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Taste masking microspheres for orally disintegrating tablets

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ABSTRACT

The purpose of this study was to evaluate the potential of microspheres for taste masking when incorporated into orally disintegrating tablets. The microspheres were produced by spray drying a mixture of the model compound (famotidine) with taste masking material. The spray process was optimized using a central composite design for two variables to obtain microspheres with desirable characteristics. Then the microspheres were mixed with other excipients to form orally disintegrating tablets. The optimal spray-drying process parameters were 34 mg/ml for solid concentration and 7 ml/min for feed rate. The drug encapsulation efficiency of the spray-dried microspheres ranges from of 37.59 to 61.56%, with a mean diameter of less than 10 μm size and low moisture content (less than 4%). Results from an evaluation by a panel of six human volunteers demonstrated that the orally disintegrating tablets with taste masking microspheres improved the taste significantly. Furthermore, an *in vivo* study in rats showed that the microspheres neither decrease the bioavailability nor retard the release of famotidine significantly. In conclusion, spray-dried microspheres can effectively mask the bitter taste of the active pharmaceutical ingredients in combination with the orally disintegrating tablets.

1. Introduction

Although tablets and capsules constitute a major portion of the drug delivery systems, some patient groups, such as pediatrics, geriatrics, and bedridden or disabled patients, may have difficulties in swallowing tablets or capsules. To meet these medical needs, formulators have devoted considerable efforts to develop a novel dosage form known as orally disintegrating tablet (ODT), which can disintegrate rapidly in the saliva without water (Abdelbary et al., 2004). However, taste masking for some pharmaceutical actives with bitter or unpleasant taste can be challenging for this dosage form to achieve patient acceptability.

The mechanisms of the taste masking methods may be summarized as following. The first is to mask the distasteful sensation by the addition of flavors, sweeteners and effervescent agents. The second is to avoid the bitter drugs coming into direct contact with patients' taste buds by coating or granulation (Lieberman et al., 1989; Ishikawa et al., 1999; Hiroyuki et al., 2003; Gao et al., 2006; Kayumba et al., 2007; Shishu and Singh, 2007). The flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. Moreover, the coatings and the granulation of the active ingredient may often rupture during compressing and chewing of the tablet, as well as contribute to a gritty feel. In recent years, microspheres and microencapsulations have been developed for taste masking by creating a physical barrier to protect the bitter drugs from coming in contact with the patients' taste buds (Robson et al., 1999, 2000a,b; Hashimoto et al., 2002; Bruschia et al., 2003; Kajiyama et al., 2003). It has also been reported that these microparticles remained intact without undergoing merging or rupturing during tabletting (Sveinsson et al., 1993; Vilivalam and Adeyeye, 1994; Soppimath et al., 2001; Raghavendra et al., 2008). The potential of microspheres for taste masking when incorporated into orally disintegrating tablets will be investigated.

Spray drying was used for the preparation of the microspheres. Spray drying is widely used in pharmaceutical processing because it requires only a one-step process and can be easily controlled and scaled up (Giunchedi et al., 2001; Alysson and Wanderley, 2007).

In this investigation, polymethacrylates (Eudragit® EPO) was applied. Eudragit® EPO is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters. The cationic copolymer dissolved in pH <5. So the copolymer dissolved fast in stomach (pH 1–3) without influence the bioavailability, but keep intact in buccal cavity (pH 5.8–7.4) with good taste masking.

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Famotidine (FMT) was applied as a model compound. It belongs to a class of medications called H_2-receptor antagonist and is used to treat ulcers (Anderson et al., 2002). As a digestive system drug, FMT is very suitable for ODT; and as a bitter taste drug, it need taste masking. Currently, a FMT ODT product (PEPCID RPD®) is already commercially available. In this paper, a FMT ODT with taste masking was prepared by directly compression to improve its market value.

In vitro and *in vivo* evaluations of FMT ODTs were performed. The potential of the taste masking microspheres incorporated in ODT and the influence of microspheres on the characteristics of the ODT are discussed in detail.

2. Materials and methods

2.1. Materials

Famotidine was obtained from Shanghai Pharmaceutical Co., Ltd. Polymethacrylates (Eudragit® EPO) was kindly donated by Degussa Co., Ltd. (Germany). Quick dissolve excipient (Pharmaburst Powder) was kindly donated by SPI Pharma, Inc. (USA). Hydroxypropyl cellulose (HXF Pharm) was kindly donated by Hercules, Inc. (USA). Sodium stearyl fumarate (Pruv®), hydroxypropyl methylcellulose (Vivapharm® type 3), and microcrystalline cellulose (Vivapur® 102) were obtained from JRS (Germany). Sodium lauryl sulfate, stearatic acid, polyethylene glycol 400, magnesium stearate, talc and colloidal silicone dioxide were obtained from Beijing Jingqiu Chemical Industry Co., Ltd. (China). Povidone K25 was obtained from Hangzhou Sunflower Technology Development Ltd. (China). Acetonitrile and methanol (HPLC grade) were obtained from Fisher Scientific UK Ltd. (UK). Other reagents were analytical grade and used as received.

2.2. Preparation of spray-dried microspheres

The aqueous dispersion of Eudragit® EPO (15%, w/v) was first prepared by dispersing 15 g Eudragit® EPO in 100 ml distilled water with 1.5 g sodium lauryl sulfate, 2.25 g stearatic acid for 30 min by high shear homogenizer (Fluko Equipment, Germany).

FMT was milled for 5 min (Retsch MM301, Germany) and the final size was about 5 μm. The FMT and the colloidal silicon dioxide were suspended in distilled water. Then the polyethylene glycol 400 and the Eugragit® EPO aqueous dispersion were added in (Krismundsdóttir et al., 1996; Raffin et al., 2006; Alysson and Wanderley, 2007). The composition of the final mixture was in the ratio of FMT:Eugragit® EPO:colloidal silicon dioxide:polyethylene glycol 400 (1:2:1:0.2). The viscosity of the final suspension ranged from 2.02 to 3.3 cP (Stress Tech, Reologica Instruments AB, Sweden).

A Büchi 290 Mini Spray Drier (Büchi, Switzerland) was used. It has a two-fluid pressure nozzle with a diameter of 0.7 mm. Experiments were carried out under the following conditions: inlet air temperature 110 °C, aspirator setting 9, air flow setting about 600 NL/h and peristaltic pumps setting 20–40%.

2.3. Design of experiment (DOE)

The design of the experiment was done by software (Design Expert®, Version 7.0.3, Stat-Ease, Inc., USA). The key response of the study was the dissolution rate in 5 min.

In the preliminary study, the composition of the suspension to be spray dried (the quantity of glidant and EPO/drug ratio) and the process parameters (inlet air temperature, aspiration, feed rate, and solid concentration) were studied by single factor design. Based on the results of preliminary study, the major factors were found to be feed rate and solid concentration.

Table 1
Factors and levels

Factors	Factor level				
	−1.41	−1	0	+1	1.41
X_1: solid concentration (mg/ml)	20	34	67.5	101	115
X_2: feed rate (ml/min)	1	2	5	8	9

Two-factor central composite design (CCD) with five center points was used to find the optimum condition. The factors and levels were shown in Tables 1 and 2. The best-fitting mathematical model was selected based on the *F*-value provided by analysis of variance (ANOVA). The optimum values of the process variables were obtained from the model.

The reproducibility of the process was studied on the optimized process by triplicate.

2.4. Dissolution test

According to FIP/AAPS (Federation International Pharmaceutique/American Association of Pharmaceutical Scientists) guidelines, dissolution values of an early time point (e.g. ≤5 min) can be used to establish the approximate baseline of taste for ODT (Siewert et al., 2003; Vikas et al., 2007). In order to achieve relatively low S.D., the sampling time was decided as 5 min.

The dissolution test was performed in triplicate by a dissolution apparatus type II (ZRS-8G, Tianjin university instrument factory, China) in 500 ml distilled water medium and at 37 ± 0.5 °C. The rotation speed was 100 rpm. Five-milliliter samples were withdrawn at 5 min, and 5 ml of the medium at the same temperature were added in. Samples were assayed by HPLC.

The HPLC method was performed on Agilent 1100 (USA) with quaternary pump, with a variable wavelength detector, autosampler and column thermostat. FMT was analyzed using a Hypersil ODS-2 C_{18} column (250 mm × 4.6 mm i.d., 5 μm, Thermo, UK). The mobile phase comprised of 30 mM potassium dihydrogen phosphate (pH 7.0) and acetonitrile (88:12, v/v) at a flow rate of 1 ml/min. The method used a detector wavelength of 254 nm, the column temperature at 30 °C and Nizatidine was chose as internal standard. The injection volume was 10 μl.

The linearity was performed with a five-point calibration curve. The method was found to be linear over the examined concentration range of 2–10 μg/ml. The average calibration equation could be described by: $y = 0.0654x - 0.0034$, with a correlation coefficient of 0.9999. Where the y is the ratio of the peak area of FMT and internal standard and x is the concentration (μg/ml). The limit of detection (LOD) was 20 ng/ml. The retention time is 8 min.

Table 2
Experimental runs

Experiment	Type	Solid concentration (mg/ml)	Feed rate (ml/min)
1	Axial	67.5	1
2	Factorial	34	2
3	Central	67.5	5
4	Axial	67.5	9
5	Central	67.5	5
6	Axial	20	5
7	Axial	115	5
8	Central	67.5	5
9	Factorial	101	2
10	Central	67.5	5
11	Factorial	34	8
12	Central	67.5	5
13	Factorial	101	8

2.5. Microspheres characterization

Many physical and chemical properties of the spray-dried microspheres may have effects on taste masking, dissolution rate, integrity, and scale-up process.

2.5.1. Moisture

Moisture was determined by loss on drying. Our preliminary study demonstrated that drying the powder by high temperature will result in recrystallization. Drying at ambient temperature can be applied by putting the 0.1 g microspheres in desiccators until the constant weight achieved, and then calculating the loss on drying.

2.5.2. Yield

The yields were calculated by dividing the weight of the microspheres by the total weight of added ingredients.

2.5.3. Drug loading and encapsulation efficiency

The drug content in the microspheres was determined in triplicate by HPLC. The drug loading and encapsulation efficiency were calculated using the following equation:

$$\text{drug loading } (\%) = \left(\frac{\text{weight of drug in microspheres}}{\text{weight of microspheres}}\right) \times 100$$

$$\text{drug encapsulation efficiency } (\%) = \left(\frac{\text{weight of drug in microspheres}}{\text{weight of drug added}}\right) \times 100$$

2.5.4. Morphology

Shape and surface characteristics of microspheres were analyzed by scanning electron micrograph (JEOL JSM5200, Japan Electron Optics Ltd., Tokyo) after gold sputtering.

2.5.5. Particle size

The product particle size distribution was determined by optical microscopy and image analysis with magnification of 400 times (Alysson and Wanderley, 2007). Powder samples were dispersed on a glass sheet and images of the powder were obtained with the aid of a COIC microscope (model XSZ-H, China) connected to a digital camera (NIKON-4500, China) (average of three determinations). The resulting images were analyzed with an image analysis system (Image Pro-Plus 6.0).

2.5.6. Thermal analysis of the microspheres

Differential scanning calorimetry (DSC) experiments were performed on plain FMT, placebo microspheres, and FMT-loaded microspheres (Perkin-Elmer, Massachusetts, USA). Accurately weighted samples (2–5 mg) were sealed in flat bottom aluminum pans and heated from ambient to 300 °C at a rate of 10 °C/min in a nitrogen atmosphere (flow rate, 10 ml/min).

2.6. Preparation of the FMT tablets

The ODTs without microspheres (formulation 1), with microspheres (formulation 2) and the marketed common tablets as control (formulation 3) were prepared by direct compression. The FMT and excipients for 50 tablets were weighted according to the ingredients listed in Table 3, and then screen by 40# mesh and blended to uniformity. Exactly weighed quantity of the powder mixture was filled into a die, and then pressure (about 5 kN) was applied to form the tablet by using the single rotary tablet press (DP30, Guoyao Longli Corporation, China).

For formulation 2, the microspheres were obtained using the optimized process parameters, described in Section 2.3.

2.7. Evaluation of the FMT tablets

2.7.1. The physical parameters

Ten randomly selected tablets were weighed individually. The average weight and the relative standard deviation were calculated. The mean weight was expressed in mg (SHIMADZU, Japan). Each tablet was crushed, and then the powder was extracted by vortex. Samples were assayed by HPLC.

For each formulation, the hardness of tablets was examined using a hardness tester to measure the crushing strength of the tablets (YPJ-200A, China). The mean hardness was calculated and expressed as N.

2.7.2. Dissolution test

The dissolution in 5 min of the tablets was performed by the method described in Section 2.4.

2.7.3. Taste masking and disintegration time

A single blind study was designed for the taste masking test and disintegration time in the buccal cavity. Six volunteers participated in the test. They were asked to rate the bitter taste of the three formulations (formulation 1–3) using a scale of 0–3. When the score was 1 or less, the taste was considered as acceptable. If the score was higher than 1, the bitterness of the formulation was

Table 3
Formulations and characteristics of the FMT tablets

	Formulation 1	Formulation 2	Formulation 3
	ODTs without microspheres	ODTs with microspheres	Marketed common tablets
Tablet components			
FMT (%)	24.5	24.5 (microspheres)	24.5
Parmaburst powder (%)	60	60	–
HPMC (%)	7.5	7.5	–
PVP (%)	5	5	–
Citric acid (%)	1	1	5
Sodium stearyl fumarate (%)	2	2	53.5
Corn starch (%)	–	–	15
Magnesium stearate (%)	–	–	2
Characteristics of the tablets for human volunteers			
Size	6 mm C	12 mm V	6 mm C
Weight (mg)	82	350–380[a]	82
Content of FMT (mg)	20	20	20

[a] According to the drug loading of the microspheres.

Table 4
The results of all the experiments

Experiment	Moisture (%)	Yield (%)	Drug loading (%)	Encapsulationefficiency (%)	Size (μm)	Dissolution in 5 min ± S.D. (%)
1	0.9 ± 0.1	33.91	33.51 ± 1.19	53.41 ± 1.90	6.26	58.10 ± 5.32
2	1.1 ± 0.1	34.06	35.01 ± 0.54	55.26 ± 0.86	6.41	45.38 ± 2.69
3	1.9 ± 0.6	41.26	28.19 ± 0.73	54.67 ± 1.42	8.52	22.31 ± 2.35
4	2.3 ± 0.2	40.89	19.56 ± 0.68	37.59 ± 1.31	8.83	38.24 ± 7.49
5	1.2 ± 0.2	40.52	27.33 ± 1.29	52.05 ± 2.46	8.33	25.18 ± 1.84
6	0.9 ± 0.1	38.05	34.42 ± 1.38	61.56 ± 2.47	5.63	28.13 ± 1.12
7	1.3 ± 0.1	33.25	25.14 ± 0.56	39.29 ± 0.88	10.76	37.87 ± 3.92
8	1.2 ± 0.2	43.80	26.56 ± 0.83	54.68 ± 1.71	8.23	29.13 ± 2.49
9	1.1 ± 0.3	34.06	28.44 ± 1.09	45.53 ± 1.74	9.04	39.98 ± 2.80
10	1.3 ± 0.1	39.17	29.17 ± 1.27	53.70 ± 2.34	8.44	20.35 ± 1.18
11	1.7 ± 0.2	41.63	24.53 ± 1.53	48.00 ± 2.99	6.98	18.29 ± 0.81
12	0.9 ± 0.3	42.33	29.09 ± 1.61	57.87 ± 3.20	8.32	18.79 ± 3.84
13	1.9 ± 0.3	40.33	20.36 ± 1.32	39.84 ± 2.63	9.82	38.44 ± 1.29

not acceptable (Kajiyama et al., 2002). An approximate time for the tablet disintegration in the buccal cavity were also recorded.

2.8. Bioequivalence study

To evaluate the effects of the microspheres on the release profile *in vivo*, the bioequivalence of formulation 1 (reference tablets) and formulation 2 (test tablets) were studied in rats. A single-dose, randomized study was conducted by 12 rats (Wistar rats, male, weight 250–350 g). The rats were divided in two groups and fasted for overnight. The tablets were dispersed in water and immediately administered at 15 mg/kg per animal through oral gavage. Heparinized samples of blood (0.5 ml, venous blood) were then collected at 15, 30, 45, 60, 90, 120, 180, 240, 360 and 480 min. Plasma samples were taken after centrifugation and stored frozen at −20 °C until HPLC analysis. The animal facilities and protocols were in accordance with the National Institute of Health's guidelines regarding the principles of animal care (2004).

The HPLC plasma samples were prepared in the following steps: a mixture of plasma (100 μl), saturated potassium carbonate solution (100 μl), ethyl acetate (200 μl), L-hydroxytryptophan at a concentration of 2 μg/ml (50 μl) was prepared using a vortex for 5 min. The mixture was then centrifuged at 10,000 × *g* for 5 min. The organic layer was separated, and then 200 μl ethyl acetate was added in the residual aqueous layer. The mixture was vortexed for 5 min and centrifuged at 10,000 × *g* for 5 min. The organic layers were combined and evaporated to dryness under a stream of nitrogen at ambient temperature. The HPLC samples were then prepared by reconstituting the extracted dry samples with 100 μl mobile phase by vortexing.

The HPLC method was performed on the same Agilent 1100 system and column as described in Section 2.4. The mobile phase was comprised of 30 mM of potassium dihydrogen phosphate (pH 7.0, containing 0.2% triethylamine, v/v) and methanol (88:15, v/v) at a flow rate of 1 ml/min. The method used a detector with a wavelength at 266 nm, a column temperature of 25 °C and L-hydroxytryptophan was used as internal standard. The injection volume was 20 μl.

The linearity was performed with a five-point calibration curve. The method was found to be linear over the examined concentration range 0.05–1 μg/ml. The average calibration equation could be described by: $y = 0.6021x + 0.0004$, with a correlation coefficient of 0.9998. Where the y is the ratio of the peak area of FMT and internal standard and x is the concentration (μg/ml). The limit of detection (LOD) was 20 ng/ml. The retention time is 12.913 min.

The pharmacokinetics and statistical analysis were computed using the Practical Pharmacokinetic Program Version 97 (the Chinese Society of Mathematical Pharmacology, China). The statistical methodology based on the U.S. Pharmacopeia (USP29) was employed. C_{max} (the maximum plasma concentration) and T_{max} (time point of maximum plasma concentration) were obtained directly from the measured data; $AUC_{0-8\,h}$ (area under the plasma concentration–time curve from 0 to 8 h) was calculated according to the trapezoidal rule, the terminal elimination rate, λ_z, was estimated by log-linear regression on the last five points, $t_{1/2}$ (half-life of drug elimination during the terminal phase) was calculated with $t_{1/2} = 0.693/\lambda_z$, and the $AUC_{0-\infty}$ (area under the plasma concentration–time curve from 0 to infinity) was the corresponding area extrapolated to infinity by $AUC_{0-8\,h} + C_{8\,h}/\lambda_z$. Bioequivalence was determined by calculating 90% confidence intervals (90% CI) for the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values, using logarithmic transformed data. The products were considered bioequivalent if the 90% CI for AUC and C_{max} fell within 80–125%.

3. Results and discussion

3.1. Characterization of microspheres

The microspheres were prepared under the spray-drying process parameters described in Section 2.2. These sets of experimental conditions were able to produce microsphere particles with moisture contents less than 4%, drug loading ranging from 19.56 to 35.01% and accepted encapsulation efficiency ranging from 37.59 to 61.56% (Table 4). The drug loading of some experiment is higher than the nominal (21.28%). The reason lies in the loss of some excipients during the process. The colloidal silicon dioxide as glidant is the one most probable to lose. The large quantity of glidant must be added in order to avoid wall sticking. The drug loading may be improved by the application of equipment with less wall sticking.

The yield is about 40% (33.25–41.23%). During the spray-drying process the non-encapsulated free drug and other excipients lost with the exhaust gas together. The yield may be further improved by preventing the loss of the smallest and lightest particles through the exhaust of the spray-dryer apparatus.

Dissolution rate of the active will determine the taste masking potential of these microspheres. Particle size, morphology and integrity of the particles have direct impact on the dissolution rate. Our preliminary studies showed that spray-drying parameters, especially the solid concentration and feed rate, have significant effects on particle size, morphology, and in turn, the dissolution rate.

The spray-dried powders generated in all experiments have mean particle sizes of less than 10 μm. In general, particle size was found to increase with an increase in solid concentration and feed rate (Fig. 1A and B). Both factors can augment the mean diameter of the atomizing drops during spray-drying contributing to the increase in size.

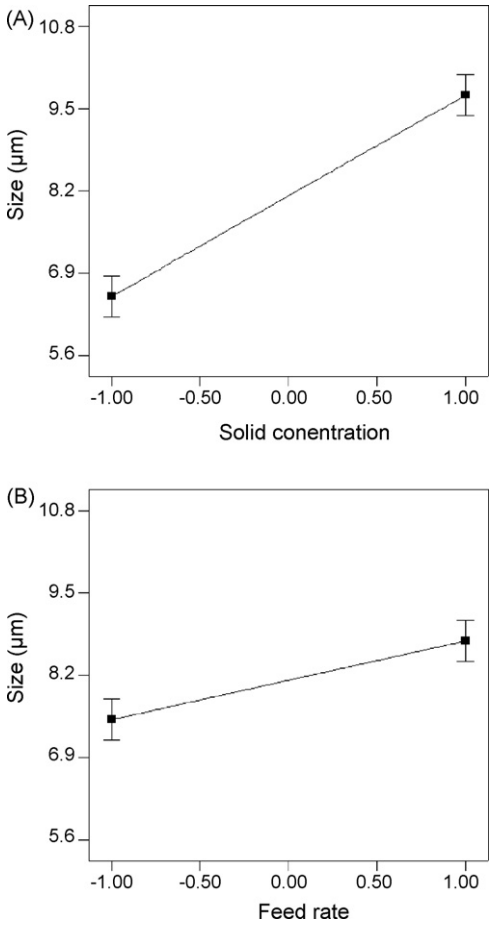

Fig. 1. Influence of the spray-drying process parameters on the size of the microspheres.

Scanning electron microscopy was used to visualize the particle structural and surface morphology of the spray-dried powders. The representative scanning electron microscopy (Fig. 2A) indicated that the taste masking microspheres are regular spherical particles with a diameter of less than 10 μm. The unevenness on the surface may form when the internal pressure rapidly increases while the moisture cannot be released (Seville et al., 2007). The morphology of the product obtained from the higher solid concentration and the feed rate (Fig. 2 B and C) showed the fractured shell and bigger size. Therefore, the solid concentration and feed rate should be carefully selected for producing desirable microspheres.

The data of dissolution in 5 min were obtained and changed from 18 to 58% (Table 4). Microspheres can mask the bitter taste by retarding the release of FMT. The high dissolution rate can be correlated to either small particle size or fractured spheres. Since dissolution rate depended on both size and morphology, unlike the particle size, it does not have a simple linear correlation with solid concentration and feed rate. Therefore, a statistically designed optimization of the process parameters was used to obtain a desirable release rate.

DSC (Fig. 3) presents the change of thermal behaviors as a result of interactions during preparation. For plain FMT, a sharp melting peak at 163 °C was observed. The DSC of FMT-loaded microspheres did not exhibit any significant melting peak. The disappearance of the peak suggests that FMT is completely entrapped in the polymer matrix and also points to possibility of significant reduction in drug crystallinity in the polymer matrix.

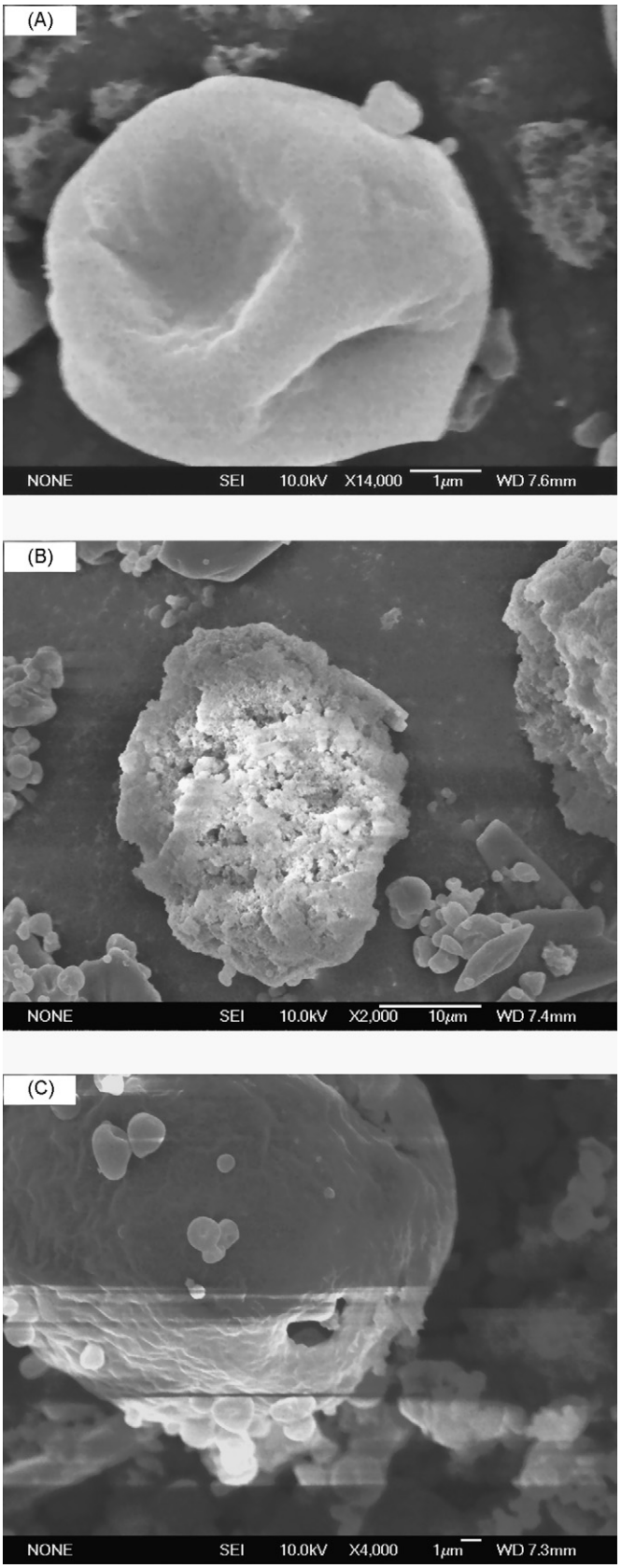

Fig. 2. Representative scanning electron micrographs of microspheres spray-dried under: (A) the solid concentration was 34 mg/ml and the feed rate was 2 ml/min; (B) solid concentration was 115 mg/ml and the feed rate was 2 ml/min; (C) solid concentration was 115 mg/ml and the feed rate was 5 ml/min.

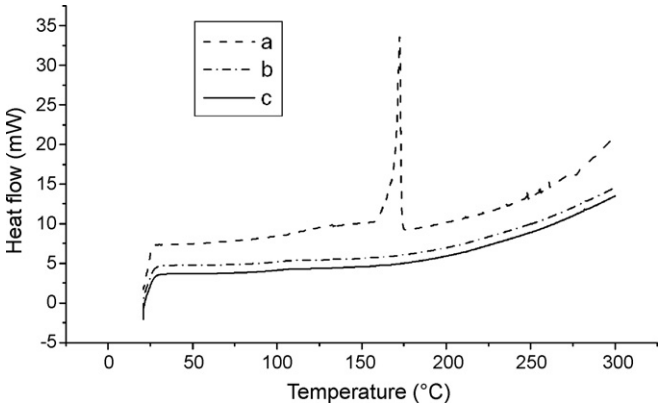

Fig. 3. DSC thermograms of (a) plain FMT; (b) placebo microspheres; (c) FMT-loaded microspheres.

3.2. Optimization of process parameters

Statistically designed experiments were performed using central composite design (CCD) to optimize the levels of solid concentration and feed rate. The quadratic model was a statistically significant model ($p = 0.0005$). The mathematical model (a polynomial equation) which was obtained by the software (Design-Expert®) was described below:

$$Y(\text{dissolution in 5 min}) = 23.15 + 3.57X_1 - 7.09X_2 + 6.38X_1X_2 + 3.66X_1^2 + 11.24X_2^2$$

ANOVA showed the F-value = 18.59, and p-value ≤ 0.05 which indicated that the effect of the corresponding factors on the response was significant. The response surface plots were shown in Fig. 4. The R^2 value of 0.9300 indicates that the model was in good fit with the R.S.D. value of 4.12, and CV of 12.75%.

An optimization procedure was used to obtain the levels of X_1 and X_2 at which minimized Y (dissolution in 5 min) by software. The optimum levels were −1 for solid concentration (34 mg/ml) and 0.6 for feed rate (7 ml/min) (Fig. 4).

The taste masking microspheres under the optimum condition were prepared in triplicate. The observed value (18.01 ± 0.63%) agreed with the predicted value (19.21%). This proved the validity of the model. The reproducibility was proved by the low S.D.

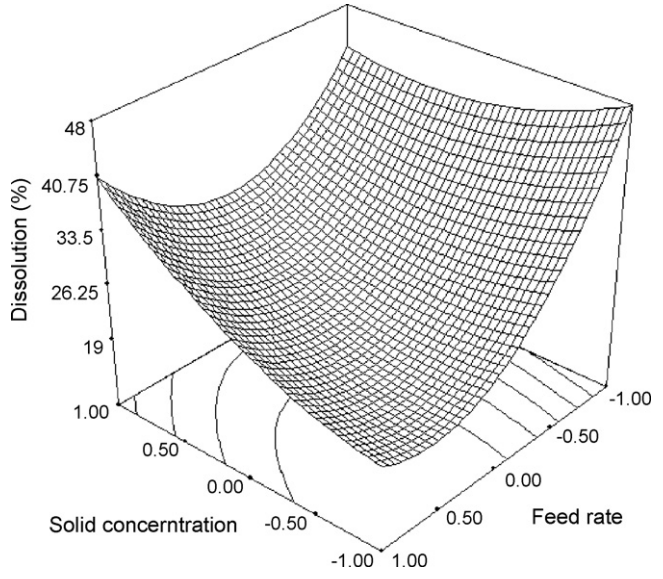

Fig. 4. The response surface plots.

Table 5
The weight uniformity, content uniform and hardness of ODTs

	Weight uniformity (%)	Content uniformity (%)	Hardness (N)
Formulation 1	81.34 ± 0.29	103.25 ± 2.78	20
Formulation 2	370.57 ± 3.14	105.33 ± 1.55	20

Table 6
Results of taste test

	Score of taste test					
	Formulation 1		Formulation 2		Formulation 3	
	Number of people	Score	Number of people	Score	Number of people	Score
No. of bitter taste	0	0	4	0	0	0
Slight bitter taste	4	4	2	2	0	0
Strong bitter taste	2	6	0	0	6	18
Mean score overall evaluation	–	1.67	–	0.33	–	3

3.3. Evaluation of the tablets

The weight uniformity, content uniformity and hardness of the prepared ODTs are satisfied (Table 5).

The values of dissolution in 5 min were 95.54 ± 5.87% for formulation 1 and 19.74 ± 7.96% for formulation 2. That demonstrate microspheres can retard the release of FMT.

The difference in dissolution rate between microspheres (18.01 ± 0.63%) and the tablets with microspheres (formulation 2) was not significant. A paired Student's t-test was performed by software (SPSS 10), and p-value of 0.756 was obtained. The fact of no significant change in dissolution rates demonstrated that the tabletted microspheres remained intact because if the microspheres break, the dissolution value is expected to increase significantly.

The disintegration time in the buccal cavity was 23.98 ± 12.20 s for formulation 1, and 31.07 ± 9.63 s for formulation 2 while the formulation 3 did not disintegrate at all. The disintegration time for the tablets with microspheres was prolonged, but it was not significant ($p = 0.258$).

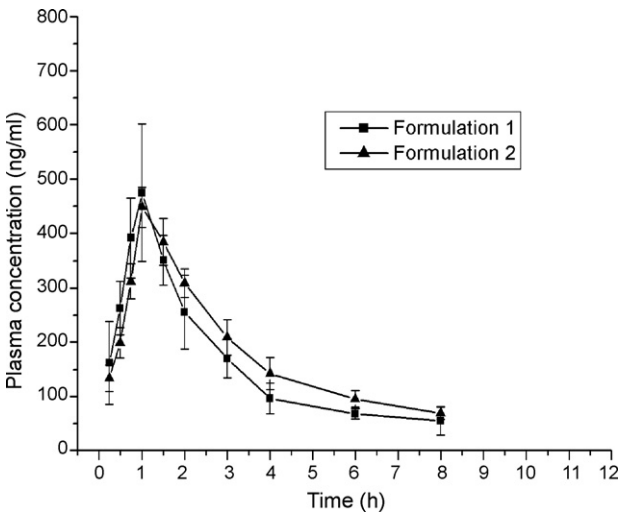

Fig. 5. FMT plasma concentration (expressed in ng/ml) vs. time profiles (mean ± S.D.) following oral administration of the formulations 1 and 2 ($n = 6$).

Table 7
Pharmacokinetic parameters of FMT (mean ± S.D.) following oral administration of the formulations 1 and 2 ($n = 6$)

	Formulation 1	Formulation 2	90% confidential interval
$AUC_{0-8\,h}$ (ng h/ml)	1253.38 ± 148.20	1437.88 ± 85.48	115.1–115.4
$AUC_{0-\infty}$ (ng h/ml)	1503.94 ± 200.20	1791.831 ± 291.9	118.7–119
C_{max} (ng/ml)	522.13 ± 129.25	450.582 ± 34.15	88.1–89.0
T_{max} (h)	1.00 ± 0.27	1.08 ± 0.20	–
$t_{1/2}$ (h)	3.06 ± 1.27	3.361 ± 2.00	–

The results of the taste masking test were listed in Table 6. The mean score less than 1 for the formulation 2 indicated that the formulation containing microspheres sufficiently alleviate the bitterness of FMT tablets.

3.4. Bioequivalence study

The plasma concentration–time profiles following oral administration of formulation 1 (reference) and 2 (test) were illustrated in Fig. 5. The pharmacokinetic parameters and 90% confidence intervals for the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, using logarithmic transformed data, were shown in Table 7. The values were within the range for bioequivalence. T_{max} for the formulations 1 and 2 were not significantly different ($p = 0.6779$). The results demonstrated formulations 1 and 2 were bioequivalent. The microspheres neither decrease the bioavailability nor delay the release of famotidine significantly.

4. Conclusions

The study indicated that both the size and the integrity of the spray-dried microspheres affected the function of taste masking. Two spray dry process parameters of solid concentration and feed rate were identified to be important for producing desirable microsphere particles. Only the microspheres spray-dried under the optimum process parameters can mask the taste effectively. The optimum solid concentration is 34 mg/ml and the optimum feed rate is 7 ml/min.

The taste masking potential of the microspheres incorporated in ODTs was evaluated by dissolution test of microsphere particles and tablets, *in vivo* rat study, and taste masking test as well as the disintegration time in the buccal cavity with a panel of human volunteers. The ODTs can disintegrate in the buccal cavity within 30 s with improved taste. The microspheres neither decrease the bioavailability nor delay the release of famotidine significantly. Based on these results, spray-dried microspheres provide an effective method for taste masking and can be incorporated in ODTs.

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