Design and optimization of artemether microparticles for bitter taste masking

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The objective of the present investigation was to reduce the bitterness of artemether (ARM). Microparticles were prepared by the coacervation method using Eudragit E 100 (EE) as polymer and sodium hydroxide solution as nonsolvent for the polymer. A 3^2 full factorial design was used for optimization wherein the amount of drug (A) and polymer (B) were selected as independent variables and the bitterness score, particle size and drug release at pH, 1.2 and 6.8 were selected as dependent variables. Optimization was carried out using the desirability function. The optimized microparticles batch was characterized by FTIR and DSC. Multiple linear regression analysis revealed that reduced bitterness of ARM can be obtained by controlling the drug release of microparticles at pH 6.8 and increasing the amount of EE. The increase in the amount of polymer leads to reduction in drug release from microparticles at pH > 5 due to its insolubility and thus reduces bitterness. However, the increase in the amount of polymer results in improved dissolution, suggesting improved availability of ARM in stomach. Optimized microparticles prepared using 0.04 g of ARM and 15 mL of 1% (*m/V*) solution of EE showed complete bitter taste masking with improved drug release at pH 1.2.

Keywords: artemether, Eudragit E 100, bitterness, 3^2 factorial design

In recent years, the use of a number of drugs, including antibiotics and antimalarials, which have undesirable tastes, has been increasing. Although antimalarials are widely administered parenterally, oral administration is more convenient and acceptable to patients. Oral administration of antimalarials, especially to children, is often hampered by their unpleasant bitter taste. This leads to non-compliance and hinders therapeutic management.

Artemether (ARM), a drug used for treatment of malaria, has an extremely unpleasant bitter taste. The exact mechanism of bitterness is unknown. However, it has been re-

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ported that drugs like ARM bind to the membrane receptor, present on the apical taste cells and thus produce bitterness (1, 2). As this is likely to give rise to non-compliance when administered orally, it would be a considerable advantage to mask the bitterness of ARM and incorporate it in a palatable formulation (3).

Various masking techniques such as the addition of sweeteners and flavors, coating with water-insoluble polymers, adsorption to ion-exchange resin, microencapsulation with various polymers, complexing with cyclodextrins, melt granulation and chemical modifications such as the use of insoluble prodrugs have been tried (4). Among the various techniques, microencapsulation has often proved to be most successful in reducing the bitterness of bitter active pharmaceutical ingredients because it is simple, economic and advantageous.

Eudragit E 100 (EE) is a cationic copolymer based on dimethyl aminoethyl methacrylate and neutral methacrylic esters soluble up to pH 5 (5). In addition, the polymer retards the drug release above pH 5 due to its insolubility. The pH inside the oral cavity has been reported to be about 6.8 (6). Thus, EE retards drug release at pH 6.8 and acts as a physical barrier between the drug and taste cells. This results in taste masking of bitter drugs.

Various methods such as coating, dispersion coating, spray drying and emulsion solvent diffusion have been reported (7, 8). In the present study, microparticles were prepared using the coacervation phase separation method. Sodium hydroxide was used as nonsolvent for the polymer.

The objective of the present investigation was to completely disguise the bitter taste of ARM by encapsulation in microparticles and to develop a palatable formulation. A 3^2 full factorial design was used for optimization of microparticles wherein the drug concentration (A) and polymer concentration (B) were selected as independent variables while the particle size, drug release at pH 1.2 and 6.8 along with bitterness score were selected as dependent variables.

EXPERIMENTAL

Materials

Eudragit E 100 (Batch no. G041131159) was a gift from Degussa India Pvt. Ltd. (India). Methanol was purchased from Qualigens Fine Chemicals (India) and was used as received. Sodium hydroxide, hydrochloric acid, potassium chloride, potassium dihydrogen phosphate, and acetic acid were purchased from S. D. Fine-Chem Ltd. (India) and were used as received.

Preparation of microparticles

Microparticles were prepared by the coacervation phase separation method. A concentrated solution of EE (1%, *m/V*) was prepared in 1%, *V/V* acetic acid. The required quantity of ARM (0.04 g in 15 mL of 1%, *m/V*, EE solution) was mixed for 5 min. 10 mL of 10%, *m/V* sodium hydroxide solution was introduced into a 10-mL glass syringe with

a flat-cut hypodermic needle and added dropwise into the EE solution. Different concentrations of ARM and EE were used as mentioned in Table I. The resulting microparticles were allowed to harden for 60 min under gentle stirring (Remi Equipments Pvt. Ltd., India) with a small magnetic bar, decanted on a Büchner funnel, rinsed with deionized doubly-distilled water, and dried to a constant mass in a hot air oven (Shree Kailash Industries, India) at 70 °C for 24 hours, and then stored in the desiccator until use.

Experimental design

A 3^2 full factorial design was employed to systematically study the joint influence of independent variables, amount of drug (A), and polymer (B), on the dependent variables such as particle size, drug release at pH, 1.2 and 6.8 along with bitterness score. In this design, 2 factors were evaluated, each at 3 levels, and experimental runs were performed in all 9 possible combinations. The experimental runs along with their measured responses (dependent variables) are reported in Table II.

Table I. *Process variables and their levels for the 3^2 full factorial design*

Coded values	Actual values	
	Amount of ARM (A) (g)	Amount of EE (B) (mL)[a]
−1	0.01	5
0	0.03	10
1	0.05	15

[a] mL of 1% (*m/V*) EE solution.

Table II. *Experimental runs for the 3^2 full factorial design with their measured responses*

Batch No.	Factor levels		Incorporation efficiency (%)[a]	Particle size (µm)[a]	Drug release		Bitterness score
	A	B			pH 1.2 (%)[a,b]	pH 6.8 (%)[a,c]	
ARM1	−1	−1	83.6 ± 1.3	44.08 ± 4.29	62.6 ± 1.1	4.4 ± 0.8	1
ARM2	0	−1	74.5 ± 1.7	45.17 ± 3.84	72.6 ± 1.0	4.2 ± 0.8	2
ARM3	1	−1	79.5 ± 1.5	45.31 ± 3.16	85.7 ± 1.0	5.4 ± 0.6	3
ARM4	−1	0	82.5 ± 1.2	142.58 ± 4.37	79.3 ± 1.3	5.7 ± 0.7	0
ARM5	0	0	78.9 ± 1.2	92.46 ± 3.52	84.3 ± 0.9	5.6 ± 0.9	0
ARM6	1	0	84.3 ± 1.4	64.49 ± 3.74	89.3 ± 1.2	6.5 ± 0.6	1
ARM7	−1	1	77.9 ± 1.2	241.84 ± 3.93	93.4 ± 1.2	3.8 ± 0.8	0
ARM8	0	1	82.8 ± 0.8	120.72 ± 3.24	90.4 ± 1.3	3.7 ± 0.8	0
ARM9	1	1	83.4 ± 1.3	54.36 ± 4.63	87.3 ± 1.0	4.5 ± 0.9	0

[a] Mean ± SD, *n* = 3.
[b,c] Percent drug released in 15 and 5 min, respectively.

A statistical model incorporating interactive and polynomial terms was used to evaluate the response (9):

$$Y = b0 + b1A + b2B + b11A^2 + b22B^2 + b12AB \qquad (1)$$

where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs while b1 and b2 are the estimated coefficients for the factors A and B. The main effects (A and B) represent the average result of changing one factor at a time from its low to high value. The interaction terms (AB) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (A^2 and B^2) are included to investigate nonlinearity.

Further, the model was evaluated for the best fit using various statistical parameters such as PRESS (predicted residual error sum of squares), Adj-R^2, Pred-R^2 and Adeq Precision. PRESS (predicted residual error sum of squares) indicates how well the model fits the data. Coefficients for the model were calculated without the first point. This new model was then used to estimate the first point and calculate the residual for point one. This was done for each data point and the squared residuals were summed.

Adj-R^2 measures the variation around the mean explained by the model, adjusted for the number of terms in the model:

$$AdjR^2 = 1 - \frac{\dfrac{SS_{residual}}{DF_{residual}}}{\dfrac{SS_{model} + SS_{residual}}{DF_{model} + DF_{residual}}} \qquad (2)$$

Pred-R^2 measures the amount of variation in new data explained by the model:

$$\Pr edR^2 = 1 - \frac{PRESS}{SS_{total} - SS_{block}} \qquad (3)$$

Adequate precision (*Adeq Precision*) is a signal to noise ratio. It compares the range of the predicted value at design points with the average prediction error:

$$Adeq \Pr ecision = \frac{pd^2}{n} \qquad (4)$$

where *p* is the number of model parameters including intercept (*b0*), *d* is the residual mean square (MS) from the ANOVA table and *n* is the number of experiments (10).

Incorporation efficiency

Microparticles containing 10 mg of the drug were weighed accurately and dissolved in methanol. Drug concentration was determined by UV spectrophotometry (UV visible spectrophotometer 1700, Shimadzu, Japan) at 256 nm. A calibration curve was used, based on standard solutions in methanol.

Particle size analysis

The average particle diameter and size distribution of microparticles were determined using Malvern (Mastersizer 2000, Malvern Instruments, UK). Approximately 10 mg of microparticles were dispersed in 2–3 mL of filtered and degassed phosphate buffer, pH 6.8, containing 0.1% Tween 80 for one minute using an ultrasonic bath. An aliquot of the microparticle suspension was then added into the small volume recirculation unit and circulated at 3500 rpm. Each sample was measured in triplicate. Particle size was expressed as the weighted mean of volume distribution.

In vitro *drug release*

The *in vitro* release profile of plain ARM and optimized microparticles was determined according to the paddle method, described in the *United States Pharmacopoeia XXIV* (11). The *in vitro* drug release study was carried out in phosphate buffer, pH 6.8, because the pH of the saliva is in the range from 6.8–7.2. Further, the *in vitro* drug release study was performed in hydrochloric acid buffer, pH 1.2, to demonstrate the availability of ARM in gastric pH. Microparticles containing an equivalent of 50 mg of ARM were suspended in 900 mL of buffer solution, and a 3 mL sample was withdrawn at 1, 5, 10, 15, 30 and 60 min and analyzed using a UV spectrophotometer at 256 nm. Each sample was replaced with fresh buffer solution of the same temperature.

Gustatory sensation test

Gustatory sensation test was carried out according to the method of Shah *et al.* (10). Twenty volunteers participated in the sensory test. One gram of microparticles was dispersed in 100 mL of water for 15 s. ARM was used as a control. Immediately after preparation, each volunteer held about 1 mL of the dispersion in the mouth for 30 s. After expectoration, the bitterness level was recorded. A numerical scale was used with the following values: 0 – tasteless, 0.5 – very slightly bitter, 1 – slightly bitter, 1.5 – slightly to moderately bitter, 2 – moderately bitter, 2.5 – moderately to strongly bitter, 3 – strongly bitter, 3+ – very strongly bitter. The threshold of bitterness of microparticles was determined as the point at which most volunteers described the taste as bitter or slightly biter.

Optimization of responses using desirability

The multiple response method makes use of an objective function called the desirability function. It reflects the desirable ranges for each response (d_i). Each response is associated with its own partial desirability function. If the value of the response is optimal, its desirability equals 1, and if it is totally unacceptable, its value is zero. Thus, the desirability for each response can be calculated at a given point in the experimental domain. The optimum is the point with the highest value of desirability (12).

The percent drug release at pH 1.2 was aimed at maximum since higher value was desired. Higher percent drug release at pH 1.2 leads to greater availability of ARM in the stomach. Moreover, microparticles showed complete release within a few minutes. Hence, the percent drug release at 15 min (t_{15}) was selected. The Ymin and Ymax values of per-

cent drug release at pH 1.2 in 15 min (t15) were 62.57 and 93.39, respectively. The desirability function of this parameter was calculated by the following equation.

$$di = \left(\frac{Yi - Y\min}{Y\max - Y\min} \right)^{s} \tag{5}$$

where di is individual desirability, Yi is the experimental result and s is used to change the shape of the desirability goal by the weight field.

To avoid grittiness of microparticles after ingestion in oral cavity, minimal particle size was desired. The observed Ymin and Ymax particle size values were 44.08 and 241.84, respectively. The problem of bitter taste of the drug is generally encountered due to dissolution of the active component in oral cavity. Microparticles remain in oral cavity for maximally 5 min. To avoid this, minimal percent drug release at 5 min was desired. The Ymin and Ymax values of percent drug release at pH 6.8 in 5 min (t5) were 3.7 and 6.47, respectively. Similarly, the lowest bitterness score value was desired for complete taste masking. Though the observed Ymax value of the bitterness score was 3, 0.5 was selected because very slight bitterness was desired. The Ymax and Ymin values of bitterness score were 0.5 and 0, respectively. Thus, the desirability function of the particle size, drug release at pH 6.8 and bitterness score was calculated using the following equation.

$$di = \left(\frac{Y\max - Yi}{Y\max - Y\min} \right)^{s} \tag{6}$$

where di is individual desirability, Yi is the experimental result and s is used to change the shape of the desirability goal by the weight field. In all the experiments performed, all the experimental values were acceptable; however, the values far from the target were penalized by choosing $0 < s < 1$ (1 in this case) in Eqs. *7*, *8* and *9*.

$$di = 1 \qquad\qquad \text{if } Yi < Y\min \tag{7}$$

$$di = \left(\frac{Y\max - Yi}{Y\max - Y\min} \right)^{s} \qquad \text{if } Y\min \leq Yi \leq Y\max \tag{8}$$

$$di = 0 \qquad\qquad \text{if } Yi > Y\max \tag{9}$$

The overall desirability was calculated from the individual values by using the following equation:

$$D = (d1 \times d2 \times d3 \times d4)^{1/4} = \left(\prod_{i=1}^{4} d_i \right)^{1/4} \tag{10}$$

where D is overall desirability and d1, d2, d3, d4 are individual desirability values of measured responses.

Fourier transform infra-red spectroscopy (FTIR)

FTIR transmission spectra of pure ARM, EE, blank microparticles and optimized microparticles were obtained using a Fourier Transform Infrared Spectrophotometer (FTIR-8300, Shimadzu, Japan). A total of 2% (*m/m*) of the sample, with respect to the potassium bromide (S. D. Fine Chem Ltd., India), was mixed with dry KBr.

Differential scanning calorimetry (DSC)

A differential scanning calorimetry study of pure ARM, EE, blank microparticles and optimized microparticles was performed using a Mettler Toledo, DSC 822e DSC (Mettler Toledo, Switzerland). All the samples were accurately weighed (5–8 mg), sealed in aluminium pans and heated at a scanning rate of 5 °C min^{-1}. Nitrogen was used as the purge gas with the flow rate set at 40 mL min^{-1}. Aluminum pans and lids were used for all samples. An empty aluminum pan was used as a reference.

RESULTS AND DISCUSSION

Experimental design

Preliminary investigations of process parameters revealed that the factors, amount of drug (A) and polymer (B), highly influenced the bitterness in human volunteers, particle size, drug release at pH 1.2 and 6.8. Hence, A and B were used for further systematic studies. The dependent and independent variables were related using mathematical relationships obtained with the statistical package DOE v6.0.5 (Stat-Ease, Inc.). The fitted polynomial equations (full and reduced model) relating the response to the transformed factors are shown in Table III. Polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries, *i.e.*, positive or negative. *F*-value compares the variance with the residual (error) variance. The terms having *Prob > F value* over 0.05 were omitted in the reduced model (13, 14).

Multiple linear regression analysis (Table III) revealed that A^2 and B^2 terms were insignificant for particle size while the A^2 term was insignificant for bitterness score and dissolution at pH 1.2. The term AB was insignificant for drug release at pH 6.8. The surface plots are shown in Fig. 1.

Table IV shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors (15). High values of the square root correlation coefficient (R^2) for all dependent variables indicate a good fit.

PRESS values for all formulations showed a good fit of the model. Adj-R^2 and Pred-R^2 values were in reasonable agreement, signifying good model fit. Further models, full model (FM) and reduced model (RM), showed the *Adeq precision value* greater than 4, indicating adequate model discrimination.

Table III. Regression analysis results

Term	Particle size (μm)				Drug release at pH 1.2 (%)[b]				Drug release at pH 6.8 (%)[c]				Bitterness score			
	FM		RM		FM		RM		FM		RM		FM		RM	
	EC	Prob > F	EC	Prob > F	EC	Prob > F	EC	Prob > F	EC	Prob > F	EC	Prob > F	EC	Prob > F	EC	Prob > F
Intercept	91.40	NA	94.56	NA	83.93	NA	84.27	NA	5.58	NA	5.58	NA	0.22	NA	0.33	NA
A (amount of ARM)	−44.06	0.0020	−44.06	0.0003	4.51	0.0007	4.51	0.0001	0.39	0.0016	0.39	0.0009	0.50	0.0079	0.50	0.0039
B (amount of EE)	47.06	0.0017	47.06	0.0003	8.36	0.0001	8.36	< 0.0001[a]	−0.52	0.0022	−0.35	0.0014	−1.00	0.0010	−1.00	0.0003
A²	12.66	0.1695	–	–	0.50	0.4228	–	–	0.52	0.0034	0.52	0.0025	0.17	0.3081	–	–
B²	−7.93	0.3674	–	–	−2.27	0.0246	−2.27	0.0129	−1.60	0.0001	−1.60	< 0.0001[a]	0.67	0.0163	0.67	0.0099
AB	−47.18	0.0030	−47.18	0.0006	−7.30	0.0003	−7.30	< 0.0001[a]	−0.08	0.1623	–	–	−0.50	0.0138	−0.50	0.0080

[a] Statistically significant ($p < 0.05$); [b,c] Percent drug released in 15 and 5 min, respectively; EC – estimated coefficient; Prob > F – probability; NA – not applicable, indicates the term is omitted in reduced model; FM – full model, RM – reduced model.

Table IV. ANOVA results showing the effect of independent variables on the measured responses

Measured response	Model	Sum of squares (SS)	DF	Mean square (MS)	F-value	(Prob > F) 100	PRESS	R^2	Adj-R^2	Pred-R^2	Adeq Precision
Particle size (μm)	FM	34282.99	5	6856.60	61.13	0.32	4090.40	0.99	0.97	0.88	22.89
	RM	33836.67	3	11278.89	72.04	0.02	2596.09	0.97	0.96	0.92	22.59
Drug release at pH 1.2 (%)[b]	FM	765.34	5	153.07	262.40	0.04	20.15	0.99	0.99	0.97	50.21
	RM	764.84	4	191.21	339.92	< 0.01[a]	16.25	0.99	0.99	0.97	56.02
Drug release at pH 6.8 (%)[c]	FM	7.34	5	1.47	194.93	0.06	0.26	0.99	0.99	0.96	40.42
	RM	7.31	4	1.83	151.72	0.01	0.24	0.99	0.98	0.96	35.00
Bitterness score	FM	9.44	5	1.89	51.00	0.42	0.83	0.98	0.96	0.91	20.15
	RM	9.39	4	2.35	56.33	0.09	0.47	0.98	0.96	0.95	20.81

[a] Statistically significant ($p < 0.05$); [b,c] Percent drug released in 15 and 5 min respectively; FM – full model; RM – reduced model. F – Fischer's ratio; R^2 – regression coefficient; df – degrees of freedom; SS – sum of squares; MS – mean of squares.
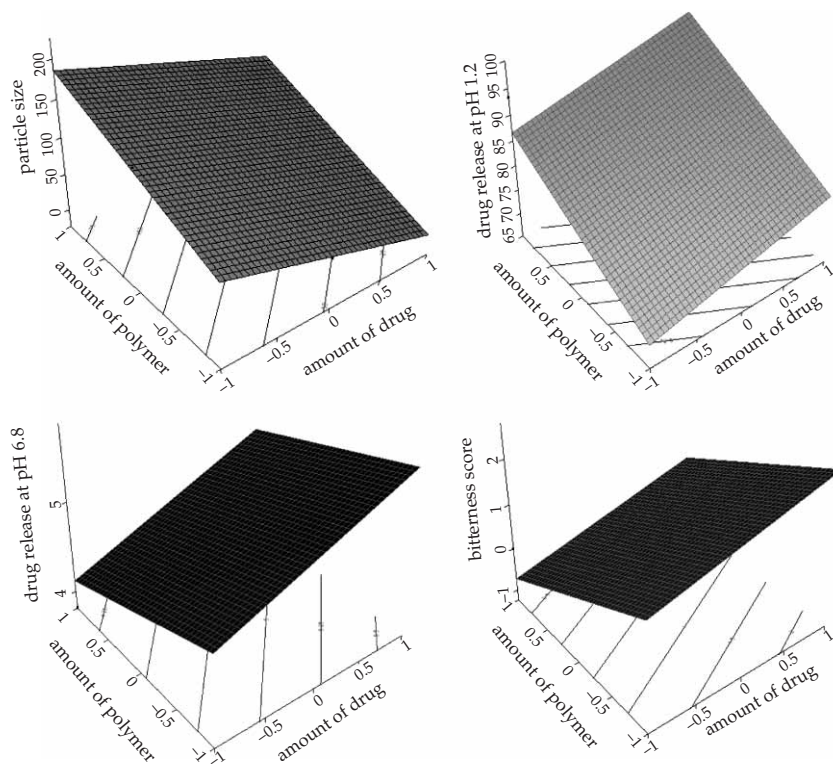
Fig. 1. Surface plots showing the effect of the amount of drug and polymer on particle size, drug release at pH 1.2 and 6.8, along with bitterness score.

Incorporation efficiency

Incorporation efficiency is an important factor in evaluation of the quality of microparticles. Incorporation efficiency varied for all batches as shown in Table II. The high ARM content in the microparticles was believed to be due to poor solubility of ARM in EE solution. Incorporation efficacy improves with an increase in polymer (16). This suggests that the present method is suitable for the preparation of microparticles of a poorly water-soluble drug, such as ARM.

Particle size

For particle size, the amount of ARM is negative while the amount of EE is positive. This indicates that on increasing the amount of EE, the particle size increases. It was observed that polymer viscosity influenced the particle size (16). Increasing the amount of EE led to an increase in its viscosity and consequently a decrease in the frequency of dissociation or separation of particles with the addition of sodium hydroxide. This resulted in an increase in the overall size of microparticles.

In vitro *drug release*

In the case of *in vitro* drug release at pH 1.2, the amounts of ARM and EE are positive. This indicates the additive effect of the amount of ARM and EE. This suggests that ARM release would be improved at acidic pH, resulting in improved availability of ARM in the stomach. ARM release from microparticles was completed within a few minute, followed by a plateau. This may be due to the high porosity of microparticles, the hydrophilic nature of EE, and improved wettability provided by the dissolved EE (17).

In the case of *in vitro* drug release at pH 6.8, the amount of ARM is positive while the amount of EE is negative. This indicates that on increasing the amount of EE, drug release from microparticles decreases. As the amount of EE increased, a thicker film was formed around the ARM particles, which retarded ARM release because of being insoluble at salivary pH (10). EE is expected to behave as an insoluble and inert material at pH 6.8 and to show decreased drug release. This is due to the decrease in drug diffusion and/or membrane infiltration (17). Fig. 2 shows the dissolution profile of ARM and optimized microparticles at pH 1.2 and 6.8.

Gustatory sensation test

In the case of bitterness score, the amount of ARM is positive while the amount of EE is negative. This indicates that on increasing the amount of EE, the bitterness score of microparticles decreases. This finding is in agreement with the *in vitro* drug release study carried out at pH 6.8, because the pH of the saliva is 6.8 (4). It has been reported that bitter drugs like ARM seem to bind G-protein coupled receptors, present on the apical taste cell membrane, and produce bitterness (1). EE is expected to behave as insoluble at pH 6.8 and to show decreased drug release in microparticles. Thus, EE forms a physical barrier between ARM and G-protein coupled receptors present on the apical taste cell membrane and reduces the bitterness score of ARM in microparticles.
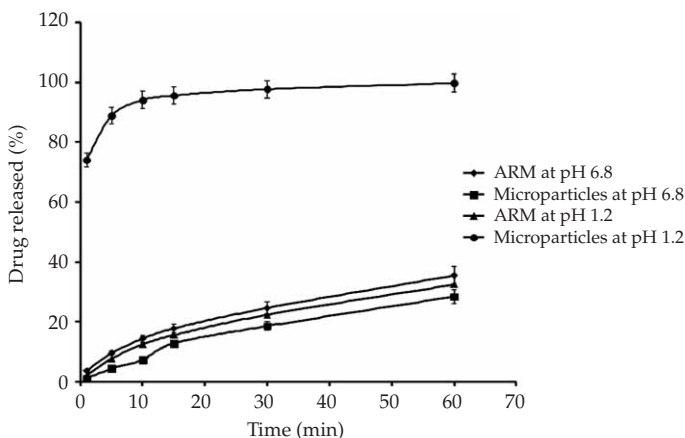

Fig. 2. Dissolution profile of ARM and optimized microparticles at pH 1.2 and 6.8 (mean ± SD, *n* = 3).

Optimization using desirability function

A process can only be authenticated when the optimum level of its variables (affecting the process) for a product of good quality characteristics is recognized. Desirability function is an excellent tool for identifying the optimum levels of variables. In this procedure, all the measured responses for independent variables that are supposed to affect the quality of the product are taken into consideration. Particle size, drug release at pH 6.8 and bitterness score have to be minimized while drug release at pH 1.2 has to be maximized in order to pour desired characteristics into the product. Using the desirability function, all the measured responses were combined to get one overall response, *i.e.*, the overall desirability. The overall desirability response was calculated from the individual desirability of each of the responses using DOE v6.0.5. The optimized batch was identified with a desirability value of 0.88. Table V lists the optimized values for independent variables and their responses.

Fourier transform infra-red spectroscopy

The FTIR spectrum of ARM, EE, blank microparticles and optimized microparticles are shown in Fig. 3. The characteristic peaks of ARM at 2873 cm^{-1} are assigned to C-H

Table V. Optimum levels of independent variables and their responses

Actual value of optimum batch		Incorporation efficiency (%)[a]	Particle size (µm)[a]	Drug release		Bitterness score	Overall desirability
A (g)	B (mL)[d]			pH 1.2 (%)[a,b]	pH 6.8 (%)[a,c]		
0.04	15	82.9 ± 1.3	85.9 ± 1.5	89.4 ± 1.3	4.2 ± 0.7	0	0.88

[a] Mean ± SD, *n* = 3.
[b,c] Percent drug released in 15 and 5 min respectively.
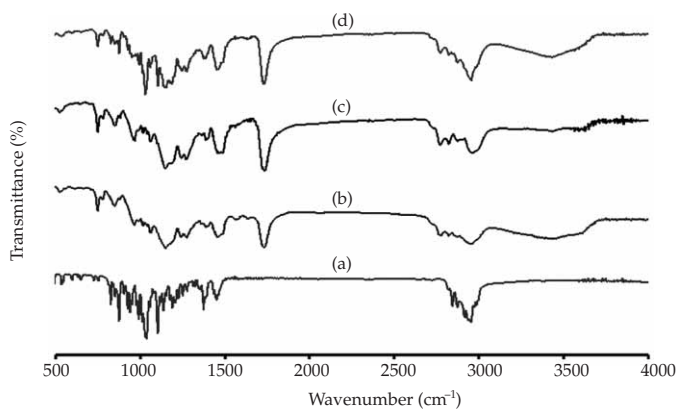[d] mL of 1% (*m/V*) EE solution.

Fig. 3. FTIR spectra of a) ARM, b) EE, c) blank microparticles and d) optimized microparticles.
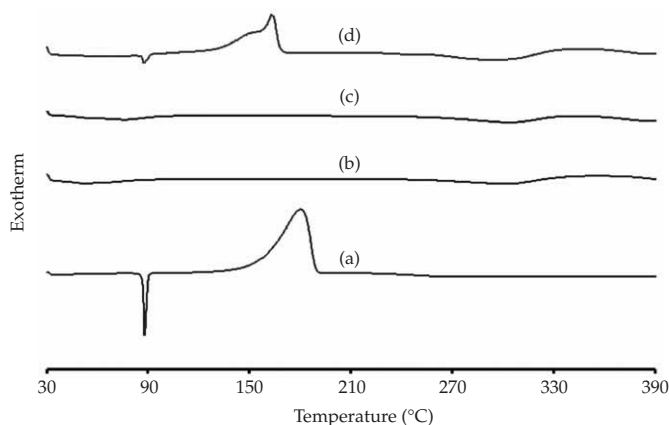
Fig. 4. DSC curve of a) ARM, b) EE, c) blank microparticles and d) optimized microparticles.

stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2844 cm^{-1} can be assigned to C-H stretching vibration in $C-O-CH_3$. The peak at 1137 cm^{-1} can be assigned to C-O stretching vibration in C-O-C. The peaks at 2953 and 2916 cm^{-1} are assigned to C-H stretching in $-CH_3$. The EE spectrum is dominated by the carbonyl (C=O) stretching vibration at 1735 cm^{-1} and the ester C-O stretching vibrations at 1148 and 1188 cm^{-1}. In addition, C-H vibrations can be discerned at 1389, 1450–1490 and 2962 cm^{-1}. The absorptions at 2772 and 2822 cm^{-1} can be assigned to the dimethylamino groups. The spectrum of microparticles corresponds to the superimposition of ARM and EE with no significant shift of major peaks. This confirms the presence of ARM in microparticles.

Differential scanning calorimety

Fig. 4 shows the DSC curve of ARM, EE blank microparticles and microparticles. Pure ARM shows an endothermic peak at 87.94 °C, followed by an exothermic peak at 180.28 °C. The endothermic peak corresponding to the melting peak of ARM was broadened and shifted towards lower temperature, with reduced intensity in microparticles. This could be attributed to higher polymer concentration and uniform distribution of the drug in the polymer crust, resulting in complete miscibility of molten drug in the polymer. The FTIR and DSC studies indicated uniform dispersion of ARM, at the molecular level, in EE microparticles.

CONCLUSIONS

The study has conclusively demonstrated complete taste masking of ARM in microparticles using EE as polymer. The present work suggests that the amount of drug (A) and polymer (B) has its own significant complementary role in enhancement of the process rather than having an exclusive effect. Application of experimental design along with desirability function can be an ideal tool to optimize independent variables like the amount

of ARM and EE, which have a significant effect on microparticles' desired properties. The bitterness of ARM was reduced successfully in EE microparticles.

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S A Ž E T A K

Dizajniranje i optimizacija mikrokapsula artemetera za maskiranje gorkog okusa

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Cilja ovog rada je bio maskirati gorki okus artemetera (ARM) mikrokapsuliranjem. Mikročestice su pripravljene metodom koacervacije pomoću Eudragita E 100 (EE) kao polimerne komponente i natrijevog hidroksida u kojem se polimer ne otapa. 3^2 faktorijalni dizajn upotrebljen je za optimizaciju. Količine ljekovite tvari (A) i polimera (B) izabrane su kao nezavisne varijable, a intenzitet gorkog okusa, veličina čestica i oslobađanje ljekovite tvari pri pH 1,2 i 6,8 izabrane su kao zavisne varijable. Optimizirane mikročestice karakterizirane su pomoću FTIR i DSC. Multipla linearna regresijska analiza otkrila je da se smanjenje gorčine artemetera može postići kontroliranjem oslobađanja ljekovite tvari pri pH 6,8 i povećanjem količine EE. Povećanje količine polimera smanjuje oslobađanje ljekovite tvari pri pH > 5 pa se smanjuje i gorčina. Međutim, povećanje količine polimera povećava topljivost ljekovite tvari, a time potencijalno i njenu raspoloživost u želucu. U optimiziranim mikročesticama pripravljenim pomoću 0,04 g ARM i 15 mL 1% *m/V* otopine EE potpuno se maskirao gorki okus, a oslobađanje ljekovite tvari pri pH 1,2 bilo je poboljšano.

Ključne riječi: artemeter, Eudragit E 100, gorčina, 3^2 faktorijano dizajniranje

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