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Preparation and evaluation of a novel delayed-onset sustained-release system of propranolol hydrochloride

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Abstract

The objective of this work was to prepare and evaluate a new delayed-onset sustained-release system, comprising a sustained-release core tablet with hydroxypropyl methylcellulose as polymer matrix and an ethylcellulose/Eudragit L coating capable of delaying the drug release. The sustained core containing propranolol hydrochloride as the model drug was prepared by granulate tableting and the polymer coating was applied in a computer-controlled coating pan. The dissolution tests demonstrated that the in-vitro drug release was pH-dependent with sufficient gastric resistance, and the lag time ($t_{10\%}$) could be controlled by adjusting the coating level. Three dosage forms including commercial tablet, sustained-release tablet and the delayed-onset sustained-release tablet were administrated to six beagle dogs and the plasma levels of propranolol hydrochloride were measured with high-performance liquid chromatography. The delayed-onset sustained-release tablet had a lag time of 3.0 h in-vitro and 3.5 h in-vivo, and a t_{max} of 7.0 h. The relative bioavailability for delayed-onset sustained-release tablet was 96.98% compared with commercial tablets. The results indicate that the new propranolol delayed-onset sustained-release system could achieve a relatively constant drug release followed by a programmed lag time, and this may provide a promising drug delivery form for chronopharmacotherapy of certain cardiovascular diseases.

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Introduction

Conventional sustained and controlled release drug delivery systems are based on single- or multiple-unit reservoir matrix systems, which are designed to provide more constant plasma levels over an extended period of time (Verma & Garg 2004; Goole et al 2007). However, a constant drug level is not always desirable for some diseases that follow temporal rhythms or for drugs with special pharmacokinetic features according to the circadian rhythms of patients (Goldbete & Claude 2002; Lemmer 2004).

Much effort has been devoted to the development of time-controlled delivery systems that can immediately release active agents after a controlled lag time (Lin et al 2001; Cao et al 2004; McConville et al 2005; Badve et al 2007; Zou et al 2008), that is a pulsatile release system. Thus, drug therapy could be used to achieve an effective drug level at a desired time, thereby minimizing adverse effects.

Clinical studies have demonstrated that the middle of the night and the morning hours are periods of high risk for cardiovascular events, including ischaemia and cerebral infarction (White 2001; Lemmer 2005, 2006). In these cases, a pulsatile release system that can release drug rapidly and completely after a lag time may not provide a sufficiently long period of therapeutic drug levels. Thus, a drug delivery system that could both delay release onset and maintain a sustained period of therapeutic drug levels has been designed. A 24-h controlled-onset extended-release delivery system (COER-24) for verapamil hydrochloride designed for bedtime administration has been approved for the treatment of hypertension and angina. It provides the highest concentration of drug in the blood during the early hours of the day when blood pressure and heart rate are rising rapidly (Carter 1998). Other chronopharmacologic delivery systems have been designed for the treatment of cardiovascular diseases. For example, a diltiazem hydrochloride delayed-onset sustained-release tablet has been developed by press coating (Ning & Jiabi 2002). The release profile was characterized by a lag time followed by steady drug release. Compression-coated time-release tablets

containing nifedipine have also been prepared by dry coating; the formulation showed a clear lag period before the initiation of nifedipine release, followed by sustained drug release lasting up to 24 h (Sawada et al 2004). However, in general, compared with liquid-based coatings (organic polymer solutions or aqueous polymer dispersions), with compression-coating techniques it is difficult to position the core in the centre of the unit, resulting in uniform retarding layers and relatively high amounts of polymer (Gazzaniga et al 1994).

Propranolol hydrochloride, a potent β-receptor blocker that has been used clinically as an anti-anginal and antihypertensive agent, has been successfully developed into types of sustained or controlled release systems (Mohammadi-Samani et al 2000; Halder & Sa 2006; Phaechamud & Ritthidej 2007) and pulsatile release systems (Ross et al 2000; Mohamad & Dashevsky 2006; Barzegar-Jalali 2007). However, no delayed-onset sustained-release system for propranolol hydrochloride has been reported to date. In this work, we focused on developing a new propranolol hydrochloride delayed-onset sustained-release system intended for chronopharmacotherapy.

Materials and Methods

Chemicals

Propranolol hydrochloride was obtained from Jiangsu Linhai Pharmaceuticals Co., (JinTan, Jiangsu, China). Hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) were from Colorcon (Shanghai) Co. Ltd., Shanghai, China. Lactose, $CaHPO_4$ and magnesium stearate were obtained from Huzhou of Zhejiang Province (China). PVP K30 and Eudragit L were gifts from ISP (Hong Kong) Ltd, Shanghai, China and Rohm (Germany), Shanghai, China, respectively. All other chemicals and solvents were of reagent grade.

Preparation of delayed-onset sustained-release tablet (DST)

The mixture for compression of the core tablets was obtained by manually granulating propranolol hydrochloride (20% w/w), HPMC K4M (10% w/w), HPMC K100LV (15% w/w), lactose (31% w/w), $CaHPO_4$ (23% w/w) with PVP K30 (15% w/w; ISP). Following drying, sieving and blending for 10 min, magnesium stearate (1%) was added to the external phase, the mixture was blended for a further 5 min, and then tableted in a rotary machine (Shanghai Huanghe Medical Machine Ltd Co., Shanghai, China), equipped with concave punches (8 mm diam.). The tablet cores were characterized by weight (balance E 400 D; Ohaus, Florham Park, NJ, USA), crushing strength (crushing tester YD-1; Tianjin Optical Instrument Factory, China), and friability (friabilometer CS-2; Tianjin Optical Instrument Factory, China). Weight measurements were performed on 20 units, while crushing strength and friability were determined on 10 units.

The coating was carried out in a computer-controlled pan with a rotation speed of 32 rev min^{-1}. EC (10 cps) and Eudragit L were dissolved in ethanol (95% v/v) by stirring overnight until a clear solution was obtained. The following process conditions were used: an inlet temperature of 45–47°C, a product temperature of 30–32°C, a nozzle diameter of 1.2 mm, an atomizing air pressure of 1.5 bar, and a spray rate of 1.5 mL min^{-1}. After the coating process, the coated tablets were further dried in the coating pan for 15 min at 40°C and then placed in an oven at 40°C for 2 h to remove residual solvent.

In-vitro dissolution studies

The dissolution test was carried out using the CP 2000 basket method, with a rotation speed of 100 rev min^{-1} and 1000 mL of medium at 37°C (n = 6). The dissolution medium was hydrochloric acid solution at pH 1.2 for the first 2 h, and was then replaced with the phosphate buffer solution, pH 7.4. The amount of propranolol hydrochloride dissolved was assayed by high-performance liquid chromatography at a detection wavelength of 290 nm. The DSTs were additionally tested in media at pH 2, 5.4, 6.8 and 7.4, to investigate the gastric resistance of the drug delivery system.

Surface morphology

Photographs of the surface of the DST coating film were taken before and after a 1.5-h release test in phosphate buffer at pH 5.4, 6.8 and 7.4 (DST-5.4, DST-6.8 and DST-7.4, respectively) using a scanning electron microscope (FEI Company, Hillsboro, OR, USA) to evaluate coating integrity. The samples were dried and coated with gold using a direct current sputter technique.

In-vivo study

Six male beagle dogs, 12 ± 1 kg, were randomly assigned to crossover treatments with a 7-day washout period. The dogs received a standard low calorie meal 2 h before administration of the tablets with 200 mL water at room temperature.

The treatments were as follows: (i) three 40-mg commercial tablets (CT); (ii) three 40-mg sustained-release core tablets (ST); and (iii) three 40-mg delayed-onset sustained-release tablets (DST). Blood samples were taken immediately before administration and at the following times after each treatment: CT 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h; ST 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h; and DST 1, 2, 3, 3.5, 4, 5, 6, 7, 8, 12 and 24 h. Plasma samples were stored at −20°C until assayed.

Plasma assay

Propranolol hydrochloride in plasma was assayed with reversed-phase high-performance liquid chromatography (Kim et al 2001; Sica et al 2003). Into each screw-cap tube (10 mL) was added 1.0 mL of plasma sample, 10 μL of internal standard solution (0.5 mg mL^{-1} procainamide hydrochloride), 0.8 mL NaOH (0.1 M) solution and 5.0 mL ether. The samples were extracted using a vortex shaker. After centrifugation (10 min, 3000 rev min^{-1}), the organic layer was collected and evaporated under N_2 flow at 50°C. Then, 100 μL of mobile phase was added to dissolve the residue and a 20-μL aliquot was injected into the reversed-phase column (Hypersil 250 mm × 4.6 mm, 10 μm) for separation. The mobile phase comprised acetonitrile and phosphate solution (pH 3.4), containing 0.2% triethylamine (60:40). At a flow rate of 1.0 mL min^{-1},

the eluate was monitored for absorbance at 232 nm and column temperate of 35°C.

Pharmacokinetic data analysis

Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and the lag time (t_{lag}), were obtained from the plasma concentration–time curve. The area under the plasma concentration–time curve (AUC) was calculated by the trapezoidal method (0–24 h). The elimination rate constant k_e was calculated from the slope of the logarithm of concentration to time at the end of the plasma concentration–time curve.

Statistical analyses were conducted using analysis of variance for repeated measurements. Bioequivalence of the tablets was evaluated by the 90% confidence interval of the ratio of DST to CT for $AUC_{0–24\,h}$ after a logarithmic transformation. Bioequivalence was rejected if the 90% confidence interval of the ratio was outside the range 0.80–1.25 and 0.7–1.45 with respect to $AUC_{0–24\,h}$, using two one-sided tests.

Results and Discussion

Preparation of delayed-onset sustained-release tablet

We sought to prepare a delayed-onset sustained-release system, an oral dosage form designed to achieve sustained delivery after a controlled lag phase. The delivery system was developed by simultaneously exploiting the prolonged release characteristics of HPMC and the pH-dependent solubility properties of the methacrylic polymer Eudragit L. The working mechanism was primarily based on exploitation of the interaction between ethylcellulose/Eudragit L polymeric coatings and aqueous gastrointestinal fluids. A single-unit system was chosen because the preparation is faster, more economical and involves fewer processing variables than a multiple-unit system, making industrial scale-up easier.

To investigate the use of ethylcellulose and Eudragit L as retarding agents for the delayed-onset sustained-release system, propranolol-containing cores were coated with polymer up to approximately 10% (w/w). This coating level was chosen as it could reasonably be reached within an acceptable process time. A solution temperature of 35°C was chosen as, by decreasing solution viscosity, it enabled the achievement of an acceptable spray rate and was easily maintainable throughout the whole coating process.

In-vitro drug release

The in-vitro release profiles of CT, ST and DST are shown in Figure 1. More than 90% of the content of the CT was released within 30 min, a typical immediate release result. The ST released more than 90% of its propranolol hydrochloride over an extended period of 5 h. With regard to DST, release of the model drug was delayed by the polymeric coating and, when it did occur, the polymers provided a delay that increased as a function of the thickness of the coating film (Figure 2).

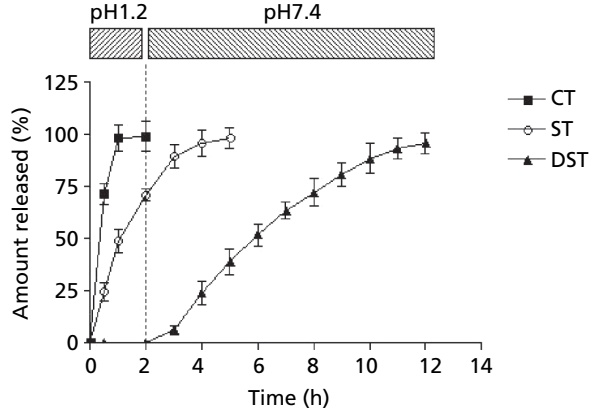

Figure 1 Release profiles obtained from commercial tablets (CT), sustained-release tablets (ST) and delayed-onset sustained-release tablets (DST) in simulated gastric (pH 1.2) and intestinal fluids (pH 7.4) (n = 6).

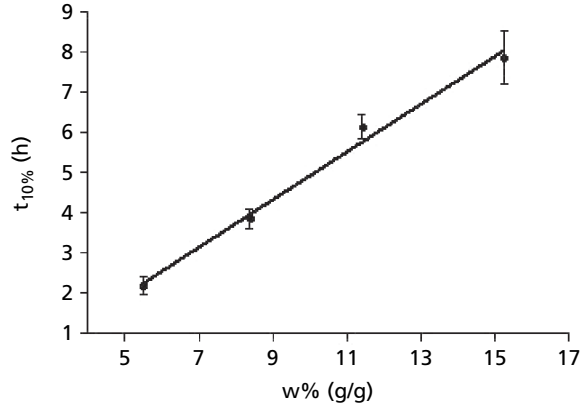

Figure 2 Relation between film weight and release lag time $t_{10\%}$. The $t_{10\%}$ increased linearly with increasing film thickness ($t_{10\%} = 0.596$ w% – 1.040, $R^2 = 0.99$) (n = 6).

The experimental data were fitted to Hixon–Crowell, Higuchi and zero-order equations (Eqns 1–3, respectively):

$$Q = 1 - (1 - kt)^3 \quad (1)$$

$$Q = b + kt^{1/2} \quad (2)$$

$$Q = a + kt \quad (3)$$

where Q is the fraction of drug released up to time t, and K is the kinetic constant. The Hixon–Crowell equation indicates an erosion-depended release mechanism. On the other hand, the Higuchi equation expresses a diffuse release mechanism. The dissolution data of ST and DST best fitted the Hixon–Crowell and, subsequently, the Higuchi equation. This indicated that the dissolution was both diffusion and erosion dependent.

A linear relation was found between coating level and lag time, the $t_{10\%}$ value increasing linearly with increasing film thickness ($t_{10\%} = 0.596$ w% – 1.040, $R^2 = 0.99$). Thus, the lag

time can be controlled by altering the thickness of the coating film.

To study the influence of pH, the DSTs were tested in media at pH 2, 5.4, 6.8 and 7.4. At pH 2 and 5.4, almost no drug delivery took place during the entire test. However, constant drug release was observed at pH values above 6, following a lag phase (Figure 3). An apparent decrease in delay duration was noticed in the tests performed at pH 7.4 compared with those carried out at pH 6.8. This suggests that enteric coating with Eudragit L can be successfully used to achieve gastric resistance and delayed-onset of the system and the in-vitro behaviour seems to be affected by pH over the physiological range for gastrointestinal fluids.

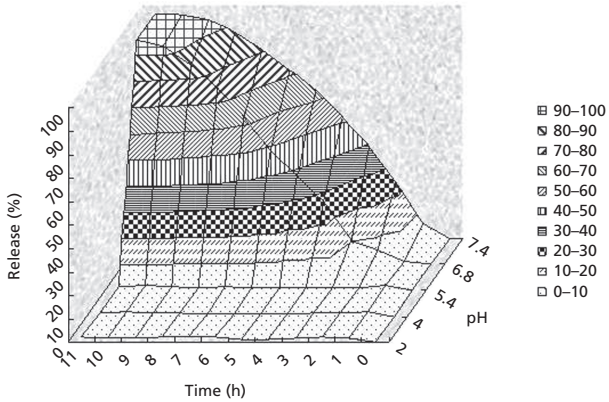

Figure 3 Three-dimensional topographic representation of drug release as a function of time and pH for delayed-onset sustained-release tablets tested in media at pH 2, 4, 5.4, 6.8 and 7.4. (n = 6)

Surface morphology

The coating film of DST-5.4 was not noticeably different from that of the intact DST; both showed a similar, homogeneous and quite compact surface (Figure 4A, B). In contrast, the surface of the DST-6.8 showed limited eroded areas, indicating that because of limited dissolution of the pH-sensitive Eudragit L, drug diffusion could take place through a porous network filled by solvent penetrating into the matrix (Figure 4C). In the case of DST-7.4, numerous pores and channels were observed. There are two possible reasons for this. First, the coating layer progressively dissolved in the pH 7.4 dissolution medium, allowing the matrix core to be exposed and allowing slow release of the drug. Second, the medium penetrated into the core during the release test, inducing swelling of the hydrophilic HPMC matrix, which may help to break the coating, producing deep fractures and irregular cavities that were apparent on the tablet surface (Figure 4D). These morphological results were consistent with the dissolution test results at different pHs (Figure 3).

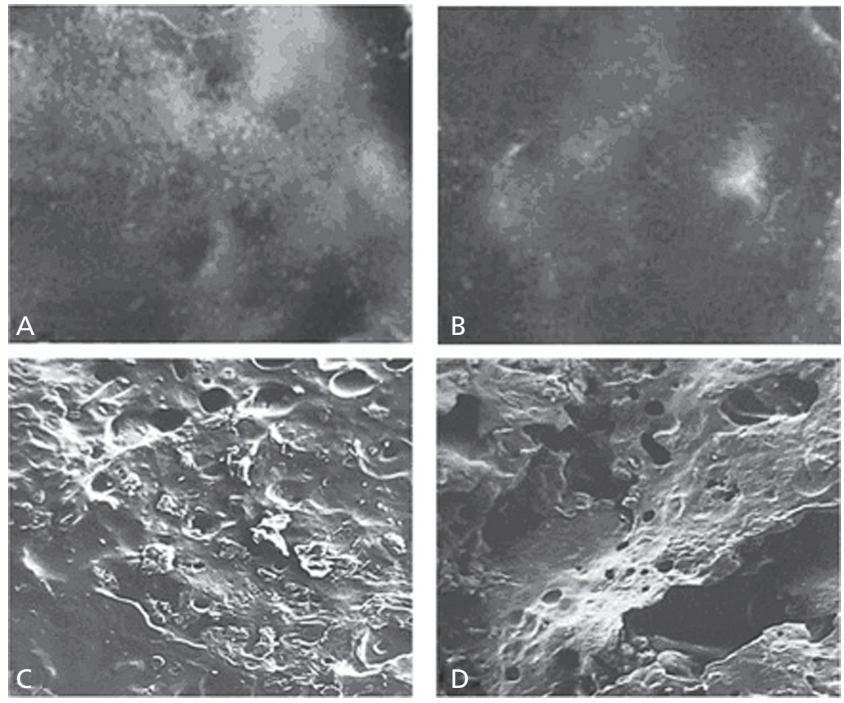

Figure 4 Scanning electron micrographs of the surface of the coating film of delayed-onset sustained-release tablets (DST). The samples are intact DST (A) and DST 1.5 h after the release test in media at pH 5.4 (B), pH 6.8 (C) and pH 7.4 (D). A. Propranolol hydrochloride release was 1.23%; the intact surface showed a smooth morphology. B. Propranolol hydrochloride release was 1.15%; the surface also showed a relatively smooth morphology as the film does not dissolve under pH 5.4; C and D. Propranolol hydrochloride release was 4.59% and 11.23%, respectively; the surface was porous due to dissolution of Eudragit L in a solution of pH above 6.

In-vivo results

The mean plasma concentration curves after oral administration of the different dosage forms to six beagle dogs are shown in Figure 5. Pharmacokinetic parameters and differences between the formulations are summarized in Table 1.

It has been reported that the age and sex of animals can influence the absorption of drugs (Katori et al 1995; Kamba et al 2002; Noble 2003; Schwartz 2003). The animals used were male dogs, aged 3 ± 0.5 years. Regardless, the drug plasma concentration displayed relatively large inter-individual variation, especially at t_{max}. This may be partly accounted for by different small intestinal motility in the dogs (Kamba et al 2002) and high inter-individual differences with propranolol (Tam 1993).

The CT and ST did not exhibit any obvious lag time before drug release, while the DST exhibited an apparent lag time of approximately 3.5 h. This lag was because of the presence of the exterior of the EC/Eudragit L film, which prevented the core tablet from being exposed during gastric residence. The in-vitro dissolution test with the ST showed that more than 90% of the drug was released within 5 h. The plasma levels resulting from the ST and DST were quite constant, being 2–8 h and 4–12 h, respectively. That is, the in-vivo therapeutic time values of DST were comparable with the corresponding in-vitro releasing time, however this needs to be further clarified.

There were significant differences in k_e and t_{lag} between ST and DST. The k_e value for DST was lower and the t_{lag} was longer, suggesting that the DST not only prolonged the lag time, but also lowered the elimination rate to some degree. The relative bioavailability was 96.98% for DST, indicating that the absorption of propranolol hydrochloride was not influenced by the in-vivo behaviour of the tablets. Nevertheless, the small intestinal motility pattern of animals does not correlate with the dissolution test (Katori et al 1995) and the lag time should be carefully adjusted and monitored to meet chronopharmacological requirements.

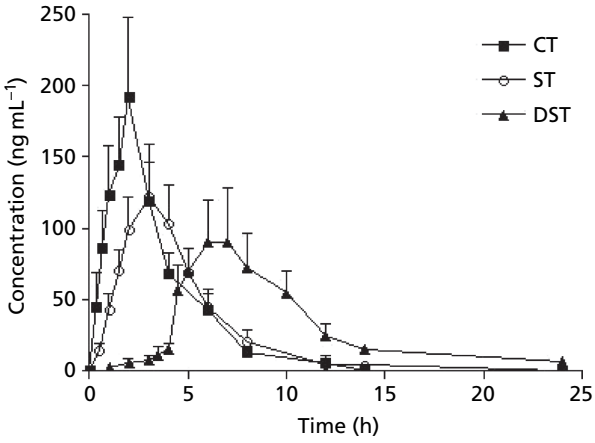

Figure 5 Propranolol hydrochloride plasma concentration–time profiles in healthy beagle dogs after oral administration of commercial tablets (CT), sustained-release tablets (ST) and delayed-onset sustained-release tablets (DST) (n = 6).

Conclusion

The delayed-onset sustained-release system is an oral dosage form designed to achieve sustained delivery after a controlled lag phase. The system consisted of a propranolol hydrochloride core with HPMC as a retarding material, and a coating film of ethylcellulose/Eudragit L. The working mechanism was largely based on the exploitation of the interaction between the ethylcellulose/Eudragit L polymeric coating and the aqueous gastrointestinal environment. The in-vitro release profile of propranolol hydrochloride from the DST Fits well the Hixon–Crowell equation after the lag time. The lag time and the release rate could be controlled by altering the thickness of the coating film. The in-vivo pharmacokinetic data demonstrate the ability of the system to release drugs after a programmed lag time in a gastro-resistant manner. By administration shortly before bedtime, the delayed-onset sustained-release system offers a promising method for the treatment and prevention of cardiovascular disorders that occur in the early morning.

Table 1 Comparison of in-vivo pharmacokinetic parameters between commercial tablets (CT), sustained-release tablets (ST) and delayed-onset sustained-release tablets (DST) (n = 6)

Parameter	CT	ST	DST
C_{max} (ng mL^{-1})	191.40 ± 56.52	121.49 ± 37.62*	60.90 ± 41.23*,†
t_{max} (h)	1.92 ± 0.204	2.83 ± 0.408	6.25 ± 0.987*,†
k_e (h^{-1})	0.157 ± 0.082	0.169 ± 0.075	0.117 ± 0.066*,†
t (h)[a]	4.41 ± 1.42	4.10 ± 1.23	6.30 ± 2.29*
t_{lag} (h)	–	–	3.5 ± 0.45*,†
$AUC_{0–24}$ (ng h mL^{-1})	697.79 ± 125.33	615.34 ± 119.25	676.74 ± 156.91
Relative bioavailability (%)	100	88.18	96.98

C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; k_e, elimination rate constant; t, the time after the lag time (t_{lag}); $AUC_{0–24}$, area under the plasma concentration–time curve 0–24 h. *$P < 0.05$ significantly different compared with the CT group. †$P < 0.05$ significantly different compared with the ST group.

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