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Research Paper

A Novel Gastro-Retentive Osmotic Pump Capsule Using Asymmetric Membrane Technology: *In Vitro* and *In Vivo* Evaluation

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Purpose. The purpose of this paper is to develop a novel gastro-retentive osmotic pump capsule using asymmetric membrane technology.
Methods. The physical characteristics of capsule walls and drug delivery behaviors of the system were compared through different coating solutions. The formulation with the glycerin and diethyl phthalate ratio of 5:4 appears to be the best. The thickness of asymmetric membranes was evaluated by withdrawing speed. The relation between the two can be fitted to a linear model. The floating abilities were investigated through filling polyethylene oxide of different molecular weight into the capsules. WSR N-80 (molecular weight 200000) is chosen for the longest floating time. Central composite design-response surface methodology was used to investigate the influence of factors on the responses. The *in vivo* pharmacokinetics were studied in beagle dogs.
Results and conclusions. A second-order polynomial equation was fitted to the data, and the actual response values are in good accordance with the predicted ones. The optimized formulation displays a complete drug delivery, zero-order release rate and 12 h floating time. The *in vivo* study results clearly indicate the controlled and sustained release of Famotidine from the system, and the relative bioavailability of this preparation is about 1.605 in comparison to that of the marketed preparation.

KEY WORDS: asymmetric membrane; central composite design; famotidine; gastro-retentive osmotic pump capsule; pharmacokinetic study.

INTRODUCTION

The osmotic pump system (OPS) is one of the most important dosage forms for orally controlled drug delivery (1). It has been widely studied for certain advantages: zero-order release rate independence of the factors of release media, pH and food; and good *in vitro*/*in vivo* correlation. The osmotic agent and suspending agent have been proved to be able to deliver water-insoluble drugs by suspending them (2). However, for drugs acting locally in the proximal part of the gastrointestinal (GI) tract, short gastric empty time will result in incomplete release from the OPS above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose (3, 4) and low drug bioavailability. Therefore, gastric residence time (GRT) (5) is an important consideration for OPS, and longer residence time will allow more of the active component to penetrate through the gastric mucus layer to produce more pronounced effect.

The asymmetric membrane technology was brought forward by Thombre (6) in the 1990s. The capsule was made by a phase inversion process in which the membrane structure was precipitated on mold-pins by dipping the mold-pins into a coating solution containing a polymer-solvent-nonsolvent system followed by dipping into a quench solution. The resulting membrane wall was composed of a thin dense region supported on a thicker porous region. The advantage of asymmetric membrane capsule is the higher rate of water influx, allowing the release of drugs with a lower osmotic pressure or lower solubility (7).

In this study, a novel gastro-retentive osmotic pump capsule was developed using asymmetric membrane technology. Famotidine (FMTD) was chosen as the model drug because its characteristics are suitable for this novel system: it has a prolonged antisecretory effect in the therapy of duodenal, gastric, and peptic ulcer, and it has a low solubility (25 μg per ml, according to USP31-NF26) with a relatively short elimination half-life time (about 3 h) in humans as well as low bioavailability (45–50%) (8). The asymmetric membrane capsule consists of a cap and a body. The cap is shorter in length and has a slightly larger diameter than the body, which is longer and has a smaller diameter. Polyethylene oxide (PEO) was used as a suspending agent that was expected to expand and suspend with drug. NaCl was used as an osmotic agent to absorb water from the medium via the CA semipermeable membrane to form osmotic pressure. FMTD, PEO and NaCl are filled directly into the capsule in the form of powders. The cap and body are snugly fitted into each other and sealed by coating solution. Then, an orifice is drilled on either side of the capsule to make the drug suspension release from it due to the pressure difference between the membranes. Because the bulk density of

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powders is quite low for the high porosity, the whole system is approximately hollow. Therefore, during controlled drug delivery in the driving force of osmotic pressure as other OPSs, this osmotic pump capsule will be floating on the medium.

A two-factor, five-level central-composite design (CCD) was used to optimize formulations of contents in the capsules. The bioavailability study in beagle dogs was carried out to evaluate the final preparation.

MATERIALS AND METHODS

Materials

FMTD (NF) was supplied by Yaoda Pharmaceutical Co. (Shenyang, China). Polyethylene oxide (PEO, NF) with molecular weight (*M*w) of 200000 (WSR N-80), 600000 (WSR N-205), 1000000 (WSR N-12K), 4000000 (WSR 301) and 7000000 (WSR 303) were provided from Dow Chemical Co. (New Jersey, U.S.A.). NaCl was obtained form Bodi Chemical Co. (Tianjin, China). Cellulose acetate (CA, 54.5–56.0 wt.% acetyl content) was from Sinopharm Chemical Reagent Co. (Shanghai, China). Acetone, ethyl alcohol, glycerin and diethyl phthalate (DEP) were from Yuwang Chemical Reagent Co. (Shandong, China). Acetaminophen purchased from Jinzhou Jiutai Pharmaceutical Co. (Jinzhou, China) was used in the *in vivo* assays as an internal standard. Commercially available FMTD tablets (20 mg) from Shanghai SCOND Pharmaceutical Co. (Shanghai, China) were chosen as the reference preparation in the bioavailability study.

Preparation of Gastro-Retentive Osmotic Pump Capsules

The coating solution was a multi-component polymer-solvent-nonsolvent system containing the film-forming polymer—CA, which was dissolved in the solvent-nonsolvent mixtures—acetone, ethyl alcohol, glycerin and DEP. The quench solution was a mixture of glycerin and water. The cylindrical glass mold-pins were about 10 cm long, with diameters of 5 mm for capsule body and 6 mm for capsule cup. The mold-pins were first dipped into the coating solution. This was followed by slowly withdrawing the mold-pins from the solution with certain constant speed and rotating them horizontally for 8 s to complete phase separation. After the polymer formed a capsular shape over the mold-pins, it was immersed into the quench bath of glycerin and water in the ratio of 1:9 (w/v). After 1 h in the quench bath, the pins were withdrawn. The capsule shells were stripped off the pins immediately and allowed to dry at room temperature. FMTD powder, PEO and NaCl were passed through an 80 mesh screen respectively and precisely weighed using an electronic balance (Shanghai Minqiao Precise Science Instrument Co., Shanghai, China) as well as mixed artificially with a plastic bottle. Then the capsule shells were trimmed to size with a razor blade and the two halves joined and sealed with coating solution, after the drug-excipient mixture was filled into the capsules in the form of powders. Finally, an orifice was drilled with a micro drill on either side of the capsule (Fig. 1(A)).

In Vitro Dissolution Test

In vitro dissolution test was conducted in a dissolution apparatus (RCZ-6B, Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China) according to the USP paddle method. The capsules were placed in stainless steel sedimentation baskets. Temperature of the test was maintained at (37±0.5)°C. The stirring rate was 100 rpm, and the dissolution medium was 900 ml artificial simulated gastric fluid (pH 1.2). Five milliliters of solution was withdrawn, and the same volume of fresh medium was added at 2 h, 4 h, 6 h, 8 h, 10 h and 12 h, respectively. Then, the solution was filtered through a 0.8 μm membrane filter immediately before being diluted, if necessary, and the drug content was determined at 266 nm using an UV-9100 spectrophotometer (Beijing Beifenruili Analytic Instrument Co., Beijing, China). The mean of six determinations was used to calculate the amount of drug released from the samples.

Determination of Coating Solution Formulation

Since the capsule membrane structure and permeability were found to be dependent on the ratio of glycerin as the pore-forming agent (7) and DEP as the plasticizer (9), capsules made by different coating solutions with various ratios of glycerin and DEP were prepared (Table I). Physical characterizations of capsules were visually observed, and dissolution tests were operated to evaluate which formulation was better. The cross-section of capsule prepared by the coating solution with the best formulation was mounted onto the stage prior to coating with gold to a thickness of about 30 nm under vacuum. The morphology was then observed under scanning electron microscopy (SEM, model SSX-550, Shimadzu, Japan).

Investigation of Thickness of Asymmetric Membranes

The withdrawing speed of mold-pins from the coating solution was investigated because it was related to the thickness of asymmetric membranes. The mold-pins were immersed 4 cm deep under the coating solution and were withdrawn constantly in 6 s, 8 s, 10 s, 12 s and 14 s to maintain the withdrawing speed of 0.67, 0.5, 0.4, 0.33 and 0.29 ($cm \cdot s^{-1}$). The capsule shells obtained were cut at 1 cm from the bottom, and the cross-sections were observed respectively using a microscope (Motic DMBA 450, Micro-Optic Industrial Group Co., Guangzhou, China), and the thickness was noted.

Selection of PEO of Different *M*w

Since the main excipients loaded into the capsules are PEO with different *M*w, the selection of the PEO *M*w is a determinant in the floating ability of the system. Drug and excipients were filled into the capsules according to formulations, followed by joining, sealing and drilling. The *M*w of PEO were chosen at 200000 (WSR N-80), 600000 (WSR N-205), 1000000 (WSR N-12K), 4000000 (WSR 301) and 7000000 (WSR 303), respectively. The floating abilities were determined using USP paddle apparatus (100 rpm, 37°C, 900 ml pH 1.2 artificial simulated gastric fluid) with a sieve plate in the dissolution vessel (Fig. 1(B)). The time to float

(A) (B)

Fig. 1. **A** Final dosage form-filled and sealed osmotic pump capsules; **B** Investigation of floating abilities of the systems filled with different PEO.

and duration of floating (floating time) were measured in 12 h by visual observation with an observation interval of 0.5 h, regarding the clinging of both capsule cap and body to the sieve plate as floating.

Experimental Design and Data Analyzing of Content Formulations in the Capsules

Central Composite Design

The independent variables in our studies were content of PEO (X_1) and content of NaCl (X_2). For each factor, an experimental range was selected (Table II) based on the results of preliminary experiments. The critical responses were ultimate cumulative release in 12 h (Y_1) and correlation coefficient of drug release profile (Y_2) because this system was developed to release drug in 12 h and to perform a zero-order release rate. The experiments were designed by Design-Expert® software, and the layout of the design was shown in Table III.

Optimization of the Formulation

Using SPSS 15.0 software, a multiple linear model and a second-order polynomial model were individually fitted to each response, which could be represented by a linear equation (Eq. 1) and a quadratic equation (Eq. 2) of the response surface.

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_4 \quad (1)$$

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}{X_1}^2 + b_{22}{X_2}^2 + b_{12}X_1X_2 \quad (2)$$

F-test was used to evaluate lack of fit within each equation and identify the fitting model. The nomial of which $P>0.3$ were selectively deleted for model simplifying (10). Graphs of surface responses were plotted by Origin 8.0 software with each response against the two factors which were significantly influential.

In Vivo Pharmacokinetic Study

The gastro-retentive osmotic pump capsule was chosen as the test preparation. Meanwhile, the commercial conventional FMTD tablet was chosen as the reference preparation. The experimental protocol was approved by the University Ethics Committee for the use of experimental animals and conformed to the Guide for Care and Use of Laboratory Animals. The study had an open, randomized and cross-over design. Six healthy male beagle dogs, with a mean age of 3± 2 years, mean weight of 13±2.5 kg, were divided into two

Table I. Formulations of Coating Solution and Characterization of Capsule Shells

	Formulation					
	A	B	C	D	E	F
Coating solution						
CA (g)	15	15	15	15	15	15
Acetone (ml)	62	62	62	62	62	62
Ethyl alcohol (ml)	35	35	35	35	35	35
Glycerin (g)	10	5	5	10	10	0
DEP (g)	0	0	8	8	12	5
Physical characterization						
Color	Opaque	Opaque	Opaque	Opaque	Opaque	Transparent
Appearance	+	+	++	++	++	–

(++) good; (+) moderate; (–) poor

Table II. Independent Variables and Their Levels Investigated in the Central Composite Design

	Factor level in coded form				
Factor	−2	−1.414	0	1.414	2
X_1 (mg)	160	171.72	200	228.28	240
X_2 (mg)	70	78.79	100	121.21	130

Independent variables—X_1: content of PEO (mg), X_2: content of NaCl (mg)

groups of 3. One was given test preparation (one capsule per dog, each gastric-resident osmotic pump capsule containing FMTD 40 mg) orally with 200 ml water, while the other was given reference drug (two tablets per dog, each commercial conventional tablet containing FMTD 20 mg) via the same route, after the dogs had fasted for at least 12 h. The dogs were not allowed to eat but allowed to drink during the test period. Then, the two groups received the other treatment schedule after a 2-week washout period. For the test group, blood samples were collected before administration and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h, 32 h and 36 h after administration. For the reference dogs, blood samples were collected before administration and at 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h and 32 h after administration. At each time-point, 4 ml blood was withdrawn from the superficial vein of the forelimbs. Plasma samples were obtained after centrifugation (4,000 rpm) for 15 min and stored in a refrigerator at 20°C until analysis.

Fifty μl internal standard solution (acetaminophen methanol solution), 100 μl 7.5% hydroxylamine hydrochloride solution and 200 μl natrium carbonicum saturated solution were added in 0.6 ml plasma. The mixture was vortexed for 2 min to allow complete mixing. Then 6 ml chromatographic pure ethyl acetate was added in, followed by vortexing for 5 min and centrifugation (4,000 rpm) for 10 min. The organic layer was separated and vacuum dried at 60°C. The enriched product was dissolved in 100 μl mobile phase for 5 min, followed by centrifugation (10,000 rpm) for 10 min. Then, a 20 μl aliquot of supernatant was directly injected into the high-performance liquid chromatography system. Chromatographic conditions were as follows: Diamonsil C_{18} column, 150 mm×4.6 mm, 5 μm (DIKMA, USA); mobile phase: 0.03 mol·L^{-1} Na_2HPO_4 (pH was adjusted by phosphonic acid to 6.5)/ acetonitrile=9/1 (v/v); flow rate 1.0 ml·min^{-1}; UV detector wavelength 266 nm.

A linear correlation (r=0.9998) between the ratio of peak areas and the plasma concentration of FMTD was obtained between the range of 0.00583 μg·ml^{-1}–0.583 μg·ml^{-1} (y=0.94x −0.005). The lower limit of quantitation (LLOQ) was 0.0058 μg·ml^{-1}. The relative standard deviations (R.S.D.) of accuracy and precision for three different plasma concentrations of FMTD (0.117 μg·ml^{-1}, 0.350 μg·ml^{-1} and 0.583 μg·ml^{-1}) were all less than 10% for intra-day and inter-day analysis. The recovery for the three plasma concentrations was found to be 94.23%, 101.73% and 99.31%, with standard deviations (S.D.) less than 4%. The concentrations of FMTD plasma were calculated, and all the data were processed by DAS statistical software. The relative bioavailability was calculated by dividing the $AUC_{0-\infty}$ of the test preparation by that of the reference preparation.

RESULTS AND DISCUSSION

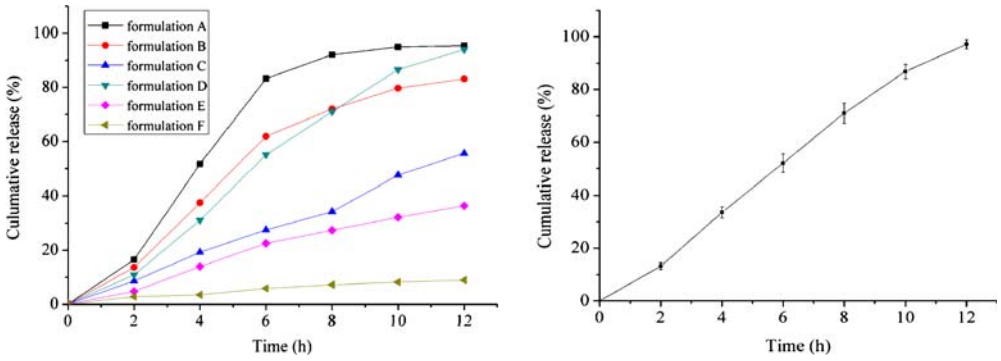
Coating Solution Formulation

The physical characteristics of asymmetric membrane capsule shells and drug delivery profiles of the system were compared by dissolving CA with adding different ratios of glycerin and DEP. The physical characteristics of capsules so obtained are shown in Table I. Formulations C, D and E appear to be better in appearance for their gloss. Formulations A and B are not as glossy as C, D and E, but easily broken, and capsules prepared with formulation F are crumpled. The capsules prepared with formulation F are transparent, whereas the capsules prepared with other five formulations are all opaque. From above we find that glycerin is essential for the coating solution formulation. Figure 2(A) shows the cumulative *in vitro* drug delivery profiles of capsules prepared with different coating solutions. When there is no DEP in the coating solution, the drug releases fast in the preliminary stage, and the profile smoothes out after about 6 h (formulation A and B). When glycerin in formulation B was replaced by DEP in formulation F, few drug releases form the system without pore-forming agent. Only when glycerin and DEP both exist in the coating solutions, the systems have a zero-order release rate (formulations C, D and E). Furthermore, formulation D with the glycerin and DEP ratio of 5:4 is the ideal, of which ultimate cumulative release is 93.96% and correlation coefficient of drug release profile is 0.9921. We concluded that glycerin is a determinant in the formation of asymmetric membrane. When coating solution makes contact with quenching solution on the outer surface, it goes through a phase inversion process (7). After the coating solution transforms from liquid phase to solid phase and the capsule shell falls into a pattern, the micro molecule glycerin goes through the asymmetric membrane into the quenching solution for the like-dissolves-like principle (11), leaving pores in the capsule shells after drying. Therefore, the amount of glycerin in the coating solution determines how much and how fast the medium will flow into the system through the asymmetric membrane capsule. Diethyl phthalate as a plasticizer is also an

Table III. Experimental Design for Two Factors and Experimental Values of the Responses

No.	X_1 (mg)	X_2 (mg)	Y_1 (%)	Y_2
1	171.72	121.21	83.93	0.9930
2	200	100	96.75	0.9985
3	171.72	78.79	86.6	0.9891
4	228.28	78.79	92.19	0.9878
5	160	100	92.48	0.9942
6	228.28	121.21	85.46	0.9934
7	200	100	96.75	0.9977
8	200	100	95.21	0.9902
9	200	130	87.93	0.9525
10	200	100	94.98	0.9946
11	200	70	96.24	0.9632
12	240	100	95.02	0.9893
13	200	100	93.96	0.9921

Factors—X_1: content of PEO (mg), X_2: content of NaCl (mg); responses—Y_1: ultimate cumulative release in 12 h (%), Y_2:correlation coefficient of drug release profile, response values: Avg., n=6



(A) (B)

Fig. 2. **A** FMTD *in vitro* cumulative release profiles of capsules prepared with different coating solutions (avg., $n=6$); **B** FMTD gastro-retentive osmotic pump capsule *in vitro* cumulative release profile of the optimized formulation A (mean ± SD, $n=6$).

important factor which counteracts the effect of glycerin for its hydrophobicity (12). More diethyl phthalate will decrease the hydrophilicity and water permeability of the membrane shell. Therefore, only an appropriate ratio of glycerin and DEP can make easy capsule appearance and good drug delivery profile. Figure 3 shows the scanning electron micrographs of asymmetric membrane capsule wall prepared by coating solution of formulation D. It illustrates that the capsule shell is generally composed of a dense and thin outer layer without pore structure and a loose and thick inner layer with pore structure. This is consistent with the asymmetric membrane prepared by A.G. Thombre using triethylcitrate (TEC) as the plasticizer (6). DEP is more easily obtained and much cheaper than TEC.

Thickness of Asymmetric Membranes

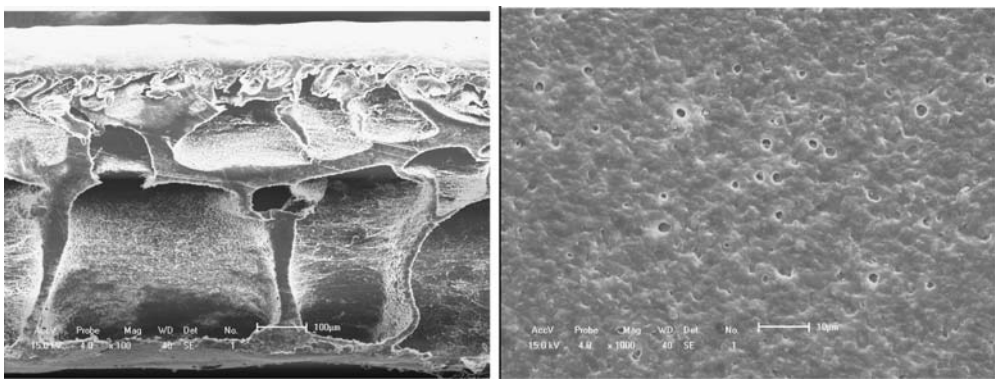
The cross-sections of capsule shells obtained by withdrawing the mold-pins from the coating solution with different speed were observed, and the photographs are displayed in Fig. 4. When the withdrawing speed is 0.29, 0.33, 0.4, 0.5 and 0.67 ($cm \cdot s^{-1}$), the thickness of the asymmetric membranes is 0.03215, 0.03753, 0.05551, 0.07451 and 0.10729 (cm), respectively. The membranes become thicker with an increase of withdrawing speed. This phenomenon can be demonstrated by theories in rheology and adsorption for macromolecular solution. The solution of CA, which is a kind of macromolecular polymer, shows a pseudoplastic flow (13). The shearing force (S, N/m^2) will increase with an increase of velocity gradient (V, S^{-1}) (Eq. 3) (14):

$$V = S^n/\eta_a (n > 1) \tag{3}$$

where η_α is apparent viscosity. If the mold-pin is quickly withdrawn from the coating solution, the velocity gradient between the liquid layers is large. Therefore, according to Eq. 3, great shearing force will conduce to the flowing of the solution, and thin CA solution layer is detained on the mold-pin. However, for the same specific surface of solid adsorbent, the saturated adsorption of the same macromolecular solution will be equal from Eq. 4 (15):

$$\Gamma_m = AsMw \Big/ \pi \left[(S_2)^{1/2} \right]^2 N_A \tag{4}$$

where Γ_m is saturated adsorption, A_s is specific surface of solid adsorbent, N_A is the Avogadro's constant, $(S_2)^{1/2}$ is average value of root mean square of macromolecular segment turning radius and π is 3.1416. Therefore, the saturated adsorptions of CA solutions on the mold-pins will be uniform



(A) (B)

Fig. 3. Scanning electron micrographs showing the cross-section (**A**, at 100× magnification) and internal surface (**B**, at 1,000× magnification) of asymmetric membrane capsule shell prepared with coating solution of formulation D.

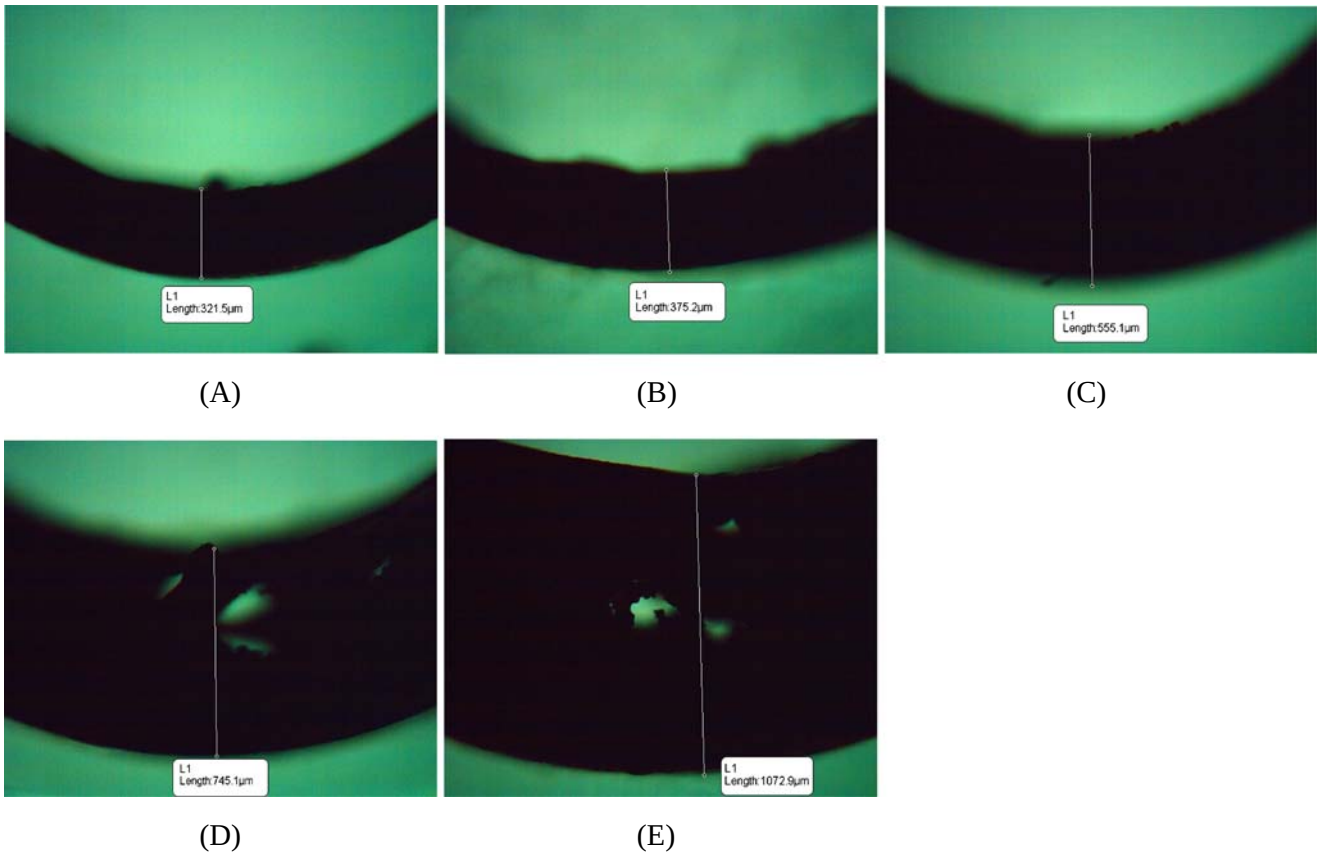


Fig. 4. Cross-sections of capsule shells obtained by withdrawing the mold-pins from the coating solution with different speed (withdrawing speed: **A**—0.29 cm·s^{-1}; **B**—0.33 cm·s^{-1}; **C**—0.4 cm·s^{-1}; **A**—0.5 cm·s^{-1}; **A**—0.67 cm·s^{-1}).

each time. If the mold-pin is withdrawn fast, the time for CA solution to flow off the mold-pin before it is horizontally rotated is short, and thick solution layer is then detained on the mold-pin. Therefore, the contributions of rheology and absorption to the thickness of asymmetric membranes are contrary and contradictive. Moreover, it seems that the function of absorption is more important, since the faster the mold-pin is withdrawn, the thicker the capsule shell will be. To make clear the relation between withdrawing speed and thickness of the asymmetric membrane, the data of the two are fitted to a linear model ($Y=-0.0265+0.2006X$, $R=0.9984$), quadratic model ($Y=-0.0353+0.2409X-0.0418X^2$, $R=0.9981$), cubic model ($Y=-0.0138+0.0917X+0.2874X^2-0.2305X^3$, $R=0.9981$), exponential model ($Y=0.5572-0.5930\times0.6622^X$, $R=0.9981$), logarithm model ($Y=ln(0.9695+0.2152X)$, $R=0.9987$) and power model ($Y=0.1903\times X^{1.3989}$, $R=0.9955$), respectively. We find that the four models all generate high correlation coefficients ($R>0.99$), and they make little difference. For the convenience of calculating, the equation ($Y=-0.0265+0.2006X$) is chosen to express the relation between withdrawing speed (X, cm·s^{-1}) and membrane thickness (Y, cm) during preparation, and the thickness of capsule wall is totally under control. In industrial manufacturing, mold-pins can be withdrawn from the coating solution at the same withdrawing speed. In this way, the reproducibility of capsule shells, preparation will be guaranteed. In this study, the withdrawing speed of 0.29 (cm·s^{-1}) is selected in further research to prepare thinner and smaller capsules.

Selection of *M*w of PEO, i.e., Investigation of Floating Ability of the System

Regarding the clinging of both capsule cap and body to the sieve plate in the dissolution vessel as floating, the time to float and floating time during 12 h of the systems filled with PEO of different *M*w were measured by visual observation

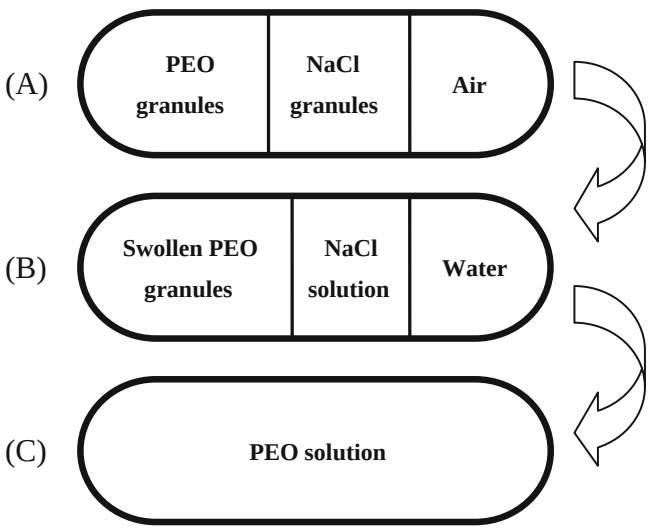
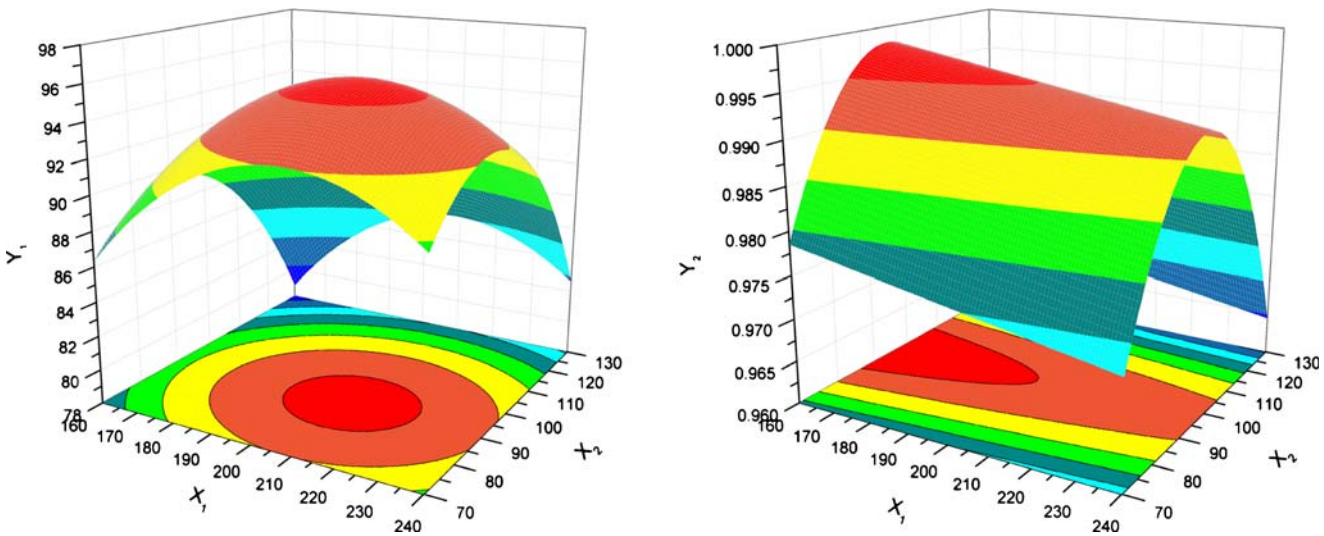


Fig. 5. Schematic diagram of the system internal change after contacting with medium.

Table IV. Regression Coefficients and Statistical Analysis

Model fitting	Factor	Factor coefficient	*P*-value	ANOVA
Multiple linear model (ultimate cumulative release in 12 h)	Intercept	95.1111	0.1905	F=1.97
	WSR N-80 content	0.0473	0.3913	R=0.5313
	NaCl content	0.1246	0.1073	
Second-order polynomial model (ultimate cumulative release in 12 h)	Intercept	−90.2833	0.0418	F=4.13
	WSR N-80 content	1.2264	0.2686	
	NaCl content	1.2934	0.0469	R=0.8209
	(WSR N-80 content)^2	-2.9477×10^{-3}	0.0867	
	(NaCl content)^2	-7.0903×10^{-3}	0.0296	
Multiple linear model (R of drug release profile)	Intercept	1.0165	0.6573	F=0.44
	WSR N-80 content	-8.0123×10^{-5}	0.5623	R=0.2837
	NaCl content	-1.2806×10^{-4}	0.4889	
Second-order polynomial model (R of drug release profile)	Intercept	0.7642	0.0004	F=17.85
	WSR N-80 content	-8.0123×10^{-5}	0.1845	
	NaCl content	5.0613×10^{-3}	0.1190	R=0.9253
	(NaCl content)^2	-2.5947×10^{-5}	<0.0001	

with an interval of 0.5 h. It is found that the time to float is all 0 h. Bulk density should be introduced to demonstrate this. Bulk density is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume (16). When the powders are filled directly into the capsules, the bulk density is quite low for the high porosity. The whole system is approximately hollow and will float immediately after contacting with the dissolution medium. The floating time of the systems filled with WSR N-80, WSR N-205, WSR N-12K, WSR 301 and WSR 303 is 12 h, 9.5 h, 8 h, 6 h and 5.5 h, respectively. It is clear that the floating time becomes shorter with an increase of the PEO *M*w. To clarify this, we regard the initial system as another form (Fig. 5(A)). Separating the inter-particle void volume and internal pore volume of the PEO and NaCl powders, the system can be divided into three parts: PEO powders without porosity, NaCl powders without porosity and air (FMTD is ignored due to its low content). In this instance, the densities of PEO and NaCl are true density, which means the mass of solid material divided by its exact volume without porosity (17). The true densities of PEO of different *M*w are from 1.15 to 1.26 (g·cm^{-3}), and the true density increases with the increase of PEO *M*w (18). The true density of NaCl is 2.16 g·cm^{-3} (14). In the beginning, the density of system is related to the density of capsule shell, the true density of PEO, the true density of NaCl as well as the density of air. It is lower than the density of water (1.004 g·cm^{-3}) because of the low density of the asymmetric membrane and the existence of air. With the medium flowing into the system from the membrane, the air area is gradually filled with water to make the density of this part equal to external environment. NaCl is dissolved, and the solution is flowing out from the orifice. PEO is going through a swelling process, which includes two stages: limited swelling and unlimited swelling (19). During limited swelling, the solvent diffuses among the PEO granules, which begin to swell slowly. At this time, the true density of PEO determines the floating ability of the system (Fig. 5(B)). When the true density is low (e.g., 1.15 g·cm^{-3}), the system density, which depends on the true



(A) (B)

Fig. 6. Response surfaces for ultimate cumulative release in 12 h (Y_1) and correlation coefficient of drug release profile (Y_2) as functions of two factors.

Table V. Composition of Optimum Formulation A, B and C, and the Predicted Values As Well As Actual Results

Formulation	X_1(mg)	X_2(mg)	Response	Predicted value	Actual value	Bias (%)
A	195	85	Y_1 (%)	95.4900	97.1937	1.7842
			Y_2	0.9913	0.9969	0.5649
B	200	90	Y_1 (%)	96.0633	98.5503	2.5889
			Y_2	0.9935	0.9989	0.5435
C	197	94	Y_1 (%)	95.8499	98.6839	2.9567
			Y_2	0.9949	0.9902	−0.4724

Bias (%)=(Actual value-Predicted value)/ Predicted value×100, factors—X_1: WSR N-80 content, X_2: NaCl content; responses—Y_1: ultimate cumulative release in 12 h (%), Y_2:correlation coefficient of drug release profile, response values: avg., n=6

density of PEO, the density of capsule shell and the density of NaCl solution, is lower than 1.004 g·cm^{-3}. The system will float in this stage. If the true density is high (e.g., 1.26 g·cm^{-3}), the system density will suddenly be higher than 1.004 g·cm^{-3} with the air part diminishing, and the system will sink. During unlimited swelling, high molecular substances disperse in the solvent, and a homogeneous solution is formed. There only exists PEO solution in the system (Fig. 5(C)). Therefore, the density of the solution will determine whether the system will continue floating. If the PEO true density is lower, the volume of needed capsule should be bigger because of loading the same weight PEO powders. Consequently, the density, i.e., the concentration of the solution formed by PEO dissolving, is lower. Therefore, the density of low *M*w PEO solution is lower than that of high *M*w PEO solution. For the system loaded with low *M*w PEO, it will still be floating (e.g., WSR N-80). Otherwise the system will sink (e.g., WSR 303). It is known that the floating time of the system loaded with WSR N-80 is longest, because the system density is lower than 1.004 g·cm^{-3} during both limited swelling and unlimited swelling. To obtain ideal floating effect, we choose WSR N-80 as the suspending agent.

Central Composite Design

The two responses were individually fitted to a multiple linear model and a second-order polynomial model. Each obtained model was validated by ANOVA. For each response, the model which generated a higher *F*-value and *R* (Correlation coefficient) was identified as the fitting model. Table IV shows that the second-order polynomial model is the better fitting model for both responses. Graphs are plotted with each response against the two factors (Fig. 6).

Influence of Factors on the Ultimate Cumulative Release in 12 h (Y_1) and the Correlation Coefficient of Drug Release Profile (Y_2)

As can be seen from (A) of Fig. 6, Y_1 decreases after increasing with an increase of X_1. That is because WSR N-80 of low percentage can not suspend the drug powder sufficiently (20), and it will impede the drug release when WSR N-80 is in excess due to its high inherent viscosity (21). Y_1 also increases followed by decreasing with an increase of X_2. More NaCl will provide better osmotic effects. Therefore, PEO is hydrated sufficiently and more drug will be released. However, if the NaCl content is high, chloride ion generated by NaCl will inhibit the ionization of HCl because of the common ion effect (22). Since FMTD belongs to basic drugs, the decrease of acidity in the internal environment of the system will cause the lowering of FMTD solubility. Thereby, drug delivery behaviors are adversely influenced. (B) of Fig. 6 shows that Y_2 decreases with an increase of X_1. It is comprehensive that WSR N-80 of high percentage will not be hydrated rapidly, and the lag time will be long. With the increase of X_2, Y_2 increases followed by decreasing. The main reason is that a low percentage of NaCl can not provide adequate osmotic pressure while a high percentage will cause high hydrating rate, making the drug release profile of later stage gentle.

Optimization of the Formulation

Since Y_1 and Y_2 have to be maximized, the regions where optimization is studied are the red domains. We seek the maximum value of Y_1 and Y_2 in this region: X_1: 195–205 (mg) and X_2: 85–95 (mg). Formulation A is chosen within the lower limit of the optimum areas. Formulation B is selected in the center of the optimum areas, and random formulation C is chosen in the experimental matrix to confirm the model adequacy for prediction. The compositions of formulation A, B, C and the predicted as well as actual values of the two responses are shown in Table V. The model proves effective,

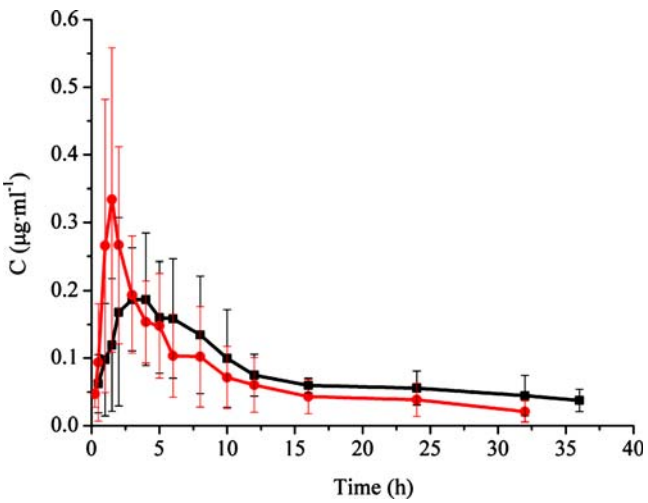


Fig. 7. Mean FMTD plasma concentration–time curves of six beagle dogs (mean ± SD, n=6). (■) test preparation; (●) reference preparation.

since an agreement exists between the predicted and actual results. The central composite design is efficient for the modeling and optimization of the system as well as for understanding how the formulation factors influence the drug release behaviors. The ultimate cumulative release and correlation coefficient of drug release profile of the optimized formulations indicate that this novel gastro-retentive osmotic pump capsule is able to deliver drug completely and performs a zero-order release rate based on the mechanism of osmotic pump (23) during floating on the medium. Although the ultimate cumulative release of formulation B and the correlation coefficient of drug release profile of formulation C are the highest, we choose formulation A as the ideal one for this drug delivery system. We made this choice because we should fill the smallest quantity of excipients in the optimum formulation areas into the capsules to obtain the smallest capsules for convenience of administration. The cumulative release profile of formulation A is illustrated in Fig. 2(B).

Pharmacokinetic Studies

Although the developed gastro-retentive osmotic pump capsule had shown ideal *in vitro* dissolution and floating behaviors, it was also evaluated for its bioavailability in beagle dogs to ascertain pharmacokinetic parameters. The mean concentration–time curves for the test and reference preparations in six beagle dogs at steady-state are illustrated in Fig. 7. In beagle dog subjects, peak plasma concentration (C_{max}) for FMTD conventional tablet is found to be 0.334 $\mu g \cdot h \cdot ml^{-1}$ as against 0.187 $\mu g \cdot ml^{-1}$ for FMTD gastro-retentive osmotic pump capsule. Similarly, time to reach peak plasma concentration (t_{max}) for FMTD conventional tablet is 2.083 h as against 4 h for osmotic pump capsule. For FMTD tablet, elimination half-life ($t_{1/2}$) is 13.178 h, whereas in case of the floating capsule, $t_{1/2}$ is 23.634 h. The comparison of these data clearly indicates that it is desirable for controlling the release of FMTD from this novel dosage form in order to prolong the drug action and minimize the frequency of drug administration. At the same time, the average peak plasma concentration is significantly lower than that of reference, and drug side effect is mitigated. *In vivo* study of prepared floating capsules confirms their ability to modify the pharmacokinetic behavior of the drug in desired manners. These results clearly indicate the controlled and sustained release of FMTD from their gastro-retentive osmotic pump formulations. What is more important, the area under the curve ($AUC_{0-\infty}$) for FMTD tablet is found to be 31.411 $\mu g \cdot h \cdot ml^{-1}$, whereas for floating capsules it is 50.4 $\mu g \cdot h \cdot ml^{-1}$. The $AUC_{0-\infty}$ is increased significantly in case of this novel preparation. The relative bioavailability is about 1.605 in comparison to that of the marketed preparation. This is owed to the floating ability of the system. GRT is an important consideration for dosage forms, which affects the drug bioavailability (5). Longer residence time allows more active components to penetrate through the gastric mucus layer and to be absorbed above the absorption zone. Therefore, the bioavailability will be significantly increased. One point is worth paying attention. The pharmacokinetic study in this paper is conducted in beagle dogs. The anatomy of canine species is different from that of humans. Hence, how this system will behave in human subjects remains to be further analyzed and studied.

CONCLUSION

The physical characteristics of asymmetric membrane capsule shells and drug delivery behaviors of the system were compared by dissolving CA using different ratios of glycerin and DEP. Formulation D with the glycerin and DEP ratio of 5:4 appears to be good in appearance for its gloss and to be ideal in drug delivery for the ultimate cumulative release and correlation coefficient of drug release profile. The thickness of asymmetric membranes was evaluated through withdrawing the mold-pins from the coating solution with different speeds. The membranes become thicker with an increase of withdrawing speed, and the relation between the two can be fitted to a logarithm model. The withdrawing speed of 0.29 $cm \cdot s^{-1}$ is selected for preparing thinner and smaller capsules. The floating abilities of the system were investigated through filling PEO of different *M*w into the capsules. The floating time of the system loaded with WSR N-80 is longest, so WSR N-80 is chosen as the suspending agent. The formulation optimization was carried out by central composite design-response surface methodology. The actual responses for the optimum formulation are in close agreement with the predicted values, indicating the excellent predictability of the optimization procedure. The optimized formulation displays a complete drug delivery and zero-order release rate during floating on the medium. The system bioavailability was evaluated in beagle dogs to ascertain pharmacokinetic parameters. The results clearly indicate the controlled and sustained release of FMTD from their gastro-retentive osmotic pump formulations. The system can prolong the drug action, minimize the frequency of drug administration and lower the average peak plasma concentration. Furthermore, the relative bioavailability of this preparation is about 1.605 in comparison to that of the marketed preparation owing to the floating ability of the system. How this system will behave in human subjects remains to be further analyzed and studied.

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