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Original research paper

Preparation and characterization of etoricoxib-polyethylene glycol 4000 plus polyvinylpyrrolidone K30 solid dispersions

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The objective of the present investigation was to study the influence of polyethylene glycol 4000 (PEG) and polyvinylpyrrolidone K30 (PVP) on *in vitro* dissolution of etoricoxib from solid dispersions. Preliminary studies were carried out using a physical mixture of the drug and carriers. Solid dispersions were prepared using the solvent evaporation method.

A 3^2 factorial design was adopted in the solvent evaporation method using the concentration of PEG and PVP as independent variables. Full and reduced models were evolved for dependant variables, such as the percentage of drug release in 10 min (Q_{10}), percentage of drug release in 30 min (Q_{30}), percentage of drug release in 45 min (Q_{45}) and percent dissolution efficiency (DE). The reduced models were validated using two check points. $Q_{10} > 65\%$, $Q_{30} > 75\%$, $Q_{45} > 85\%$ and DE > 80% were used as constraints for the selection of an optimized batch. Contour plots are presented for the selected dependant variables.

PEG was found to be more effective in increasing the drug dissolution compared to PVP. Wettability study was carried out for the pure drug and optimized batch. FT-IR spectroscopy, microscopic study, differential scanning calorimetry and X-ray diffraction study were carried out in order to characterize the drug in solid dispersions. Improved dissolution was attributed to decreased crystallinity of the drug, improved wetting and solubilizing effects of carriers such as PEG and PVP from the solid dispersion of etoricoxib. In conclusion, dissolution of etoricoxib can be modulated using appropriate levels of hydrophilic carriers.

Keywords: etoricoxib, solid dispersions, dissolution, polyethylene glycol, polyvinylpyrrolidone, factorial design

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Solid dosage forms such as tablets and capsules hold the highest share in the pharmaceutical market despite the advancement in innovative dosage forms, such as liposomes and transdermal delivery systems. Drugs dissolution from oral solid dosage forms

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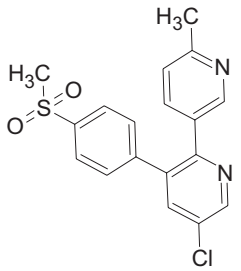
depends on the release of the drug from the dosage form and subsequent solubilization of drug particles in physiological fluid. The dissolution characteristic of poorly water-soluble drugs has been and still remains a problem to the pharmaceutical industry because dissolution is the rate-limiting process in the absorption of these drugs from solid dosage forms. Among the various approaches employed to improve the dissolution of poorly soluble drugs, solid dispersion has been proven successful. Fast or immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles, existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles (1, 2). Literature shows that the solvent evaporation method has been used for the preparation of solid dispersions for dissolution enhancement (3–7). Earlier studies show that solid dispersion systems increased the drug dissolution due to improved solubility, wettability and dispersibility using hydrophilic carriers (8–14).

The poor aqueous solubility and wettability of etoricoxib (CAS Registry No. 202409-33-4, molecular formula $C_{18}H_{15}ClN_2O_2S$, molecular mass 358.84, Scheme 1), a non-steroidal anti-inflammatory cyclo-oxygenase-II inhibitor drug, cause difficulties in the formulation of oral dosage forms and lead to variable bioavailability.



Scheme 1

To the best of our knowledge, no information is available on the improvement of etoricoxib dissolution from solid dispersion systems using hydrophilic carriers. In order to improve its solubility, dispersibility and wettability, hydrophilic carriers (polyethylene glycol 4000, polyvinylpyrrolidone K30) were tested in our laboratory to formulate a solid dispersion system.

EXPERIMENTAL

Materials

Etoricoxib was obtained as a gift sample from Sun Pharmaceuticals Limited (India). Polyvinyl pyrrolidone K30 and polyethylene glycol 4000 were purchased from Laser Laboratories (India), potassium dihydrogen phosphate, sodium hydroxide and 2-propanol from S. D. Fine-Chemicals Ltd. (India). Distilled water was used throughout the study.

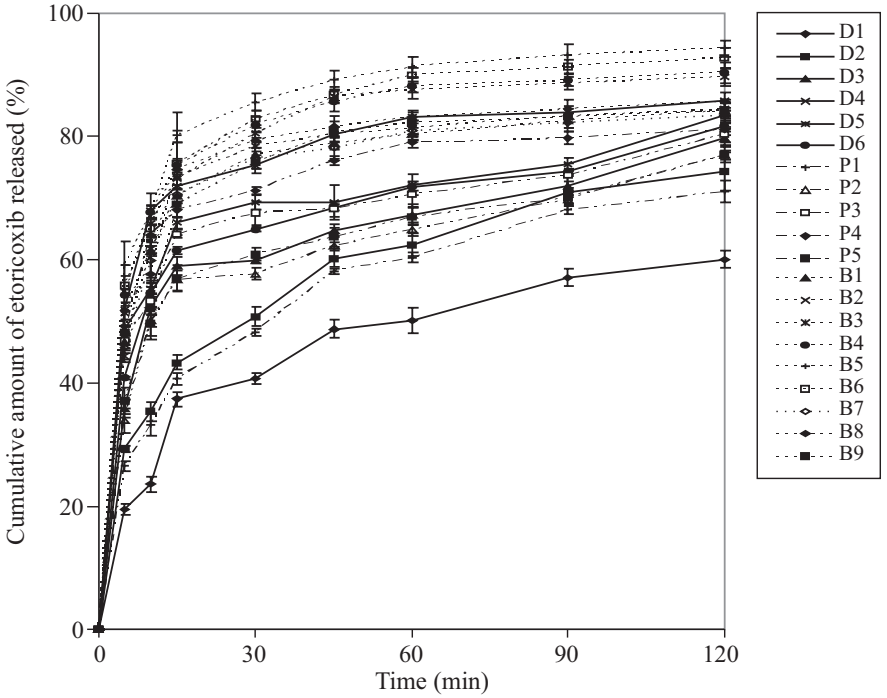


Fig. 1. Dissolution profile of the preliminary and factorial design batches (mean ± SD, $n = 3$). For abbreviations see Table I.

Methods

Physical mixing method. – A physical mixture was prepared by mixing etoricoxib (250 μm) with PEG (1:5 ratio), PVP (1:5 ratio) or drug/PEG/PUP (1:2:2 ratio) in a glass mortar by trituration for 10 min.

Solvent evaporation method. – Solid dispersions of etoricoxib and PEG/PVP were prepared in drug to PEG/PVP ratios 1:1, 1:2, 1:3 and 1:5 (*m/m*) by the solvent evaporation method. Etoricoxib was dissolved in 2-propanol to get a clear solution. PEG/PVP was then dispersed as fine particles and the solvent was removed by evaporation on a water bath at 60 °C. The dried mass was stored in dessicator until constant mass was obtained, pulverized and passed through 250 μm sieve.

Experimental design (15). – A 3^2 factorial design was adopted in the present study using PEG and PVP concentrations as independent variables at three levels: low, medium, high. The batches of experimental design B_1-B_9 were prepared by the solvent evaporation method and their composition is presented in Table I.

Dissolution study. – Dissolution of etoricoxib powder as such and from its physical mixture or solid dispersions equivalent to 60 mg of etoricoxib was carried out with the

Table I. Composition and wetting time of all batches

Batch No.	Etoricoxib (mg)	PEG (mg)	PVP (mg)	Wetting time (min)
D_1	60	–	–	149
D_2	60	60	–	86
D_3	60	120	–	77
D_4	60	180	–	68
D_5	60	300	–	61
D_6[a]	60	300	–	82
P_1	60	–	60	98
P_2	60	–	120	89
P_3	60	–	180	82
P_4	60	–	300	70
P_5[b]	60	–	300	92
B_1	60	60	60	46
B_2	60	60	120	41
B_3	60	60	180	39
B_4	60	120	60	40
B_5	60	120	120	36
B_6	60	120	180	37
B_7	60	180	60	38
B_8	60	180	120	37
B_9	60	180	180	39
M_1	60	180	120	37
M_2	60	180	180	38

[a] Physical mixture of drug/PEG (1:5).
[b] Physical mixture of drug/PVP (1:5).

USP 23 Dissolution Test Apparatus (paddle) at 37 ± 0.5 °C and 50 rpm using 900 mL phosphate buffer (pH 7.4) as dissolution medium ($n = 3$) (16). Samples of dissolution medium (5 mL) were withdrawn at predetermined time intervals and an equal amount of fresh dissolution medium was added. Test samples were filtered through Whatman filter paper No. 41 (Whatman Paper Limited, UK), suitably diluted and assayed for etoricoxib at 284 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (Model 160A, Shimadzu, Japan). The cumulative percentage of etoricoxib dissolved was calculated using a regression equation generated from standard data.

Wettability study. – Drug powder, physical mixture or solid dispersion (3 g) was placed in a sintered glass funnel (55 mm i.d.). The funnel was plunged into a beaker containing water so that the surface of the water in the beaker remained at the same level as the powder in the funnel (17). Methylene blue powder (100 mg) was poured onto the surface of the test sample. The time required for wetting the methylene blue powder was measured. The average of three observations was calculated.

Infrared spectra. – Fourier transform infrared (FT-IR) spectra of etoricoxib, carriers, physical mixtures and solid dispersions in carriers were obtained using potassium bromide as the pellet making substance (Model 8400S, Shimadzu, Japan).

Microscopic analysis. – Photographs of the drug, carriers, physical mixtures and solid dispersions were taken by placing a drop of their suspensions in cedar wood oil on a glass slide with cover slip and viewing under the microscope fitted with a camera at the required magnification.

X-ray diffraction study. – The X-ray diffraction study was carried out to characterize the physical form of etoricoxib in solid dispersions of selected batches. Vacuum grease was applied onto the glass slide to stick the sample. The sample was allowed to spread on the slide to approximately 0.5 mm thickness. The slide was then placed vertically at 0° angle in an X-ray diffractometer (Model X''Pert, Philips, The Netherlands) so that the X-ray beam fell on it properly. The results were recorded over 0–100° (2θ) using a Cu-target X-ray tube and Xe-filled detector.

Differential scanning calorimetry study. – The powder sample was analyzed by differential scanning calorimetry (Model DT-60, Shimadzu) at a constant scanning speed of 10 °C min^{-1} from 0–300 °C. The 5–7 mg samples were accurately weighed into solid aluminum pans without seals.

RESULTS AND DISCUSSION

Only 60% of etoricoxib was released from the etoricoxib powder (batch D_1) in 2 h. Possible reasons for poor dissolution are its low aqueous solubility and poor wettability (wetting time of etoricoxib 149 min) as compared to the etoricoxib – PEG (1:5) or etoricoxib-PVP (1:5) physical mixture with wetting time of 82 and 92 min, respectively). Eighty-two and seventy-seven percent of the drug were released from the physical mixtures (batch D_6 and batch P_5, respectively). Marginal improvement of the drug dissolution may be attributed to the hydrophilic nature of the polymers. The solvent evaporation method was adopted for preparation of the solid dispersion because it is economical as compared to the other methods. The etoricoxib-PEG dispersions have a higher percentage of drug released compared to etoricoxib-PVP dispersions. This may be due to the more solubilizing and wetting effect of PEG compared to PVP. None of the formulated batches (Fig. 1) showed ≥ 75% of drug release in 30 min. Hence, combinations of PEG and PVP were used in the experimental design.

It was arbitrarily decided to obtain at least 75% drug release within 30 min from the formulated dispersions. PEG or PVP were explored as hydrophilic carriers to improve drug dissolution in the trials at different concentrations (Table I).

A 3^2 factorial design was adopted, using the amounts of PEG (X_1) and PVP (X_2) as independent variables. The results of dependant variables, such as the percentage of drug release in 10 min (Q_{10}), percentage of drug release in 30 min (Q_{30}), percentage of drug release in 45 min (Q_{45}) and percentage dissolution efficiency (DE) are shown in Table II and Fig. 1.

Table II. Experimental runs and measured responsesa

Batch No.	X1	X2	Q_{10} (%)[b]	Q_{30} (%)[c]	Q_{45} (%)[d]	*DE* (%)[e]
B_1	–1	–1	61.32	77.04	78.92	76.24
B_2	–1	0	65.88	80.50	86.48	81.33
B_3	–1	1	61.76	78.44	80.34	77.36
B_4	0	–1	67.82	81.97	85.73	83.86
B_5	0	0	67.61	85.61	89.15	86.00
B_6	0	1	65.09	82.87	86.78	82.46
B_7	1	–1	59.87	76.49	78.11	75.81
B_8	1	0	57.71	79.46	81.63	78.34
B_9	1	1	52.03	75.75	80.77	76.11

Factors and levels in the factorial design

Independent variables	Level		
	Low (–1)	Medium (0)	High (+1)
PEG 4000 (X_1, mg)	60	120	180
PVP K30 (X_2, mg)	60	120	180

[a] Detailed composition of batches B_1-B_9 is shown in Table I.
[b] Q_{10} – drug released in 10 min.
[c] Q_{30} – drug released in 30 min.
[d] Q_{45} – drug released in 45 min.
[e] *DE* (%) – percentage dissolution efficiency in 120 min.

Response surface curvature can be examined when the two variables are investigated at three levels. The design provides the following empirical second order equation (full model):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$

where Y is the response, b_0 is the intercept, b_1 and b_2 are coefficients of the main effects. The coefficients with second order terms (b_{11} and b_{22}) indicate the quadratic nature and b_{12} is the regression coefficient for the interaction term. The estimated non-significant coefficients should be omitted from the full model by adopting the significance test for the regression coefficients. Microsoft EXCEL® may be used to identify non-significant terms. A coefficient is significant if $t_{calculated} > t_{crit(v)}$, where v denotes the degree of freedom of residual variances. The refined model ($p < 0.05$) for the Q_{10}, Q_{30}, Q_{45} and *DE* (%) is shown in Table III.

It was arbitrarily decided to obtain $Q_{10} > 65\%$, $Q_{30} > 75\%$, $Q_{45} > 85\%$ and $DE > 80\%$ from the formulated dispersions. A coefficient with a positive sign shows a synergistic effect whereas a coefficient with a negative sign shows an antagonistic effect. The main effects and the coefficient of the quadratic term b_{22} were found to be significant. Hence, one cannot draw conclusions by considering the mathematical signs (positive or negative) of the main effects, such as b_1 and b_2. The refined model shows that the main effects, b_1 and b_2, and the quadratic term b_{11} are significant for Q_{10}, Q_{30}, Q_{45} and *DE* (%)

Table III. Regression analysis of batches in the factorial design – summary

Response	Model	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Q_{10}	Full	68.45	3.23	1.69	–7.08	–2.42	–2.07	0.9807
	Refined	66.84	3.23	1.69	–7.08	–	–2.07	0.9257
Q_{30}	Full	85.55	0.71	–0.26	–5.53	–3.10	–0.53	0.9973
	Refined	85.55	0.71	–0.26	–5.53	–3.10	–	0.9839
Q_{45}	Full	89.88	0.87	0.85	–6.18	–3.98	–0.31	0.9308
	Refined	89.88	0.87	0.85	–6.18	–3.98	–0.31	0.9308
DE (%)	Full	86.25	0.74	–0.49	–6.54	–3.27	–0.21	0.9831
	Refined	86.25	0.74	–0.49	–6.54	–3.27	–	0.9815

while the interaction term b_{12} is significant only for Q_{30} and quadratic term b_{22} is significant for Q_{30}, Q_{45} and *DE* (%). PEG seems to be more effective compared to PVP in controlling Q_{10}, Q_{30}, Q_{45} and *DE* (%), since coefficient b_1 (3.2, 0.71, 0.87 and 0.74 for Q_{10}, Q_{30}, Q_{45} and *DE* (%), respectively) is greater in magnitude compared to b_2 (1.7, –0.26, 0.85 and –0.49 for Q_{10}, Q_{30}, Q_{45} and *DE* (%), respectively). The improved drug dissolution is attributed to increased surface area or superior wetting of drug particles in the case of Q_{30} and Q_{45}. The decreased drug dissolution at high levels of variables (both PEG and PVP 180 mg) in the case of Q_{30} and Q_{45} was attributed to the increased viscosity of dissolution medium due to the presence of hydrophilic carriers. Fig. 2 shows the contour plots for Q_{10}, Q_{30}, Q_{45} and *DE* (%). The area that falls under the contour lines of $Q_{10} > 65\%$, $Q_{30} > 75\%$, $Q_{45} > 85\%$ and $DE > 80\%$ shows different combinations of X_1 and X_2 that can give acceptable drug dissolution.

Batches B_2 and B_4 to B_6 met the selection criteria for Q_{10}, Q_{30}, Q_{45} and *DE* (%). Batch B_5 shows the highest dissolution efficiency among the selected batches (Table IV) and hence it was considered to be an optimized batch in the present study.

The similarity factor (f_2) (19) was calculated using B_5 as a reference batch. Table V shows that non-significant differences were observed between B_5 and B_2, B_4, B_6. The wetting time for the pure drug and batch B_5 was found to be 149.5 and 36.0 min, respectively. It may be assumed that improved drug dissolution was obtained due to increased wetting.

The FTIR spectra of pure etoricoxib showed characteristic peaks at 1599 cm^{-1} (C=N stretching vibration), 1433 cm^{-1}, 1300 cm^{-1}, 1130 cm^{-1} and 1084 cm^{-1} (S=O stretching vibrations), and 839 cm^{-1}, 781 cm^{-1} and 638 cm^{-1} (C-Cl stretching vibration), respectively. The spectra of physical mixtures were equivalent to the spectra obtained by the addition of polymers and the crystalline drug spectrum. This indicated that no interaction occurred with simple physical mixing of the drug and hydrophilic polymers. The FTIR spectrum of solid dispersion of etoricoxib with PEG and PVP showed a significant boarding O-H stretching vibration peak characteristic of PEG (large band between 3483 cm^{-1} and 3119 cm^{-1}) and a C-N stretching vibration peak characteristic of PVP (1238 cm^{-1}) and S=O stretching vibration characteristic of etoricoxib (1130 cm^{-1}). This indicated that no interaction occurred in dispersion of etoricoxib with PEG and PVP.

Photomicrographs of etoricoxib, PEG, PVP, their physical mixtures and solid dispersion are shown in Fig. 3. Analysis of photomicrographs revealed that the relatively

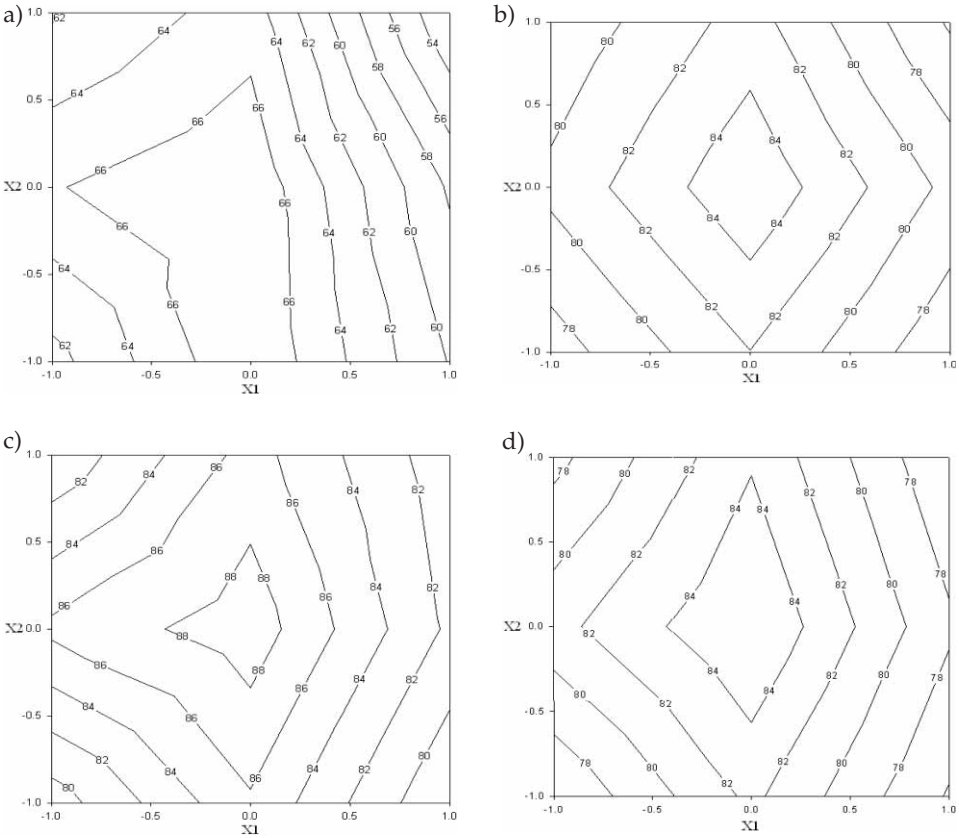


Fig. 2. Contour plots for: a) Q_{10}, b) Q_{30}, c) Q_{45} and d) *DE* (%). Note: Transformed value [–1, 1] for X_1= [60,180] mg PEG, transformed value [–1, 1] for X_2 = [60,180] mg PVP.

Table IV. Dissolution efficiency

Batch No.	Dissolution efficiency (%)[a]
B_2	81.3
B_4	82.5
B_5	86.0
B_6	83.8

[a] Defined as the area under the dissolution curve up to a certain time, expressed as percentage of the area of the rectangle described by 100% dissolution during the same time (18).

Table V. Student's t*-test and similarity factor*

Batch	t_{calc}	f_2[a]
B_5-B_2	0.77	58.42
B_5-B_4	0.54	70.50
B_5-B_6	0.38	77.13

t_{crit} = 1.89
[a] Similarity factor.

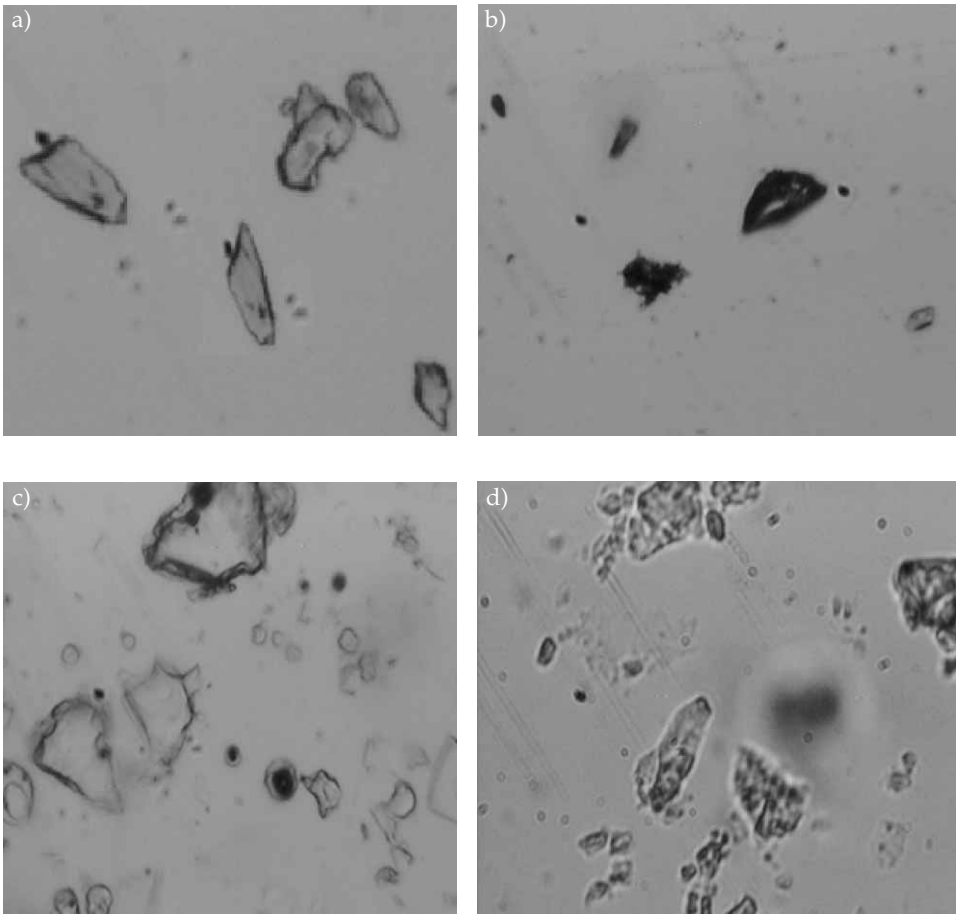


Fig. 3. Photomicrographs of: a) pure etoricoxib, b) PEG, c) PVP, d) batch B_5.

larger polyhedral crystalline forms of PEG and PVP and the elongated/oval crystals of etoricoxib, clearly visible in their physical mixtures, were transformed to less crystalline structures in their solid dispersions. These observations provided the evidence of solid dispersion formation (20).

The X-ray diffraction pattern (XRD) of the pure drug and batch B_5 are shown in Fig. 4. Characteristic peaks appeared in the XRD pattern of the drug at a diffraction angle of

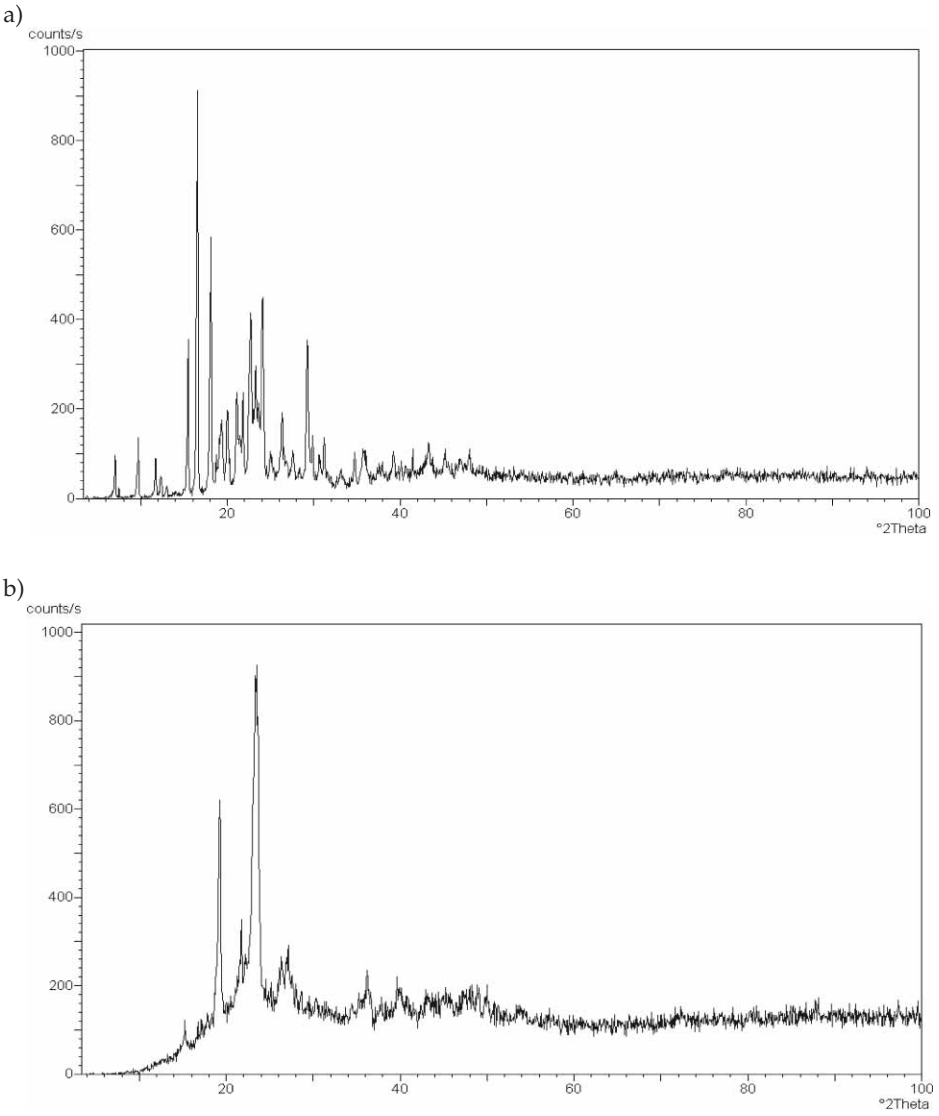


Fig. 4. X-ray diffraction of: a) batch D_1, b) batch B_5.

9.6, 11.7, 15.4, 16.4, 18.1, 19.4, 22.7, 24.1, 29.3, 31.2, 39.2, 43.3 and 45.1° suggesting that the drug is present as a crystalline material. Solid dispersion showed all the peaks shown by the drug (15.2, 19.2, 21.7, 23.4, 27.0, 36.2, 39.8 and 43.3); however, the intensity of the peaks found was slightly reduced when compared to that of the drug. It was also observed that some peaks shown by pure etoricoxib are absent and the intensity of peaks found was markedly reduced in the XRD patterns of solid dispersion. The result indicates that the drug in solid dispersion is amorphous as compared to the pure drug. Hence, increased dissolution of the drug was observed (21).

DSC curves of the pure drug (batch D_1) and its solid dispersion (batch B_5) are shown in Fig. 5. DSC curve of batch D1 showed one sharp endothermic peak at 140.68 °C corresponding to etoricoxib. The DSC curve of batch B5 showed two endothermic peaks, a sharp peak at 57.31 °C corresponding to PEG and a broad peak at 125.88 °C corresponding to etoricoxib in solid dispersion. Peak temperature in solid dispersions

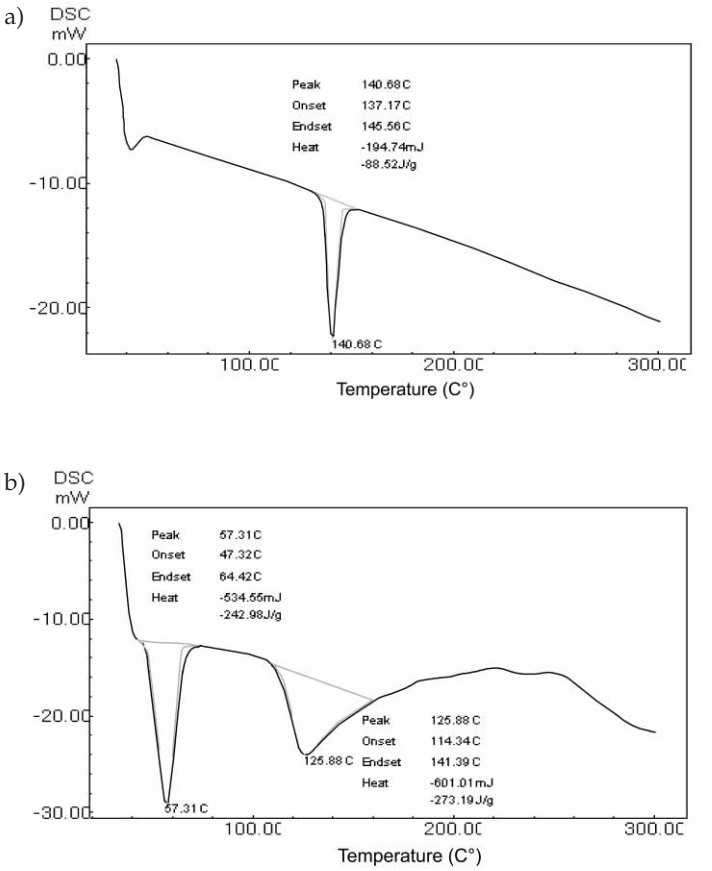


Fig. 5. DSC scans of: a) batch D_1, b) batch B_5.

Table VI. Observed and predicted results of check points

Response	Batch M_1 (X_1 = 0.5, X_2 = 0.5)		Batch M_2 (X_1 = 0.75, X_2 = 0.5)	
	Observed	Predicted	Observed	Predicted
Q_{10} (%)	64.3	63.1	60.9	59.8
Q_{30} (%)	83.6	83.0	81.5	81.1
Q_{45} (%)	89.0	87.4	85.7	85.3
DE (%)	84.9	83.5	82.7	83.5

For abbreviations see Table II.

shifted slightly to lower temperature with respect to the drug alone and there was a decrease in ΔH value of batch B_5 (–273.19 J g^{-1}) compared to the pure drug (–88.52 J g^{-1}). These phenomena could be attributed to the amorphous form of the drug in solid dispersions (22).

The mixture of PEG and PVP in dispersion systems rendered the drug more hydrophilic and more wettable in the dissolution medium. This is the prime reason for rapid and complete drug dissolution from solid dispersion systems. Decreased crystallinity and increased wetting of the particles may be considered as major contributors to the enhanced etoricoxib dissolution from a solid dispersion system containing PEG and PVP.

To validate the evolved mathematical models [(reduced models for Q_{10}, Q_{30}, Q_{45} and *DE* (%)], two check points were selected. Two batches (M_1 and M_2, Table I) were prepared and evaluated. The observed and predicted values are shown in Table VI. Good agreement was found between the observed and predicted values. Thus, it may be concluded that the evolved models may be used for theoretical prediction of responses within the factor space.

CONCLUSIONS

Solid dispersions prepared from hydrophilic polymers using the solvent evaporation method were effective in improving drug dissolution. The dispersion containing PEG and PVP (batch B_5) shows acceptable dissolution compared to the PEG or PVP dispersion or pure drug. The study revealed that optimum levels of hydrophilic carriers ensure a prompt and complete dissolution of etoricoxib from solid dispersions that are used in oral pharmaceutical formulations.

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REFERENCES

1. K. P. R. Chowdary, K. V. R. Murthy and C. D. S. Prasad, Solid dispersions of nimodipine: Physico-chemical and dissolution rate studies, *Indian Drugs* **32** (1995) 537–542.
2. J. Kerc, S. Srcic and B. Kofler, Alternative solvent-free preparation methods for felodipine surface solid dispersions, *Drug Dev. Ind. Pharm.* **24** (1998) 359–363.
3. I. Delneuville, J. P. Dechesne and L. Delattre, Preparation and study of the characteristics of dithranol: polyvilylpyrrolidone coevoporates, *Int. J. Pharm.* **168** (1998) 109–118.
4. G. F. Palmieri, F. Cantalamessa, P. D. Martino, C. Nasuti and S. Martelli, Lonidamine solid dispersions: in vitro and in vivo evaluation, *Drug Dev. Ind. Pharm.* **28** (2002) 1241–1250.
5. V. Tantoshaiyakul, N. Kaewnopparat and S. Ingkatawornwong, Properties of solid dispersions of piroxicam in polyvilyl pyrrolidone K-30, *Int. J. Pharm.* **143** (1996) 59–66.
6. M. Iwata and H. Veda, Dissolution properties of glibenclamide in combinations with polyvinylpyrrolidone, *Drug Dev. Ind. Pharm.* **22** (1996) 1161–1165.
7. G. P. Bettinetti and P. Mura, Dissolution properties of naproxen in combinations with polyvinylpyrrolidone, *Drug Dev. Ind. Pharm.* **20** (1994) 1353–1366.
8. M. C. Gohel and L. D. Patel, Processing of nimesulide-PEG 400-PG-PVP solid dispersions: preparation, characterization and *in vitro* dissolution, *Drug Dev. Ind. Pharm.* **29** (2003) 299–310.
9. G. R. Lloyd, D. Q. M. Craig and A. Smith, A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions, *Eur. J. Pharm. Biopharm.* **48** (1999) 59–65.
10. D. Q. M. Craig and J. M. Newton, The dissolution of nortryptiline HCl from polyethylene glycol solid dispersions, *Int. J. Pharm.* **78** (1992) 175–182.
11. J. W. Lu, M. Z. Wang, P. Ding and Z. S. Pan, Preparation and dissolution of nimodipine-PEG solid dispersion, *Chinese Pharm. J.* **30** (1995) 23–25.
12. H. Suzuki and H. Sunada, Influence of water soluble polymers on the dissolution of nifedipine solid dispersion with combined carriers, *Chem. Pharm. Bull.* **46** (1998) 482–487.
13. D. F. Temeljotov, M. Mohar, B. Kofler, S. Kotnik and A. Resman, Solubilization and dissolution enhancement for sparingly soluble fenofibrate, *Acta Pharm.* **46** (1996) 131–136.
14. M. C. Gohel and L. D. Patel, Improvement of nimesulide dissolution from solid dispersions containing crosscarmellose sodium and Aerosil® 200, *Acta Pharm.* **52** (2002) 227–241.
15. S. Bolton, *Practical and Clinical Applications*, in *Pharmaceutical Statistics*, 2nd ed., Marcel Dekker, New York 1990, pp. 308–337.
16. *United States Pharmacopoeia*, 23, NF 18, The USP Convention, Rockville 1995, pp. 1791–1799.
17. C. Lefebvre, A. M. Barthelemy and G. Hermann, An attempt at bringing to light a phase inversion in a binary mixture of two dimensional rounded particles, *Drug Dev. Ind. Pharm.* **14** (1988) 2443–2465.
18. K. A. Khan, The concept of dissolution efficiency, *J. Pharm. Pharmacol.* **27** (1975) 48–49.
19. J. W. Moore and H. H. Flanner, Mathematical comparison of dissolution profiles, *Pharm. Technol.* **20** (1996) 64–74.
20. G. M. Khan and Z. Jiabi, Preparation, characterization, and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (PEG), talc, and PEG-talc as dispersion carriers, *Drug Dev. Ind. Pharm.* **24** (1998) 455–462.
21. S. Y. Lin, Y. H. Kao and J. C. Yang, Grinding effect on some pharmaceutical properties of drugs by adding ß-cyclodextrin, *Drug Dev. Ind. Pharm.* **14** (1988) 99–118.
22. M. Wulff and M. Alden, Solid state studies of drug-cyclodextrin inclusion complexes in PEG 6000 prepared by a new method, *Eur. J. Pharm. Sci.* **8** (1999) 269–281.

S A Ž E T A K

Priprava i karakterizacija čvrstih disperzija etorikoksiba s polietilenglikolom 4000 i polivinilpirolidonom K30

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U radu je proučavan utjecaj polietilenglikola 4000 (PEG) i polivinilpirolidona K30 (PVP) na *in vitro* oslobađanje etorikoksiba iz čvrstih disperzija. Preliminarni pokusi provedeni su sa smjesom ljekovite tvari i polimernih nosača. Čvrste disperzije pripravljene su metodom uparavanja otapala. Za ovu metodu razvijen je 3^2 faktorijalni dizajn koristeći koncentraciju PEG i PVP kao nezavisne varijable. Za zavisne varijable razvijeni su potpuni i reducirani modeli, kao što su postotak oslobođene ljekovite tvari u 10 (Q_{10}), 30 (Q_{30}) ili 45 minuta (Q_{45}) i postotak učinkovitosti oslobađanja (DE). Reducirani modeli su validirani pomoću dviju kontrolnih točaka. $Q_{10} > 65\%$, $Q_{30} > 80\%$, $Q_{45} > 85\%$ i $DE > 80\%$ su uporabljeni kao ograničenja za izbor optimirane serije. Prikazane su konturne linije za pojedine zavisne varijable.

Oslobađanje lijeka bilo je učinkovitije iz pripravaka s PEG-om. Vlaženje je proučavano za čistu ljekovitu supstanciju i optimiranu seriju. Za karakterizaciju ljekovite tvari u čvrstim disperzijama korištene su FT-IR spektroskopija, mikroskopske studije, diferencijalna pretražna kalorimetrija i difrakcija rentgenskim zrakama. Povećano oslobađanje posljedica je smanjene kristaliničnosti ljekovite tvari, pojačanog vlaženja i solubilizacijskog učinka polimernih nosača u disperzijama. Zaključeno je da se oslobađanje etorikoksiba može modulirati promjenom količine hidrofilnih nosača.

Ključne riječi: etorikoksib, čvrsta disperzija, oslobađanje, polietilenglikol, polivinilpirolidon, faktorijalni dizajn

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