubility increases with decreasing pH (pK_a = 8.8), the lower solubility can be attributed to binding onto the insoluble complex. The assayed potencies were close to the theoretical values, indicating both little loss in preparation and complete elution from the complex.

Preliminary taste testing of the various ratios did not reveal a clear cut difference. Therefore the 5:1 drug:Carbopol complex, which minimized the percentage polymer and degradation potential, was selected for further evaluation.

Clarithromycin/Carbopol Complex Formation

Clarithromycin is considerably more acid stable than erythromycin, although degradation was still of concern in preparing the complex. Since clarithromycin was less soluble than erythromycin in water-miscible organic solvents, a slurry procedure was generally used to prepare the complex mixtures. The drug was slurried in acetone or alcohol mixtures with the polymer, the solvent was allowed to evaporate, and the wet solids were dried in an oven.

As with erythromycin, a series of complexes using various drug:polymer ratios was prepared. The equal weight ratio did not have the physical characteristics desired and was not considered further. Table II compares the solubilities of the clarithromycin–Carbopol complexes to pure drug at comparable pH levels. The studies showed a rank-order decrease in drug solubility with increasing Carbopol when 5:3, 5:2, and 5:1 ratios were compared. The assayed potencies were likewise close to the theoretical values, indicating both little loss in preparation and complete elution from the complex.

A bioavailability study in dogs comparing the three ratios, shown in Fig. 1, showed little difference in bioavailability, reflected by the area under the curve values. Bitterness testing correlated well with the solubility studies, with the following initial taste scale values: 5:1 ratio, 2.0 (moderate); 5:2 ratio, 1.5 (slight to moderate); and 5:3 ratio, 0 (none). We therefore concentrated on the 5:3 weight ratio of clarithromycin:Carbopol for further evaluation.

Dissolution Properties

Dissolution of drug from the Carbopol complexes may be considered an equilibrium phenomenon where counterions displace the erythromycin or clarithromycin from the carboxylic acid sites of the polymer. Table III emphasizes the effect of hydrogen ion (from hydrochloric acid) and sodium ion (from sodium chloride) on erythromycin—Carbopol complex. Both show an increase in drug dissolution with counterion concentration. However, the proton effect is much greater. This may be attributed to the pK_a of the carboxylic acid polymer, which results in the most sites being undissociated at the low pH levels induced by the HCl. The reduced ionic character may translate to rapid elution in the stomach.

A more extensive evaluation of pH effect on elution is illustrated in Fig. 2, which shows dissolution properties of clarithromycin from uncoated complex as a function of both pH and time. At low pH levels dissolution of drug is rapid

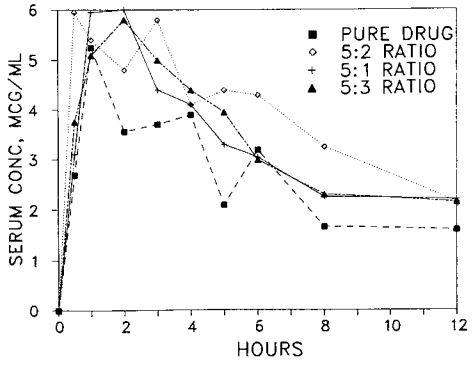

Fig. 1. Bioavailability of clarithromycin in dogs from Carbopol complexes with different drug:polymer ratios and uncomplexed drug.

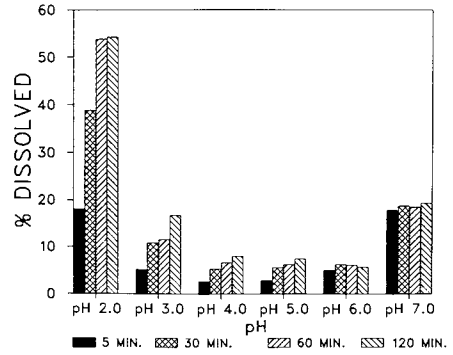

Fig. 2. Dissolution of clarithromycin from Carbopol complex as a function of pH and time.

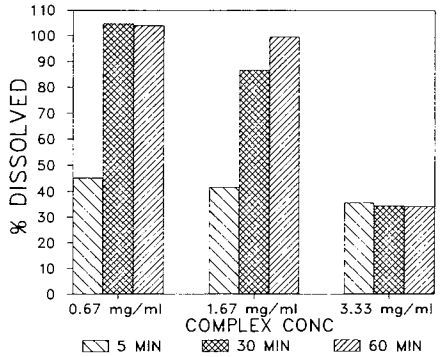

Fig. 3. Dissolution of clarithromycin from Carbopol complex using various volumes of pH 7.0 buffer.

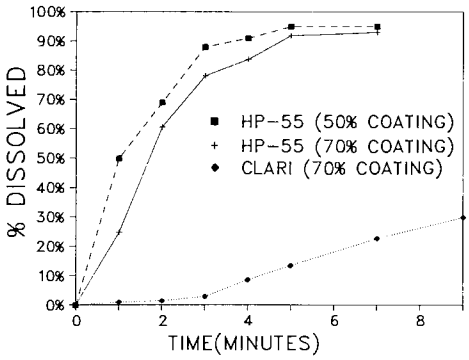

Fig. 5. Dissolution of HP-55 and clarithromycin from coated Carbopol complex (coated with 50 and 70% HP-55) in pH 7.0 buffer.

and complete, promoted by high clarithromycin solubility and the Carbopol equilibrium lying primarily toward undissociated carboxylic acids. Significant drug degradation was encountered at pH 2.0, so that the percentages shown actually underestimate the percentages actually released. At intermediate pH levels (pH 4–pH 6) the equilibrium is not as strongly shifted toward drug elution, and counterion concentrations are inadequate to displace all the drug from the insoluble Carbopol. Above pH 7.0 dissolution increases, although with the concentrations of 20 mg complex/ml buffer used in this study complete release could not be achieved.

Figure 3 demonstrates the buffer conditions needed to provide sink conditions for dissolution testings. With a sufficient drug:buffer ratio, essentially complete drug release can be achieved rapidly. However, with insufficient volume the clarithromycin solubility limits complete dissolution. At 0.67 and 1.67 mg/ml clarithromycin, close to half the drug dissolved in 5 min and greater than 85% dissolved in 30 min. At 3.33 mg/ml dissolution ceased after about 35% release in 5 min. The results are consistent with the belief that low drug concentrations should be maintained in the solution phase of a suspension as long as the cation concentration is minimized. Likewise, very rapid dissolution should occur in the body, especially above pH 7 (intestine). However, the fast pH 7 dissolution translates into bitterness problems if the particles are not cleared from the mouth rapidly.

Polymer-Coated Particles

Although the erythromycin and clarithromycin–Carbopol complex provided considerable improvement in taste through reduced solubility, a bitter aftertaste was still present. Coating of the particles with polymers provided additional taste protection by delaying dissolution and extending the time for clearing the particles from the mouth. Extensive studies were carried out to select the best polymer coating. A particle size range of 40–80 mesh was selected as best for both the coating operation and palatability. Larger particles impart too much grittiness to the suspension, while excess smaller particles caused problems in the coating procedure. The desired range was prepared by separating the 40- to 80-mesh particles with screens.

Several polymers applied as coatings gave improved taste protection. However, hydroxypropyl methylcellulose phthalate (HP-55), a polymer which is insoluble below pH 5.5 or in the absence of cations appeared to offer the best potential in terms of both taste protection and bioavailability. Castor oil was included in the coating solution as a plasticizer. To determine the optimum amount of polymer to apply, a series of coated clarithromycin–Carbopol particles was prepared by application of 20–70% HP-55. Figure 4 shows release rates of clarithromycin from the coated particles using pH 3.0 and pH 7.0 buffers. The low percentages dissolves after 1 hr at pH 3.0 (less than 0.2% with coatings above 30%) illustrate the effectiveness of the HP-55 coating. Without this acid-insoluble coating encapsulating the particles, a substantial percentage of clarithromycin would be released. At pH 7.0 the release is much faster but still dependent on the coating level.

While the coating remains intact at low pH and in cat-

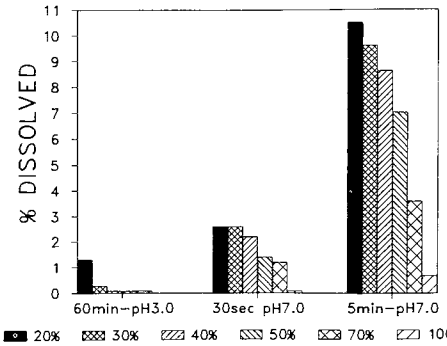

Fig. 4. Release rate of clarithromycin from Carbopol complex with various coating levels in pH 3.0 and pH 7.0 buffers.

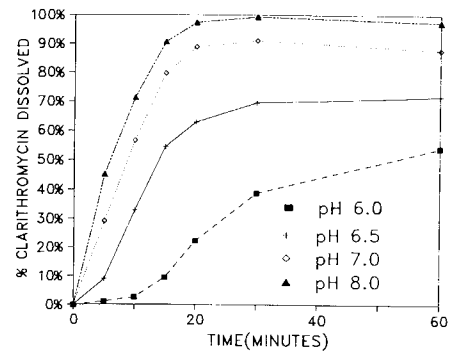

Fig. 6. Release rate of clarithromycin from coated Carbopol complex in various pH buffers.

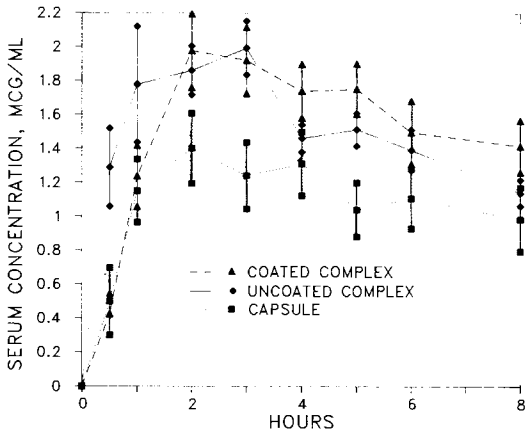

Fig. 7. Bioavailability of clarithromycin (mean ± SE) in dogs from two suspensions (100 mg/5 ml) of coated and uncoated Carbopol complexes and 100 mg capsule of unformulated drug.

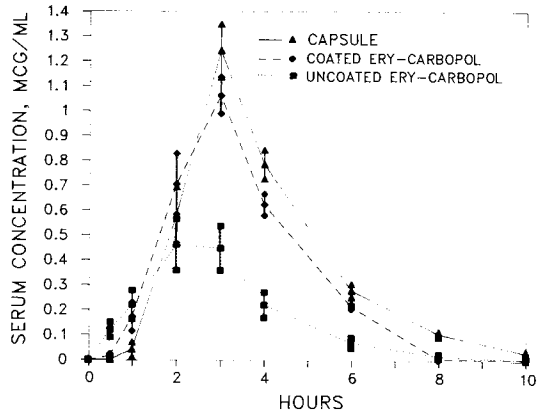

Fig. 8. Bioavailability of erythromycin (mean ± SE) in human from two suspensions (250 mg/10 ml) of coated and uncoated Carbopol complexes and a commercial formulation of coated erythromycin-base particle capsule (250 mg in two capsules).

ion-free water, rapid dissolution occurs above pH 7.0. This is illustrated in Fig. 5, which shows nearly quantitative coating dissolution in 3 min for a 50% HP-55 application and 5 min for 70% HP-55. Both the dissolution rate and the actual percentage of coating polymer were determined by UV spectral assays at 282 nm. Dissolution of clarithromycin at pH 7.0 follows the coating dissolution at a comparatively slower rate. Figure 6 illustrates the rapid dissolution rate as the pH increases above pH 6.0. This occurs from both dissolution of the HP-55 coating and swelling of Carbopol. The latter effect probably results in faster dissolution of clarithromycin from the complex than could be achieved with crystalline drug and should translate to rapid absorption in the intestine. Thus, the pH-dissolution properties obtained with the HP-55-coated clarithromycin/Carbopol complex *in vitro* studies appear nearly ideal for good bioavailability.

The rapid pH 7.0 dissolution, so advantageous for bioavailability, can have an adverse effect on taste. Figure 4 shows results from a pH 7.0 release test designed to simulate mouth availability. Some drug is released after 30 sec. However, the greater the coating, the less drug released. Taste screening studies confirmed that bitterness protection improved with increased coating level.

Incorporation into Suspension

Maintaining palatability in a suspension requires minimizing the cation concentration. Soluble cations can displace drug from the Carbopol as well as dissolve the HP-55 coating polymer if present. In pharmaceutical practice the use of dry blends which allow preparation of suspensions at the time of dispensing would minimize disruption of the complex. Only a small percentage of the drug enters the solution phase of a suspension. A high sucrose concentration reduces the drug level even more, in addition to providing sweetness and suspendablility. Assays of the filtrate from a 25 mg/ml clarithromycin suspension formulated using coated complex showed 26 μg/ml (0.10%) in solution after 2 weeks refrigeration and 45 μg/ml (0.18%) after 2 weeks at ambient temperature. *In vitro* dissolution tests in 0.1 *N* HCl and pH 6.8 phosphate buffer showed no rate changes over a 2-week period. When clarithromycin suspension was tested by a flavor panel, no meaningful changes in bitterness were observed over a 4-week period.

Table IV. Bioavailability of Clarithromycin in Dogs from Suspensions of Carbopol Complex and Drug Capsules: Three-Way Crossover, 100 mg/Dog

Formulation	Mean (SD)		
	T_{max} (hr)	C_{max}* (μg/ml)	AUC* (μg/ml × hr)
Uncoated complex in suspension	2.0 (0.9)	2.27 (0.58)	12.04 (2.86)
Coated complex (20%) in suspension	2.8 (0.8)	2.19 (0.61)	12.19 (3.40)
Capsule of pure drug	3.0 (1.6)	1.51 (0.65)	8.76 (3.81)

* No significant difference between coated and uncoated complex: both significantly higher than capsule (P = 0.05).

Bioavailability of Clarithromycin in Dogs

A three-way complete-crossover study using nine dogs after overnight fasting was run to assess bioavailability from two suspensions (100 mg/5-ml doses) made using coated and uncoated clarithromycin–Carbopol complex. A 100-mg capsule containing unformulated drug was used as a control.

Table V. Bioavailability of Erythromycin in Humans from Suspensions of Carbopol Complex and Particle-Coated Drug in Capsules: Three-Way Crossover, 24 Subjects, Fasting Regimen, 250-mg Doses

Formulation	Mean (SD)		
	T_{max} (hr)	C_{max}* (μg/ml)	AUC* (μg/ml × hr)
Uncoated complex in suspension	2.3 (0.6)	0.53 (0.49)	1.64 (1.76)
Coated complex (20%) in suspension	2.6 (0.5)	1.19 (0.41)	3.41 (1.27)
Coated drug in capsule	2.9 (0.5)	1.34 (0.49)	3.83 (1.35)

* No significant difference between coated complex and capsule: both significantly higher than uncoated complex (P = 0.05).

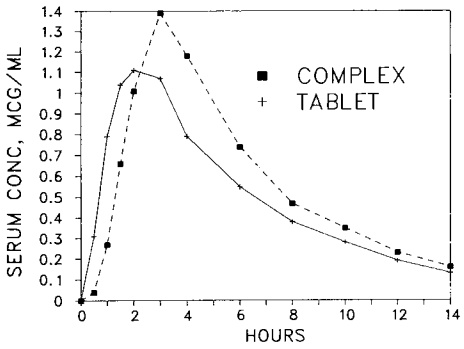

Fig. 9. Bioavailability of clarithromycin in human from a suspension of coated Carbopol complexes (250 mg/10 ml) and a conventional tablet (250 mg) using fasting regimens.

The curves are shown in Fig. 7 and the pharmacokinetic parameters are listed in Table IV. Except for an initial delay as reflected by the T_{max}, very similar bioavailability results were obtained from uncoated and HP-55-coated (20%) clarithromycin/carbopol complex. Both gave significantly higher AUC and C_{max} values than the capsule.

Bioavailability of Erythromycin in Humans

A three-way complete-crossover single-dose study using 24 human volunteers was run to compare the bioavailability of both coated and uncoated erythromycin/Carbopol given as suspensions of erythromycin base. The formulations used were a suspension containing 250 mg erythromycin/5 ml as the uncoated complex, a second suspension containing 250 mg/5 ml as a HP-55-coated (20%) complex, and a commercial particle-coated erythromycin base capsule (Eryc) containing 250 mg in two capsules. The serum level curves are shown in Fig. 8 and the results are summarized in Table V. Statistical analysis showed no significant difference in bioavailability between the coated erythromycin–Carbopol suspension and the commercial erythromycin-base capsules. However, both gave significantly higher levels than the uncoated complex. In this case, the enteric coating appeared necessary to protect erythromycin from gastric acid degradation.

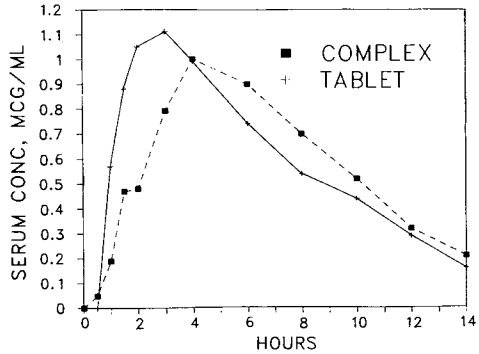

Fig. 10. Bioavailability of clarithromycin in human from a suspension of coated Carbopol complexes (250 mg/10 ml) and a conventional tablet (250 mg) using nonfasting regimens.

Table VI. Bioavailability of Clarithromycin in Humans from Suspensions of Carbopol Complex and Drug Tablets, from Two Four-Way Crossover Studies Using Both Fasting and Nonfasting Regimens

		Mean (SD)		
Formulation	Regimen	T_{max} (hr)	C_{max}* (μg/ml)	AUC* (μg/ml × hr)
Coated complex	Fasted	2.9 (0.6)	1.46 (0.27)	8.16 (1.90)
250-mg tablet	Fasted	2.3 (0.8)*	1.27 (0.42)*	7.30 (1.94)*
Coated complex	Nonfasted	4.8 (1.6)	1.17 (0.22)	8.10 (1.36)
250-mg tablet	Nonfasted	3.3 (1.8)*	1.35 (0.45)*	8.42 (2.43)*

* Significant difference from coated complex value (above), at $P = 0.05$.

Bioavailability of Clarithromycin in Humans

A suspension containing coated clarithromycin–Carbopol (41% HP-55) was evaluated as part of two four-way complete-crossover single-dose studies using healthy human volunteers. One study utilized a fasting regimen (16 subjects) and the other a nonfasting regimen (13 subjects). The serum level curves for the fasting and nonfasting regimens are shown in Figs. 9 and 10, respectively, while the primary bioavailability values are listed in Table VI. With the fasting regimen the HP-55-coated Carbopol complex showed a delay compared to the tablet (T_{max}, 2.9 vs 2.3 hr). However, it gave a 14% higher C_{max} and 12% higher AUC mean than the tablet. In the nonfasting study the coated complex gave a 5% lower AUC (nonsignificant) and a 16% lower C_{max} than the tablet along with the T_{max} delay.

ACKNOWLEDGMENTS

The authors wish to thank Drs. Sou-yie Chu and Alex Chun for their inputs in the design and interpretation of the bioavailability studies and Mrs. Nancy Ramer for the microbiological assays.

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