European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08 Issue 7, 2021

Original Research Article

Design And Optimization Of Ciprofloxacin Dry Suspension For Bitter Taste Masking

Satish Agrawal[l]*, Aniruddh Singh Deora[2]

[1]*Professional Address: Research Scholar, Department of Pharmaceutics, Bhupal Nobles' College of Pharmacy, Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan.

[2]Professional Address: Professor, Department of Pharmaceutics, Bhupal Nobles' College of Pharmacy, Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan.

***Corresponding author:** Satish Agrawal

*Professional Address: Research Scholar, Department of Pharmaceutics, Bhupal Nobles' College of Pharmacy, Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan.
Email id: satishagrawal050@gmail.com

ABSTRACT

The objective of the present investigation was to reduce the bitterness of ciprofloxacin (CIPRO). Dry suspension was prepared by the coacervation method using Eudragit E 100 (EE) as polymer and sodium hydroxide solution as non-solvent for the polymer. A 32 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 dry suspension batch was characterized by FTIR and DSC. Multiple linear regression analysis revealed that reduced bitterness of CIPRO can be obtained by controlling the drug release of dry suspension at pH 6.8 and increasing the amount of EE. The increase in the amount of polymer leads to reduction in drug release from dry suspension at pH > 5 due to its insolubility and thus reduces bitterness. However, the increase in the amount of polymer results in improved dissolution, suggesting im- proved availability of CIPRO in stomach. Optimized microparticles prepared using 0.04 g of CIPRO and 15 mL of 1% (m/V) solution of EE showed complete bitter taste masking with improved drug release at pH 1.2.

Keywords: ciprofloxacin, Eudragit E 100, bitterness, 32 factorial design

INTRODUCTION

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.

Ciprofloxacin (CIPRO), 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- ported that drugs like CIPRO 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 CIPRO and incorporate it in a palatable formulation (3).

ISSN 2515-8260 Volume 08 Issue 7, 2021

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 metha- crylate 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 sol- vent diffusion have been reported (7, 8). In the present study, dry suspension was pre- pared using the coacervation phase separation method. Sodium hydroxide was used as nonsolvent for the polymer.

The aim and objective of present study was to develop a formulation which should be tasteless upon administration and not release drug at pH of saliva but should release the drug rapidly in to the stomach (pH 0.9-1). Hence for masking the taste of Ciprofloxacin (CIPRO) various techniques and materials were used on the basis of formulation design. The objective of present investigation was to completely disguise the bitter taste of drug by encapsulation in microparticles and to develop a palatable formulation.

EXPERIMENTAL

Materials

Eudragit E 100 was a gift from Degussa India Pvt. Ltd. Methanol was purchased from Qualigens Fine Chemicals (India) and was used as received. Sodium hydroxide, hydrochloric acid, potassium chloride, potassium dihydro- gen phosphate, and acetic acid were purchased from S. D. Fine-Chem Ltd. (India) and were used as received.

Preparation of dry suspension

Dry suspension was 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 CIPRO (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 drop wise into the EE solution. Different concentrations of CIPRO 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 per- formed in all 9 possible combinations. The experimental runs along with their measured responses (dependent variables) are reported in Table II.

ISSN 2515-8260 Volume 08 Issue 7, 2021

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

Coded values	Amount of CIPRO (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 32 full factorial design with their measured responses

Batch	Factor levels		Incorporation	Particle size	Drug release		Bitterness
No.	A	B	efficiency (%)[a]	(mm)[a]	pH 1.2 (%)[a,b]	pH 6.8 (%)[a,c]	score
CIPRO1	–1	–1	83.6 ± 1.3	44.08 ± 4.29	62.6 ± 1.1	4.4 ± 0.8	1
CIPRO2	0	–1	74.5 ± 1.7	45.17 ± 3.84	72.6 ± 1.0	4.2 ± 0.8	2
CIPRO3	1	–1	79.5 ± 1.5	45.31 ± 3.16	85.7 ± 1.0	5.4 ± 0.6	3
CIPRO4	–1	0	82.5 ± 1.2	142.58 ± 4.37	79.3 ± 1.3	5.7 ± 0.7	0
CIPRO5	0	0	78.9 ± 1.2	92.46 ± 3.52	84.3 ± 0.9	5.6 ± 0.9	0
CIPRO6	1	0	84.3 ± 1.4	64.49 ± 3.74	89.3 ± 1.2	6.5 ± 0.6	1
CIPRO7	–1	1	77.9 ± 1.2	241.84 ± 3.93	93.4 ± 1.2	3.8 ± 0.8	0
CIPRO8	0	1	82.8 ± 0.8	120.72 ± 3.24	90.4 ± 1.3	3.7 ± 0.8	0
CIPRO9	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):

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

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 (A2 and B2) 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-R2, Pred-R2 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-R2 measures the variation around the mean explained by the model, adjusted for the number of terms in the model:

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

Pred-R2 measures the amount of variation in new data explained by the model:

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

$$Pred R^2 = 1 - \frac{PRESS}{SS_{total} - SS_{block}} \quad (3)$$

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:

$$Adeq\,Precision = \frac{pd^2}{n} \quad (4)$$

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

Dry suspension 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, ba- sed on standard solutions in methanol.

Particle size analysis

The average particle diameter and size distribution of dry suspension were determi- ned using Malvern (Mastersizer 2000, Malvern Instruments, UK). Approximately 10 mg of dry suspension 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 ex- pressed as the weighted mean of volume distribution.

***In vitro* drug release**

The in vitro release profile of plain CIPRO and optimized dry suspension 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 CIPRO in gastric pH. Dry suspension containing an equivalent of 50 mg of CIPRO 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 dry suspension was dispersed in 100 mL of water for 15 s. CIPRO was used as a control. Immediately after preparation, each volunteer held about 1 mL of the dispersion in the mouth for 30 s. After ex- pectoration, 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 dry suspension was determined as the point at which most volunteers described the taste as bitter or slightly bitter.

ISSN 2515-8260 Volume 08 Issue 7, 2021

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 (di). Each response is associated with its own partial desirability function. If the value of the response is opti- mal, 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 do- main. 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 CIPRO in the stomach. Moreover, dry suspension showed complete release within a few minutes. Hence, the percent drug release at 15 min (t15) was selected. The Y_{min} and Y_{max} 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.

$$di = \left(\frac{Yi - Ymin}{Ymax - Ymin} \right)^{s} \qquad (5)$$

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 dry suspension after ingestion in oral cavity, minimal particle size was desired. The observed Y_{min} and Y_{max} particle size values were 44.08 and 241.84, respectively. The problem of bitter taste of the drug is generally encountered due to dis- solution of the active component in oral cavity. Dry suspension remains in oral cavity for maximally 5 min. To avoid this, minimal percent drug release at 5 min was desired. The Y_{min} and Y_{max} 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 Y_{max} value of the bitterness score was 3, 0.5 was selected because very slight bitterness was desired. The Y_{max} and Y_{min} values of bitterness score were 0.5 and 0, respectively.

Fourier transforms infra-red spectroscopy (FTIR)

FTIR transmission spectra of pure CIPRO, EE, blank dry suspension 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 CIPRO, EE, blank dry suspension and optimized dry suspension was performed using a Mettler Toledo, DSC 822e DSC (Mettler Toledo, Switzerland). All the samples were accurately weighed (5–8 mg), sealed in aluminum 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 fit- ted polynomial equations (full and reduced model) relating the response to the trans- formed 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 A2 and B2 terms were in- significant for particle size while the A2 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 (R2) for all dependent variables indicate a good fit.
PRESS values for all formulations showed a good fit of the model. Adj-R2 and Pred-R2 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.

Incorporation efficiency

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

Particle size

For particle size, the amount of CIPRO 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 dry suspension.

***In vitro* drug release**

In the case of in vitro drug release at pH 1.2, the amounts of CIPRO and EE are positive. This indicates the additive effect of the amount of CIPRO and EE. This suggests that CIPRO release would be improved at acidic pH, resulting in improved availability of CIPRO in the stomach. CIPRO release from dry suspension was completed within a few minute, followed by a plateau. This may be due to the high porosity of dry suspension, 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 CIPRO is positive while the amount of EE is negative. This indicates that on increasing the amount of EE, drug release from dry suspension decreases. As the amount of EE increased, a thicker film was formed around the CIPRO particles, which retarded CIPRO 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 CIPRO and optimized dry suspension at pH 1.2 and 6.8.

Gustatory sensation test

In the case of bitterness score, the amount of CIPRO is positive while the amount of EE is negative. This indicates that on increasing the amount of EE, the bitterness score of dry suspension 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 CIPRO 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 dry suspension. Thus, EE forms a physical barrier between CIPRO and G-protein coupled receptors present on the apical taste cell membrane and reduces the bitterness score of CIPRO in dry suspension.

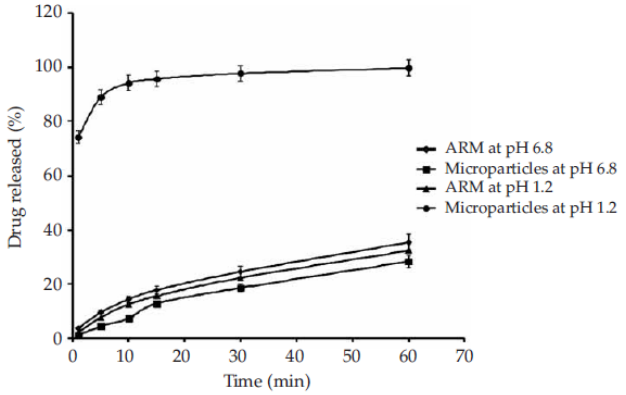

Fig. 2. Dissolution profile of CIPRO and optimized dry suspension at pH 1.2 and 6.8 (mean ± SD, n = 3).

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 CIPRO, EE, blank dry suspension and optimized dry suspension are shown in Fig. 3. The characteristic peaks of CIPRO 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.

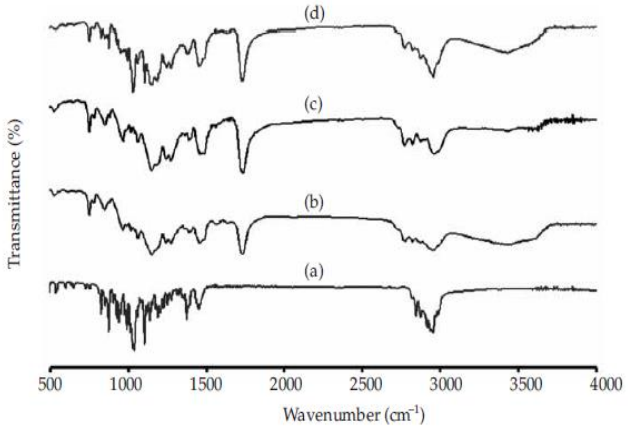

Fig.3. FTIR spectra of a) CIPRO, b) EE, c) blank microparticles and d) optimized microparticles.

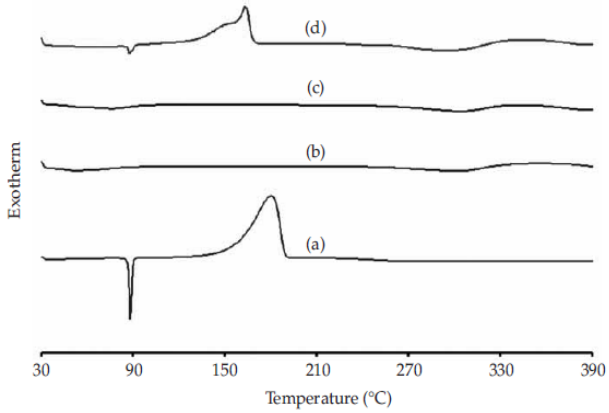

Fig.4. DSC curve of a) CIPRO, b) EE, c) blank microparticles and d) optimized microparticles.

Stretching vibration in CH3, CH2. In addition, the absorption peak at 2844 cm–1 can be assigned to C-H stretching vibration in C-O-CH3. 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 -CH3. 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 CIPRO and EE with no significant shift of major peaks. This confirms the presence of CIPRO in microparticles.

Differential scanning calorimety

Fig. 4 shows the DSC curve of CIPRO, EE blank microparticles and microparticles.

Pure CIPRO 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 CIPRO 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 CIPRO, at the molecular level, in EE microparticles**.**

ISSN 2515-8260 Volume 08 Issue 7, 2021

CONCLUSIONS

The study has conclusively demonstrated complete taste masking of CIPRO in micro- particles 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 CIPRO and EE, which have a significant effect on dry suspension' desired properties. The bitterness of CIPRO was reduced successfully in EE dry suspension.

REFERENCES

1. T. Yamamoto, T. Nagai, T. Shimura and Y. Yasoshima, Roles of chemical mediators in taste sys- tem, Jpn. J. Pharmacol. 76 (1998) 325–348.

2. P. P. Shah, R. C. Mashru, A. R. Thakkar and A. C. Badhan, Effect of chitosan crosslinking on bit- terness evaluation of ciprofloxacin using response surface methodology, J. Pharm. Pharmacol. 60 (2008) 421–427; DOI: 10.1211/jpp.60.4.0003.

3. P. P. Shah and R. C. Mashru, Development and evaluation of ciprofloxacin taste masked rapid dis- integrating tablets with improved dissolution using solid dispersion technique, AAPS Pharm- SciTech 9 (2008) 494–500; DOI: 10.1208/s12249-008-9066-4.

4. H. Sohi, Y. Sultana and R. K. Khar, Taste masking technologies in oral pharmaceuticals: recent deve- lopments and approaches, Drug. Dev. Ind. Pharm. 30 (2004) 429–448; DOI: 10.1081/DDC-120037477.

5. E. Esposito, R. Rancarati, R. Cortesi, F. Cervellati and C. Nastruzzi, Production of Eudragit mi-croparticles by spray-drying technique: Influence of experimental parameters on morphological and dimensional characteristics, Pharm. Dev. Tech. 5 (2000) 267–278; DOI: 10.1081/PDT-100100541.

6. Y. Hashimoto, M. Tanaka, H. Kishimoto, H. Shiozawa, K. Hasegawa, K. Matsuyama and T. Uchida, Preparation, characterization and taste masking properties of polyvinylacetal diethylamino ace- tate microsphere containing trimebutine, J. Pharm. Pharmacol. 54 (2002) 1323–1328.

7. T. Ishikawa, Y. Watanabe, N. Utoguchi and M. Matsumoto, Preparation and evaluation of tab-lets rapidly disintegrating in saliva containing bitter taste-masked granules by direct compres-sion method, Chem. Pharm. Bull. 47 (1999) 1451–1454.

8. Y. Gao, F. Cui, Y. Guan, L. Yang, Y. Wang and L. Zhang, Preparation of roxithromycin-polymeric microspheres by the emulsion solvent diffusion method for taste masking, Int. J. Pharm. 318 (2006) 62–69; DOI: 10.1016/j.ijpharm.2006.03.018.

9. Y. M. Rane, R. C. Mashru, M. G. Sankalia and J. M. Sankalia, Effect of hydrophilic swellable polymers on dissolution enhancement of carbamazepine solid dispersion studied using respon-se surface methodology, AAPS PharmSciTech 8 (2007) article 27; DOI: 10.1208/pt0802027.

10. P. P. Shah, R. C. Mashru, Y. M. Rane and A. R. Thakkar, Design and optimization of mefloquine hydrochloride dry suspension for bitter taste masking, AAPS PharmSciTech 9 (2008) 377–389; DOI: 10.1208/s12249-008-9052-x.

11. United States Pharmacopoeia XXIV, National Formulary XIX, USP Pharmacopoeilal Convention, Rockville 2000, pp. 1941–1943.

12. Y. M. Rane, R. C. Mashru, M. G. Sankalia, V. B. Sutariya and P. P. Shah, Investigation on factors affecting chitosan for dissolution enhancement of oxcarbazapine by spray dried microcrystal formulation with an experimental design approach, Drug. Dev. Ind. Pharm. 33 (2007) 1008–1023; DOI: 10.1080/03639040601179749.

13. M. C. Gohel and M. K. Panchal, Novel use of similarity factor f2 and Sd for the development of diltiazem HCl modified release tablets using a 32 factorial design, Drug. Dev. Ind. Pharm. 28 (2002) 77–87; DOI: 10.1081/DDC-120001488.

14. T. J. Shah, A. F. Amin, J. R. Parikh and R. H. Parikh, Process optimization and characterization of poloxamer solid dispersion of a poorly water soluble drug, AAPS PharmSciTech 8 (2007) arti- cle 29; DOI: 10.1208/pt0802029.

15. S. Bolton and S. Charles, Pharmaceutical Statistics, Marcel Dekker, New York 2004.

16. P. M. Satturwar, P. M. Mandaogade and A. K. Dorle, A novel method for preparation of Eudragit RL microcapsules, J. Microencapsul. 19 (2002) 407–413;
DOI: 10.1080/02652040210140454.

17. H. Valizadeh, A. Nokhodchi, N. Qarakhani, P. Zakeri-Milani, S. Azarmi, D. Hassanzadeh and R. Lobenberg, Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin and Eudragit E100, Drug. Dev. Ind. Pharm. 30 (2004) 303–317; DOI: 10.1081/DDC-120030426