Polyvinyl Alcohol–Methyl Acrylate Copolymers as a Sustained-Release Oral Delivery System

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Low crystalline and crystalline polyvinyl alcohol–methyl acrylate (PVA-MA) copolymers were examined, because of their excellent flow and compressibility properties, as matrices for sustained-release tablets using phenylpropanolamine hydrochloride (PPA.HCl) as a model drug. Crystallinity of the copolymer affected the release characteristics from the tablet. Tablets made with low-crystalline PVA-MA provided sustained release of PPA, both in vitro and in vivo in dogs. PPA absorption from the low-crystalline PVA-MA tablet formulation was biphasic. An initial rapid phase was followed by a second, slower absorption phase which continued over 16 hr. Plasma PPA concentrations then declined with a half-life roughly parallel to the oral immediate-release half-lives. Oral bioavailability from the low-crystalline PVA-MA tablet formulation was 78.8 ± 3.9%.

KEY WORDS: polyvinyl alcohol–methyl acrylate copolymers; crystalline; low crystalline; phenylpropanolamine; sustained release; pharmacokinetics.

INTRODUCTION

Hydrogels have been studied extensively as materials for drug delivery systems. These gels are capable of releasing entrapped drugs in aqueous medium and are able to regulate the release of drugs by swelling. The swelling and permeability of most hydrogels can be affected by the molecular weight, cross-linking density, and crystallinity of the hydrogel (1,2).

In swellable drug delivery systems, polymeric matrices are prepared with drug dispersed throughout, forming a solid hydrophilic delivery system of variable porosity. Upon swelling in aqueous environments, a gel-like phase is formed and the bioactive agent is released. Depending on the rate of polymer relaxation at the glassy/rubbery sorption front, the swelling process and the associated drug release may exhibit Fickian or non-Fickian behavior. Typically, for a hydrogel slab, Fickian diffusion is characterized by a square root time dependence in both the amount diffused and the penetrating diffusion front position from the surface. In most cases, the front separates an undissolved core containing drug from a partially extracted region with dissolved drug diffusing through the swollen layer into the dissolution medium (3).

Many polymers have been observed to have properties analogous to swellable systems. They include materials derived from monomers such as methacrylates, vinyl acetates, and vinyl pyrrolidones. Others have been formed from polyesters and polyamides.

Hydrophilic polymers which have been used in oral sustained-release drug delivery systems include hydroxypropylmethylcellulose (4), hydroxypropylcellulose, acrylic polymers, and polypyrrolylpyrrolidone (5). The swelling properties of polyvinyl alcohol (PVA) have been extensively studied (2). The effect of molecular weight, degree of hydrolysis, and cross-linking density on swelling of PVA in controlled-release systems has been reported (2). The effect of heat treatment on the crystallinity of films of PVA was studied (6). Slabs of polyvinyl alcohol containing theophylline were cross-linked with glutaraldehyde. The resultant films showed a decrease in the rate of theophylline release with an increase in cross-linking (2). PVA tablets (15-mm diameter × 2 mm) containing PPA.HCl were prepared in a hydraulic press at 50 kN. The sustained release of the drug was dependent on the degree of hydrolysis (2). Partially hydrolyzed PVA homopolymer was capable of faster drug release due to an increase in solubility relative to fully hydrolyzed PVA polymer (7). It has been determined that when PVA homopolymer films are subjected to heat treatment, their crystallinity increases and their permeability to small molecules decreases (6). Also, crystallinity of heat-treated PVA homopolymer can readily be increased by both duration and temperature of annealing (8). PVA–MA copolymers described in this paper have excellent flow and compressibility properties compared to other commercially available hydrogel polymers (D. CoffinBeach, unpublished data). For these reasons, it is possible to dry blend the active ingredients and excipients and form tablets by direct compression.

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In this report, PPA.HCl was incorporated into crystalline and low-crystalline PVA-MA copolymer tablet formulations and release studies in vitro and in vivo in dogs were performed.

EXPERIMENTAL

Materials and Methods

Polyvinyl alcohol containing 6% methylacrylate (PVA-MA), crystalline and low-crystalline copolymers were provided by Polymer Products Department (DuPont Co.) having $M_w = 101,000$ and $M_n = 46,000$. Phenylpropanolamine hydrochloride and magnesium stearate were purchased from Sigma Chemical Company.

Wide-angle X-ray scans were performed on a Phillips wide-angle diffractometer.

X-Ray Diffraction

Wide-angle X-ray diffraction was performed on the powder of the copolymers. The powder was loosely placed in an aluminum tray with an opening measuring $5.08 \times 1.77 \times 0.152$ cm. The scan was performed employing a reflection diffractometer having a nickel filter or monochromating crystal and pulse-height analysis set to pass symmetrically 90% of the characteristic copper K-alpha radiation.

Tablet Preparation

Tablets were prepared containing the following: PPA.HCl (60 mg), PVA-MA copolymer (237 mg), and magnesium stearate (3 mg). The ingredients were dry blended via geometric dilution. The powder mixture was compressed into tablets using a Manesty F-3 single-punch tabletting machine with 7/32-in. diameter standard concave tooling and compression pressure of $4.8 \times 10^6$ kg/m² to form compacts at the target weight of 300 mg; tablet hardness = 12 SCU.

Dog Studies

Three female dogs were fasted overnight prior to dosing. PPA.HCl in PVA-MA tablets were administered orally followed by 40 ml of water. Blood (5 ml) was collected by jugular venipuncture into evacuated tubes containing Na₂EDTA as an anticoagulant. Plasma was stored frozen. These dogs were also administered in crossover fashion with the PPA.HCl in PVA-MA, PPA.HCl i.v. and orally in an immediate-release formulation (30 mg PPA.HCl packed in a hard gelatin capsule). Animals were fasted overnight prior to each experiment. The data for the latter studies were published elsewhere (9). Plasma PPA concentrations were determined by HPLC after solvent extraction using a previously described method (9).

The terminal decay constant, $k$, and the terminal half-life, $t_{1/2}$, were calculated by linear regression of the terminal portion of individual lnCp (plasma PPA concentration) vs time plots. The area under the $C_p$ vs time curve (AUC$_{0-\infty}$) was calculated for each dog using the trapezoidal method, with the residual area calculated by dividing $C_p$ at the time of the last sample by $k$. Oral bioavailability (F) was calculated from the i.v. dose normalized AUC$_{0-\infty}$ after oral and i.v. dosing using individual AUC$_{0-\infty}$ values.

The Wagner–Nelson method was used to calculate the fractional oral absorption of the bioavailable dose at each sample time:

$$\% \text{ absorbed} = \frac{C_p t + \text{AUC}_{0-\infty} K}{\text{AUC}_{0-\infty} K} \times 100$$

where $k$ was the elimination rate constant after i.v. dosing.

RESULTS AND DISCUSSION

PVA-MA copolymers were examined as a sustained-release matrix in tablets containing PPA.HCl.

The release characteristics were dependent on the crystallinity of the copolymer. Low-crystalline copolymer can be converted to crystalline copolymer by heat treatment. Cryst-