DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(4), 385-394 (1992)

SPRAY-DRIED ENTERIC SOLID DISPERSION AS A NOVEL ORAL DELIVERY SYSTEM FOR A PENTAPEPTIDE ANALOG OF THYMOPENTIN

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ABSTRACT

IRI-426 (Ac-Arg-Pro-Asp-Val-Phe-NH_2) is a biologically active and enzyme-resistant analog of thymopentin (Arg-Lys-Asp-Val-Tyr), a pentapeptide corresponding to an active site of the thymic hormone thymopoietin. Enteric formulation of this enzyme resistant pentapeptide could be valuable for oral administration by providing protection from acid proteolysis in the gastric juice and release and absorption in the duodenum. Using a drug-to-polymer ratio of 1 to 10, an enteric solid dispersion of IRI-426 was prepared with an acid-insoluble, pH-sensitive polymer Eudragit S-100, by the spray-drying technique. The USP rotating paddle method

and 190 proof ethyl alcohol, USP were used as received. All solvents used in the analytical procedure were of HPLC grade.

Analytical Procedure

A Waters isocratic, reverse-phase HPLC system (Millipore Corp., Milford, MA) comprising a 610E Pump, 600E Powerline Controller, 712D Wisp, 484 UV/VIS detector set at 220 nm, and 745B Integrator was used. The mobile phase consisted of a binary mixture of 0.05 M aqueous potassium dihydrogen phosphate solution and acetonitrile in the ratio of 82 to 18 v/v. Analyses were performed at ambient temperature on a 4.6 mm x 15 cm Spherisorb column (Phase Separation Inc., Norwalk, CT) containing 3-micron octadecylsilane bond packing material (S3 ODS 2), using a flow rate of 1 ml/min.

Spray-Dried Enteric Solid Dispersion Powder

A laboratory bench top model GA-31 spray-dryer (Yamato USA, Inc., Northbrook, IL), with a 0.4 mm diameter standard spray nozzle orifice, was used. A drug-to-polymer ratio of 1 to 10 was used in the preparation of a 10% w/v solution of the drug/polymer mixture in 190 proof ethyl alcohol, for spray-drying. The feed solution was pumped at the rate of 2 ml/min, and sprayed in the drying chamber at a pressure of 2 bar. The inlet and outlet air temperatures were 50-55 and 30-40°C, respectively; and the flow rate of the drying air was maintained at the aspirator setting of 7.

Preparation of Pellet-Filled Capsules

A 50/50 blend of spray-dried enteric solid dispersion powder and Avicel PH-102 was directly compressed into 1/2 inch round flat-faced slugs on a Carver laboratory press (Fred S. Carver, Inc., Menomonee Falls, WI) at 2 ton pressure. The compressed slugs were reduced to dry granules by milling through a TG 2S Dry Granulator (Erweka Instruments, Inc., Milford, CT). The dry granulation was screened through standard sieves, and a 16/18 mesh fraction collected for filling into No. 1 Clear Posilok hard gelatin capsules (Elanco Qualicaps, Indianapolis, IN), on a Minicap capsule filler (Scientific Instruments and Technology Corp., Piscataway, NJ).

Enteric Coating of Powder-Filled Capsules

Using the Minicap capsule filler, a 50/50 blend of spray-dried enteric solid dispersion powder and Avicel PH-102 was filled into No. 1 Clear Posilok hard gelatin capsules. The filled hard gelatin capsules were then enteric coated by immersing in a 30% alcohol solution of polyvinyl acetate phthalate (Opaseal), and air-drying at ambient temperature. The immersion and air-drying process for enteric coating the hard gelatin capsules was repeated twice.

In Vitro Drug Release

Release profiles were generated on a Vanderkamp 600 Dissolution Tester (VanKel Industries, Inc., Edison, NJ) as per the USP rotating paddle

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method (apparatus II). Each formulation was tested in triplicate, using 900 mL of the corresponding dissolution medium containing 0.1% Tween 80, at 37°C and 50 RPM. In order to prevent hard gelatin capsules from floating, stainless steel springs were used to hold capsules at the bottom. At predetermined time intervals, 3 mL aliquots of the dissolution medium were aspirated, filtered through 0.45 micron, low protein binding, acrodisc membrane (Gelman Sciences, Ann Arbor, MI), and analyzed by the HPLC technique. Each aliquot withdrawn was immediately replaced with an equal volume of fresh dissolution medium previously equilibrated to 37°C.

RESULTS AND DISCUSSION

One rate limiting step for the bioavailability of a drug product is the dissolution of the drug itself. The faster and more complete the dissolution, the more bioavailable the drug product becomes. The principle site for drug absorption usually resides in the small intestine. In order to protect peptide drugs from degradation in the stomach, acid-insoluble, pH-sensitive polymers with ionizable groups can be used to delay the onset of drug release and target drug delivery to the upper small intestine for absorption where pH is 6 or above.

A number of pH-sensitive polymers including cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxpropyl methylcellulose phthalate, and methacrylic acid/methyl methacrylate copolymer were screened for their amenability to form "enteric solid dispersions" by spray-drying technique.

The methacrylic acid/methyl methacrylate copolymer Eudragit S-100 alone showed promise as a potential candidate for further investigation.

Preliminary dissolution studies in 0.1N HC1 (pH 1.2) and Sorensen phosphate buffer (pH 7) indicated that the drug-to-polymer ratio of 1 to 10 was more effective than that of 1 to 5 in retarding release at pH 1.2 without adversely affecting release at pH 7. In the present study, the drug-to-polymer ratio of 1 to 10 was used to prepare enteric solid dispersions of IRI-426 with the Eudragit S-100 polymer by the spray-drying technique.

Figure 1 depicts dissolution profiles of IRI-426 from the spray-dried enteric solid dispersion powder at various pHs. As expected, drug release at pH 7 and 8 was rapid, while it was retarded at pH 1.2 and 5.

Dissolution profiles of powder-filled versus pellet-filled capsules were generated as shown in Figure 2 to determine if compaction affected the release properties. Although densification effectively retarded release from 32 to 11% after 6 hours at pH 1.2, it also somewhat dampened rapid-release characteristics at pH 7 by slowing down release after 1 hour from 95 to 77%.

We therefore filled the hard gelatin capsules with spray-dried enteric solid dispersion powder and the filled capsules were enteric coated with Opaseal. Release profiles for enteric-coated and noncoated capsules filled with enteric solid dispersion powder are presented in Figure 3. Enteric coating of the capsules slowed down drug release at both pH 7 and 1.2,

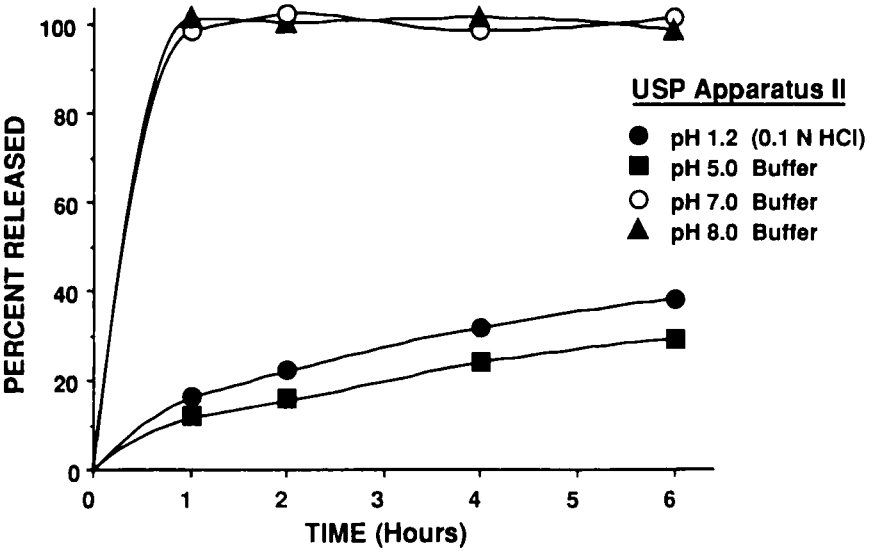

FIGURE 1

Release of IRI-426 from spray-dried enteric solid dispersion powder at various conditions of pH.

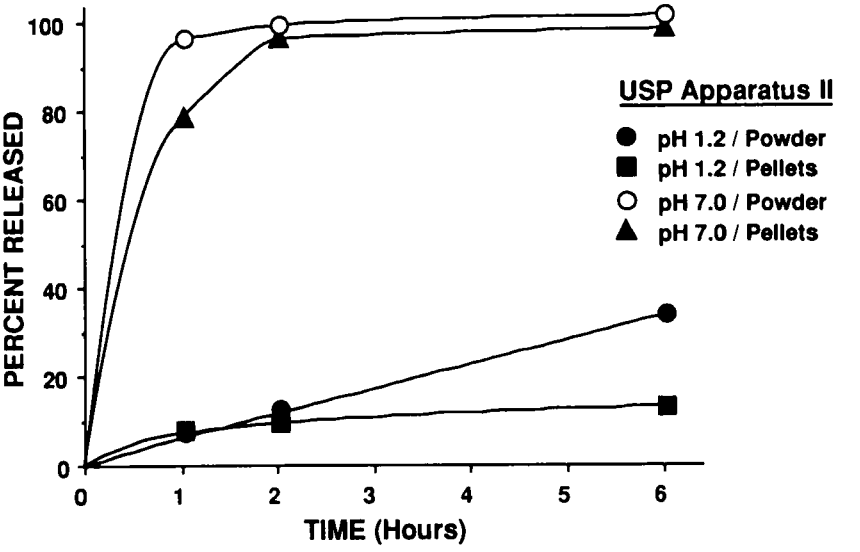

FIGURE 2

Release of IRI-426 from powder-filled versus pellet-filled capsules.

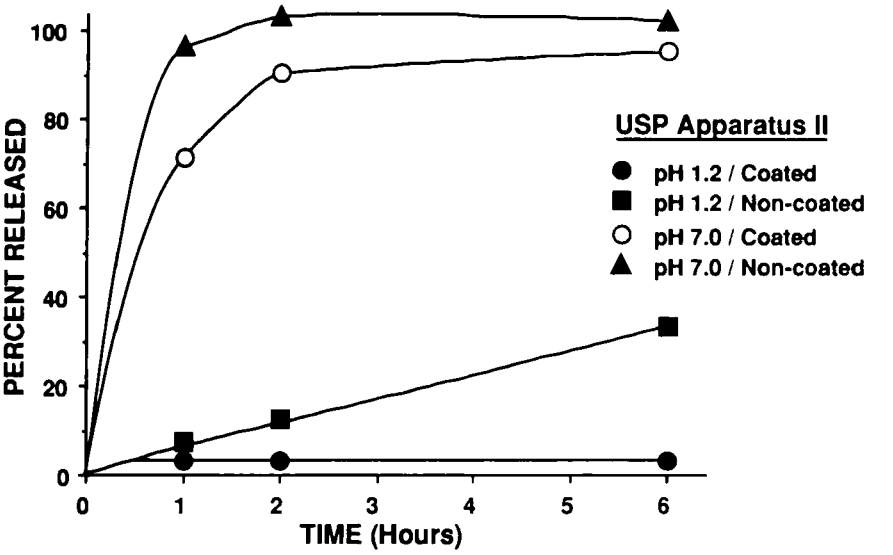

FIGURE 3

Release of IRI-426 from noncoated versus enteric coated capsules.

but did maintain the distinctions conferred by the original spray-dried enteric solid dispersion powder.

A solid dispersion of IRI-426 coated by spray-drying with a pH-sensitive polymer Eudragit S-100 in the drug-to-polymer ratio of 1 to 10 exhibits rapid release at pH 7 and slow release at pH 1.2. Compaction of the spray-dried enteric solid dispersion powder or enteric coating of the capsules filled with the spray-dried enteric solid dispersion powder causes retardation of drug release at pH 1.2 as well as pH 7. Spray-dried enteric coated solid dispersion powder in uncoated gelatin capsules appears to be the best formulation to deliver this peptide to the upper small intestine.

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