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Report

Hollow Fibers as an Oral Sustained-Release Delivery System

Munir A. Hussain,[1,2] Robert C. DiLuccio,[1] and Eli Shefter[1]

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Phenylpropanolamine (PPA) bound to ion-exchange resin was encapsulated in hollow fibers made of segmented polyurethane. This system was examined as an oral sustained-release delivery system. The fibers were spun by the phase inversion process and cut into different aspect ratios (length/diameter). The U.S.P. basket dissolution method was used to evaluate the *in vitro* drug release kinetics and the effect of the aspect ratio on the release. For *in vivo* evaluation, selected fibers were orally administered to dogs in gelatin capsules. The fiber delivery system provided a sustained-release profile of plasma PPA and a longer terminal half-life when compared to an oral immediate-release formulation.

KEY WORDS: hollow fibers; segmented polyurethane; oral delivery system; sustained release; phenylpropanolamine.

INTRODUCTION

Hollow fibers are interesting drug delivery systems due to their high surface area to volume ratio, loading flexibility, membrane permeability, and potential slower gastrointestinal tract (GIT) transit time. The latter may be greatly dependent on the aspect ratio (length/diameter) of the fibers as compared to the transit time of other geometries (tablets, capsules, spheres). These characteristics may provide a method to obtain controlled release for drugs in the small intestine and/or in the colon.

Because of the great flexibility in the design of hollow fibers, it is possible to have agents delivered by "sustained" or "controlled" release through their ends or through the membrane sheath. They can also be made to deliver agents through control of osmotic pressure gradient, diffusivity, pH, density, hydrophilicity, and porosity.

Very little work appears in the literature exploiting the use of fibers as delivery systems for pharmaceuticals or agrichemicals. Some literature can be found reporting the incorporation of tetracycline (1), progesterone (2), and antimicrobial agents (3). Biodegradable hollow fibers were reported as implants for subdermal drug delivery (4).

The spinning of fibers from polymers can be achieved by various routes. These are referred to as wet-, dry-, or melt-spinning processes (5). Melt-spinning involves heating a polymer above its melting point and extruding it through an orifice (usually referred to as a spinneret) which can be designed to form a monolithic fiber or hollow fiber. Once extruded, the melt is cooled (via a quenching process), which allows the polymer to solidify into a filament. In the dry-spinning process, a solution of the polymer is extruded through a desired orifice and is fed into a heated column, which allows for evaporation of the solvent and subsequent formation of a filament. In the wet-spinning process, a solution of the polymer is extruded through an orifice and quenched in a coagulant for the polymer, resulting in the formation of a fiber. Of the above-mentioned spinning techniques, wet-spinning allows the greatest flexibility in terms of production of hollow porous fibers.

In this report, the wet-spinning technique was used to encapsulate ionically bound phenylpropanolamine (PPA). Hollow fibers open at both ends were studied *in vitro* and *in vivo* in dogs.

EXPERIMENTAL

Materials

Segmented polyurethane, MW 50,000, was obtained from the Du Pont Co.; polyvinylpyrrolidone (PVP), MW 15,000, was purchased from GAF. Dowex 50W was purchased from Dow Chemical. Dimethylacetamide (DMAC) and phenylpropanolamine hydrochloride were purchased from Sigma Chemical Company.

Fiber Preparation and Spinning Equipment

PPA was ionically bound to Dowex 50W resin (2% cross-linked sulfonated polystyrene resin, 200–400 mesh) by a method similar to that described previously (6,7). The ion exchange–PPA complex was suspended in a 3.6% solution of polyurethane in DMAC (1:2).

A spinning (extrusion) device was designed to accept separate streams of polymer and drug suspension simultaneously (see Fig. 1) to form a solid fiber having a core and a sheath as shown in the cross section (Fig. 2). The composition of the sheath was 18% (w/w) PVP and 18% (w/w) polyurethane dissolved in DMAC. PVP was used to render the fiber hydrophilic. The sheath and the core were pumped at

[1] E. I. du Pont de Nemours & Company, Medical Products Department, Chemical & Pharmaceutical Development, Experimental Station, Building 400, Wilmington, Delaware 19898.
[2] To whom correspondence should be addressed.

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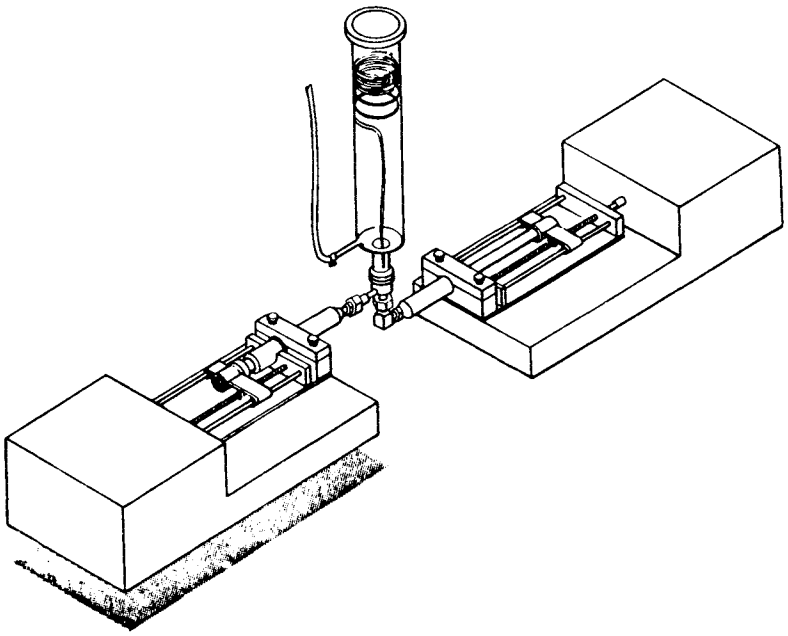

Fig. 1. Upward configuration of a wet-spinning apparatus for preparation of fibers containing a core of ion exchange–PPA complex.

0.2 and 0.123 ml/min, respectively, through a coextrusion die and quenched into a vertical bath containing deionized water to form a continuous fiber (Fig. 3); the quench time was approximately 5 min. The quench caused the solvent to be removed from the extrudate, causing phase inversion of the polymer and formation of the fiber. The fiber was then post-treated with acetone overnight to remove any residual solvent and was air-dried for 24 hr. The product was manually cut into uniform lengths by the use of a razor. (The lengths were 0.32, 0.64, and 1.28 cm; all were 0.071 cm in diameter).

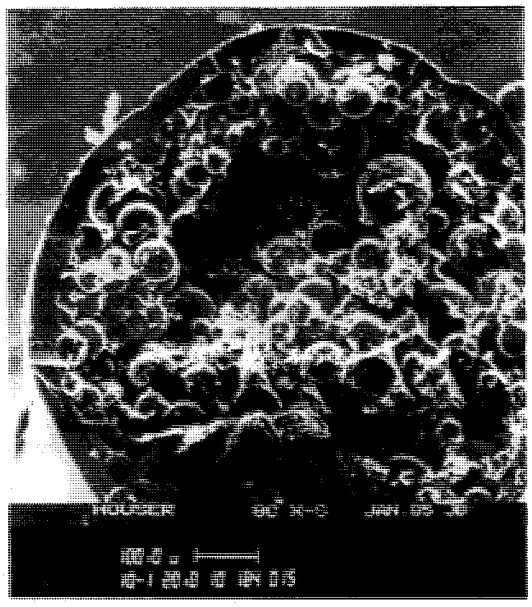

Fig. 2. Cross-section SEM of a hollow fiber containing ion exchange–PPA complex.

The percentage drug loading was determined by dissolving aliquots of the ion exchange–PPA encapsulated fibers in triplicate in DMAC. Subsequently, 1 *N* HCl was added to allow the drug to be removed from the resin. The mixture was filtered through a 0.45-μm Millipore filter and analyzed for PPA by high-performance liquid chromatography (HPLC).

In Vitro Release

The release rate of PPA from the fibers in 0.1 *N* HCl was determined using the rotating-basket technique (100 rpm at 37°C). Samples of the fibers at different aspect ratios of 4.5, 9, and 18 (equivalent to 60 mg PPA hydrochloride) were used for the *in vitro* dissolution studies. The volume of dissolution media used was 1 liter. Aliquots of the dissolution medium were assayed for PPA by HPLC.

Dog Studies

Three female dogs were administered the fiber delivery system (equivalent to 60 mg PPA hydrochloride having an

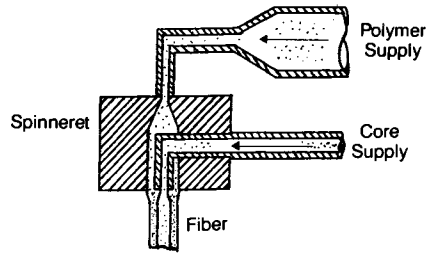

Fig. 3. Schematic of a spinneret permitting coextrusion of a sheath and a core.

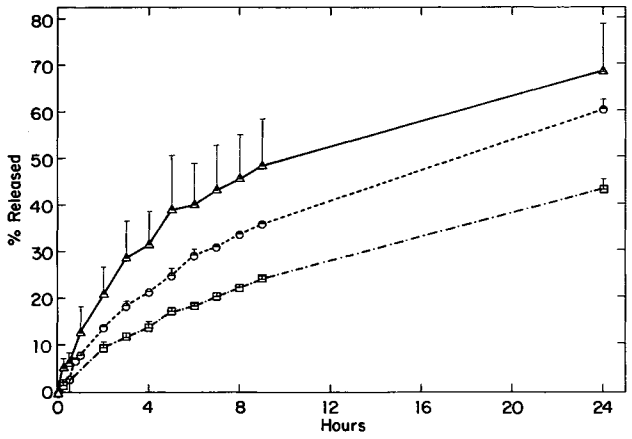

Fig. 4. *In vitro* release of PPA from fibers with aspect ratios of 4.5 (△), 9 (○), and 18 (□) into 0.1 *N* HCl.

aspect ratio of 4.5) packed in a hard gelatin capsule. Blood (5 ml) was collected by jugular venipuncture into evacuated tubes containing Na_2EDTA as an anticoagulant. Plasma was separated and stored frozen. These dogs were also administered, in a crossover fashion with the fiber delivery system, PPA i.v. and orally in an immediate-release formulation (30 mg PPA hydrochloride packed in a hard gelatin capsule). Animals were fasted overnight prior to each experiment. The data for the latter studies were published elsewhere (8). Plasma PPA concentrations were determined by HPLC after solvent extraction using a previously published method (8).

The terminal decay rate 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 dose-normalized $AUC_{0-\infty}$ after oral and i.v. dosing using individual $AUC^{i.v.}_{0-\infty}$ 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 is the elimination rate constant after i.v. dosing.

Table I. Pharmacokinetic Parameters (Mean ± SD) of Oral Phenylpropanolamine in Dogs Administered as Immediate Release (30 mg PPA Hydrochloride) and in the Fiber Delivery System (Equivalent to 60 mg PPA Hydrochloride)

	Immediate release	Fiber delivery system
C_{max} (ng/ml)	1274 ± 183	472 ± 17.9
t_{max} (hr)	0.89 ± 0.44	6.0 ± 2.8
F (% dose)	98.2 ± 6.9	64.9 ± 13.1
Terminal $t_{1/2}$ (hr)	5.06 ± 1.41	7.4 ± 0.9

RESULTS AND DISCUSSION

The PPA content of the fibers was equivalent to 60 ± 3 mg PPA hydrochloride per 150 mg fibers.

The fibers in this study allow exchanging ions to enter the ends of the fibers and diffuse through the channels within the matrix core. Once the PPA is exchanged, it must diffuse through the channel within the polymer matrix and escape through the ends of the fiber segments. The sheath structure of these fibers allows them to wet, however, diffusion of the drug through the sheath is minimal as was observed in *in vitro* studies on fibers closed at the ends (data are not shown). PPA release profiles of various lengths (aspect ratios) of fibers into 0.1 *N* HCl are shown in Fig. 4. The aspect ratios were 4.5 (0.32 cm long), 9 (0.64 cm long), and 18 (1.28 cm long). As the length decreased, the release rate of the drug from the fiber increased, indicating that diffusion of the drug through the polymer matrix core and out the ends is the most significant factor in the overall release process. Release of PPA from the ion exchange–PPA complex, not encapsulated in fibers, was immediate (data are not shown).

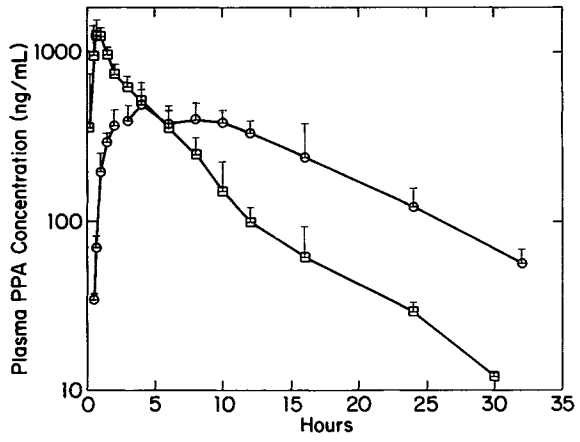

Fig. 5. Average (+SD) plasma PPA concentrations in three dogs orally administered 30 mg in an immediate-release capsule (□) or 60 mg in the fiber delivery system (○).

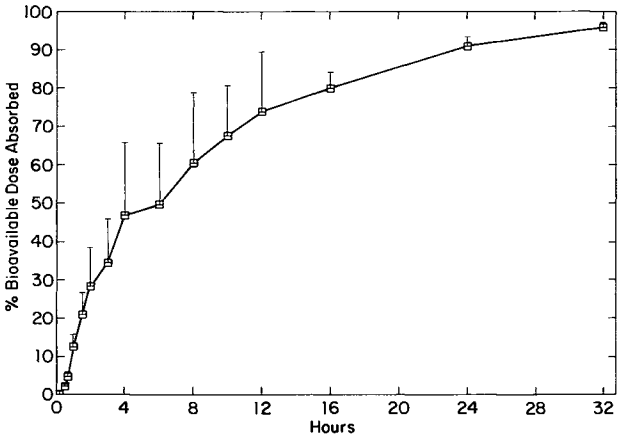

Fig. 6. Cumulative percentage (mean + SD) of the bioavailable dose absorbed vs time after an oral dose of ion exchange–PPA complex in the fiber delivery system.

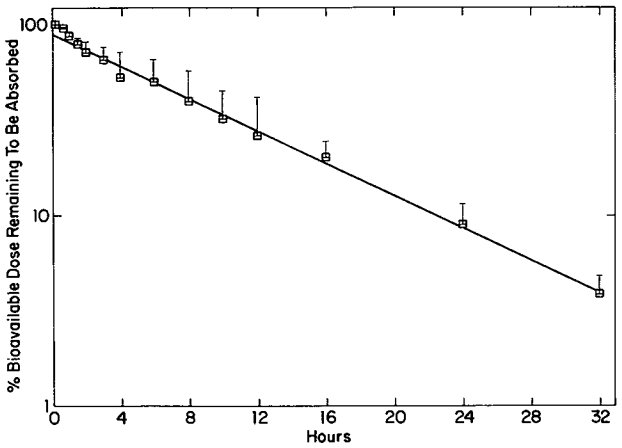

Fig. 7. Average percentage (mean + SD) of the bioavailable dose remaining to be absorbed after an oral dose of ion exchange–PPA complex in the fiber delivery system.

We have shown previously that PPA is rapidly absorbed in dogs after administering an immediate-release dosage form and the plasma concentration decayed with a half-life of ~5 hr. Bioavailability from the immediate-release dosage form was ~98% (8). (The profile is shown in Fig. 5 for comparison.)

The average plasma PPA concentration vs time in dogs administered the fiber delivery system (equivalent to 60 mg PPA hydrochloride and with an aspect ratio of 4.5) is shown in Fig. 5. Plasma PPA concentrations peaked within the first several hours and then plateaued, reflecting the continuous delivery from the fibers. Finally, the plasma PPA decayed with a half-life of 7.4 ± 0.9 hr. Other pharmacokinetic parameters are given in Table 1.

Oral absorption data were evaluated using the Wagner–Nelson approach. The percentage absorption of the bioavailable dose vs time plot (Fig. 6) shows that the fiber delivery system provided approximately 50% of the bioavailable dose in the initial 4–8 hr and 90–95% within 24 hr. Absorption from the fast-release formulation was very fast (8). The absorption profile from the controlled-release fiber delivery system was biphasic when plotted as the percentage remaining to be absorbed vs time. If first-order absorption (Fig. 7) is assumed, the absorption half-life is 7 hr.

The fiber delivery system provided a bioavailability of ~65% and a longer terminal half-life, indicating that the content of the fibers was not completely depleted within 32 hr. This may be advantageous for delivery to the colon. Gamma scintigraphic studies using ^{153}Sm-radiolabeled hollow fibers (0.32 cm long), performed in four dogs, showed that all the fibers had been excreted by 48 hr in three dogs, and in the fourth dog they were eliminated completely in 60 hr (M. A. Hussain and G. A. Digenis, unpublished results).

In summary, a method to prepare hollow fibers encapsulating an ion exchange–PPA complex was presented. These fibers provided *in vitro* and *in vivo* a sustained-release profile and a longer plasma PPA terminal half-life.

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