Process Optimization and Characterization of Poloxamer Solid Dispersions of a Poorly Water-soluble Drug

Submitted: April 1, 2006; Accepted: October 1, 2006; Published: April 13, 2007

Tejal J. Shah,[1] Avani F. Amin,[1] Jolly R. Parikh,[2] and Rajesh H. Parikh[3]

[1]Institute of Pharmacy, Nirma University of Science & Technology, Ahmedabad, Gujarat, India.
[2]A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar,Gujarat, India.
[3]Ramanbhai Patel College of Pharmacy, Changa, Gujarat, India.

ABSTRACT

The objective of the present investigation was to improve the dissolution rate of Rofecoxib (RXB), a poorly water-soluble drug by solid dispersion technique using a water-soluble carrier, Poloxamer 188 (PXM). The melting method was used to prepare solid dispersions. A 3^2 full factorial design approach was used for optimization wherein the temperature to which the melt-drug mixture cooled (X_1) and the drug-to-polymer ratio (X_2) were selected as independent variables and the time required for 90% drug dissolution (t_{90}) was selected as the dependent variable. Multiple linear regression analysis revealed that for obtaining higher dissolution of RXB from PXM solid dispersions, a low level of X_1 and a high level of X_2 were suitable. The differential scanning calorimetry and x-ray diffraction studies demonstrated that enhanced dissolution of RXB from solid dispersion might be due to a decrease in the crystallinity of RXB and PXM and dissolution of RXB in molten PXM during solid dispersion preparation. In conclusion, dissolution enhancement of RXB was obtained by preparing its solid dispersions in PXM using melting technique. The use of a factorial design approach helped in identifying the critical factors in the preparation and formulation of solid dispersion.

KEYWORDS: Solid dispersion, factorial design, poloxamer, poorly water-soluble drug.

INTRODUCTION

The sparingly water-soluble drugs often show an erratic dissolution profile in gastrointestinal fluids, which consequently results in variable oral bioavailability.[1] To improve the dissolution and bioavailability of sparingly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants, and others.[2,3] Chiou and Rigelman[4] and Serajuadin et al.[5] have used the solid dispersion technique for dissolution enhancement of poorly water-soluble drugs. Among the various approaches, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous.[6]

Sekiguchi and Obi[7] were the first to propose the solid dispersion method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs. In this method, the drug is thoroughly dispersed in a water-soluble carrier by melting, solvent, or solvent-melting methods.[4] Many water-soluble carriers have been employed for preparation of solid dispersion of poorly soluble drugs. The most common are polyethylene glycols,[8,9] polyvinyl pyrrolidone,[10,11] lactose,[12] β-cyclodextrin,[13,14] and hydroxypropyl methylcellulose.[15] Recently, poloxamers, a group of block copolymer nonionic surfactants, have attracted considerable attention for application in preparation of solid dispersions.[16-18] These polymers are widely used as emulsifiers, solubilizing agents, and suspension stabilizers in liquid, oral, topical, and parenteral dosage forms and also act as wetting agents and plasticizers, and have been reported for enhancing the solubility and bioavailability of sparingly soluble drugs in solid dosage forms.[19,20] Nine grades of poloxamers have been evaluated by Saettone and coworkers[21] as solubilizers for tropicamide, a poorly water-soluble drug. Solubility was found to increase as the oxyethylene content increased. Poloxamer 188 (PXM) is a nonionic block copolymer composed of 2 hydrophilic polyoxyethylene chains and connected by a hydrophobic polyoxypropylene chain and has been used by researchers to increase the aqueous solubility of poorly water-soluble drugs.[22-24] PXM was thus selected as a carrier for dissolution enhancement of a poorly water-soluble drug.

Rofecoxib (RXB), belonging to BCS Class II, is a cyclooxygenase-II (COX-2) inhibitor used in osteoarthritis, rheumatoid arthritis, and in management of acute pain in adults. RXB is a selective COX-2 inhibitor with 1000-fold selectivity for COX-2 relative to COX-1. It shows high anti-inflammatory and analgesic activities in addition to low toxicity, moderate incidence of gastric side effects, and high therapeutic

Corresponding Author: Rajesh H. Parikh, Principal, Ramanbhai Patel College of Pharmacy, Education Campus, Changa, Ta: Petlad, Dist: Anand, Gujarat- 388 421, India. Tel: 91-2697-247500; Fax: 91-2697-247100; E-mail: rhp59@rediffmail.com

index.[25,26] However, RXB is practically insoluble in aqueous fluids; and as such its oral absorption is dissolution rate limited. The aqueous solubility of RXB was found to be 0.01 mg/mL.[27] Therefore, it displays poor solubility in gastrointestinal (GI) fluids, which results in low and erratic oral bioavailability. It was selected as a model drug for dissolution enhancement studies in the present investigation. Attempts were devised to enhance the dissolution of RXB using a solid dispersion technique. Solid dispersions of PXM-RXB were prepared using the melting method and studied systematically using an optimization technique. A 3^2 full factorial design approach was used for optimization of process variables on dissolution characteristics. The aim of the present work was to study the joint influence of the independent variables, temperature to which the melt-drug mixture cooled (X_1), and the drug-to-polymer ratio (X_2) on the dependent variable t_{90} (time required for 90% drug dissolution) in solid dispersions. Physicochemical characterization was performed to evaluate the occurrence of chemical interaction between the drug and polymer.

Materials and Methods

Materials

RXM and PXM were received as gift samples from Torrent Research Centre, Ahmedabad, India. Sodium lauryl sulfate (SLS)(analytical reagent grade) was obtained from SD Fine Chem. Pvt. Ltd, Mumbai, India.

Preparation of solid dispersions

The solid dispersions of PXM-RXB were prepared by the melting method.[4] PXM was heated at a temperature of 55°C ± 0.5°C using a thermostatically controlled water bath (Labtronik, Ahmedabad, India). RXB in a 1:2, 1:5, and 1:8 drug-to-polymer ratio was dispersed in the melted polymer. The resultant mixture was immediately cooled to 5°/15°/25°C using an ice-water mixture and was maintained at the specified temperature for a period of 2 hours. The solidified mass was then removed from the ice-water mixture and allowed to attain the room temperature (25-30°C). It was stored at room temperature for 24 hours and then pulverized using a glass mortar and pestle. The pulverized mass was sifted through a #120 sieve, weighed, and transferred to amber-colored Type-I glass vials, stored at 30°C ± 1°C and the yield was determined using following formula:

$$Yield = \left(\frac{a}{b+c}\right) \times 100, \quad (1)$$

where, a is the weight of the solid dispersion sifted through a #120 sieve, b is the weight of RXB taken for solid dispersion preparation, and c is the weight of PXM taken for solid dispersion preparation.

Experimental design

A 3^2 full factorial design was employed to systematically study the joint influence of the effect of independent variables X_1 and X_2 on the dependent variable t_{90}. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations.[28,29] A statistical model incorporating interactive and polynomial terms is used to evaluate the response.

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

where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The composition of the factorial design batches SD1 to SD9 are shown in Table 1.

Characterization

In Vitro Dissolution Studies

Drug/physical mixture/solid dispersion equivalent to 25 mg of RXB was used for the dissolution studies. The study was performed using USP XXIV basket apparatus at 37°C ± 0.5°C at 75 rpm, and using 900 mL of 0.1N HCl containing 0.6% wt/vol SLS as dissolution medium (n = 3). A 5-mL amount of dissolution medium was withdrawn at intervals of 5, 10, 20, 30, 40, 60, 90, and 120 minutes. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Test samples were filtered through a 0.45-μm membrane filter (Sartorius, Hamburg, Germany) and suitably diluted. The absorbance of each diluted sample was measured at 262 nm using a double beam UV-Visible spectrophotometer (Elico, 174, Hyderabad, India).

Fourier Transform Infrared Spectroscopy

Fouier transform infrared spectroscopy (FTIR) spectra of the RXB, PXM, and solid dispersion was recorded using a Fourier Transform Infrared spectrophotometer (Jasco Model: 5300, Tokyo, Japan). Samples were prepared using KBr (Spectroscopic grade) disks by means of hydraulic pellet press at a pressure of 7 to 10 tons. The samples were scanned from 4000 to 600 cm^{-1}.

Thermal Analysis

Differential scanning calorimetry (DSC) study of RXB, PXM, and solid dispersion was performed using Differential Scanning Calorimeter (Perkin Elmer, Pyris-I, Waltham, MA). The

Table 1. Composition of Factorial Design Batches*

	Variable Levels in Coded Form			
Batch Code	X_1	X_2	t_{90} ± SD, min†	%Yield ± SD†
SD1	–1	–1	62.92 ± 0.70	79.6 ± 2.16
SD2	–1	0	21.48 ± 0.49	77.4 ± 1.07
SD3	–1	+1	19.26 ± 0.30	67.4 ± 2.05
SD4	0	–1	64.12 ± 0.62	63.4 ± 0.74
SD5	0	0	32.89 ± 0.31	65.8 ± 1.92
SD6	0	+1	30.91 ± 0.33	72.2 ± 2.70
SD7	+1	–1	93.36 ± 0.44	62.6 ± 0.86
SD8	+1	0	64.62 ± 0.36	70.8 ± 2.03
SD9	+1	+1	58.60 ± 0.56	65.4 ± 0.86
SD10 (Check point)	–0.5	+0.33	26.58 ± 0.43	74.6 ± 1.01
SD11 (Check point)	+0.5	–0.33	51.30 ± 0.24	67.2 ± 0.65

	Actual Values	
Coded Values	X_1	X_2
–1	5	1:2
0	15	1:5
1	25	1:8

*X_1 indicates the temperature to which the melt-drug mixture cooled (°C); X_2, drug-to-polymer ratio; t_{90}, time required for 90% drug dissolution.
†Values represent the mean ± SD of 3 experiments.

weighed amount of the sample was first cooled to –10ºC and was held at that temperature for 1 minute. The sample was then heated to 250ºC at a rate of 5ºC/min.

X-Ray Diffraction (XRD) Studies

Vacuum grease was applied over a glass slide to stick the sample. About 100 mg of sample was sprinkled over it to make a layer having a thickness of ~0.5 mm. All the experiments were performed on an X-ray diffractometer (Philips X'Pert MPD, Eindhoven, The Netherlands) having a sensitivity of 0.1 mg. The sample slide was placed vertically at an angle of zero degree in the sample chamber. An x-ray beam (Philips Cu target x-ray tube) of 2 kW was allowed to fall over the sample. As the slide moves at an angle of theta degree, a proportional detector detects diffracted x-rays at angle of 2-theta degrees. XRD patterns were recorded using Philips JPCD software for powder diffractometry.

Results and Discussion

The drug release from pure RXB was found to be only 27.2% in 2 hours during the in vitro dissolution study, suggesting a strong need to enhance the dissolution of RXB. Therefore, a solid dispersion technique using PXM was employed for dissolution enhancement of RXB in the present investigation.

Preliminary investigations of the process parameters revealed that factors X_1 and X_2 highly influenced the rate of in vitro dissolution and, hence, were used for further systematic studies. The t_{90} for the 9 batches (SD1 to SD9) showed a wide variation of 93.36 to 19.26 minutes (Table 1). The data clearly indicate that X_1 and X_2 strongly influence the t_{90}. All the batches of factorial design exhibited yield greater than 60% (Table 1). The fitted polynomial equations (full and reduced model) relating the response t_{90} to the transformed factors are shown in Table 2. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, ie, positive or negative. The significance level of coefficient b_{12} was found to be P equals .2837 and hence it was omitted from the full model equation to generate the reduced model equation. Table 2 shows the results of regression analysis. The coefficients b_1, b_2, b_{11}, and b_{22} were found to be significant at P is less than .05 and thus, were retained in the reduced model.

Table 3 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. The

Table 2. Results of Regression Analysis

Response t_{90}	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Full model (FM)	32.51	18.82	–18.61	10.73	15.20	2.23	0.9929
Reduced model (RM)	32.51	18.82	–18.61	10.73	15.20	___	0.9889

___ indicates b_{12} term is omitted in reduced model.

Table 3. The Results of ANOVA*

Response t_{90}	df (1,3)	SS	MS	F	R^2	
Regression						
FM	5	4914.22	982.84	84.20	0.9929	F_{cal} = 1.6967
RM	4	4894.42	1223.61	89.28	0.9889	F_{table} = 10.13
Error						
FM	3	35.02	11.67			
RM	4	54.82	13.70			

*ANOVA indicates analysis of variance; df, degrees of freedom; SS, sum of squares; MS, mean of squares; *F*, Fischer's ratio; R^2, regression coefficient; FM, full model; RM, reduced model.

high values of correlation coefficients for t_{90} indicate a good fit. The critical value of *F* for $\alpha = 0.05$ is equal to 10.13 (df = 1, 3). Since the calculated value (*F* = 1.6967) is less than the critical value (*F* = 10.13), it may be concluded that the interaction term b_{12} does not contribute significantly to the prediction of t_{90} and hence can be omitted from the full model.

The change in t_{90} as a function of X_1 and X_2 is depicted in the form of response surface plot (Figure 1) based on full factorial design. The data of all the 9 batches of factorial design were used for generating interpolated values using Sigma plot software (Systat Software Inc., Version 3.0, Richmond, CA). Low level of X_1 and high level of X_2 were found to be favorable conditions for obtaining faster dissolution.

Multiple linear regression analysis (Table 2) revealed that coefficient b_1 is positive and b_2 is negative. This indicates that on increasing X_1, t_{90} increases. It was observed that as the temperature decreases, the amount of drug dissolved increases, which may be attributed to a higher energy state for drug particles at low temperature, resulting in a more amorphous form. The release studies of batches with increasing concentration of PXM (X_2) revealed that as the concentration of PXM increases, t_{90} decreases (Table 1). This could be because RXB may exist in the solid dispersion in 2 different forms, namely crystalline and amorphous. The rate of dissolution of the drug from solid dispersion depends on the proportion of the 2 forms, which in turn depends on the proportion of PXM in the solid dispersion. As the weight fraction of PXM increases, the proportion of the amorphous form of RXB may increase, which in turn results in enhancement of dissolution of RXB. A similar argument has been offered by Kapsi and Ayers[30] for enhancement in dissolution of itraconazole from its solid dispersion with polyethylene glycol (PEG) and by Chutimaworapan et al[16] for enhancement in dissolution of nifedipine from its solid dispersion with different water-soluble carriers like PEG, hydroxyl propyl β-cyclodextrin (HP-β-CD), and PXM. Checkpoint batches SD10 and SD11 were prepared at $X_1 = -0.5$ and 0.5 and X_2 = 0.33 and –0.33 levels, respectively. The theoretical t_{90} of batches SD10 and SD11 were 21.29 and 52.40 minutes, respectively. The experimental values are 26.58 and 51.30 minutes (Table 1), which are in good agreement with theoretical values.

Batch SD2 (1:5 ratio) and SD3 (1:8 ratio) exhibited least t_{90} values, ie, 21.48 and 19.26 minutes, respectively. The t_{90} of

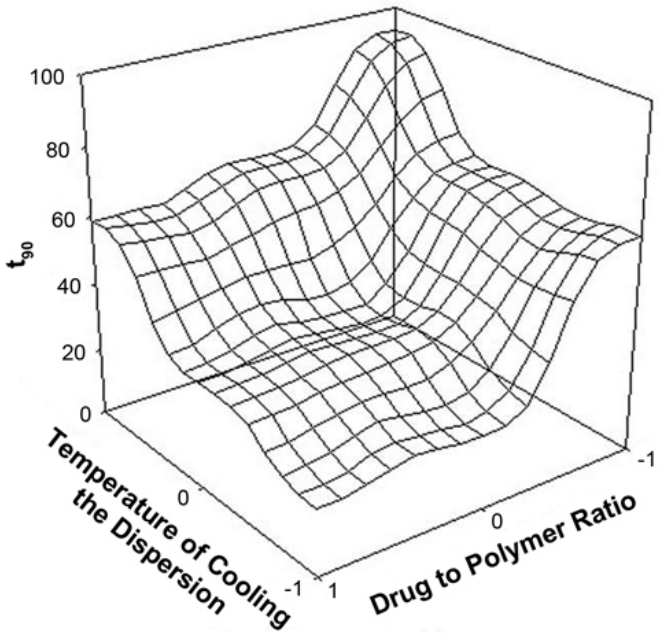

Figure 1. Response surface plot.

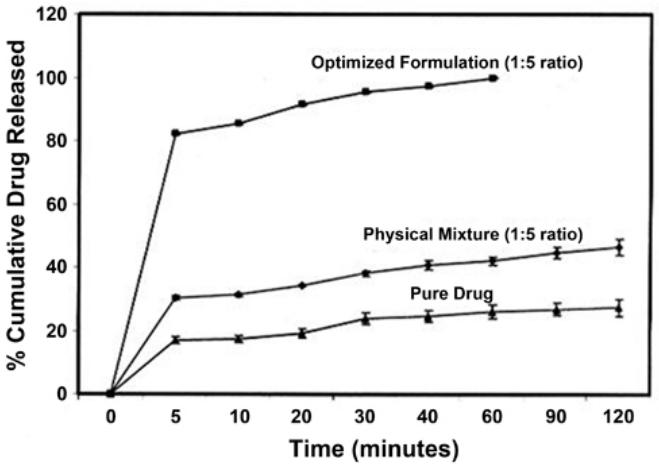

Figure 2. Dissolution profile of optimized formulation, physical mixture, and pure drug.

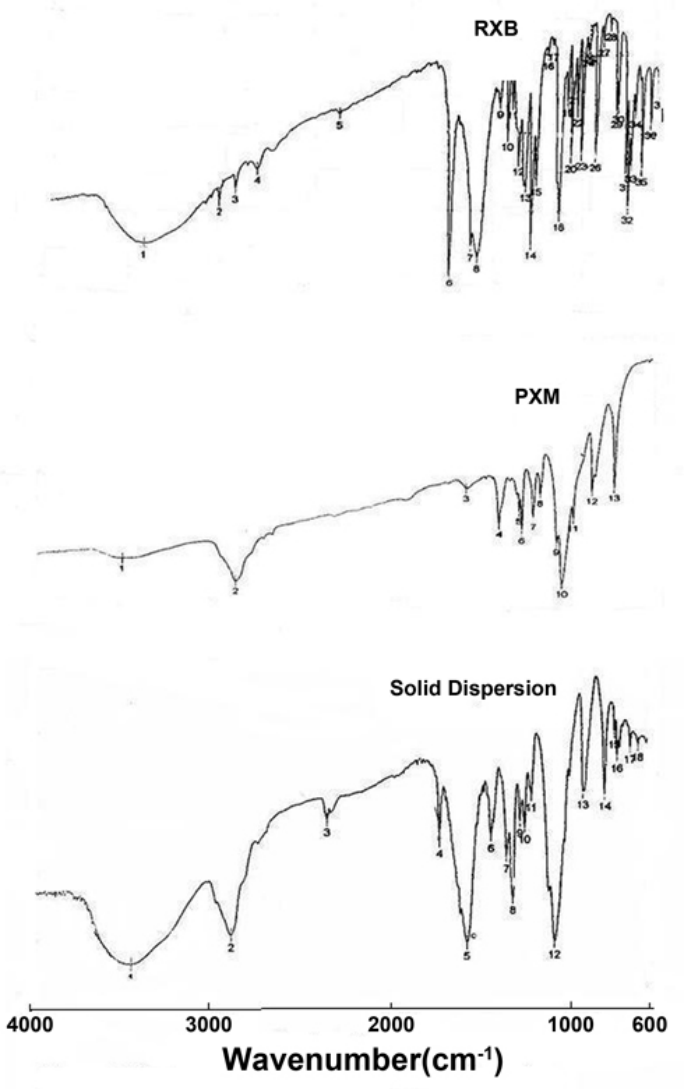

Figure 3. FTIR spectra of RXB, PXM, and FTIR spectra of solid dispersion.

both these batches were almost similar and exhibited an insignificant difference as confirmed by Student *t* test (t_{cal} = –0.459, t_{table} = 2.776). Moreover, the yield of batch SD2 was higher as compared with batch SD3. Therefore, batch SD2 may be considered as a promising formulation batch for dissolution enhancement of RXB. Hence, this batch was further selected for physical characterization. The dissolution profiles of optimized formulation (1:5 ratio, Batch SD2), physical mixture (1:5 ratio), and pure drug are shown in Figure 2. It is clearly evident from the figure that the dissolution rate of pure drug and physical mixture is very low as compared with the optimized formulation. It is also observed from the dissolution profile of optimized formulation that the total quantity of the drug present in the solid dispersion gets dissolved within 60 minutes.

The solid dispersion of best batch SD2 was evaluated for physical characterization viz FTIR, DSC, and XRD. Pure RXB and pure PXM were also run as control. The samples used for the study were prepared (before 48 hours) and preserved in desiccator before use. The FTIR spectrum of RXB, PXM, and solid dispersion is shown in Figure 3. The characteristic peaks of pure RXB at 1748, 1383, and 1148 cm^{-1} are assigned due to stretching of C = O and O = S = O

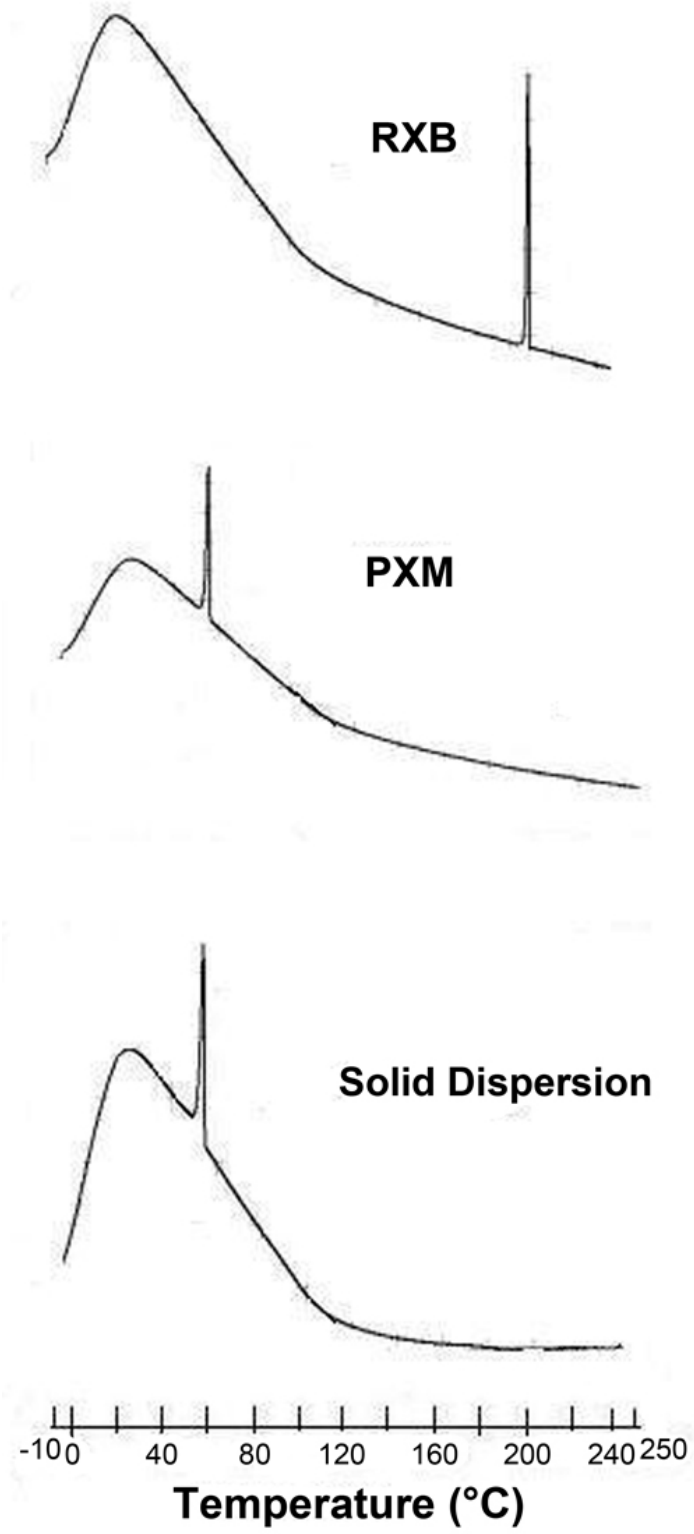

Figure 4. DSC curves of RXB, PXM, and solid dispersion.

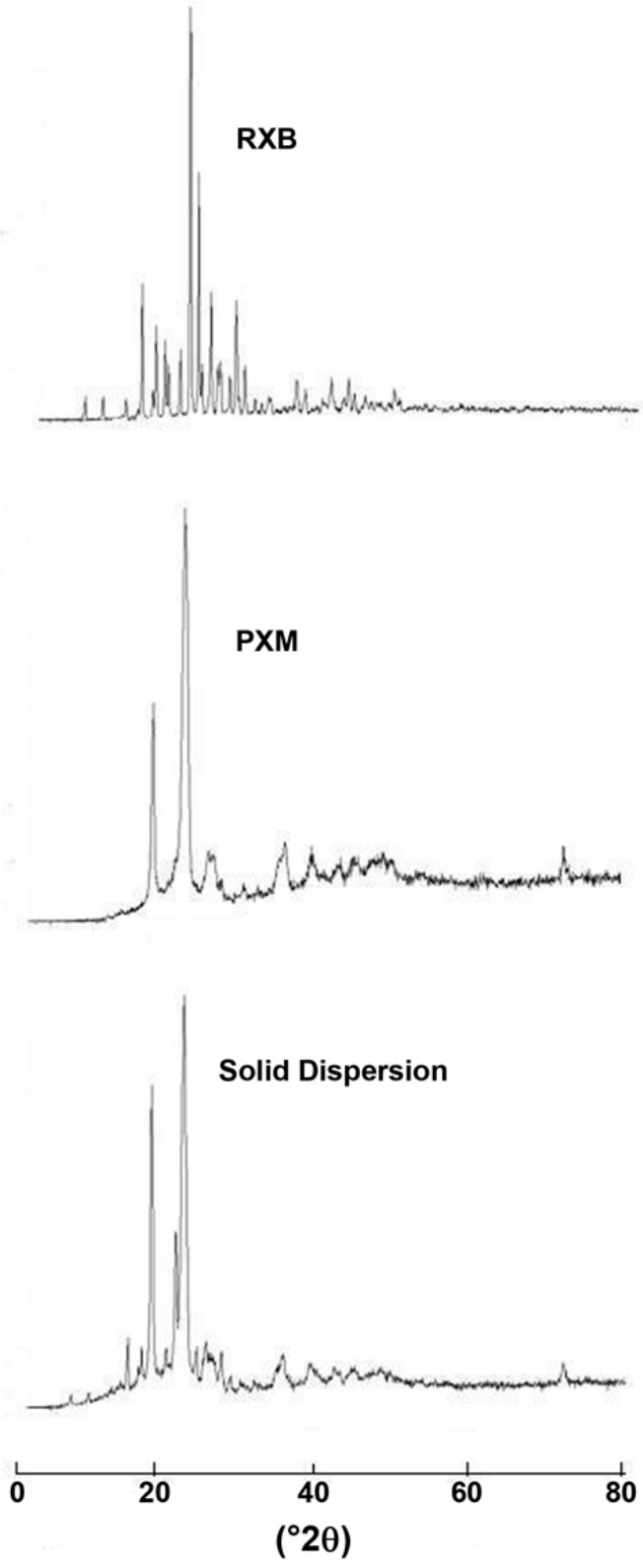

Figure 5. XRD patterns of RXB, PXM, and solid dispersion.

groups. The PXM exhibits characteristic peaks at 3503, 2884, and 1114 cm^{-1} due to stretching of O-H, C-H, and C-O groups. The peak at 1148 cm^{-1} of the O = S = O, ie, stretching of the sulphonyl group, is the important characteristics of RXB. The characteristic sulphonyl stretching band of pure drug was absent in FTIR spectra of batch SD2. Rather, this peak is shifted to a lower frequency 1113 cm^{-1} in the solid dispersion. The lowering of shift to 35 cm^{-1} could be attributed to the physical interaction of Van der Waals forces of drug with polymer moiety, which may result in dissolution enhancement of RXB.

Figure 4 shows the DSC curve of RXB, PXM, and solid dispersion. The RXB, PXM, and solid dispersion show endothermic peaks at 209°C, 55°C, and 54°C, respectively. The endothermic peak corresponding to melting of RXB was absent in the DSC thermogram of solid dispersion. It might be due to the presence of the amorphous form of RXB in the solid dispersion or the dissolution of crystalline RXB into the molten carrier.

XRD analysis was performed to confirm the results of DSC studies. XRD patterns of RXB, PXM, and solid dispersion is shown in Figure 5. In the x-ray diffractograms of RXB, sharp peaks at a diffraction angle (2θ) of 16.01°, 22.26°, 23.35°, 24.88°, and 28.19° indicate the presence of crystalline drug, while solid dispersion shows sharp peaks at 19.08°, 22.19°, and 23.28°. These data reveal that the typical drug crystalline peaks were still detectable (with reduced intensity and less number) in the solid dispersion. This finding confirms the presence of little amount of crystalline drug in the solid dispersion despite the complete disappearance of its melting peak in the corresponding DSC curves; however, the sharp drug peaks corresponding to drug are absent in the solid dispersion. The XRD patterns of RXB, PXM, and solid dispersion showed a total 29, 10, and 22 peaks, respectively. The XRD of solid dispersion exhibits 17 peaks less than the sum of the number of peaks of RXB and PXM in their pure forms. This suggests that crystallinity of both drug and polymer is reduced in the solid dispersion. Decrease in crystallinity of the drug and polymer may contribute to enhancement of dissolution of the drug.

CONCLUSIONS

The results of the experimental study confirm that the factors X_1 and X_2 significantly influence the dependent variable t_{90}. Characterization studies revealed that solid dispersion of RXB-PXM showed enhancement of RXB dissolution due to the conversion of RXB into a less crystalline and/or amorphous form. The application of experimental design techniques for optimization of formulation helps in reaching the optimum point in the shortest time with minimum efforts.

ACKNOWLEDGMENT

The authors are thankful to Torrent Research Centre, Ahmedabad, for providing gift samples of Rofecoxib and Poloxamer. Help, support, and assistance received from Professor Y. K. Agrawal (Director, Institute of Pharmacy, Nirma University

of Science and Technology, Ahmedabad), Professor A. K. Saluja (Principal, A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar), and Mr Y. B. Solanki (Lecturer, Ramanbhai Patel College of Pharmacy, Changa) are gratefully acknowledged.

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995;12:413–420.

2. Garad SD. How to improve the bioavailability of poorly soluble drugs. *Am Pharm Rev.* 2004;7: Available at: http://www.varianinc.com.cn/products/dissolution/shared/ir2004_5.pdf. Accessed April 5, 2007.

3. Nokhodchi A, Javadzadeh Y, Reza M, Barzegar Jalali M. The effect of type and concentration of vehicles on the dissolution rates of a poorly water soluble drug (indomethacin) from liquisolid compacts. *J Pharm Pharm Sci.* 2005;8:18–25.

4. Chiou WL, Rigelman S. Pharmaceutical application of solid dispersion system. *J Pharm Sci.* 1971;60:1281–1302.

5. Serajuddin A. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. *J Pharm Sci.* 1999;88:1058–1066.

6. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000;50:47–60.

7. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture-I. *Chem Pharm Bull (Tokyo).* 1961;9:866–872.

8. Liu C, Liu C, Desai KGH. Enhancement of dissolution rate of valdecoxib using solid dispersions with polyethylene glycol 4000. *Drug Dev Ind Pharm.* 2005;31:1–10.

9. Verheyen S, Blaton N, Kinget R, Van den Mooter G. Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. *Int J Pharm.* 2002;249:45–58.

10. Hirasawa N, Ishise S, Miyata H. An attempt to stabilize nivaldipine solid dispersion by the use of ternary systems. *Drug Dev Ind Pharm.* 2003;29:997–1004.

11. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Miscibility behavior and formation mechanism of stabilized felodipine-polyvinylpyrrolidone amorphous solid dispersions. *Drug Dev Ind Pharm.* 2005;31:473–489.

12. Hirasawa N, Danij K, Haruna M, Otsuka A. Physicochemical characterization and drug release studies of naproxen solid dispersions using lactose as a carrier. *Chem Pharm Bull (Tokyo).* 1998;46: 1027–1030.

13. Zheng Y, Haworth IS, Zuo Z, Chow MS, Chow AH. Physicochemical and structural characterization of Quercetin-β-Cyclodextrin complexes. *J Pharm Sci.* 2005;94:1079–1089.

14. Rawat S, Jain SK. Rofecoxib-beta-cyclodextrin inclusion complex for solubility enhancement. *Pharmazie.* 2003;58:639–641.

15. Okimoto K, Miyake M, Ibuki R, Yasumura M, Ohnishi N, Nakai T. Dissolution mechanism and rate of solid dispersion particles of nivaldipine with hydroxypropylmethylcellulose. *Int J Pharm.* 1997;159:85–93.

16. Chutimaworapan S, Ritthidej GC, Yonemochi E, Oguchi T, Yamamoto K. Effect of water soluble carriers on dissolution characteristics of nifedipine solid dispersions. *Drug Dev Ind Pharm.* 2000;26:1141–1150.

17. Chen Y, Zhang G, Neilly J, Marsh K, Mawhinney D, Sanzgiri Y. Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. *Int J Pharm.* 2004;286:69–80.

18. Mehta K, Kislalioglu S, Phuapradit W, Malick W, Shah N. Multi-unit controlled release systems of Nifedipine and Nifedipine:Pluronic F-68 solid dispersions: characterization of release mechanisms. *Drug Dev Ind Pharm.* 2002;28:275–285.

19. Schmolks IR. Poloxamers in controlled drug delivery. In: Tarcha PJ, ed. *Polymers for Controlled Drug Delivery.* Boca Raton, FL: CRC Press; 2000:189–214.

20. Seo A, Holm P, Kristensen HG, Schaefer T. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int J Pharm.* 2003;259:161–171.

21. Saettone MF, Giannacini B, Delmonte G, Campigli V, Tota G, La Marca F. Solubilization of tropicamide by poloxamers:physicochemical data and activity data in rabbits and humans. *Int J Pharm.* 1988;43:67–76.

22. Passerini N, Albertini B, Gonzalez-Rodriguez ML, Cavallari C, Rodriguez L. Preparation and characterization of ibuprofen-poloxamer 188 granules obtained by melt granulation. *Eur J Pharm Sci.* 2002;15:71–78.

23. Kwon GS. Polymeric micelles for delivery of poorly water-soluble compounds. *Crit Rev Ther Drug Carrier Syst.* 2003;20:357–403.

24. Yong CS, Yang CH, Rhee JD, et al. Enhanced rectal bioavailability of ibuprofen in rats by poloxamer 188 and menthol. *Int J Pharm.* 2004;269:169–176.

25. Merck & Go, Inc. Vioxx (Rofecoxib tablets and oral suspension). In: Walsh P, ed. *Physicians Desk Reference.* 57th ed. Montvale, NJ: Thomson-PDR; 2003:2120–2125.

26. Mukherjee D, Nissen SE, Topol E. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA.* 2001;286:954–959.

27. Chavanpatil M, Dawre FD, Shakleya DS, Vavia PR. Enhancement of oral bioavailability of Rofecoxib using β-Cyclodextrin. *J Incl Pheno Macro Chem.* 2002;44:145–149.

28. Bolton S, Charles S. *Pharmaceutical Statistics*. New York, NY: Marcel Dekker Inc; 2004.

29. Franz RM, Browne JE, Lewis AR. Experiment design, modeling and optimization strategies for product and process development. In: Libermann HA, Reiger MM, Banker GS, eds. *Pharmaceutical Dosage Forms: Disperse Systems.* vol. 1. New York, NY: Marcel Dekker Inc; 1988:427–519.

30. Kapsi SG, Ayers JW. Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. *Int J Pharm.* 2001;229:193–203.