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Report

Hollow Fibers as an Oral Sustained-Release Delivery System Using Propranolol Hydrochloride

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Fibers were spun by the downward configuration of the wet spinning technique. This configuration is capable of encapsulating nonspherical and/or coarse particles. We examined encapsulation of propranolol hydrochloride and the ability of the fibers to act as a sustained-release delivery system for propranolol hydrochloride as a model drug. The U.S.P. basket dissolution method was used to evaluate the *in vitro* drug release kinetics and the effect of the aspect ratio (length/diameter) on drug release. For *in vivo* evaluation, selected fibers were administered to dogs in gelatin capsules. The results of these *in vitro* and *in vivo* studies were compared to those obtained with a marketed sustained-release propranolol product (Inderal LA). The fiber delivery system provided a sustained-release profile of plasma propranolol concentrations similar to that observed with Inderal LA.

KEY WORDS: hollow fibers; downward configuration; oral delivery system; sustained release; propranolol.

INTRODUCTION

There is great flexibility in the processing of hollow fiber drug delivery systems. We recently examined the upward configuration of the wet-spinning technique by encapsulating phenylpropanolamine bound to an ion-exchange resin within the core of hollow fibers (1). Those fibers provided *in vitro* and *in vivo* (in dogs) a sustained-release profile and a longer phenylpropanolamine plasma terminal half-life. In the upward configuration, controlling the diameter of the fiber is solely dependent on the diameter of the spinneret orifice. The ion-exchange–PPA fibers were easily made using the upward configuration technique due to the fine spherical suspension of particles which easily flows through a small diameter spinneret. However, in the case of nonspherical particles, such as propranolol hydrochloride, which is used as a model drug in this report, a large-diameter spinneret is required. In the downward configuration, it is possible to use a large-diameter spinneret to form a uniform, fine fiber by drawing down the extrudate under the influence of gravity. Therefore, the advantage of the downward configuration is encapsulation of a suspension of nonspherical or coarse, irregular particles into fine fibers. If, however, a large-diameter spinneret is used in the upward configuration, the fiber would have to be drawn mechanically.

In this report, the wet-spinning technique was used in a downward configuration to encapsulate propranolol hydrochloride within hollow fibers. *In vitro* and *in vivo* studies in dogs were performed and compared to those observed with a marketed long-acting propranolol hydrochloride formulation, Inderal LA (Ayerst, ICI). Inderal LA is a hard gelatin capsule containing film-coated spheroids. The spheroid comprises a mixture of propranolol hydrochoride and microcrystalline cellulose. The spheroid film coat comprises a mixture of ethyl cellulose and hydroxypropylmethyl cellulose with a plasticizer (2).

EXPERIMENTAL

Materials

Segmented polyurethane, MW 50,000, was obtained from the Du Pont Company. Hydroxypropyl cellulose (Klucel HF) was obtained from Hercules Incorporated. Dimethylacetamide (DMAC) and propranolol hydrochloride were purchased from Sigma Chemical Company.

Fiber Encapsulation

A spinning (extrusion) device previously described (1) was used to accept separate streams of the polymer solution and drug suspension simultaneously and form a solid fiber having a core and a sheath as shown in Fig. 1. The coagulant bath was fashioned so that the fiber could be spun downward (Fig. 2). In this configuration, the fiber is allowed to free fall for a specified distance from the end of the spinneret prior to entry into the coagulant bath. The composition of the sheath solution was 36% (w/w) polyurethane dissolved in DMAC. The core was a suspension of 50% (w/w) propranolol hydrochloride in DMAC containing 2% (w/w) Klucel HF. The sheath and the core were pumped at 0.123 and 0.049 ml/min, respectively, through a coextrusion die and quenched in a

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Fig. 1. Cross-section SEM of a hollow fiber containing propranolol hydrochloride.

vertical coagulant bath 20 cm from the exit of the spinneret. The bath contained 60% aqueous ethanol, which quenched the fiber for approximately 80 sec. The fiber was then removed upward into another bath containing acetone. This step removed any residual solvent. The fiber was left in the acetone bath for 16 hr; it was then removed and air-dried for 24 hr. The fiber was then manually cut into uniform lengths using a razor. The lengths (0.32, 0.64, and 1.28 cm) were 0.091 cm in diameter. These lengths corresponded to aspect ratios (length/diameter) of 3.5, 7.0, and 14, respectively.

The percentage drug loading was determined by dissolving aliquots of the encapsulated fibers in quadruplicate in DMAC. HCl (1 *N*) was subsequently added to precipitate the polymer. The suspensions were filtered through Millipore filters and the filtrate was analyzed for propranolol by high-performance liquid chromatography (HPLC).

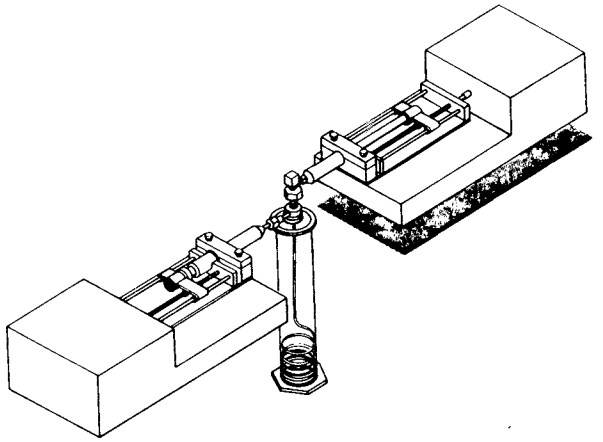

Fig. 2. Downward configuration of a wet-spinning apparatus for preparation of fibers containing a core of propranolol hydrochloride.

In Vitro Release

The release rate of propranolol from the fibers into 0.1 *N* HCl was determined using the rotating basket technique (100 rpm at 37°C). Samples of the fibers at aspect ratios of 3.5, 7.0, and 14 (equivalent to 80 mg propranolol hydrochloride) were used for the dissolution studies. The release of propranolol from Inderal LA was also examined under the same conditions. The volume of the dissolution medium used was 1 liter. Aliquots of the dissolution medium were assayed for propranolol by HPLC using UV detection at 290 nm, a reverse-phase column (Zorbax C8, DuPont), and a mobile phase containing 36% acetonitrile in 0.05 *M* phosphate buffer (pH 2.2), delivered at 3 ml/min. Retention time for propranolol was 6.8 min.

Dog Studies

Three female dogs were administered propranolol hydrochloride intravenously and orally in crossover experiments. The protocol was for each dog to receive propranolol hydrochloride i.v., an oral immediate-release propranolol HCl dose, an oral controlled-release propranolol HCl tablet, and propranolol HCl encapsulated in fibers. There was a washout period of 2 weeks between experiments. For i.v. dosing, propranolol HCl was dissolved in water and 1 mg/kg (0.5 ml/kg) was injected via the cephalic vein. The immediate-release oral dose was 40 mg propranolol HCl packed into a hard gelatin capsule. The controlled-release tablet (Inderal LA) contained 80 mg propranolol HCl. The fiber delivery system contained 80 mg propranolol HCl, having an aspect ratio of 3.5, and was 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. Animals were fasted overnight prior to each experiment. Plasma propranolol concentrations were determined by HPLC after solvent extraction using fluorometric detection as previously described (3).

The elimination rate constant, K, and the elimination half-life, $t_{1/2}$, were calculated by linear regression of the terminal portion of individual ln C_p (plasma propranolol concentration) vs time plots. All data points after i.v. doses were included in the regression. The terminal slope after the immediate-release oral doses began at t_{max} (the time of maximum C_p). The area under the C_p vs time curve (AUC_{0-t}) was calculated for each dog and treatment using the trapezoidal method, with the residual area calculated by dividing C_p at the time of the last samples by K. After Inderal LA and the hollow fiber delivery system $AUC_{0-32\ hr}$ was calculated rather than $AUC_{0-\infty}$. Oral bioavailability (F) was calculated from the dose-normalized AUC after oral and i.v. dosing using individual AUC values.

RESULTS AND DISCUSSION

The preparation of the hollow fiber delivery system re-

ported here involved the use of a process allowing the encapsulation of drugs that cannot form fine spherical particles. This method involved spinning the fiber in a downward fashion (Fig. 2). In this downward fashion, a suspension of the drug was pumped simultaneously with the sheath polymer through a large-diameter spinneret core. A gap between the end of the spinneret and the coagulant bath allowed the fiber to be drawn down to a uniformly small diameter. Once the fiber extrudate entered the coagulant, it was quickly quenched in the coagulant bath. The fiber remained in the coagulant bath long enough for the sheath to set. In order to remove residual solvent from the core, the fiber was postquenched with acetone. The propranolol hydrochloride content of the fibers was equivalent to 80 ± 8 mg per 310 mg fibers.

The release profiles of propranolol hydrochloride from the various lengths (aspect ratios) of fibers and from Inderal LA into 0.1 *N* HCl are shown in Fig. 3. The aspect ratios were 3.5 (0.32 cm long), 7 (0.64 cm long), and 14 (1.28 cm long). As the length decreased, the release rate of the drug from the fiber increased, indicating that diffusion of the drugs through the polymer matrix core and out the ends is the most significant factor in the overall release process. Similar behavior was observed previously with fibers encapsulated with phenylpropranolamine–ion-exchange resin complex (1). Therefore, these fibers allow the dissolution medium to enter the ends, diffuse through the channels within the matrix core, dissolve the drug, and escape through the ends of the fiber segments. We have shown previously that diffusion of drugs through the sheath is minimal (1). Release of propranolol from Inderal LA was sustained over 24 hr. Fibers having an aspect ratio of 3.5 nearly resembled the release profile observed with Inderal LA. These fibers were compared to Inderal LA *in vivo* in dogs.

The average plasma propranolol concentrations vs time in dogs administered propranolol hydrochloride i.v. (1 mg/kg) and an oral immediate-release capsule (40 mg propranolol HCl) are shown in Fig. 4. After i.v. administration,

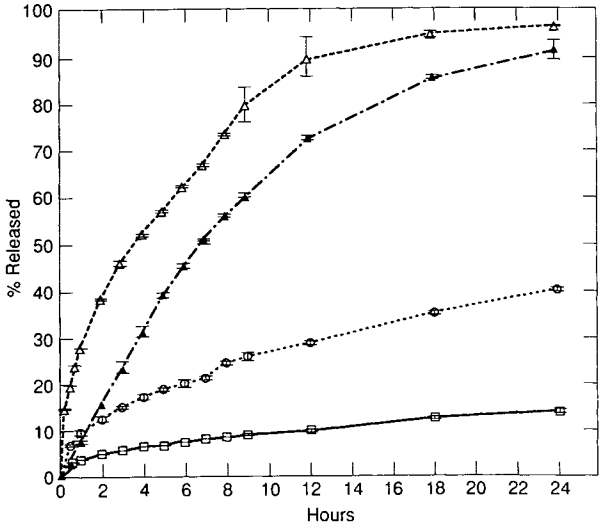

Fig. 3. *In vitro* release of propranolol hydrochloride from Inderal LA (▲) and fibers with aspect ratios of 3.5 (△), 7.0 (○), and 14 (□) into 0.1 *N* HCl.

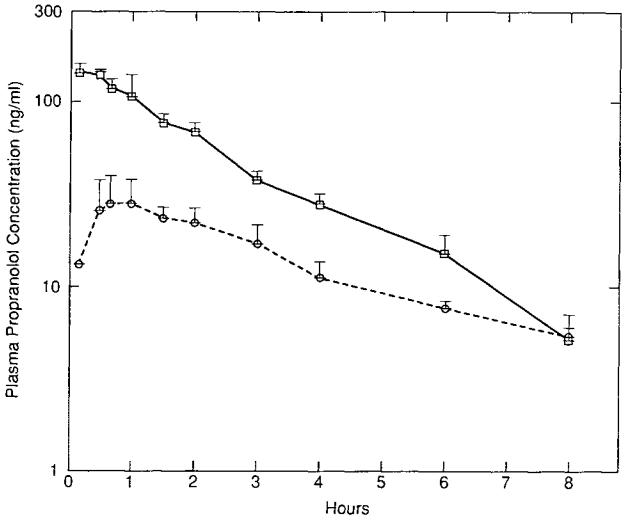

Fig. 4. Average (+SD) plasma propranolol concentrations in three dogs administered propranolol · HCl i.v. (□) (1 mg/kg) and orally in an immediate-release capsule (○) (40 mg).

plasma propranolol concentrations decayed with a half-life of 1.64 ± 0.17 hr. Following 40-mg doses of propranolol hydrochloride in an immediate-release formulation, the average maximum plasma concentration (C_{max}) was 34.5 ± 6.6 ng/ml and occurred at 1.0 ± 0.7 hr postdosing. Plasma propranolol concentrations decayed with a half-life of 2.6 ± 0.14 hr. The longer plasma decay half-life after oral doses relative to that after intravenous dosing has been observed previously in dogs (4) and in man (5). Oral bioavailability after the oral immediate-release formulation was 7.6 ± 0.7%, similar to that previously reported (6). The average plasma propranolol concentration vs time profiles after Inderal LA (80 mg propranolol HCl) and the fiber delivery system (equivalent to 80 mg propranolol HCl and with an aspect ratio of 3.5) are shown in Fig. 5. After Inderal LA administration, the C_{max} was 18.66 ± 1.24 ng/ml and occurred at 2.66 ± 0.47 hr postdosing. Average propranolol plasma levels remained between 10 and 15 ng/ml over 24 hr. After the fiber delivery

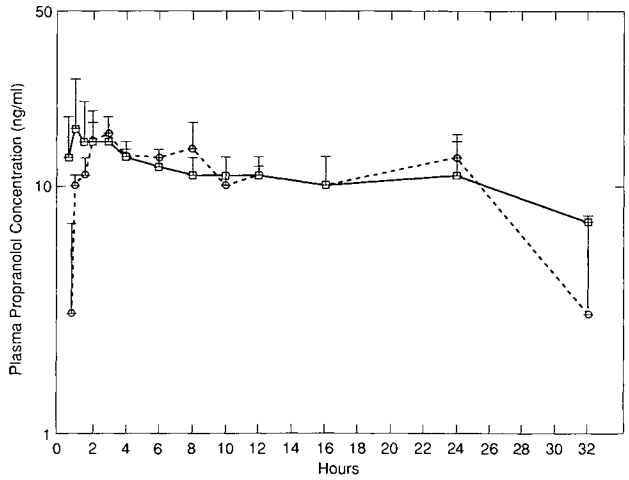

Fig. 5. Average (+SD) plasma propranolol concentrations in three dogs orally administered 80 mg propranolol hydrochloride as Inderal LA (○) and in the fiber delivery system (□).

system, the average C_{max} was 20 ± 7.5 ng/ml and occurred at 1.55 ± 1.03 hr postdosing. Average propranolol plasma levels remained between 10 and 17 ng/ml over 24 hr. Identification of a terminal log-linear elimination phase was not possible after either Inderal LA or the fiber delivery system, because continued absorption masked the true elimination. Similar behavior was observed in humans treated with Inderal LA (7). Thus, the bioavailability of the sustained-release formulation was estimated from the area under the plasma concentration vs time curve from 0 to 32 hr. Calculated in this way, the oral bioavailabilities of propranolol after administration of Inderal LA and the fiber delivery system were 9.7 ± 1.8 and 9.5 ± 1.5%, respectively. These were not significantly different from the immediate-release formulation (t test).

In summary, the downward configuration of the wet-spinning technique was employed to encapsulate propranolol hydrochloride within hollow fibers. These fibers provided a sustained-release profile for propranolol both *in vitro* and *in vivo* in dogs.

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