—Regular Articles—

A Novel Osmotic Pump Tablet Using Core of Drug-resin Complexes for Time-controlled Delivery System

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A novel elementary osmotic pump tablet was developed. The system uses the core of drug-resin complexes (DRCs) loaded with propranolol hydrochloride (PNH) for time-controlled delivery. In traditional osmotic pump tablets (OPTs), the lag time was always minimized. However, in the DRCs osmotic pump tablet (DRCOPT), the lag time was increased to achieve the time-controlled delivery. The quantity of osmotic agent in the core and channeling agent in the coating solution as well as weight gain were confirmed to be essential for the release behavior. A spherical symmetric design was applied to the optimization of the DRCOPT. The optimal formulation mainly consisted of DRC 100 mg, polyethyleneoxide (N80) 182 mg, and NaCl 30 mg. The ratio of cellulose acetate (CA)/polyethylene glycol 4000 was 15 : 3 (w/w) in coating solution, and the weight gain was 8%. The release behavior of the optimal DRCOPT was evaluated in media with different pH, rotation speeds, and ionic strength. It was found to generate a 2-h lag time, to deliver PNH at a rate of zero order from 2 h to 14 h in the medium of NaCl 0.15 mol/l, and the cumulative release at 24 h was 94%. Drug relee was independent of pH and rotation speed, but was proportional to ionic strength. In summary, the lag time could be used in therapeutic regimens with the characteristics of chronotherapy because of the lag time and provides a new concept for the development of osmotic pumps.

Key words——drug-resin complexes; osmotic pump tablet; time-controlled delivery; chronotherapy; spherical symmetric design; propranolol hydrochloride

INTRODUCTION

The osmotic pump tablet (OPT) is an advanced drug-delivery technology that uses osmotic pressure as the driving force to deliver pharmacotherapy, usually once daily, in several therapeutic areas, which was developed as an oral drug-delivery system. In the historical development of the OPT, there were many achievements for its promotion, including the Rose-Nelson pump,[1] Higuchi-Leeper pump,[2,3] elementary osmotic pump tablet (EOPT),[4] and push-pull system.[5] In recent years, many novel technologies and formulations related to the OPT have been developed, such as osmotic drug delivery using swellable-core technology,[6] effervescent OPT from a traditional Chinese medicine compound recipe,[7] (SBE) 7m-β-CD in controlled-porosity OPT,[8] and other new approaches.

Ion-exchange resins (IERs) are crosslinked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and for controlled-release systems in liquid or solid form.[9–11] IERs behave, for some drugs, as reliable, controlled drug-delivery systems.[12] However, improvements of their release properties can be affected by coating the resin beads and further controlling the rate of drug release.[13–16] In these forms, the pattern of drug release is governed by the degree of cross-linking of the resins and by the properties of the coat.

Propranolol hydrochloride (PNH) was chosen as the model drug. PNH is a nonselective Beta-adrenergic blocking agent and has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders.[17] Patients with cardiovascular disease are at the greatest risk of heart attack and stroke during the early hours of the morning (02:00), and there is a need for adequate control of hypertension during this vulnerable period. It is necessary to develop a time-controlled system to achieve an effective drug level only at the demanded time.

In previous studies, drug-resin complex (DRCs) have been employed in controlled release with numer-

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ous types of materials such as poly (4-vinylpyridine), sulphonic acid cation-exchange resin, and sodium polystyrene sulfonate, and there were several reports on PNH-resin complexes, for example, calcium alginate beads loaded with PNH-resin complexes,[18] poly (acrylic acid) grafted poly (vinylidene fluoride) membrane,[19] and polymeric microparticles.[20] The first report concerning the use of a DRC to modulate osmotic pump tablets was published in 1990.[21] Furthermore, the effects of IERs on the release of PNH-matrix tablets were studied in 1998.[22] The paper focused on the combination of an OPT and IER to prepare a novel osmotic pump tablet for time-controlled delivery. Unlike other EOPT systems,[23,24] this delivery system showed a steady zero-order release profile after an initial lag time, which is the difference between the DRCOPT and other approaches.

In this study, cores consisting mainly of DRCs, polyethyleneoxide (PEO), and sodium chloride were coated with a semipermeable membrane and an orifice was drilled. A 2-h lag time was observed and steadier drug release behavior was achieved in *in vitro* experiments. The DRCOPT not only improved the application of the OPT in the direction of time-controlled release by combinating the EOPT and IER, but also controlled the drug-release rate. In addition, the lag time provided a new concept for preparing a novel EOPT for a time-controlled system. It could also provide a method to achieve an effective drug level only at the demanded time using the DRCOPT.

MATERIALS AND METHODS

Materials Propranolol HCl (Rouz Darou Co.) and the cation-exchange resin Amberlite IRP69 (sodium polystyrene sulfonate) was obtained from Rohm and Haas Company, Philadelphia, PA, USA; sodium chloride, mannitol, and lactose (Tianjin Bo-di Chemical Industry, Tianjin, China), cellulose acetate (CA, Shanghai Chemical Reagent, Shanghai, China), and hydroxypropylmethylcellulose (HPMC, K4M Colorcon, UK), sodium carboxymethyl cellulose (CMC-Na, Colorcon), polyethyleneoxide (PEO, Dow Chemical, NJ, USA), and polyethylene glycol 1500, 4000, and 20000 (PEG, Shenyang Chemical Reagent, Shenyang, China), polycinylpyrrolidone K30, K90, S630 (PVP, ISP Technologies Inc.) were employed in the experiments. All other reagents used were of analytical grade.

PREPARATION OF DRCOPT

Preparation of Cores DRCs were prepared using the batch method. In this experiment, IERs were suspended in a specific concentration of PNH dissolved in deionized water under magnetic stirring at constant temperature and thereafter sampled and the concentration determined at predetermined time points. After exchange reached the balance point, the DRCs were washed free of the exchange salt and any free drug with deionized water. The drug-loaded resin beads obtained were dried in a fluid bed at 40°C.

Tableting and Coating The dried drug-loaded resin beads (100 mg), and other excipients were sieved through 160 mesh separately and mixed (except for magnesium stearate) for 10 min. To the mixture, sieved magnesium stearate (3 mg) was added and the blend continued for 10 m longer. The dried powders were directly compressed using a single-punch tableting machine (Shanghai Huanghai Drug Inspection Instrument, Shanghai, China) with a 9.0-mm bulgy-faced punch to yeild a 0.33-g tablet each time. The hardness of the tablets was kept constant (3 kg, hardness tester, Idem, Shanghai, China). The tablet core was coated with coating fluid composed of different ratios of CA to PEG, forming a semi permeable membrane. A 0.6 mm orifice was drilled on the membrane surface mechanically. In this study, formulation 1 was coated to a weight gain of 6%, 8% and 10% of the core, respectively, while the other formulations were 8% of the core. Different core formulations and coating solutions are listed in Table 1.

Optimization of the Formulation The spherical symmetric design was applied to optimize the formulation. This experimental design required 15 experiments in total (2^n+2n+1, where n is the number of factors). The ranges of three factors and five levels were determined based on preliminary experiments. The cumulative release during 24 h (Q_{24}), linear degree of zero order from 2 h to 14 h by the means of the least-squares method, and ratio of the cumulative release at 16 h (Q_{16}) to that at 24 h (Q_{24}) were set as indexes to optimize the formulations.

***In Vitro* Drug Release** The release of drug from the core of the DRCOPT (equivalent to PNH 40 mg) was determined using the paddle method of the USP Pharmacopoeia Dissolution Apparatus test (50 rpm, 37°C). The dissolution medium (900 ml) was NaCl

Table 1. Different Core Formulations and Coating Solutions

Ingredient (mg)	Composition number														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Drug-resin complexes	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
PEO (N10)	182														
PEO (N80)		182				192	172	182	182	192	172	182	182	182	182
PEO (N750)			182												
CMC-Na				182											
HPMC					182										
NaCl	30	30	30	30	30	20	40			30	30	30	30	30	30
Lactose								30							
Mannitol									30						
PVP	15	15	15	15	15	15	15	15	15	5	25	15	15	15	15
Coating material (g)	Composition ratio of coating material														
Cellulose acetate	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
PEG 1500												6			
PEG 4000	6	6	6	6	6	6	6	6	6	6	6			2	4
PEG 20000													6		

F : 1～15, formulations 1～15.

0.15 mol/l solution. Medium 5.0 ml was withdrawn at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, and 24.0 h and replaced with 5.0 ml of fresh dissolution media. The mean of three tablets was used to calculate the amount of drug released from the samples. The amount of drug release was determined by measuring the absorbance with a spectrophotometer (UV9100, Beijing Ruili Analytical Apparatus, Beijing, China) at 290 nm.

Effects of Dissolution Medium To investigate the effects of the pH value of the dissolution medium on DRCOPT release behavior, release tests were carried out in 1) simulated gastric fluid (SGF), pH 1.2; 2) simulated intestinal fluid (SIF), pH 6.8; 3) SGF for 2 h and SIF for up to 24 h; 4) simulated colonic fluid (SCF), pH 7.4.[25] All were adjusted to the same ionic strength with NaCl.

Effects of Ionic Strength Sodium chloride solutions with different ionic strengths of 0.05 mol/l, 0.10 mol/l, and 0.15 mol/l were prepared to study the effects of ionic strength on release behavior.

Effects of Rotation Speed Dissolution tests were conducted at different rotation speeds of 50 rpm, 75 rpm, and 100 rpm to investigate the effects of rotation speed on release behavior.

Lag Time To compare the lag time of the DRCOPT with that of the conventional OPT, different tablet cores were designed. One was the optimal the DRCOPT formulation, and the other was the same formulation in which only the DRCs were replaced with PNH with equal PNH content. After being coated with the specific coating solution, both were compared in an *in vitro* drug release test. At the same time, the DRCOPT cores without coating and DRCs were also examined in the same trial.

RESULTS AND DISCUSSION

***In Vitro* Characterization of Formulations** *In vitro* drug release profiles of different formulations under sink conditions are shown in Figs. 1–5. As evident from the dissolution profiles, differences in drug release behaviors were observed with the types and amounts of suspension agent, osmotic agent, binder, composition of coating solution, and weight gain. The similarity factor f_2 was used to evaluate the release behaviors among the different formulations.[26]

$$f_2 = 50 \times 1\ \mathrm{g}\{[+(1/T)\sum_{i=1}^{T}(\bar{x}_{ti}-\bar{x}_{ri})^2]^{-1/2} \times 100\}$$

Where, $\bar{x}_{ti}$ and $\bar{x}_{ri}$ represent the average percentage of drug released from the three test tablets and three reference tablets at the ith time point, respectively, and T is the number of time points tested. When the two profiles are identical, $f_2 = 100$. An average difference of 10% at all measured time points results in an f_2 value of 50. The US Food and Drug Administration has set a public standard of an f_2 value between 50

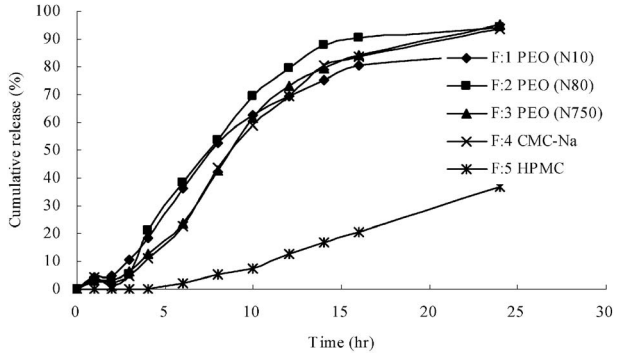

Fig. 1. Dissolution Release Profile of Propranolol Hydrochloride in the DRCOPT of Formulations 1–5 (n=3, mean)

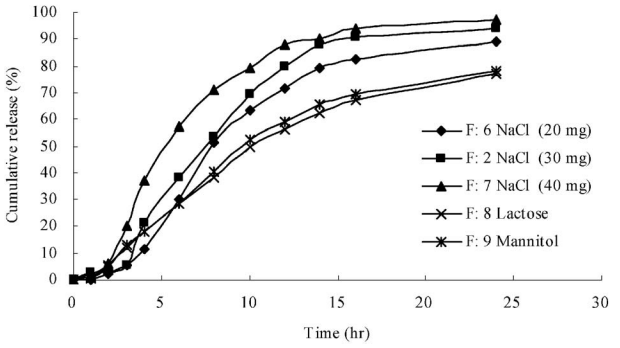

Fig. 2. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Formulations 2 and 6–9 (n=3, mean)

and 100 to indicate similarity between two dissolution profiles.

Restrictions associated with the use of the f_2 estimate include:

1) The dissolution measurements of the test and reference batches must be done under exactly the same conditions.

2) There should only be one measurement considered after either product has achieved 85% dissolution.

3) The percent coefficient of variation (CV) at the earliest points (*e.g.*, 15 min) should not exceed 20%, and the% CV should not exceed 10% at all other time points.

An f_2 value of 50 or greater (50–100) ensures the sameness or equivalence of the two curves, and thus the performance of the two products.[27,28]

As shown in Fig. 1, the cores of PEO (N80) exhibited a better release profile compared with those of HPMC (f_2=24.01), indicating that PEO (N80) had a better suspension function, because in the good suspension agent the DRC was suspended uniformly in the core when water entered. A microenvironment occurrs, in which NaCl gradually exchanges the drug with the DRCs. Thereafter, the exchanged drug is exported from the orifice. Although the cores of CMC-Na expressed a similar release behavior (f_2=58.56), the compressibility was inferior to that of PEO (N80). To compare the effects of different types of PEO on release behavior, PEO (N80) was replaced with PEO (N10) and PEO (N750), and similar profiles were obtained. The f_2 values with PEO (N80) were 65.70 for PEO (N10) and 60.70 for PEO (N750), respectively, demonstrating that the influence of PEO was minute. As a result, PEO (N80) was chosen as suspension agent in the core.

As shown in Fig. 2, varying the categories and quantity of osmotic agents in the cores had an obvious effect on the release behavior from formulations. Compared with NaCl, drug released from cores of lactose (f_2=47.45) and mannitol (f_2=48.88) as osmotic agents appeared to be more incomplete, which could be explained as follows. NaCl has two aspects of function. First, NaCl dissolved in the core created a constant osmotic pressure difference between the core ingredients and external environment, which could produce sufficient osmotic pressure to guarantee the impetus of drug release. In addition, NaCl is an ionic osmotic agent, which could provide the DRC with Na^+ to exchange drug, and this may cause the distinction in drug release between NaCl and other nonionic osmotic agents in the DRCOPT. To adjust the appropriate drug release, the quantity of NaCl was also studied to determine whether it influenced the release behavior. It was noted that the cumulative release increased as the quantity of NaCl rose. However, NaCl 30 mg in the core displayed a better zero-order profile than 20 mg (f_2=41.50) and 40 mg (f_2=71.54).

Because the core contained the DRC, the compressibility was very poor. PVP K30, PVP K90, and PVP S630 were used as binders to improve the compressibility. However, PVP K30 and PVP S630 could not produce sufficient binding power for direct tableting. As a result, PVP K90 was chosen as the binder. PVP can interfere with the drug release when an inappropriate quantity is used. Figure 3 shows no significant differences among different quantities of PVP. As far as the amount of PVP K90 was concerned, the core containing PVP K90 5 mg had poor

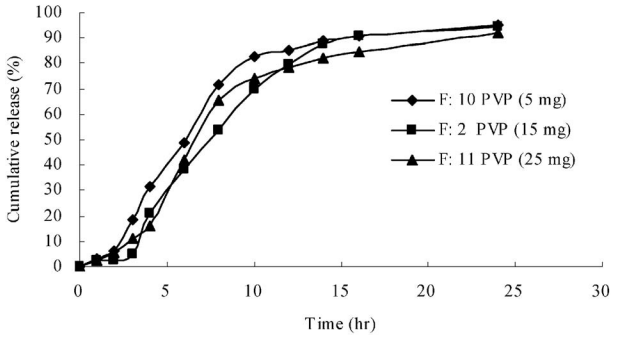

Fig. 3. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Formulations 2 and 10–11 (n=3, mean)

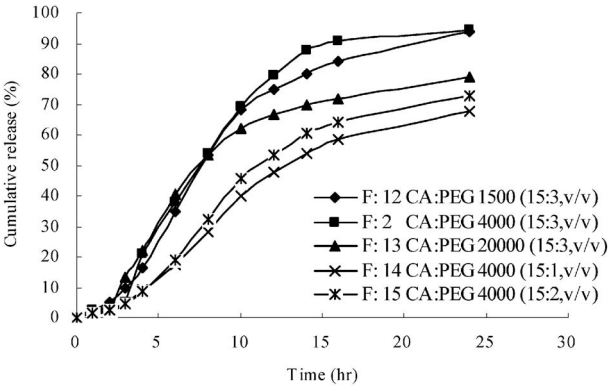

Fig. 4. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Formulations 2 and 12–15 (n=3, mean)

friability, while the core containing PVP K90 25 mg had high viscosity. Taking tableting and coating into account, 15 mg was chosen as the binder quantity.

In the case of coating factors, the types of PEG and CA/PEG ratio together with the weight gain were investigated to determine the effects on the drug release behavior from the same core. When the ratio of CA/PEG was kept constant, the types of PEG appeared to have an appreciable influence on the drug release rate. As the molecular weight (MW) of PEG increased, the drug release decreased. This is attributed to the dissolution of PEG in the medium, because the speed at which PEG dissolved was inversely proportional to MW. When PEG dissolved, the microspores in the coating membrane appeared, and the rate of water ingress was directly related to the drug release rate. As shown in Fig. 4, the release profile was the same before 10 h, and after that time point, PEG 4000 as the channeling agent manifested an advantage over PEG 1500 (f_2=63.86) and PEG 20000 (f_2=46.43), which could be elucidated as follows. In the initial period, all types of PEG have almost the same dissolving rate, and this tendency reached a critical time point, when the disparity in the rate of dissolving increases as the MW of PEG becomes greater. Generally, the components used in the DRCOPT should be common in pharmaceutical products, and therefore PEG 4000 was chosen as the channeling agent. Furthermore, the CA/PEG ratio used in the coating solution had an apparent effect on the drug release profiles because water intake through the coating depended on the quantity of PEG in the coating solution. The f_2 values of the CA/PEG ratio (15∶3) between ratio (15∶1) and ratio (15∶2) were 28.03 and 31.98, respectively. Coatings with the lower CA/PEG ratio released drug more quickly. The more PEG used in the solution, the more micropores occurred at the same time, leading to higher cumulative release. Thus the CA/PEG ratio can be regarded as a variable to control the drug release profile. All the f_2 values given in Figs. 1–4 are the results of other formulations compared with formulation 2 (F: 2).

The general expression for the drug delivery rate from an OPT tablet can be described as the following Eq. (1) of F. Theeuwes.[29]

$$dm/dt = AS/hLp\sigma\Delta\Pi + PAS/h \qquad (1)$$

Here, A is the OPT surface area, h is the thickness of coating, S is the solubility of drug, $Lp\sigma$ is the fluid permeability of the coating, P is the permeability coefficient of the active ingredient through the coat, and $\Delta\Pi$ is the osmotic pressure difference between the core inside and outer circumstance. From Eq. (1), we can see that the delivery rate is inversely proportional to membrane thickness, and quicker drug release occurs with decreasing coating thickness. For the same cores, coating thickness was related to the coating weight. Figure. 5 shows that the coating weight was a significant factor governing drug delivery. A comparison of different weights gain illustrated that the thicker coating had a lower release rate at corresponding time points, because water penetration was slower in cores with a thicker coating, which required a relatively longer time for sufficient water to fluidize the extruded drug. An 8% weight gain yielded better release behavior; on the contrary, irregular profiles were obtained when wei ght gain was 6% (f_2=39.93) and 10% (f_2=37.43) compared with 8% of the core. This is explained as follows. The thinner coating (6%) always reflects worse reproducibility, which in turn results in many disadvantages in experimental

operation and the further development for practical manufacture. In addition, the drug release profile with thicker coating (10%) could contribute to slower drug release, it takes a longer time to carry out the coating operation, and it requires more energy consumption to complete the experiment. Drug release is also hampered by a thicker coating, which may be responsible for the results in Fig. 5.

Optimization of Formulations Using the Spherical Symmetric Method According to the results of the *in vitro* characterization of formulations, the quantity of NaCl in the core, PEG in the coating solution and coating thickness had effects on the drug release behavior. That is, osmotic pressure attributes to the quantity of NaCl and CA/PEG ratio, and membrane permeability is attributed to coating thickness and the CA/PEG ratio.

A spherical symmetric design was applied to the optimization of the DRCOPT, and the levels and factors of spherical symmetric design are represented in Table 2.

As mentioned above, the cumulative release during 24 h (Q_{24}) could reflect the ultimate release of the DRCOPT. The linear degree of zero order from 2 h to 14 h expressed the minimum value, which was calculated by the sum of the square of distance for each point in the release profile to the straight line fitted by Excel. The smaller the values, the closer the release behavior approached zero order. The ratio of the cumulative release at 16 h (Q_{16}) to that at 24 h (Q_{24}) showed the drug release during the latter period. Therefore, the three parameters were set as indices to optimize the formulations. The experimental values are summarized in Table 3.

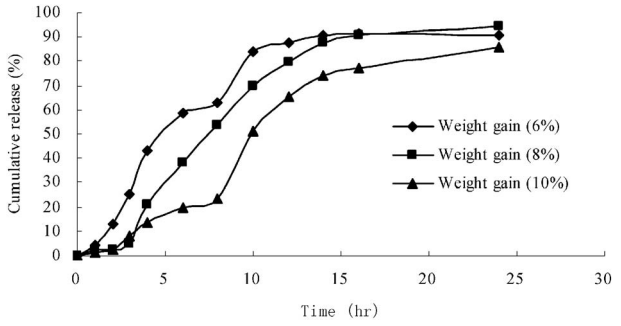

Fig. 5. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Different Coating Weight Gain (n=3, mean)

The purpose of the spherical symmetric design is to define the function relationship between indices investigated and chosen factors, which can be expressed as $y=f(x_1, x_2, x_3, \ldots\ldots)$. When applying the equation, the corresponding rule f is fitted by the regression of x and y, and any function can be extended as a polynomial, and thus $f(x)$ should be assumed to be a polynomial as follows.[30–32]

$$y=b_0+\Sigma b_i x_i+\Sigma b_{ij} x_i x_j+\Sigma b_{ijk} x_i x_j x_k+\ldots\ldots \quad (2)$$

Lingo software 8.0 (Lindo System Inc. USA) was used to fit each coefficient to Eq. (2), as shown in Table 4.

From the critical value of the F test, the F (n, m–n–1) of 99% significance level is 6.122, and the F values of the three indices are all greater than 6.122, which means that the polynomial fitting is reasonable. The limitations of three indices are regulated as follows. Q_{24} (y_1) should be greater than 90%, linear degree (y_2) was less than 0.00875 (the optimal value fitted by Lingo software), and Q_{16}/Q_{24} (y_3) was set to be greater than 95%. The regression of Eq. (2) was on the basis of experimental data, and each coefficient was obtained. The relationship between indices and factors is given below.

$$y_1=0.820126+0.036875x_1+0.030781x_2-0.02390x_3+0.008221x_1^2+0.011413x_1x_2+0.008284x_1x_3+0.018918x_2^2-0.00507x_2x_3-0.00905x_3^2.$$

$$y_2=0.00479+0.000825x_1+0.0014x_2-0.317x_3-1.260x_1^2+0.000208x_1x_2-0.000195x_1x_3+0.000348x_2^2-0.0066x_2x_3-0.001060x_3^2.$$

$$y_3=0.00835+0.00751x_1+0.0042x_2-0.00284x_3-0.00319x_1^2+0.00491x_1x_2+0.00745x_1x_3$$

Table 2. Levels and Factors in Spherical Symmetric Design

Factor	Factor levels in coded form				
	$-\sqrt{3}$	−1	0	1	$\sqrt{3}$
x_1 (NaCl, g)	20.000	24.226	30.000	35.744	40.000
x_2 (CA : PEG 4000)	15 : 1.000	15 : 1.164	15 : 1.500	15 : 2.109	15 : 3.000
x_3 (WG, %)	6.000	7.268	9.000	10.732	12.000

Table 3. Experimental Design for Three Factors and Experimental Values

Formulation	Factor levels in coded form			Experimental value		
	x_1	x_2	x_3	Q_{24} (%)	Linear degree ($\times 10^{-3}$)	Q_{16}/Q_{24} (%)
1	−1	−1	−1	81.7544	1.730	85.9532
2	−1	−1	1	76.4713	0.688	74.1908
3	−1	1	−1	85.0638	1.507	91.2344
4	−1	1	1	80.8722	2.805	82.0546
5	1	−1	−1	83.2631	2.844	85.2481
6	1	−1	1	84.4167	3.122	79.9901
7	1	1	−1	94.2611	8.434	96.0284
8	1	1	1	90.2648	1.093	86.2922
9	$-\sqrt{3}$	0	0	76.7031	0.244	83.6185
10	$-\sqrt{3}$	0	0	90.3205	1.855	81.5284
11	0	$-\sqrt{3}$	0	81.3710	1.797	83.2136
12	0	$\sqrt{3}$	0	92.0704	9.974	99.7383
13	0	0	$-\sqrt{3}$	84.4335	0.966	82.7953
14	0	0	$\sqrt{3}$	72.2276	2.338	80.5637
15	0	0	0	82.0132	4.792	83.4613

Table 4. Estimated Regression Coefficient of Second-order Polynomial Equation for Each Objective Variable Determined from Multiple Regression Analysis with the Lingo Program

Parameter	Q_{24}	Linear degree	Q_{16}/Q_{24}
b_0	0.820126	0.004790	0.00835
b_1	0.036875	0.000825	0.00751
b_2	0.030781	0.001400	0.0042
b_3	−0.02390	−0.000317	−0.00284
b_{11}	0.008221	−0.001260	−0.00319
b_{12}	0.011413	0.000208	0.00491
b_{13}	0.008284	−0.000195	0.00745
b_{22}	0.018918	0.000348	0.00265
b_{23}	−0.00507	−0.000660	−0.00238
b_{33}	−0.00905	−0.001060	−0.00617
$Q_{surplus}$	0.002882	0.0000288	0.00797
Q_{total}	0.052448	0.000109	0.05748
$Q_{regress}$	0.049566	0.0000804	0.04950
r	0.970491	0.881264	0.916037
F	63.05822	10.24276	22.79193

$$+0.00265x_2^2-0.00238x_2x_3-0.00617x_3^2.$$

The four optimal formulations (Table 5) were obtained from the inequality qualified by the conditions that $y_1>0.9$, $y_2<0.00875$, and $y_3>0.95$. Q_{24}, linear degree and Q_{16}/Q_{24} were anticipated values.

The four distinct formulation principles for the DRCOPT were prepared to verify the results of optimal formulations, which are illustrated in Table 6 and Fig. 6. It was found that there was good agreement between the experimental and predicted values. In addition, formulation *b* exhibited better *in vitro* release behavior, which was in line with every index. As a result, formulation *b* was determined to be the optimal formulation. In other words, there were DRCs 100 mg, PEO (N80) 182 mg, NaCl 30 mg and PVP K90 15 mg in the core. The ratio of CA/PEG 4000 was 15 : 3 in coating solution and the weight gain was 8%.

Table 5. Results of Optimal Formulations

Formulation	Parameter		
	X_1	X_2	X_3
a	25	5	6
b	30	5	8
c	35	5	10
d	40	5	12

Effects of Dissolution Medium To elucidate the effect of the dissolution medium on the DRCOPT release characteristics, the release profile of the optimal formulation in different media was obtained. The results were not statistically significant ($p<0.05$). As illustrated in Fig. 7 linear correlation of zero order could be achieved in different pH gradients, indicating that the release behavior of the DRCOPT was not affected by the simulated pH en-

Table 6. Results of Predicted Values (PV) and Experimental Values (EV)

Formulation	Parameter		
	Q_{24} (PV/EV)	Linear degree (PV/EV)	Q_{16}/Q_{24} (PV/EV)
a	0.929153/0.936512	0.004264/0.006518	1.019973/0.965623
b	0.946020/0.949615	0.008748/0.007612	1.003959/0.957662
c	0.967643/0.942611	0.006686/0.009145	0.981607/0.940284
d	0.994022/0.903205	0.001921/0.004531	0.952918/0.815282

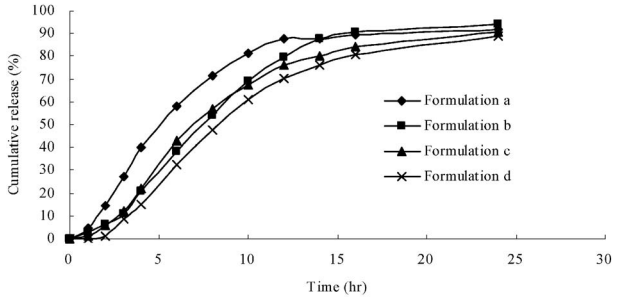

Fig. 6. Verification of Optimal Formulations (n=3, mean)

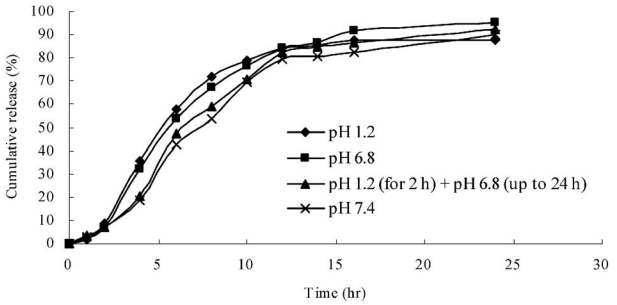

Fig. 7. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Different Dissolution Medium (n=3, mean)

vironment in the human body, which was consistent with the characteristics of the OPT.

Effects of Ionic Strength The drug release studies were performed in sodium chloride solution of different ionic strengths. Based on the results shown in Fig. 8, drug release exhibited consonance before 6 h, when the cumulative release began to increase as the ionic strength increased. A possible reason for the effect of ionic strength on drug release is that when water entered the core through the semipermeable membrane, PEO (N80) swells gradually. During the first 6 h, PEO (N80) acts as an excellent suspension agent, which provides NaCl with the proper conditions to exchange PNH in the core. Thereafter, the exchanged drug is released from the orifice under the osmotic pressure. The more water taken in, the more the PEO swells. A portion of the DRCs are driven away to the medium solution. It was noted that greater ionic strength provides the DRCs with more opportunities to exchange drug. Consequently, the DRC expelled in higher ionic strength solution exhibited a better release profile than that in lower ionic strength solution.

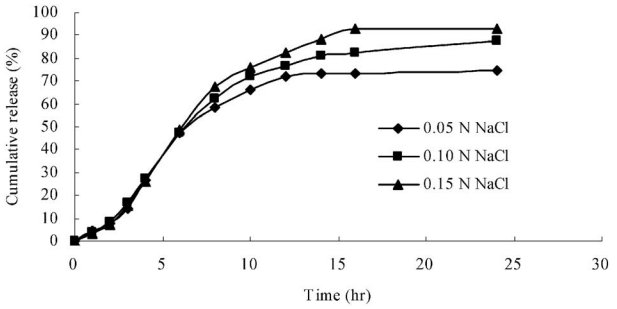

Fig. 8. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Different Ionic Strengths (n=3, mean)

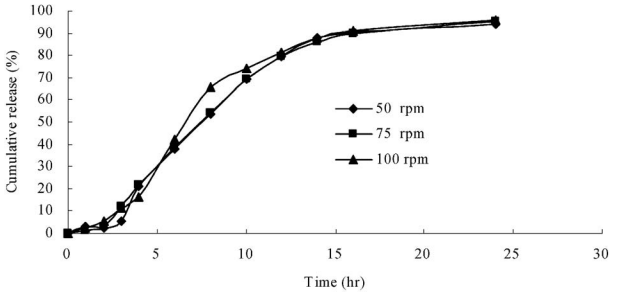

Fig. 9. Dissolution Profile of Propranolol Hydrochloride in the DRCOPT of Different Rotation Speeds (n=3, mean)

Effects of Rotation Speed To investigate the effects of stirring speed on the drug release behavior, dissolution experiments with the optimal DRCOPT were carried out at stirring rates of 50, 75, and 100 rpm. As shown in Fig. 9, no significant effect of rotation speed on the drug release profile was observed. Thus the mobility of the gastrointestinal tract may only slightly affect the drug release of the DRCOPT,

meaning that the DRCOPT will remain in the gastrointestinal tract in a reliable and reproducible manner.

Evaluation of Lag Time in the DRCOPT Delivery System Lag time is a normal phenomenon in the OPT delivery system. In previous studies, the main purpose was always to shorten the lag time. On the contrary, the lag time was utilized to achieve the aim of time-controlled delivery system in this investigation.

Compared with the conventional OPT, the DRCOPT gained an advantage in terms of lag time. Figure 10 shows the release profiles of different formulations, and the release rate increased from resin-loaded drug (PNH) to the DRCOPT. When the DRCs were exposed to the dissolution medium, the exchange reaction occurred immediately, the cumulative release was 98.43% within 2.5 h, and rapid release behavior can be achieved. As for the DRC tablet, a relatively slower drug release rate was observed, because the DRC tablet was a type of matrix tablet with PEO (N80) as the hydrophilic matrix material. Furthermore, drug release from conventional OPT and DRCOPT formulations could be controlled and the DRCOPT sustained a longer zero-order drug release period, ranging from 2 h to 14 h, than that of the conventional OPT, ranging from 0 h to 10 h. Additionally, the DRCOPT had a 2-h lag time in the *in vitro* dissolution test, which may accommodate such diseases as hypertension and angina pectoris occurring during certain period.

In the current study, the lag time was due to two factors. On one hand, the influx of water into tablets customarily requires a certain time. On the other hand, the DRCs in cores that exchanged drug with sodium chloride also consumed time. As a result, a relatively longer lag time of the DRCOPT compared to the conventional OPT occured.

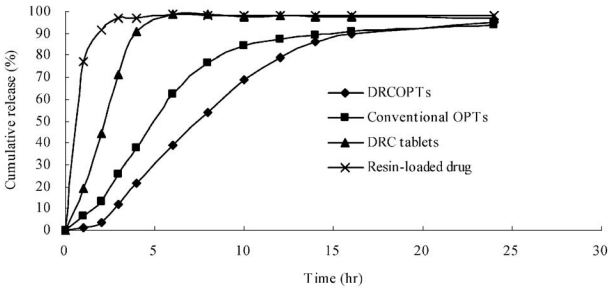

Fig. 10. Dissolution Profile of Different Preparations in Lag Time Investigation ($n=3$, mean)

CONCLUSIONS

A time-controlled release system that met the requirements for chronopharmaceutical drug delivery was developed based on the combination of the DRC and OPT. The quantity of osmotic agent in the core and channeling agent in the coating solution as well as weight gain were shown to be essential for the release behavior. Compared with other formulations, an obvious lag time was achieved. The system can be used in therapeutic regimens for diseases with characteristics of chronotherapy. In further investigations, more experiments are needed to describe the *in vivo* release behavior. On the whole, the DRCOPT preparation will provide a novel method for time-controlled delivery systems and provide a new concept for the development of osmotic pumps.

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