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A novel gastric-resident osmotic pump tablet: In vitro and in vivo evaluation

Jin Guan, Liying Zhou, Shufang Nie, Tingxu Yan, Xin Tang, Weisan Pan*

Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China

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ABSTRACT

A novel famotidine gastric-resident osmotic pump tablet was developed. Pharmaceutical iron powder was used as a gas-formation and density-increasing agent. Central composite design-response surface methodology was used to investigate the influence of factors, i.e., polyethylene oxide (*M*w 1,000,000) content, NaCl content, iron powder content and weight gain, on the responses including ultimate cumulative release and correlation coefficient of drug release profile. A second-order polynomial equation was fitted to the data and actual response values are in good accordance with the predicted ones. The optimized formulation displays a complete drug delivery and zero-order release rate. Gamma scintigraphy was selected as the method to monitor in vivo gastric residence time of the ^{99m}Tc-labeled system in Beagle dogs. It was observed that the system can retain in stomach for an extended period of 7 h after administration compared with conventional tablets. The present investigation suggests that water-insoluble drug can be delivered from single-layer osmotic pump tablets completely due to the push power of the hydrogen gas generated by the reaction of the iron and gastric fluid. And iron powder can increase the system density which is over 2.5 g cm^{-3}, making the system resident in stomach to prolong the drug delivery time in absorption zone.

1. Introduction

The osmotic pump tablet (OPT) is one of the most important dosage forms for orally controlled drug delivery (Liu and Xu, 2007). Elementary osmotic pump (EOP) developed by Theeuwes (1975) is only suitable for water-soluble drugs. Two of the major problems caused by drugs with low water solubility are the inadequacy of cumulative release and the lack of zero-order release character, and cannot be solved by EOP. Therefore, two-compartment (Theeuwes, 1978), two-layer push–pull (Cortese and Theeuwes, 1982) and three-layer (Stephens and Wong, 1989) osmotic pump tablets have been developed to overcome the limitation of EOP. But these three systems demand certain sophisticated techniques compared to single-layer OPTs. Thus it is a technically challenge to produce single-layer OPTs for water-insoluble drugs. Xue et al. prepared an effervescent single-layer OPT (Xue et al., 2009). Since the model drug was acidic, they used $NaHCO_3$ as effervescent to generate CO_2, forcing the drug to release completely. Besides, an important consideration for dosage forms is gastric residence time (GRT) which affects the drug bioavailability (Desai and Bolton, 1993). For drugs acting locally in the proximal part of gastrointestinal (GI) tract, short gastric empty time can result in incomplete release from the drug delivery system above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose (Chueh et al., 1995; Iannuccelli et al., 1998). Therefore, longer residence time will allow more of the active component to penetrate through the gastric mucus layer to produce a more pronounced effect. The studies on both high-density pellets (Clarke et al., 1993) and low-density microballoons (Sato et al., 2003) aimed at obtaining longer GRT. Bearing in mind these facts above, we set out to develop a desired OPT in order to overcome difficulties of producing single-layer OPTs for water-insoluble drugs and prolong the residence time of the system in the stomach.

In this study, a novel high-density gastric-resident osmotic pump tablet was developed using pharmaceutical iron powder in the core tablets as a gas-formation agent and density-increasing agent. Famotidine (FMTD) was chosen as the model drug because its characteristics are suitable for this kind of new dosage form: 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%) (McCallum et al., 1985). On the one hand, the pharmaceutical iron powder reacts with the gastric fluid flowing into the core tablet through semipermeable membrane owing to osmotic pressure and transforms into ferrous ion which is beneficial and easy to be assimilated. This will generate hydrogen gas which forces the drug suspension outwards. Accordingly, water-insoluble FMTD will deliver from single-layer OPTs more completely. On the other hand,

* Corresponding author. Tel.: +86 24 23953241; fax: +86 24 23953241.
E-mail address: ppwwss@163.com (W. Pan).

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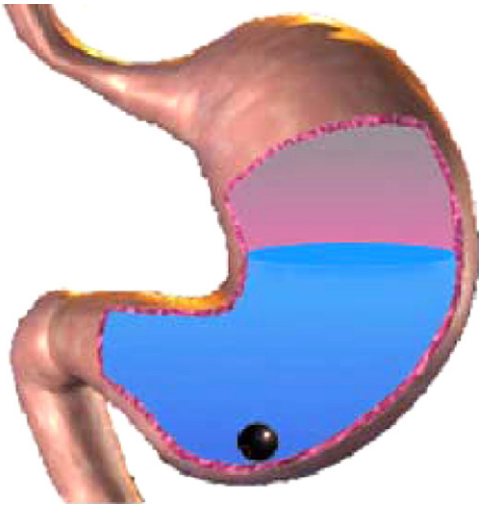

Fig. 1. Schematic localization of a high-density system in the stomach. High-density system (density ≈ 2.5 g cm^{-3}) (Bardonnet et al., 2006).

gastric contents have a density close to water (about 1.004 g cm^{-3}). Small high-density systems will sink to the bottom of the stomach (Fig. 1) where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall (Bardonnet et al., 2006). A density close to 2.5 g cm^{-3} seems necessary for significant prolongation of GRT (Clarke et al., 1993). Presence of the pharmaceutical iron powder increases the system density which is over 2.5 g cm^{-3}, prolonging the drug delivery time in absorption zone and improving the bioavailability. Therefore, the iron powder is the innovation of this design and the key for the success of this preparation.

A four-factor, five-level central composite design (CCD) was used to optimize formulations of this new kind of OPTs. Gamma scintigraphy was selected as the method to monitor GRT of the radio-labeled systems in Beagle dogs.

2. Materials and methods

2.1. Materials

FMTD (NF) was supplied by Yaoda Pharmaceutical Co. (Shenyang, China). Pharmaceutical iron powder (100 mesh) was purchased from Hongjian Powder Material Co. (Hangzhou, China). Polyethylene oxide (PEO, NF) with *M*w of 1,000,000 (WSR N12K) was provided from Dow Chemical Co. (New Jersey, USA). NaCl was obtained from Bodi Chemical Co. (Tianjin, China). Cellulose acetate (CA, 54.5–56.0 wt.% acetyl content) was from Sinopharm Chemical Reagent Co. (Shanghai, China). Acetone and polyethylene glycol 4000 (PEG 4000, average molecular weight) were from Yuwang Chemical Reagent Co. (Shandong, China). Technetium-99m ($^{99m}TcO_4^-$) was obtained from The General Hospital of Shenyang Military Command, Department of Nuclear Medicine (Shenyang, China). Commercially available FMTD conventional tablets from Shanghai SCOND Pharmaceutical Co. (Shanghai, China) were chosen as the reference preparation in the gamma scintigraphy study. All the chemicals used were of analytical grade.

2.2. Preparation of high-density gastric-resident osmotic pump tablets

FMTD powder, pharmaceutical iron powder, WSR N12K and NaCl were passed through an 80 mesh screen, respectively. Then they were precisely weighed using an electronic balance (Shanghai Minqiao Precise Science Instrument Co., Shanghai, China) and mixed artificially with a plastic bottle. Then the resultant power mixture was compressed into tablets by a single-punch tableting machine (Shanghai No. 1 Pharmaceutical Device Co., Shanghai, China) using a 7 mm diameter concave punch. The hardness of the core tablets was precisely kept at 8 kg by a hardness tester (Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China). CA in acetone (3%, w/v) containing plasticizer PEG-4000 (0.6%, w/v) was used as coating solution. The coating was carried out in a coating pan (Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China) whose interior temperature was 30 °C and rotating rate was 30 rpm. The coated tablets were then dried at 50 °C for 24 h to remove the residual solvent before a 0.7 mm orifice was drilled by a microdrill on both sides of the tablets.

2.3. 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. 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 milliliter of solution was withdrawn and the same volume of fresh medium was added at 2, 4, 6, 8, 10 and 12 h, respectively. Then the solution was filtered through a 0.8 μm membrane filter immediately before 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.

2.4. Experimental design and data analyzing

2.4.1. Central composite design

The independent variables in our studies were: content of WSR N12K (X_1), content of NaCl (X_2), content of pharmaceutical iron powder (X_3), weight gain of the tablet which indicates the level of coating (X_4), and for each factor an experimental range was selected (Table 1) 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 2.

2.4.2. 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. *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 (Gan et al., 2007). Graphs of surface responses were plotted by Origin 8.0 software with each response against the two factors which were significantly influential.

Table 1
Independent variables and their levels investigated in the central composite design[a].

Factor	Factor level in coded form				
	−2	−1	0	1	2
X_1 (mg)	30	45	60	75	90
X_2 (mg)	20	35	50	65	80
X_3 (mg)	100	112.5	125	137.5	150
X_4 (%)	5	6	7	8	9

[a] Independent variables—X_1: WSR N12K, X_2: content of NaCl, X_3: content of pharmaceutical iron powder, and X_4: weight gain of the tablet.

Table 2
Experimental design for four factors and experimental values of the responses[a,b].

No.	X_1 (mg)	X_2 (mg)	X_3 (mg)	X_4 (%)	Y_1 (%)	Y_2
1	45	65	112.5	6	49.67	0.9892
2	45	65	112.5	8	47.92	0.9632
3	60	50	125	7	88.25	0.9950
4	60	20	125	7	98.86	0.9875
5	75	35	137.5	8	61.14	0.9866
6	30	50	125	7	46.41	0.9870
7	60	50	125	7	79.72	0.9977
8	45	35	112.5	8	72.03	0.9912
9	75	35	137.5	6	74.00	0.9821
10	90	50	125	7	81.81	0.9925
11	60	50	100	7	81.88	0.9940
12	75	65	112.5	6	73.93	0.9961
13	60	50	150	7	76.20	0.9925
14	75	35	112.5	8	97.31	0.9915
15	75	65	137.5	6	74.59	0.9970
16	45	65	137.5	6	43.38	0.9891
17	45	35	137.5	8	30.39	0.9904
18	60	80	125	7	79.29	0.9766
19	75	35	112.5	6	79.62	0.9860
20	45	35	112.5	6	63.63	0.9814
21	60	50	125	7	87.99	0.9895
22	75	65	137.5	8	86.50	0.9922
23	75	65	112.5	8	68.80	0.9925
24	60	50	125	7	78.26	0.9956
25	60	50	125	9	77.17	0.9931
26	60	50	125	7	78.75	0.9955
27	45	35	137.5	6	59.70	0.9904
28	60	50	125	7	78.99	0.9954
29	60	50	125	5	84.45	0.9899
30	45	65	137.5	8	67.17	0.9918

[a] Factors—X_1: WSR N12K, X_2: content of NaCl, X_3: content of pharmaceutical iron powder, and X_4: weight gain of the tablet; responses—Y_1: ultimate cumulative release in 12 h (%) and Y_2: correlation coefficient of drug release profile.
[b] Response values: avg., $n = 6$.

2.5. Gamma scintigraphy study

2.5.1. Choice of radio-label

Technitium-99m was the radioisotope of choice for Gamma scintigraphy studies. It had a short half-life of 6.03 h and was easy and inexpensive to produce. ^{99m}Tc was eluted as pertechnetate ($^{99}TcO_4^-$) with sodium chloride 0.9% from a molybdenum-99 generator (this process was operated by a professional staff in the department of nuclear medicine, General Hospital of Shenyang Military Command (Shenyang, China)).

2.5.2. Preparation of the radio-labeled dosage form

The preparation of radio-labeled osmotic pump tablet was almost the same as in Section 2.2. The only difference was about the tablet compressing. Half of the mixed powder was compressed lightly before 20 μl ^{99m}Tc solution was injected in the centre to give an activity of 10 millicuries per dose. After drying the ^{99m}Tc solution, the other half powder was added and the whole powder was compressed into tablet. This operation will keep the ^{99m}Tc in the core the tablet, causing no loss of the ^{99m}Tc during coating and will have the ^{99m}Tc all coated inside the membrane. The whole process should be as soon as possible and the coated tablet was blew to dry instead of drying at 50 °C for 24 h to make sure that the radioactivity changed little before administration. To label the commercially conventional tablet, the tablet was firstly ground into powder. Similarly, half of the powder was compressed lightly before 20 μl ^{99m}Tc solution was injected in the centre. After drying, the other half powder was added and the whole powder was compressed into tablet.

2.5.3. In vivo gamma scintigraphy study

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 was made in the department of nuclear medicine, General Hospital of Shenyang Military Command (Shenyang, China). Healthy male Beagle dogs, having a mean age of 3 ± 2 years, mean weight of 13 ± 2.5 kg, were used for the gamma scintigraphy study. Radio-labeled test preparation (high-density gastric-resident osmotic pump tablet) and reference preparation (commercially conventional tablet) were administered, respectively, with 200 ml of water after the dogs had fasted for at least 12 h. The dogs were not allowed to eat or drink during the imaging period. Each dog was in a prone position beneath the gamma camera during imaging. At all other times they were able to move freely. Scintigrams of test preparation were recorded by a single-photon emission computed tomography (SPECT) apparatus with dual search units (General Electric Company, USA) at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after administration and the ones of reference preparation were recorded at 0.25, 0.75, 1.5, 2 and 3 h. The scintigrams taken by the post search unit were selected. Collimators were of the LEHR (low energy high resolution) type.

3. Results and discussion

3.1. 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 3 shows that the second-order polynomial model is a better fitting model for both responses. Graphs were plotted with each response against the two factors which were significantly influential (Fig. 2).

3.1.1. Influence of factors on the ultimate cumulative release in 12 h (Y_1)

As can be seen from (a)–(c) of Fig. 2, Y_1 decreases after increasing with an increase of X_1. That is because WSR N12K of low percentage cannot suspend the drug and iron powder sufficiently (Tetsuya et al., 1999) and it will impede the drug release when N12K is excess due to its high inherent viscosity and low hydrating rate (Liu et al., 2000). (a) and (d) of Fig. 2 demonstrates that Y_1 decreases when X_2 increases and the reason is that more and more chloride ion generated by NaCl will inhibit the ionization of HCl because of the common ion effect (Larsena et al., 2007). Thus less hydrogen gas cannot push the drug suspension efficiently. In (b) and (e) of Fig. 2, Y_1 shows a trend of first increase and then decrease with an increase of X_3. When the iron powder content is low, the push power is not enough to deliver drug completely. And, excess iron powder will prevent N12K form suspending the drug powder due to its high density. From (c) and (e) of Fig. 2 we find that with an increase of X_4, Y_1 also increases followed by decreasing. The main reason is that low weight gain makes the core tablets hydrate rapidly (Ofori-Kwakye and Fell, 2003) and leads to the loss of iron powder which is released with drug before reaction. When weight gain is high, low hydrating rate of core tablets causes insufficiency of drug release in 12 h.

3.1.2. Influence of factors on the correlation coefficient of drug release profile (Y_2)

(g) of Fig. 2 shows that Y_2 increases with an increase of X_1. It is comprehensive that more N12K will sufficiently suspend the drug powder. From (f) and (h) of Fig. 2, we know that with an increase of X_2, Y_2 increases followed by decreasing. Low percentage of NaCl cannot provide adequate osmotic pressure while high percentage will cause high hydrating rate of the core tablets, making the drug release profile of later stage gentle. (g) in Fig. 2 indicates that Y_2

Table 3
Regression coefficients and statistical analysis.

Model fitting	Factor	Factor coefficient	*P*-value	ANOVA
Multiple linear model (ultimate cumulative release in 12 h)	Intercept	67.7683	0.0090	$F = 4.27$, $R = 0.4787$
	N12K content	0.7022	0.0007	
	NaCl content	−0.1806	0.3284	
	Iron powder content	−0.2247	0.3112	
	Weight gain of the tablet	−0.0758	0.9780	
Second-order polynomial model (ultimate cumulative release in 12 h)	Intercept	−109.7525	0.0002	$F = 6.84$, $R = 0.8501$
	N12K content	4.1848	<0.0001	
	NaCl content	−6.4351	0.2068	
	Iron powder content	2.2731	0.1912	
	(NaCl content) (iron powder content)	0.0396	0.0085	
	(NaCl content) (weight gain)	0.1871	0.2827	
	(N12K content)^2	−0.0290	0.0029	
	(Iron powder content)^2	−0.0179	0.1610	
	(Weight gain)^2	−2.3548	0.2347	
Multiple linear model (R of drug release profile)	Intercept	0.9741	0.6373	$F = 0.64$, $R = 0.0932$
	N12K content	1.3417×10^{-4}	0.1779	
	NaCl content	-2.8611×10^{-5}	0.7700	
	Iron powder content	8.5000×10^{-5}	0.4711	
	Weight gain of the tablet	-2.2917×10^{-4}	0.8758	
Second-order polynomial model (R of drug release profile)	Intercept	0.8405	0.0008	$F = 5.49$, $R = 0.8225$
	N12K content	1.9424×10^{-3}	0.0559	
	Iron powder content	4.8800×10^{-4}	0.2958	
	(N12K content) (NaCl content)	1.4361×10^{-5}	0.0152	
	(N12K content) (iron powder content)	-1.4967×10^{-5}	0.0317	
	(NaCl content) (iron powder content)	9.9000×10^{-6}	0.1416	
	(NaCl content) (weight gain)	-2.1458×10^{-4}	0.0155	
	(N12K content)^2	-5.4618×10^{-6}	0.1917	
	(NaCl content)^2	-1.4017×10^{-5}	0.0025	

decreases when X_3 increases. That is because excess iron powder will not react with HCl promptly, resulting in irregularity of drug release.

3.1.3. Optimization of the formulation

Since Y_1 and Y_2 have to be maximized, the region where optimization is studied is the red domain. We seek the maximum value of Y_1 and Y_2 in this region: X_1: 60–85; X_2: 30–35; X_3: 110–120 and X_4: 6.25–7.75. Formulation A was chosen in the centre of the optimum areas. Two additional random formulations B and C were chosen in the experimental matrix to confirm the model adequacy for prediction. The compositions of formulations A–C and the predicted as well as actual values of the two responses are shown in Table 4. The model is proved to be effective since an agreement exists between the predicted and actual results. The cumulative release profiles of the optimized formulation A and reference preparation (commercially conventional tablet) are illustrated in Fig. 3. The ultimate cumulative release (99.25%) and correlation coefficient of drug release profile (0.9928) of this preparation indicate that this novel osmotic pump tablet using pharmaceutical iron powder as a gas-formation agent is able to deliver drug completely in 12 h and perform a zero-order release rate in contrast with normal tablet. Hydrogen gas is generated due to the reaction of pharmaceutical iron powder and gastric fluid, and this increase the push power in the core tablet. The joint action of push power of gas as well as swelling force of PEO makes the drug release more completed. This system has the same effect as multiple-layer osmotic pump tablets for water-insoluble drugs but the techniques are simpler for single-layer tablet compression. Meanwhile, the addition of iron and generation of gas do not interfere the drug release behavior. The whole system functions basing on the mechanism of osmotic pump (Lu et al., 2003) and has a zero-order release rate. Of course, the gas generation needs gastric fluid flowing into the core tablet. This requires retention of the system in the stomach. Therefore, the gastric residence time is a determinant in this research.

3.2. In vivo evaluation by gamma scintigraphy

The purpose of this gamma scintigraphy study is to determine the GRT of the radio-labeled test preparation compared with reference preparation in Beagle dogs and to assess this high-density gastro-retentive system. Gamma scintigraphic images are shown in Figs. 4 and 5. After finding the bright spot, i.e., the radio-labeled

Table 4
Composition of optimum formulation A and two other random formulations B and C, and the predicted values as well as actual results of them[a,b,c].

Formulation	X_1 (mg)	X_2 (mg)	X_3 (mg)	X_4 (%)	Response	Predicted value	Actual value	Bias (%)
A	73	33	115	7	Y_1 (%)	96.0821	99.2554	3.3027
					Y_2	0.9901	0.9928	0.2727
B	72	36	112	8	Y_1 (%)	90.4354	86.5503	−4.2960
					Y_2	0.9951	0.9789	−1.6549
C	66	30	127	6	Y_1 (%)	87.7562	90.6839	3.3362
					Y_2	0.9826	0.9746	−0.8142

[a] Bias (%) = (actual value − predicted value)/predicted value × 100.

[b] Factors—X_1: WSR N12K, X_2: content of NaCl, X_3: content of pharmaceutical iron powder, and X_4: weight gain of the tablet; responses—Y_1: ultimate cumulative release in 12 h (%) and Y_2: correlation coefficient of drug release profile.

[c] Response values: avg., $n = 6$.

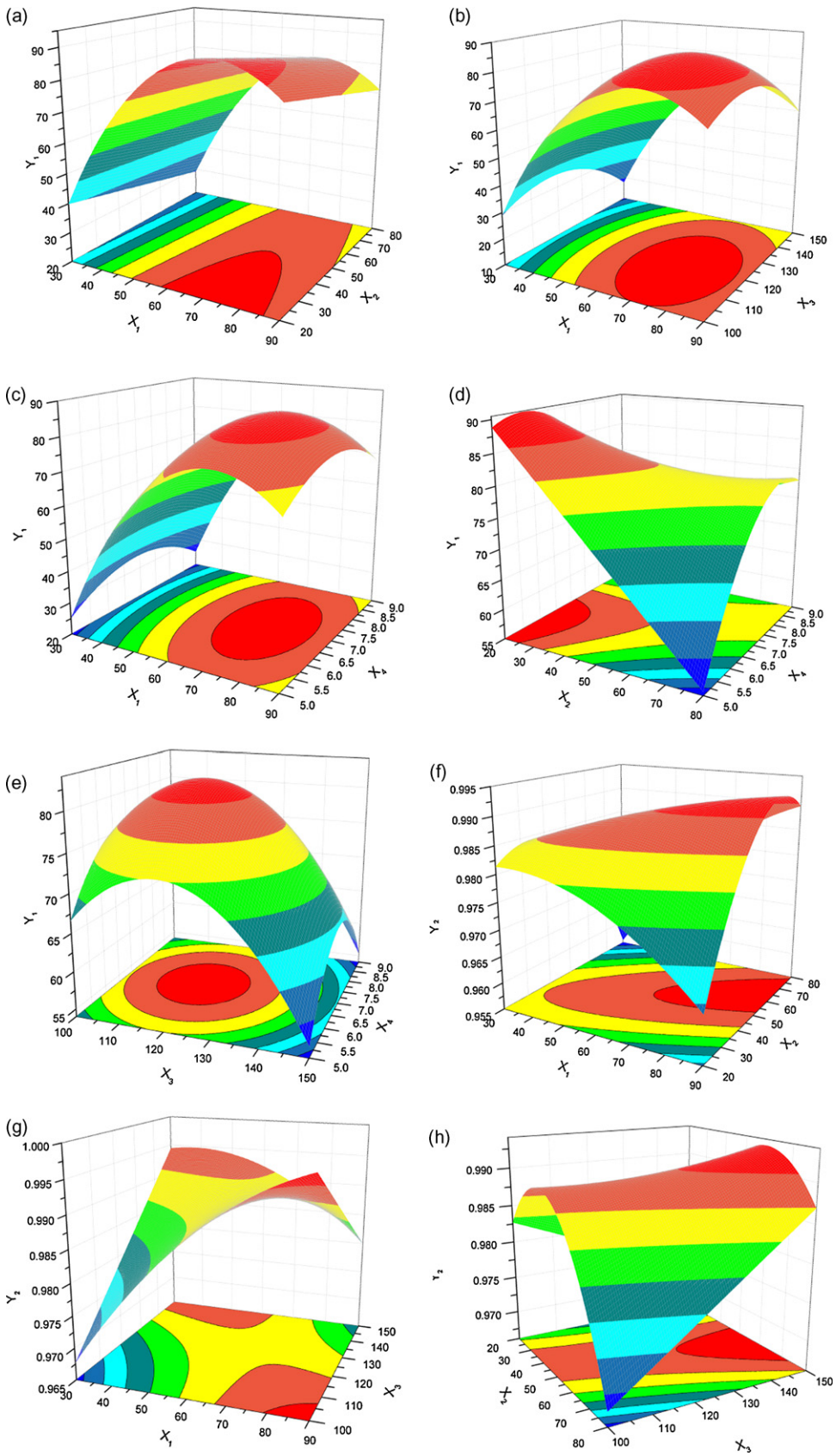

Fig. 2. Response surfaces for ultimate cumulative release in 12 h (Y_1) and correlation coefficient of drug release profile (Y_2) as functions of two factors which were significantly influential.

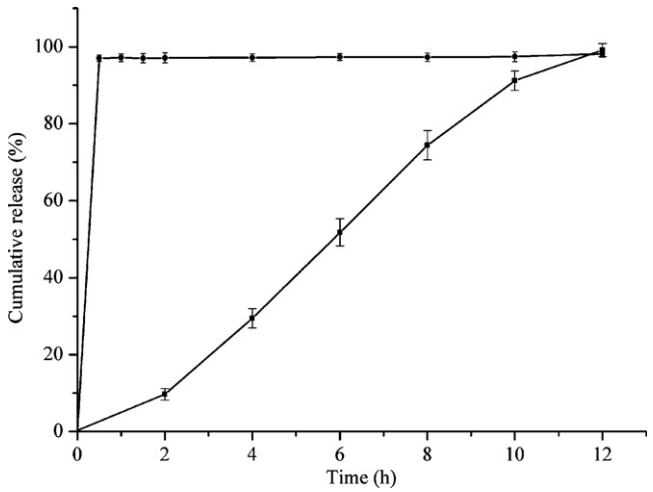

Fig. 3. FMTD in vitro cumulative release profile of the optimized formulation A and reference preparation (commercially conventional tablet) (mean ± SD, $n = 6$).

tablet at 30 min after administration, we fixed the dog. Later scintigrams were recorded at the same anatomical location. The location of the bright spot did not change, which indicated that the radio-labeled tablet was in the stomach all the time. Furthermore, radio-labeled drug and excipients were released from the system after a few hours. The boundary of the stomach became clearer and again proved that the system was in the stomach. The test preparation is retained in the bottom of the stomach for an extended period of 7 h after administration. According to Fig. 3, about 60% cumulative release was achieved in this 7 h in stomach, and the residue was released in intestinal tract in the next few hours. However, the reference preparation only exists in the stomach for 15 min before entering into the intestinal tract. Regarding the tablet as a cylinder, we can calculate the volume of the high-density gastro-retentive tablet ($V = \pi r^2 \times h = 3.142 \times 0.35^2 \times 0.2 = 0.077\ \mathrm{cm}^3$). Therefore, we obtain the initial density of the tablet prepared by formulation A: $\rho = M/V = (40 + 73 + 33 + 115) \times (1 + 7\%)/0.077 = 3.63\ (\mathrm{g\,cm}^{-3})$. This density will cause the test system immediately sink to the bottom of the stomach after administration. The gamma scintigraphic result proves it and is consistent with the conclusions of Clarke et al. (1993). Along with the reaction of pharmaceutical iron powder with gastric fluid, the system density decreases. After 7 h, the residual iron is not heavy enough to withstand the peristaltic waves of the stomach wall and the system empties from the stomach rapidly. It should be noted that during the gastric residence time the density of the text preparation is the summation of the densities of iron, drug, hydrated and unhydrated excipients, gastric fluid in the core tablet, coating membrane, as well as generating gas. In case gas is evolved, the density of the system will be lowered. But the adverse impact seems little, for the system can still sink in the stomach for about 7 h from the

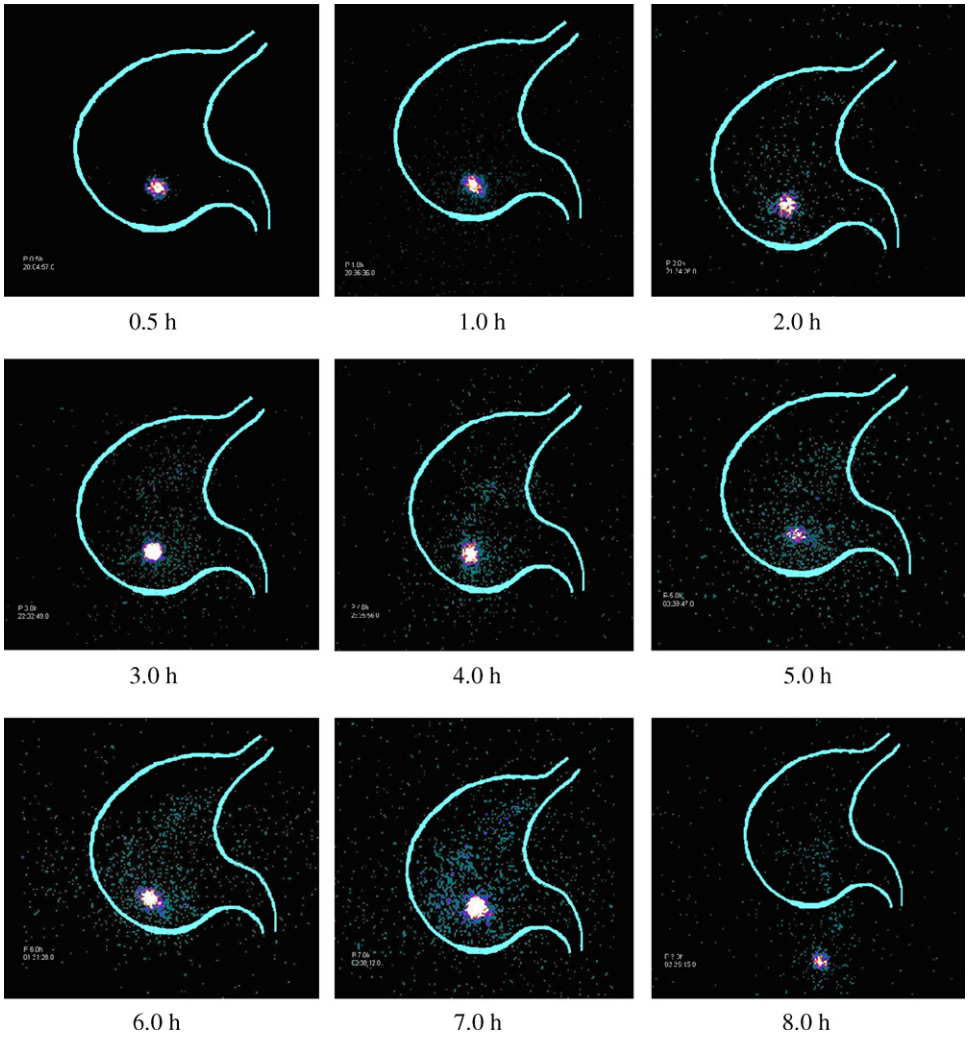

Fig. 4. Scintigraphic images of the in vivo behavior of the radio-labeled test preparation (high-density gastric-resident osmotic pump tablet) in Beagle dogs.

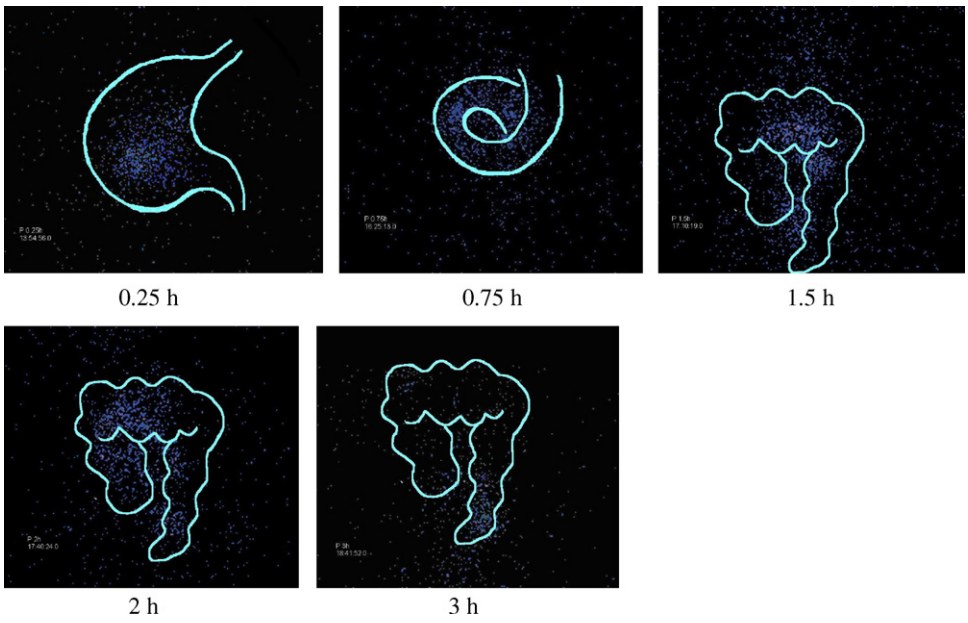

Fig. 5. Scintigraphic images of the in vivo behavior of the radio-labeled reference preparation (commercially conventional tablet) in Beagle dogs.

scintigraphic images. The main reason is that the initial generation of gas will lower the system density but the gas bubbles will vanish immediately after they contact the contents of the tablet to make the density comeback. So gas cannot counteract the contribution of increasing system density of iron. One point is worth paying attention. The gamma scintigraphy study in this paper has been conducted in Beagle dogs. The anatomy of canine species is a little different from that of humans. Hence how this system will behave in human subjects remains to be further analyzed and studied.

4. Conclusion

The optimization of FMTD novel high-density gastric-resident osmotic pump tablet formulation 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. It is proved that 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. Gamma scintigraphy was selected as the method to monitor GRT of the radio-labeled systems in Beagle dogs. Gamma scintigraphic images demonstrate that the system are retained in stomach for 7 h following administration and achieves gastric-resident purpose. How this system will behave in human subjects remains to be further analyzed and studied.

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