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 Cmax, higher values of tmax, 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 glycercyl 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 ecum 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 ecum, 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-
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 Indoausturanat 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_e 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_e was added to get AUC_0–∞. AUMC_0–∞ 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 1 cup and bob assembly of a Haake Rotovisco 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.](image-url)