Stereoselective Dissolution of Propranolol Hydrochloride from Hydroxypropyl Methylcellulose Matrices

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Since many chiral pharmaceutical excipients, such as cellulose polymers and cyclodextrins, are used as stationary phases for the separation of enantiomers by high performance liquid chromatography (HPLC), it is hypothesized that one enantiomer of a chiral drug will be released faster than the other from a pharmaceutical formulation containing a racemic drug and a chiral excipient. The mechanism of such an event may arise from preferential intermolecular interaction between the chiral excipient and one of the enantiomers. To test this hypothesis, the release of the enantiomers of propranolol hydrochloride into water from formulations containing the chiral excipients, hydroxypropyl methylcellulose (HPMC) or β-cyclodextrin, was investigated by stereospecific HPLC analysis of the dissolved concentrations of each of the enantiomers from the formulations. The release of the enantiomers of propranolol hydrochloride from the formulations containing HPMC, although variable, was found to be stereoselective. However, the release of propranolol hydrochloride enantiomers from the β-cyclodextrin complex was found to be nonstereoselective.

KEY WORDS: chiral excipient; chiral drug; β-cyclodextrin; hydroxypropyl methylcellulose matrix; propranolol hydrochloride enantiomers; stereoselective release.

INTRODUCTION

Chirality is one of the key issues in current pharmaceutical research (1,2). It is also of a major concern in the development, regulation (3), and administration of drugs (4). Although much work has been done on the pharmacokinetic, pharmacodynamic, and toxicological aspects of chirality (5–7), the implications of chirality in physical pharmacy are poorly understood. Apart from influencing the methods for resolving racemates (8,9), chirality and chiral purity can influence salt formation (10) and the properties of optically active crystals (11). However, the interaction of chiral drugs with chiral excipients has not yet been reported. A wide variety of chiral excipients, such as cellulose polymers and cyclodextrins, is used as excipients in pharmaceutical formulations. Some of the commonly used chiral excipients employed in the pharmaceutical industry are listed in Table I. These compounds and their derivatives are also used as chiral stationary phases to resolve enantiomers chromatographically because of their ability to interact preferentially with one enantiomer.

Since the chiral excipients mentioned above are obtained from natural sources, they are optically pure. The interaction of the enantiomers of a chiral drug with these chiral excipients may lead to the formation of diastereomers, usually transient, with different physical and chemical properties. The same principle is applied to the resolution of enantiomers on a column packed with chiral material, such as cellulose and/or its derivatives. Hesse and Hagel (12) have suggested that resolution of compounds with an aromatic ring may be achieved by the formation of weak bonds, such as hydrogen bonds, and the inclusion of the aromatic ring(s) in crystalline acetyl cellulose in the swollen state. Considering these possibilities, we hypothesize that chiral excipients may interact preferentially with one enantiomer leading to a stereoselective dissolution from a formulation containing a racemate. The possibility of such a stereoselective release of the two enantiomers from a formulation containing a racemic drug and a chiral excipient appears, hitherto, to have been ignored. Since many drugs are chiral and are still administered as racemates, we have studied the effect of chiral excipients on the release of the enantiomers of a chiral drug molecule.

To test the above hypothesis, the present study examines the possibility of stereoselective release of the enantiomers of a model drug, propranolol hydrochloride, from two formulations containing the chiral excipients, hydroxypropyl methylcellulose (hereafter HPMC) and β-cyclodextrin. The reasons for this choice of model drug are that (a) propranolol can be resolved on a chiral cyclodextrin-bonded stationary phase for which (*R*)-propranolol preferentially interacts with β-cyclodextrin (13) and (b) propranolol enantiomers are high-extraction drugs and undergo stereoselective first-pass metabolism. As a result, their bioavailability may be affected by their rates of absorption.

One of the formulations consisted of a matrix, composed of HPMC, in which enantiomers may undergo stereoselective intermolecular interactions of differing strength with the chiral excipient prior to dissolution. The other formulation was a tablet composed of the β-cyclodextrin complexes formed from racemic propranolol hydrochloride. This compact presumably consists of two diastereomer complexes formed between each of the drug enantiomers and the chiral excipient. The release rates of the two enantiomers of racemic propranolol hydrochloride from these formulations were determined by HPLC, and the reasons for stereoselectivity of release, or lack of it, were examined.

MATERIALS AND METHODS

Materials

Racemic propranolol hydrochloride and β-cyclodextrin were obtained from Sigma Chemical Company (St. Louis,

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Table I. List of Chiral Excipients Commonly Used in the Pharmaceutical Industry

Excipient	Application
1. Alginic acid	Disintegrant, tablet binder
2. Carboxymethylcellulose calcium	Disintegrant
3. Carboxymethylcellulose sodium	Disintegrant
4. Microcrystalline cellulose	Binder, diluent, disintegrant
5. Dextrin	Adhesive, stiffening agent
6. Dextrose	Sweetening agent, binder
7. Ethylcellulose	Binder, coating material
8. Guar gum	Binder
9. Hydroxyethylcellulose	Binder, film former
10. Hydroxypropylcellulose	Granulating agent, binder
11. Hydroxypropyl methylcellulose	Film former, in sustained-release formulations
12. Hydroxypropyl methylcellulose phthalate	Binder, in preparation of granules with sustained-release properties
13. Lactose	Diluent, filler
14. Mannitol	Carrier, lubricant
15. Methylcellulose	Binder
16. Ascorbic acid	Antioxidant
17. Starch	Diluent
18. Sucrose	Sweetener
19. Cyclodextrins, their derivatives	Complexing agents, dissolution enhancers

MO). HPMC (grade E4M) was obtained from Dow Chemical Company (Midland, MI).

Methods

Preparation of the Matrix Containing Racemic Propranolol Hydrochloride and HPMC. Racemic propranolol hydrochloride (160 mg) and HPMC (70 mg) were mixed in a glass vial with a spatula. The matrix, in the form of a compact (1 cm in diameter), was prepared by weighing 150 mg of the mixture into the sample holder, which is a part of the intrinsic dissolution apparatus, described below, followed by compression under a hydraulic press (Carver Laboratory Press, Model C, Menomonee, WI) at 125 MPa pressure for 60 sec.

Preparation of the β-Cyclodextrin Inclusion Complex. The method used for the preparation of the complex was similar to that used by Kurozumi *et al.* (14). Racemic propranolol hydrochloride (295.8 mg) and β-cyclodextrin (1135 mg) were dissolved in 70 mL of distilled water and the solution was freeze-dried for 48 hr. Thus, the product consisted of 5×10^{-4} mol of (*R*)-propranolol hydrochloride, 5×10^{-4} mol of (*S*)-propranolol hydrochloride, and 1×10^{-3} mol of β-cyclodextrin. The intrinsic dissolution rate of the product (termed the "complex") was carried out on compacts (weight 250 mg) prepared in the same way as the HPMC matrices described above.

Differential Scanning Calorimetry (DSC). A Du Pont Model 910 instrument equipped with a Data Station (Thermal Analyst 2000, Du Pont Instruments, Wilmington, DE) was used to record the DSC curves. The temperature axis and the cell constant were calibrated with indium (10 mg, 99.99% pure, peak maximum at 156.6°C, and heat of fusion = 28.4 J/g). Samples were weighed into aluminum open pans and loosely covered with a lid. A heating rate of 10°C/min with nitrogen purge was employed throughout the study.

Powder X-Ray Diffraction. The powder X-ray diffraction patterns were determined using an X-ray generator (Model 500, Siemens) at 50 mA and 45 kV with a CuK_α radiation. The samples were placed in an aluminum holder and scanned at $5° < 2\theta < 35°$ in increments of 0.05°. The Bragg-Brentano focusing geometry was used with a 1° incident aperture, a 0.5° detector slit, and a scintillation counter as a detector. A single-crystal graphite monochromator was used to enhance the signal-to-noise ratio.

Characterization of the β-Cyclodextrin Inclusion Complex of Racemic Propranolol Hydrochloride. The DSC curves of the freeze-dried inclusion complex, the freeze-dried racemic propranolol hydrochloride, the freeze-dried β-cyclodextrin, and the physical mixture of freeze-dried racemic propranolol hydrochloride and freeze-dried β-cyclodextrin, with the same overall composition as the complex, are shown in Fig. 1. The formation of an inclusion complex by the freeze-drying method was suggested by the absence of the melting endotherm of racemic propranolol hydrochloride at 165°C in the DSC curve of the inclusion complex. Freeze-dried racemic propranolol hydrochloride gave a sharp melting endotherm at 165°C, suggesting that, after freeze-drying, it remains in the same crystalline form as that of the starting material.

The powder X-ray patterns of the inclusion complex, the freeze-dried racemic propranolol hydrochloride, and the freeze-dried β-cyclodextrin are shown in Fig. 2. The X-ray diffraction patterns confirmed the formation of an inclusion complex. Although racemic propranolol hydrochloride and β-cyclodextrin remained crystalline after freeze drying, the inclusion complex formed was found to be X-ray amorphous. Thus, both (*R*)- and (*S*)-propranolol hydrochloride are completely included in β-cyclodextrin to form an amorphous material which is termed the "complex." Since each molecule of β-cyclodextrin can include in its cavity only one molecule of propranolol hydrochloride (13), the "complex" actually consists of an equimolecular mixture of the two diastereomeric complexes, i.e., (*R*)-propranolol-β-cyclodextrin (1:1) hydrochloride and (*S*)-propranolol-β-cyclodextrin (1:1) hydrochloride.

Intrinsic Dissolution Rate. The intrinsic dissolution rate was determined using the intrinsic dissolution apparatus described of Doherty and York (15), based on that of Collett *et al.* (16). The sample holder containing the compact was screwed into the center of the cell base so that a single face of the compact (diameter, 1 cm; area, 0.7854 cm^2) was exposed to 600 mL distilled water out-gassed and equilibrated at 25 ± 0.2°C. Directly above the compact, a three-paddle stirrer was rotated at 50 rpm by a synchronous motor (Slo Syn, Superior Electric Co., Bristol, CT). The samples were analyzed for the dissolved concentrations and hence for the dissolved amounts of each of the enantiomers by stereospecific HPLC.

Stereospecific High-Performance Liquid Chromatography. The concentration of each enantiomer of propranolol in samples obtained from dissolution experiments was determined by a stereospecific HPLC procedure (17). Following

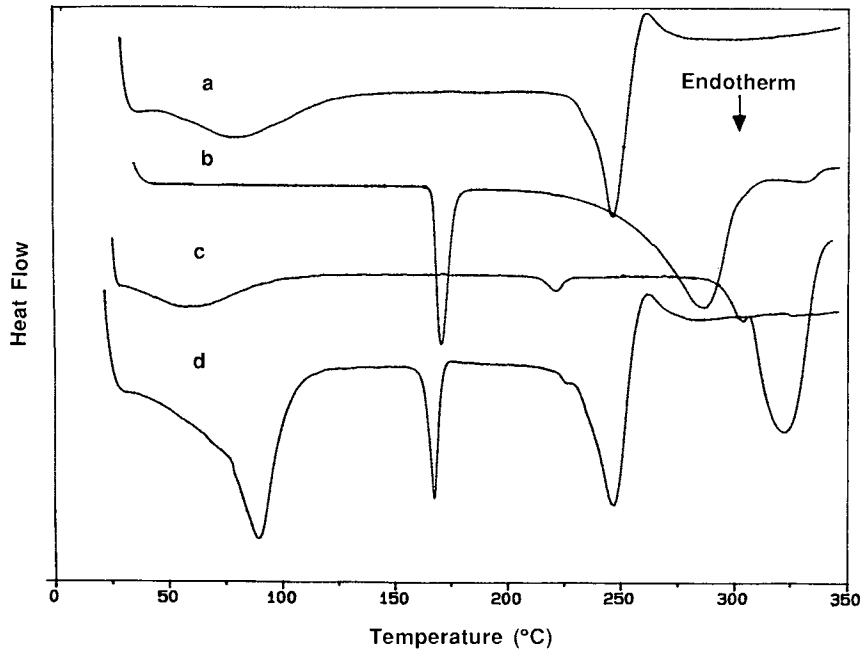

Fig. 1. DSC curves of (a) the freeze-dried equimolecular mixture of the diastereomeric inclusion complexes formed between β-cyclodextrin and racemic propranolol hydrochloride (1:1), (b) freeze-dried racemic propranolol hydrochloride, (c) freeze-dried β-cyclodextrin, and (d) the physical mixture of freeze dried-racemic propranolol hydrochloride and freeze-dried β-cyclodextrin of the same overall composition as for the inclusion complexes.

addition of the internal standard, bupranolol, 0.1 ml of sample was basified by the addition of 1 *M* NaOH and then extracted with ether. The organic layer was transferred to a glass tube and evaporated to dryness. The residue was derivatized with 0.2 mL of 0.015% (v/v) *S*-(+)-1-(1-naphthyl)ethyl isocyanate in chloroform:hexane (50:50). The mobile phase was hexane:chloroform:methanol (75:25:0.4) and the flow rate was adjusted to 2 mL/min. The stationary phase was a 25-cm Partisil 5 column. Fluorescence detection was set at 225 nm for excitation and 280 nm for emission. The peaks corresponding to (*R*)- and (*S*)-propranolol were eluted at approximately 12 and 19 min, respectively. Peak area ratios of each enantiomer and the internal standard were used to quantitate the concentrations of the enantiomers.

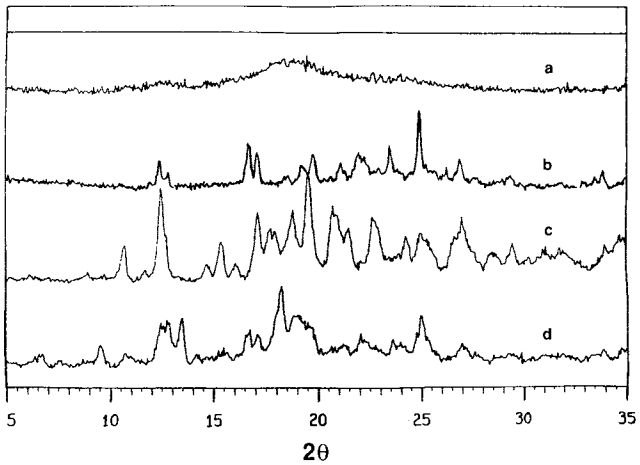

Fig. 2. Powder X-ray diffraction patterns of (a) the freeze-dried equimolecular mixture of the diastereomeric inclusion complexes formed between β-cyclodextrin and racemic propranolol hydrochloride (1:1), (b) freeze-dried racemic propranolol hydrochloride, (c) freeze-dried β-cyclodextrin, and (d) the physical mixture of freeze-dried racemic propranolol hydrochloride and freeze-dried β-cyclodextrin of the same overall composition as for the inclusion complexes.

Data Analysis. Prior to each dissolution experiment, the racemate, and not the individual enantiomers, was incorporated into the formulations. Therefore, the two-sample *t* test is inappropriate to examine the difference between the enantiomers released. This is because the assumption of independent samples is not valid in the present study since the concentrations have been measured in pairs (18). Hence, the difference between the two enantiomers released was evaluated for statistical significance using the paired *t* test ($\alpha = 0.05$). The paired *t* test was deemed more appropriate than the two-sample *t* test because only the paired *t* test compares the concentrations of the two enantiomers in a given experiment and is not influenced by variations between experiments.

RESULTS AND DISCUSSION

Dissolution of the Enantiomers from HPMC Matrices

Two types of dissolution profiles were observed: (a) a sigmoidal profile (e.g., Fig. 3a) in four of the six dissolution experiments and (b) nonsigmoidal profiles with plateaus and burst effects (Fig. 4) in two of the six dissolution experiments. Similar burst effects with HPMC matrices have also been observed recently by Railkar *et al.* (19). These authors (19) reported that the burst effects are more pronounced with

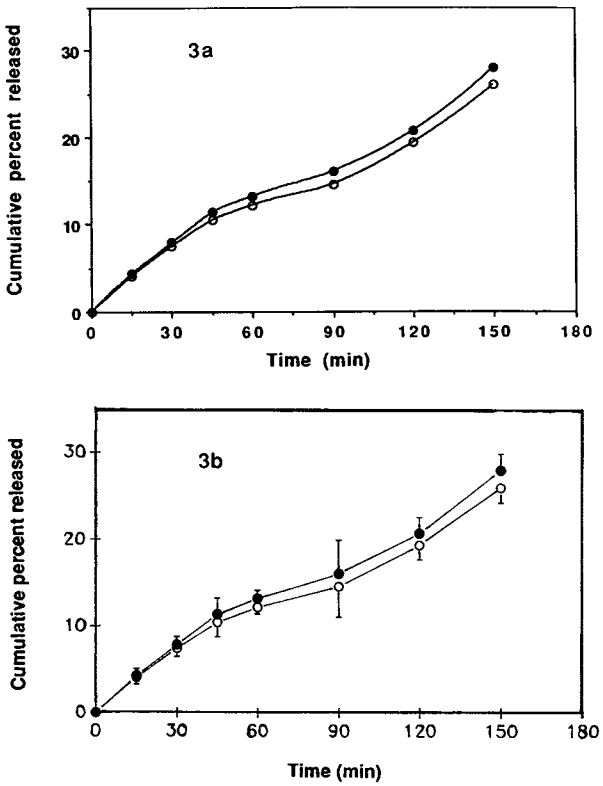

Fig. 3. Time plot of the cumulative percentages of (*R*)-propranolol hydrochloride (open circles) and (*S*)-propranolol hydrochloride (filled circles) released from hydroxypropyl methylcellulose matrices in the experiments showing stereoselectivity in dissolution: (a) a typical dissolution experiment showing stereoselectivity in the release of the enantiomers; (b) mean cumulative percentages released in all four experiments showing stereoselectivity in the release of the enantiomers. The vertical bars represent the standard deviations (n = 4).

the E4M-grade HPMC, the same grade as used in the present study, and in tablets made by direct compression. The origin of such burst effects, which is a variable characteristic of this particular grade of HPMC, is not yet completely understood. Particle size, chain length, and degree of substitution may influence the release kinetics (19). In addition, minor changes in the processing of the dosage form may also alter the release kinetics in an unpredictable manner.

A typical sigmoidal release profile exhibiting stereoselectivity is shown in Fig. 3a. Three other dissolution experiments showed very similar stereoselective release profiles. A time plot of the cumulative percentages of each enantiomer released in all the four experiments exhibiting stereoselectivity is shown in Fig. 3b. This stereoselectivity, although small (S:R ratio, 1.07 ± 0.01), is statistically significant (paired t test, P value < 0.05 in each of the four experiments typified by Fig. 3a). The percentage coefficient of variation (CV) for the cumulative amounts of each enantiomer released, at each time point, was found to be 13.5% and was essentially independent of the time of contact of the compact with the dissolution medium. Figure 5 shows the ratio of the cumulative amount of the (*S*)-enantiomer released to that of the (*R*)-enantiomer plotted against time. Over the time period of the dissolution experiments, the ratio was found to be

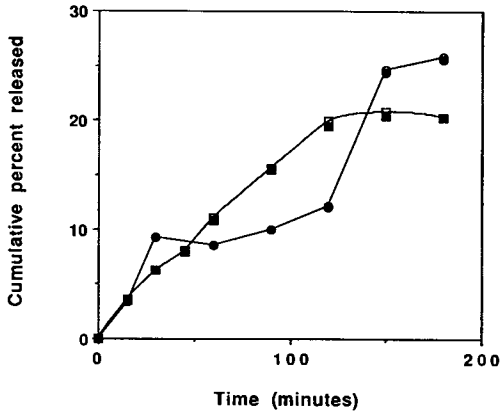

Fig. 4. Time plot of the cumulative percentages of the propranolol hydrochloride enantiomers released from hydroxypropyl methylcellulose matrices in two individual experiments in which insignificant stereoselectivity was observed. The open and filled symbols represent the (*R*)- and (*S*)-enantiomers, respectively, and are coincident in most data points.

greater than unity and independent of time. Although there are differences in the total amounts of the enantiomers released from one dissolution experiment to another, in any given experiment showing a sigmoidal release profile, Fig. 5 shows that the amount of (*S*)-enantiomer released is always greater than that of the (*R*)-enantiomer. Since propranolol is a drug which undergoes significant stereoselective first-pass metabolism, even low stereoselectivity in dissolution may affect the interpretation of its pharmacokinetic data.

HPMC, the polymer used in the present study, is employed in sustained-release formulations. The overall release of a water-soluble drug from a matrix composed of HPMC depends on the following three processes: (a) diffusion of water, a nonstereoselective process, through the matrix, thereby hydrating it; (b) diffusion of the enantiomers of the drug through the hydrated chiral matrix, presumably a stereoselective process; and (c) erosion of the hydrated matrix, a nonstereoselective process.

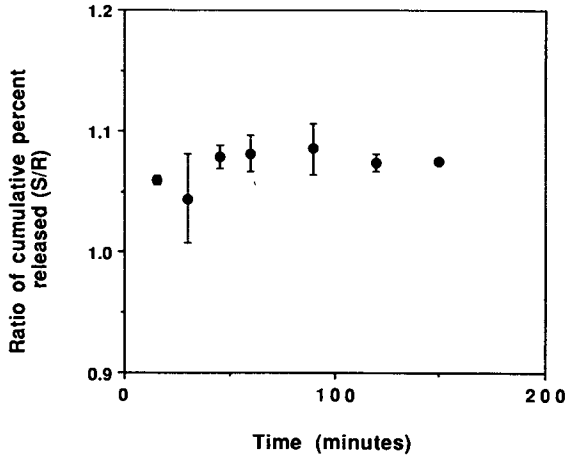

Fig. 5. Time plot of the mean ratio (*S*/*R*) of the cumulative percentages of (*R*)- and (*S*)-propranolol hydrochloride enantiomers released from hydroxypropyl methylcellulose matrices in the four experiments showing stereoselectivity in dissolution. The vertical bars represent the standard deviations (n = 4).

The general equation that describes the kinetics of solute release from a controlled-release polymer (20) is given by Eq. (1).

$$R = kt^n \quad (1)$$

where R is the fraction of drug released, k is the kinetic constant, t is the release time, and n is the release exponent. The best fits of the data to this equation afford the following: for (*R*)-propranolol hydrochloride, $k = 0.523$, $n = 0.767$, $r^2 = 0.990$; and for (*S*)-propranolol hydrochloride, $k = 0.538$, $n = 0.777$, $r^2 = 0.990$. The magnitudes of the n values are between 0.5 and 1, suggesting that the release is controlled by both diffusion of the drug in the hydrated matrix and the erosion of the matrix itself (21). The stereoselective release observed in the present study may arise from a difference in the diffusivities of the two enantiomers in the chiral translucent hydrated layer next to the chiral matrix and/or may reflect a difference in complexation constant of each enantiomer with the chiral excipient in the hydrated layer. Such a difference in complexation constant would correspond to a difference in the partition coefficient of each enantiomer between the bulk water and the hydrated layer of HPMC.

The two dissolution experiments exhibiting irregular, nonsigmoidal release did not exhibit any significant difference between the (*R*)- and the (*S*)-enantiomers (Fig. 4). The lack of stereoselectivity may arise from an irregular, non-diffusion-controlled release from the matrices. The lack of stereoselectivity in these two experiments emphasizes that the stereoselectivity observed in the four experiments showing a sigmoidal release profile is not an analytical artifact but is a real effect.

Dissolution of the Enantiomers from the β-Cyclodextrin Complex

The β-cyclodextrin complex of racemic propranolol hydrochloride was found to be in the amorphous state (Fig. 2) and hence is expected to have a high aqueous solubility. Compacted disks prepared from the amorphous complex gave constant dissolution rates for 15 min, during which the surface area remained constant. However, the dissolution rate was so high that, after 20 min, the surface area of the dissolving disk no longer remained constant and the shape of the disk became concave, with the subsequent formation of a hole at the center. The disk dissolved completely in 30 min. From the cumulative amounts released as functions of time, the release rates of the individual enantiomers, during the first 15 min while the surface area of the disk remained constant, were 1.42 ± 0.16 mg/min cm^2 for *R* and 1.45 ± 0.18 mg/min cm^2 for *S*, with no significant difference ($P > 0.05$). Thus, no stereoselectivity in release of the two enantiomers from the β-cyclodextrin complex was observed.

The computer-generated projections of the lowest free energy inclusions of the propranolol enantiomers with β-cyclodextrin show that the enantiomers are almost completely included in the cavity of β-cyclodextrin and differ only in the interaction of their secondary amine group with the 2- and 3-hydroxyl groups of β-cyclodextrin (13). Since the molecules are almost completely included in the cavity, the solubility of the complex will be influenced more by the interaction of the water molecules with β-cyclodextrin than by their interaction with the individual enantiomers. Thus, the complexes of the two enantiomers with β-cyclodextrin are expected to have similar, if not the same, solubilities. Further, it appears that the lack of stereoselectivity may also arise from the rapidity of dissolution which renders difficult the analytical detection of any difference between the intrinsic dissolution rates. Therefore, a deliberate reduction in the solubility of the "complex" by utilizing a more hydrophobic derivative of β-cyclodextrin, such as ethylated β-cyclodextrin, may render the analytical detection of the difference easier. This hypothesis is currently under investigation.

In conclusion, the sigmoidal release profile of propranolol hydrochloride enantiomers from the E4M-grade HPMC matrices containing the racemic drug was found to be stereoselective (S:R ratio equals 1.07 ± 0.01), probably because of stereoselective diffusion of the enantiomers through the chiral environment of the hydrated matrix and/or stereoselective complexation of the enantiomers with the hydrated chiral polymer. When the release from this type of system exhibited plateaus or burst effects, a loss of stereoselectivity, corresponding to an S:R ratio equal to unity, was observed. There was no significant difference in the release rates of the two enantiomers of propranolol hydrochloride from the amorphous inclusion "complex" prepared from β-cyclodextrin and racemic propranolol hydrochloride.

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