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Report

Zero-Order Release Formulation of Oxprenolol Hydrochloride with Swelling and Erosion Control

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Zero-order release of oxprenolol hydrochloride was obtained by controlling the swelling and erosion of the matrix. This formulation involves only mixing of drug, hydroxypropylmethylcellulose (HPMC), and sodium carboxymethylcellulose (Na CMC) at the ratio of 1:0.4:1.6, respectively, and compressing the mixture directly into tablets. The *in vitro* release pattern from this optimized matrix tablet was reproducible. Accelerated stability studies revealed that the optimized formulation remains stable for an approximately 2-year shelf life. This sustained-release (SR) tablet was evaluated in dogs, and for comparison a conventional (CV) formulation was also given at the same dose level. Plasma oxprenolol levels were monitored by a sensitive and specific high-performance liquid chromatographic (HPLC) method. Significant differences in the pharmacokinetic parameters, i.e., lower C_{max}, higher values of t_{max}, MRT, AUC, and plasma concentration at 24 hr, and nearly constant plasma levels over 12 hr, indicated that the SR matrix tablet is superior to the CV rapid-releasing formulation. The *in vitro* release parameters and *in vivo* pharmacokinetics correlated well.

KEY WORDS: zero-order release; swelling and erosion controlled; cellulose ethers; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; oxprenolol hydrochloride; *in vivo* evaluation; stability evaluation; *in vitro–in vivo* correlation.

INTRODUCTION

Oxprenolol, (±)-1-(*o*-allyloxyphenoxy)-3-isopropylaminopropan-2-ol, is a β-adrenergic blocking agent with a short half-life (1.3 to 2 hr). It is frequently used in the treatment of hypertension in pregnancy, cardiac arrhythmias, and angina pectoris. Prolonged pharmacodynamic activity and better patient compliance were reported with once-a-day administration of the sustained-release (SR)[4] oxprenolol to patients (1) and healthy volunteers (2). A multicenter evaluation of 6000 angina patients revealed that once-daily therapy with the SR oxprenolol (160 mg) is helpful in the management of angina pectoris (3). In another double-blind multicenter trial, SR oxprenolol reduced the total and weighted number of anginal attacks and glyceryl trinitrate consumption compared with the placebo (4). Chronic administration of SR oxprenolol delayed the onset of exercise-induced anginal pain and extended the exercise tolerance compared with the rapid-release formulation at the same dose level (5). The transit time of most conventional dosage forms from mouth to cecum varies from 2 to 7 hr (6,7). The gastric retention time of conventional dosage forms can be increased significantly by administering them with food (8). Oxprenolol was reported to be absorbed even from the cecum, as its bioavailability was 82% compared with the oral dosing (9). The systemic availability of two Oros systems of oxprenolol releasing the drug at two different rates was found to be comparable to that with the rapid-release tablets, which suggests that slow delivery of the drug is not associated with greater first-pass loss. Similar results were reported earlier with the SR propranolol formulations (10,11). Therefore, formulation of the SR dosage forms of oxprenolol is advantageous compared with the conventional dosage forms.

Among the various types of controlled-release dosage forms, swelling-controlled release systems are becoming popular because of the several advantages they offer (12). Among the various polymers which may be used for controlling the release of drugs, two water-swellable cellulose ethers, namely, hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (Na CMC), were selected for this study as matrix materials. The ease of compression, nontoxic nature, ability to accommodate a large percentage of the drug, and negligible influence of the processing vari-

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[4] Abbreviations used: AUC, area under the plasma concentration curve; AUMC, area under the first moment curve; C_{max}, measured maximum plasma concentration; CV, conventional; ELS, extended least squares; HPLC, high-pressure liquid chromatography; HPMC, hydroxypropylmethylcellulose; K_a, absorption rate constant; K_{el}, elimination rate constant; MRT, mean residence time; Na CMC, sodium carboxymethylcellulose; OH, oxprenolol hydrochloride; SR, sustained release; t_{max}, time to C_{max}; $t_{1/2}$, half-life.

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ables on the release of drug from the matrices are some of the reasons for their popularity (13,14). The release profiles of freely soluble drugs through these matrices normally follow the classical square root of the time relationship (15,16). Recently, we reported (14,17–23) a novel and simple method of preparing zero-order release tablets by synchronizing the swelling and erosion rates of the matrix. In this method, anionic and nonionic cellulose ethers were mixed with the very soluble drug at an optimum ratio and compressed into tablets. The purpose of this study is to prepare a zero-order release tablet dosage form of oxprenolol hydrochloride (80 mg) based on the same principle using HPMC and Na CMC and to evaluate its performance *in vivo,* so that this formulation, when administered twice a day, may maintain the desired plasma level and thus optimum beta blockade in angina patients.

EXPERIMENTAL

Materials and Methods

Oxprenolol hydrochloride (OH) and Methocel K4M Premium (HPMC) were generously supplied by Ciba-Geigy, Basel, Switzerland, and by Colorcon, Orpington, U.K., respectively. Na CMC, high-viscosity grade, was procured from Loba Chemie Indoaustranat Co., Bombay, India. All other chemicals were of analytical reagent or HPLC grade.

Plasma samples were analyzed for the intact oxprenolol by the specific and sensitive high-pressure liquid chromatographic (HPLC) method of Padmalatha Devi *et al.* (24). For determining the values of the elimination and absorption rate constants (K_{el} and K_a, respectively) the data were fitted with ELSFIT (25), a program based on the extended least-squares (ELS) method. The area under the curve (AUC) and the area under the first moment curve (AUMC) were calculated by the trapezoidal rule. To the value of AUC_{0-24}; the ratio of plasma concentration at 24 hr to K_{el} was added to get $AUC_{0-\infty}$. $AUMC_{0-\infty}$ was calculated according to the method of Benet and Galeazzi (26). The mean residence time (MRT) is the ratio of $AUMC_{0-24}$ to AUC_{0-24}. In order to evaluate the data statistically, the paired *t* test was applied between the pharmacokinetic data of the SR and those of the CV formulations.

Standardization of Na CMC

Pseudoplastic properties (27) of 2% (w/v) aqueous dispersions were determined using the MVI cup and bob assembly of a Haake Rotovisko viscometer (1965 model). At 20°C, the mean ± SD (N = 6) flow and consistency indices were found to be 0.501 ± 0.01 and 166.61 ± 6.12 P, respectively. Viscosity of 2% (w/v) aqueous dispersion of Methocel K4M Premium was reported by the manufacturer to be about 40 P at 20°C.

Preparation of the Tablets and *In Vitro* Dissolution Studies

Oxprenolol hydrochloride was mixed manually with HPMC or Na CMC (<120 mesh) at different ratios and compressed into flat-faced, 9.5-mm-diameter tablets, containing 80 mg of drug, at 10 kN, using a hand-operated single-punch tablet machine. Three tablets of each formulation were subjected to dissolution using a USP dissolution apparatus 1 at 37 ± 1°C for 3 hr in diluted HCl (pH 3.0) and later in 0.2 M phosphate buffer (pH 7.4) for another 9 hr. The basket was rotated at 100 rpm. Samples were drawn at regular intervals and assayed for the drug spectrophotometrically by measuring the absorbance of the drug at 273 nm. Results are shown in Figs. 1 and 2.

Similar studies were carried out using a mixture of the drug, HPMC, and Na CMC. By changing the ratios between the drug and the total polymer and also between HPMC and Na CMC, different batches were prepared and subjected to dissolution as before, until 100% of the drug was released in about 12 hr at a nearly zero-order rate. The optimized formulation contained the drug:HPMC:Na CMC at the ratio of 1:0.4:1.6. The reproducibility of the release pattern of this formulation was confirmed by studying the release pattern of one tablet from each of the 10 different batches prepared in the same manner. The mean release profile is shown in Fig. 3.

Accelerated Stability Studies

Accelerated stability studies were conducted as previously described by us (28); they revealed that the optimized formulation may remain stable for a shelf life of about 2 years.

In Vivo Evaluation of the Optimized SR Formulation

Five healthy mongrel dogs weighing 16–20 kg were acclimatized to the laboratory environment by keeping them in the laboratory for 1 week. They were administered a conventional (CV) capsule containing 80 mg of OH along with standard food (0.5 kg each of bread, whole milk, and water). To make sure that the tablet or capsule was ingested in an intact manner, five or six sweetened balls (ca. 5 g each) made from wheat flour were fed at intervals of ca. 5 sec so that the dog swallowed them instantaneously. The SR tablet or CV capsule was embedded in one of the balls. Blood samples (5 ml) were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hr into heparinized tubes by repeated venipuncture. The blood samples were centrifuged immediately and

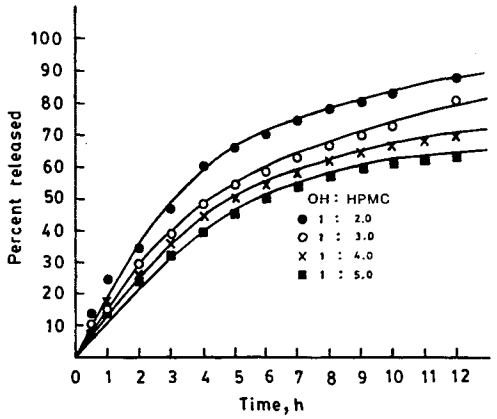

Fig. 1. Release of oxprenolol hydrochloride (cumulative percentage), as a function of time, from tablets containing the drug and HPMC at the ratios given.

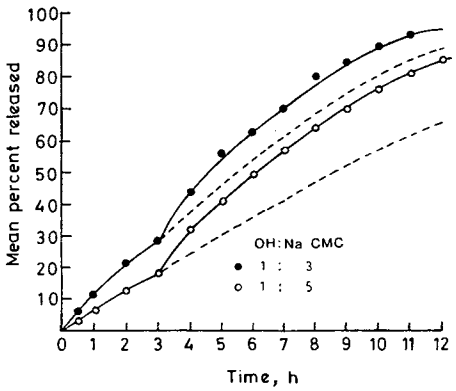

Fig. 2. Release of oxprenolol hydrochloride (cumulative percentage), as a function of time, from tablets containing the drug and Na CMC at the ratios given.

the plasma was separated and frozen at −20°C until analyzed. After a washout period of 1 week, the same dogs were administered in an identical manner one tablet of the SR formulation containing an equivalent amount of the drug. Plasma samples were also drawn and assayed in an identical manner. The mean plasma concentration versus time plots of both the conventional (CV) and the SR formulations are shown in Fig. 4.

RESULTS AND DISCUSSION

In formulations containing OH and HPMC, an increase in the ratio of polymer to drug decreased the release rate in a nonlinear manner (Fig. 1). Also, the release rate was faster in the beginning and decreased with time, and only 90% of the drug was released in 12 hr even when the polymer-to-drug ratio was 2. Owing to slow erosion of the outer gel layer of the HPMC matrices, the diffusional path length for the drug increased with time and hence the release rate decreased with time. The drug release in alkaline medium was faster through the Na CMC matrices compared with the HPMC matrices with the same ratio of polymer to drug. This may be because of the faster erosion rate of Na CMC compared with HPMC. Also, when Na CMC alone was used, the

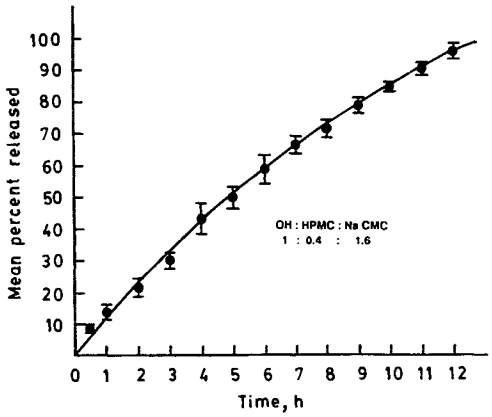

Fig. 3. Release of oxprenolol hydrochloride (mean cumulative percentage), as a function of time, from tablets of different batches (N = 10) containing the drug, HPMC, and Na CMC at the ratios given. Vertical bars indicate ±SD.

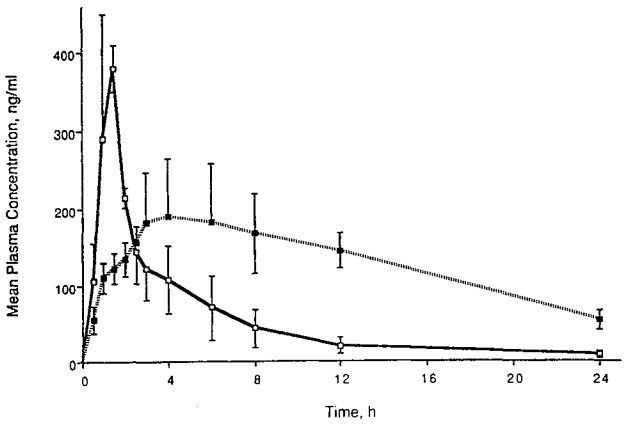

Fig. 4. Mean (N = 5) plasma concentrations of oxprenolol at various times in dogs following oral administration of 80 mg of oxprenolol hydrochloride as conventional (□) and sustained-release (■) formulations. Vertical bars indicate ±SD.

release in acidic medium was slower than that in alkaline medium (Fig. 2). Owing to the ionic nature of the polymer, its packing might be different in acidic and alkaline media and hence the release pattern. When the ratio of drug: HPMC:Na CMC was 1:0.4:1.6, the entire drug was released in 12 hr at a nearly zero-order rate, as shown in Fig. 3.

The constant release rate observed in such formulations was explained earlier (17–23) and was later modified by Ranga Rao and Padmalatha Devi (12). According to the former, by optimizing the ratio between the drug and the polymers, the rates of advancement of the swelling front into the glassy core and the attrition of the rubbery state polymer were made equal so that the diffusional path length for the drug remained constant. This hypothesis was modified (12) to explain the constant release rate observed even when the size of the matrix was significantly less (due to erosion) compared with its initial size. Accordingly, as the size of the matrix decreased with time owing to rapid erosion of the outer rubbery (gel) layers, the diffusional path length for the drug decreased with time. It was also reported earlier (27) that the penetration of the solvent front into the glassy core of a cylinder decreased with time. Hence the rate of formation of the gel also decreased with time. We reported earlier that the erosion rate of cellulose matrices was fairly constant (22). This also supports the hypothesis (12) that the diffusional path length for the drug decreases with time. Hence

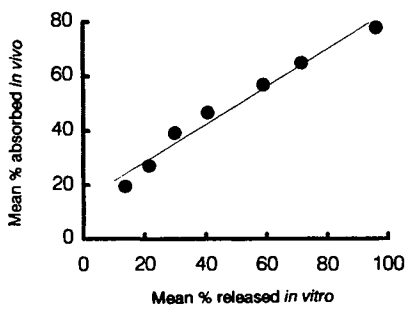

Fig. 5. Mean (N = 5) percentage absorbed (*in vivo*) versus mean (N = 10) percentage released (*in vitro*) at the times indicated from the sustained-release formulation of oxprenolol hydrochloride.

Table I. Pharmacokinetic Parameters (Mean ± SD) of Oxprenolol in Dogs Following Oral Administration of Conventional (CV) and Sustained-Release (SR) Formulations Containing 80 mg of Oxprenolol Hydrochloride

Pharmacokinetic parameter	CV	SR	t value ($P < 0.05$)
C_{max} (ng/ml)	410 ± 114	218 ± 61	5.110
t_{max} (hr)	1.4 ± 0.224	3.8 ± 1.44	3.639
K_{el} (hr^{-1})	0.2137 ± 0.0998	0.0782 ± 0.0411[a]	2.422
$t_{1/2}$ (hr)	3.4 ± 1.8	11.6 ± 6.7[a]	2.341
K_a (hr^{-1})	1.6595 ± 0.9758	0.7445 ± 0.5442	3.655
AUC_{0-24} (ng · hr/ml)	1,312 ± 483	2,997 ± 587	8.926
$AUC_{0-\infty}$ (ng · hr/ml)	1,348 ± 509	3,964 ± 265	9.778
$AUMC_{0-24}$ (ng · hr^2/ml)	6,749 ± 3,190	29,052 ± 3,992	12.734
$AUMC_{0-\infty}$ (ng · hr^2/ml)	7,837 ± 4,000	73,882 ± 36,267	3.797
MRT_{0-24} (hr)	4.97 ± 0.62	9.81 ± 0.89	7.765

[a] Apparent values.

the release rate from the matrix increases with time. But this increase in the release rate is compensated by the decrease in the size of the matrix with time; hence, the net effect is the delivery of a constant amount of the drug into the dissolution medium.

Plasma concentration–time profiles (Fig. 4) clearly demonstrate the slow release and sustaining ability of the SR formulation *in vivo* for about 12 hr. The mean pharmacokinetic parameters are given in Table I. The peak plasma concentration (C_{max}) and the time at which this peak appears (t_{max}) were read from the plasma concentration–time data.

The mean C_{max} value for the CV formulation was 1.88 times higher than that for the SR formulation ($P < 0.05$). On the other hand, as expected, the mean t_{max} value for the SR formulation was 2.7 times higher compared with the CV formulation ($P < 0.05$). The ratios of MRT and AUC_{0-24} of the SR to CV formulations were 1.97 and 2.28, respectively ($P < 0.05$). In addition to this, it is obvious from Fig. 4 that the plasma concentration at 24 hr was much higher for the SR formulation compared with the CV formulation. These data clearly indicate that the SR formulation is superior to the CV formulation.

In order to correlate the mean *in vitro* release pattern of the SR formulation with that *in vivo*, a plot of the percentage absorbed at different times versus the percentage released *in vitro* at those times was made (Fig. 5). The cumulative percentage absorbed was calculated using the modified Wagner–Nelson equation (30) and the cumulative percentage released *in vitro* at those times was noted from Fig. 3. For calculating the percentage absorbed *in vivo* following administration of the SR formulation, the K_{el} of the CV formulation was used. The linear relationship between the two ($r^2 = 0.9723$) indicates that the rate of absorption of the drug is almost constant. This means that the release rate from the SR formulation is practically constant in the gastrointestinal tract.

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