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 macroide to the high molecular weight polycrylic 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 macroide–Carbopol complexes were prepared by dissolving or slurryng 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 macroide 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 proprio 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 resin form insoluble adsorbates or resinate through weak ionic bonding with oppositely charged drugs. The adsorbate 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 polycrylic acid polymer, as a means to obtain taste protection. As with conventional ion-exchange resins, the Carbopol ionically binds the macroide antibiotic, keeping almost all drug out of solution in an ion-free suspension:

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

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

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

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
macrolide–Carbopol system. It includes studies related to the 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.