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Report

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 pyrollidones. 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 polyvinylpyrollidone (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 a $\overline{M}_w$ = 101,000 and $\overline{M}_n$ = 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 × 1.77 × 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 symetrically 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 tableting machine with ⅜-in. diameter standard concave tooling and compression pressure of 4.8×10^6 kg/m^2 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 Na_2EDTA 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).

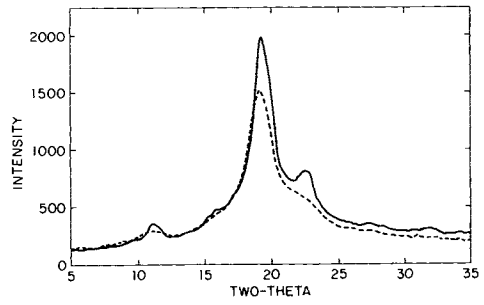

Fig. 1. Wide-angle X-ray diffraction scans performed on powders of crystalline PVA-MA (——) and low crystalline PVA-MA (---).

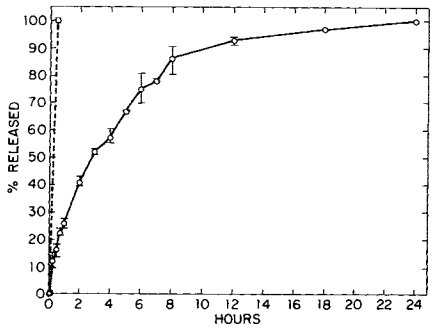

Fig. 2. *In vitro* release of PPA from crystalline PVA-MA (□) and low-crystalline PVA-MA (○) tablet formulations.

The terminal decay constant, k, and the terminal half-life, $t_{1/2}$, were calculated by linear regression of the terminal portion of individual $\ln C_p$ (plasma PPA concentration) vs time plots. The area under the C_p vs time curve (AUC_{0-t}) 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:

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

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. Crys-

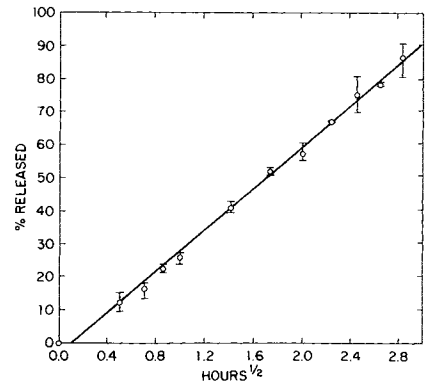

Fig. 3. *In vitro* cumulative percentage (±SD) release of PPA vs square root of time from low-crystalline PVA-MA tablet formulation.

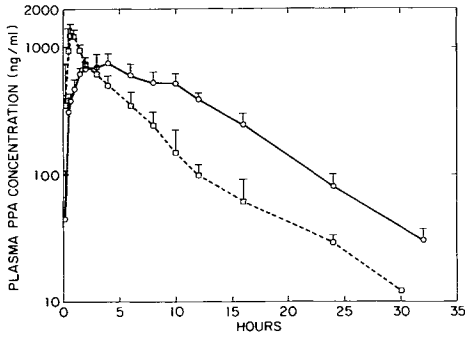

Fig. 4. Average (+SD) plasma PPA concentrations in three dogs orally administered 30 mg in an immediate-release capsule (□) or 60 mg in a low-crystalline PVA-MA tablet formulation (○).

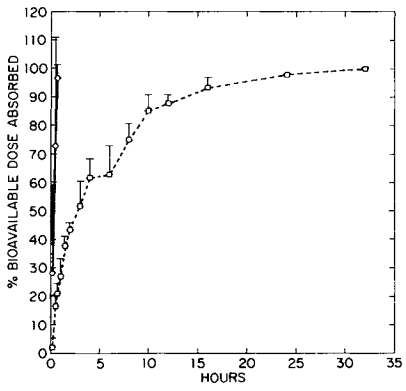

Fig. 5. Cumulative percentage (mean + SD) of the bioavailable dose absorbed vs time after an oral immediate release PPA (○) and PPA in a low-crystalline PVA-MA tablet formulation (□).

tallinity of the copolymer was determined by wide-angle X-ray scan performed on the crystalline and low-crystalline powder of the polymers. These scans showed that the crystalline copolymers exhibited characteristic peaks at 2-theta = 11 and 23°. These peaks were not observed with the low-crystalline (non-heat-treated) copolymer (see Fig. 1). Heat treatment of polyvinyl alcohol homopolymers and copolymers has been reported to decrease water solubility and decrease degree of swelling due to water uptake. When fashioned into a tablet, crystalline PVA-MA copolymers resulted in a formulation that will disintegrate immediately upon contact with an aqueous environment. Conversely, the low-crystalline copolymers will remain intact and start forming a gelatinous layer that swells to a finite thickness.

In vitro release of PPA.HCl (60 mg) from tablets containing crystalline or low-crystalline copolymer in 0.1 *N* HCl is shown in Fig. 2. PPA release from the tablet containing crystalline copolymer was very fast (100% in <0.5 h). However, tablets having a matrix of low-crystalline copolymer exhibited sustained-release behavior of PPA over 12 hr.

The accumulated release of PPA from the tablet containing low-crystalline PVA-MA was proportional to the square root of time (see Fig. 3), suggesting a Fickian diffusion-controlled mechanism (10). It is reported that the release of water-soluble drugs from initially dehydrated hydrogel matrices generally involves simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism (3).

We have shown previously that PPA is rapidly absorbed in dogs when administered in an immediate release dosage form. PPA plasma concentration decayed with a half-life of ~5 hr. Bioavailability from the immediate-release dosage form was ~98% (9). (For comparison, the profile is shown in Fig. 4.)

Average plasma PPA concentration versus time in dogs administered the sustained-release tablet (equivalent to 60 mg PPA.HCl) is shown in Fig. 4. Plasma PPA concentrations peaked within the first several hours and then plateaued, reflecting continuous delivery from the tablet. Thereafter, plasma PPA concentrations decayed with a half-life similar to that observed after the immediate-release preparation. Oral PPA bioavailability in this dosage form was 77.8 ± 3.9% of the dose. Other pharmacokinetic parameters are given in Table I.

Oral absorption data were further evaluated using the Wagner–Nelson approach. Percentage absorbed versus time plots (Fig. 5) reflect rapid PPA absorption from the gelatin capsule. The controlled-release tablet provided approximately 50% of the bioavailable dose in the initial 2 to 4 hr and 90 to 95% within 16 hr. The absorption profile from the sustained-release tablet was biphasic when plotted as the percentage remaining to be absorbed versus time. If first order absorption (Fig. 6) is assumed, the absorption half-life is 4.5 hr.

In summary, crystallinity of PVA-MA copolymer affected the release characteristics of PPA.HCl from a tablet formulation. Crystalline PVA-MA provided an immediate release of PPA.HCl. In contrast, low-crystalline PVA-MA

Table I. Pharmacokinetic Parameters (Mean ± SD) or Oral Phenylpropanolamine in Dogs Administered as Immediate Release (30 mg PPA Hydrochloride) and in a Low-Crystalline PVA-MA Tablet Formulation (60 mg PPA Hydrochloride)

	Immediate release	Low-crystalline PVA-MA tablet formulation
C_{max} (ng/ml)	1274 ± 183	756 ± 138
t_{max} (hr)	0.89 ± 0.44	3 ± 0.82
F (% dose)	98.2 ± 6.9	78.8 ± 3.9
Terminal $T_{1/2}$ (hr)	5.06 ± 1.41	5.3 ± 0.1

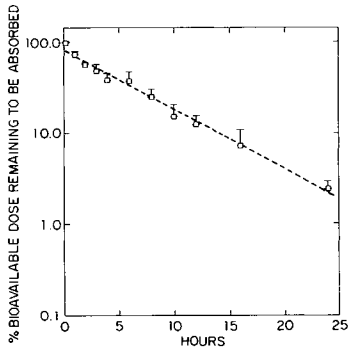

Fig. 6. Average percentage (mean + SD) of the bioavailable dose remaining to be absorbed vs time after an oral dose of PPA in a low-crystalline PVA-MA tablet formulation.

provided a sustained release profile of PPA *in vitro* and *in vivo* in dogs.

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