Int. J. Chem. Sci.: 6(4), 2008, 1858-1866

STUDIES ON SOLID DISPERSED ETORICOXIB WITH NEWER CARRIERS

A. PRAMEELS RANI*, R. SANTOSH KUMAR and N. SARAT BABU

K. V. S. R Siddhartha College of Pharmaceutical Sciences, VIJAYAWADA-10 (A. P.) INDIA

ABSTRACT

Etoricoxib (ETO) is a non-steroidal anti-inflammatory drug, which is widely used in symptomatic relief of osteoarthritis and rheumatoid arthritis. One of the major problems of this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersion of ETO with newer carriers i. e., croscarmellose sodium (CCS) and crospovidone (CP) were prepared using CCS and CP in three ratios (1 : 1, 1 : 2 and 1 : 3) employing physical mixing method and solvent evaporation method. The drug release profile for pure drug as such and its solid dispersions was determined. ETO was released at much higher rate from its solid dispersions as compared to that of pure drug. Faster dissolution rate was observed in drug : CCS (1 : 3) prepared by co-evaporation method. The increase in dissolution rate of drug may be due to increase of wettability, hydrophilic nature of carrier and also due to reduction in drug crystallinity, which is supported by DSC thermograms.

Key words: Etoricoxib, Dispersion, Co-evoperates.

INTRODUCTION

Solid dispersion techniques can be used to increase dissolution and bioavailability of several insoluble drugs[1-2]. Todate, a number of drugs are not showing complete therapeutic effect because of their poor solubility and dissolution, which in turn leads to poor bioavailability of the drug[3,4]. So in the modern days, top most importance is given for increasing the dissolution rate of poorly soluble drugs which enhances their bioavailability.

Etoricoxib (ETO) is a novel, selective, second generation cyclooxygenase-2 inhibitor administered orally as analgesic and anti-inflammatory drug. Chemically, it is 5-chloro-2[6-methyl pyridine-3-yl]-3-[4-methyl sulfonyl phenyl] pyridine having a formula $C_{16}H_{15}ClN_2O_2S$. The drug is practically insoluble in water (< 70µg/mL)[5,6]. Since the dissolution rate of a drug from surface is affected by the carrier in solid dispersion, the

* Author for correspondence; E-mail: drapr@rediffmail.com; radasantosh@rediffmail.com

carrier has an ultimate influence in the dissolution of the dispersed drug. Therefore, newer carriers like croscarmellose sodium and crospovidone were used as carriers in this study. These solid dispersions were prepared in different ratios of the drug and the carrier using techniques i. e., physical mixing method and co-evaporation method.

EXPERIMENTAL

Materials and methods

Etoricoxib, crospovidone and croscarmellosesodium were obtained as gift samples from Hetero Drugs Ltd, Hyderabad, A. P. All other materials used are of pharmacopoeial grade.

Estimation of etoricoxib

An UV spectrophotometric method based on the measurement of absorbance at 235 nm in distilled water containing 1% SLS was used in the estimation of ETO. The method obeyed Beer's law in the concentration range of 0-10 µg/mL. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of ETO content in various products and *in vitro* dissolution studies.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors[7]. Excess of drug was added to 15 mL of triple distilled water with pH 6.8 containing various concentrations of polymer (CCS and CP in percentages) taken in a series of 25 mL stoppered conical flask and the mixtures were shaken for 72 hrs at room temperature on a rotary flask shaker. After 72 hrs of shaking to achieve equilibrium, 2 mL aliquots were withdrawn at 1 hr interval and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assessed for drug content by U. V. spectrophotometric method at 235 nm. The solubility experiments were conducted in triplicate. The results are given in Fig. 1.

Preparation of solid dispersions of etoricoxib

Solid dispersions of ETO-CP and ETO-CCS were prepared in 1 : 1, 1 : 2 and 1 : 3 ratios by two methods :

(i) Physical mixing.

(ii) Co-evaporation.

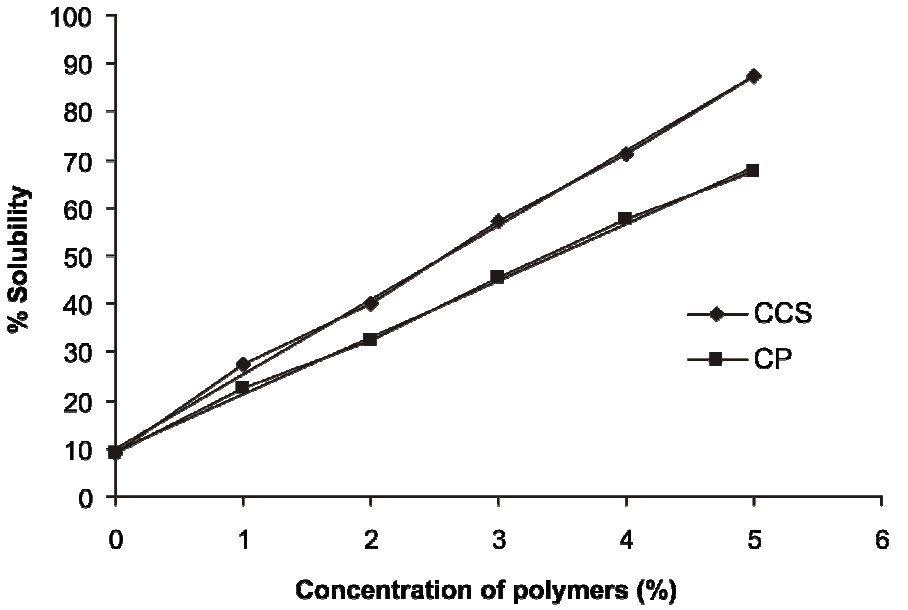

Fig. 1: Effect of CCS and CP on the solubility of ETO

Preparation of physical mixtures (PM) of etoricoxib

Physical mixtures of the drug (ETO) with the excipients in the 1 : 1, 1 : 2 and1 : 3 ratios were prepared by mixing them thoroughly for 5 min in a mortar until a homogeneous mixture was obtained. This was passed through mesh No #100 and stored in desiccated environment.

Preparation of co-evaporates (CE) of etoricoxib

The co-evaporates were prepared by using the solvent evaporation method. Etoricoxib was dissolved in a solvent blend of methanol and dichloromethane (1 : 1) to get a clear solution in a 100 mL round bottom flask. The aqueous solution of excipients (CP and CCS) was then added and dispersed. The solvent in the mixture was removed by evaporation at 50^0C under pressure while mixing the contents. The mass obtained was pulverized, mixed and passed through mesh no#100.

Estimation of drug content in the solid dispersions

The powder from solid dispersions equivalent to 50 mg of drug (ETO) was taken in a 50 mL volumetric flask. About 40 mL methanol was added and mixed thoroughly. The contents were repeatedly warmed in a hot water bath while mixing to dissolve the drug in

the solvent. The solution was made up to volume with methanol. The solution was then suitably diluted and assayed for the drug content at 235nm by the UV spectrophotometer method described above.

Dissolution rate studies on etoricoxib solid dispersions

Dissolution rate of etoricoxib as such and from solid dispersions was studied using Lab India Disso 2000, an 8 stage dissolution rate testing apparatus, with a paddle stirrer. The dissolution fluid was 900 mL of distilled water containing 1% SLS. Dissolution studies were carried out by taking solid dispersion equivalent to 50 mg of ETO. A speed of 75rpm and a temperature at 37 ± 1.0 ^{0}C were used in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for ETO by measuring absorbance at 235 nm. The dissolution experiments were conducted in triplicate and the results are shown in the Fig. 3.

Physico chemical compatibility between ETO and its solid dispersion with CCS using differential scanning calorimetry (DSC)

Sieko japan DSC 220C Model differential scanning calorimeter was used. Samples (1-4 mg) in weight were sealed hermetically in flat bottomed aluminium cells. These samples were then heated over a temperature of 35-300 ^{0}C in an atmosphere of nitrogen 50 mL/minute using alumina as reference standard.

RESULTS AND DISCUSSION

The aqueous solubility of ETO was increased linearly as a function of the concentration of polymer (CCS and CP). All the mixtures were found to be fine powders. Low SD in % drug content values indicated uniformity of drug content in each batch of physical mixtures / co-evaporates. The results are given in Table 1.

Table 1 : Drug content of ETO solid dispersions

Solid dispersion systems		Percent ETO content (mean ± s. d., n=3)	
		Physical mixtures	Co-evaporates
ETO : CP	(1 : 1)	99.66 ± 0.12	98.65 ± 0.12
ETO : CP	(1 : 2)	99.46 ± 0.25	98.68 ± 0.23
ETO : CP	(1 : 3)	98.26 ± 0.23	99.63 ± 0.32

Cont…

Solid dispersion systems	Percent ETO content (mean ± s. d., n=3)	
	Physical mixtures	Co-evaporates
ETO : CCS (1 : 1)	99.68 ± 0.16	96.58 ± 1.20
ETO : CCS (1 : 2)	98.60 ± 0.28	98.45 ± 0.98
ETO : CCS (1 : 3)	98.46 ± 0.12	99.95 ± 0.11

DSC thermograms of ETO and its solid dispersion in CCS are shown in Fig. 2 and 3, respectively. DSC thermogram of ETO exhibited a sharp endothermic peak at 134.96 ^{0}C corresponding to its melting point. In the DSC thermograms of solid dispersion, the endothermic melting point peak was shifted to a lower temperature i. e., 131.56 ^{0}C in the case of CCS (1 : 3) solid dispersion. The intensity of peak also gradually reduces, as the concentration of CCS was increased. The DSC patterns thus suggest an interaction between ETO and the carrier (CCS) and physical conversion of ETO into solution form (solid solution) at higher concentration of carrier. The rapid dissolution and higher dissolution efficiency values observed with solid dispersion is due to this interaction and physical conversion of ETO to solid solution form.

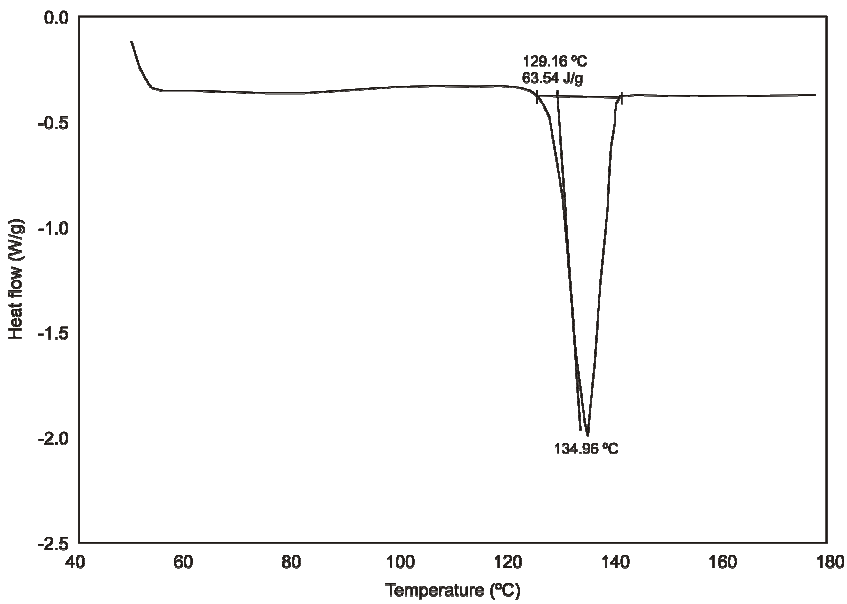

Fig. 2 : DSC thermogram of etoricoxib

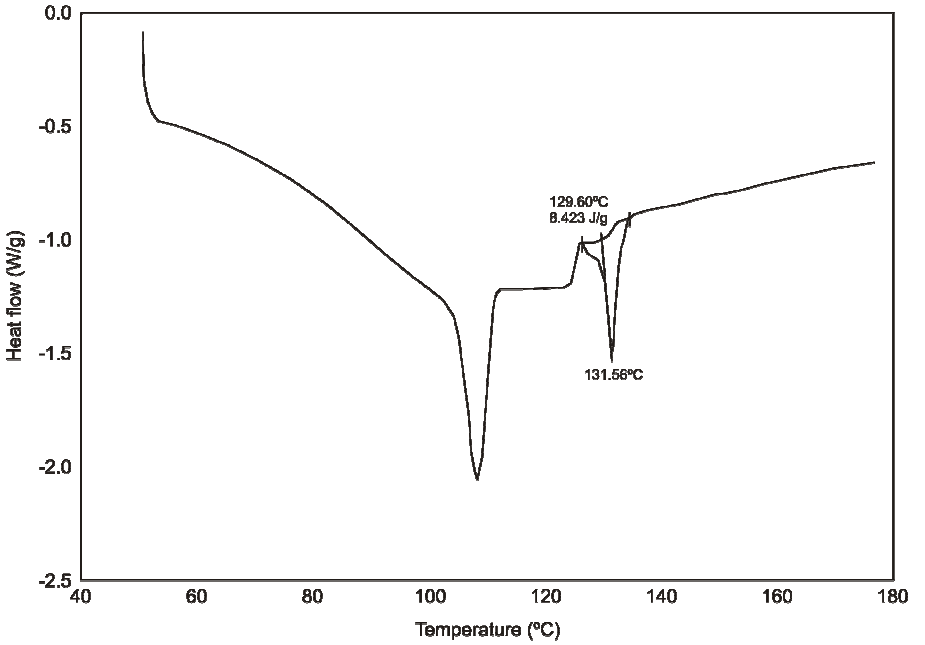

Fig. 3 : DSC thermogram of etoricoxib solid dispersion in CCS

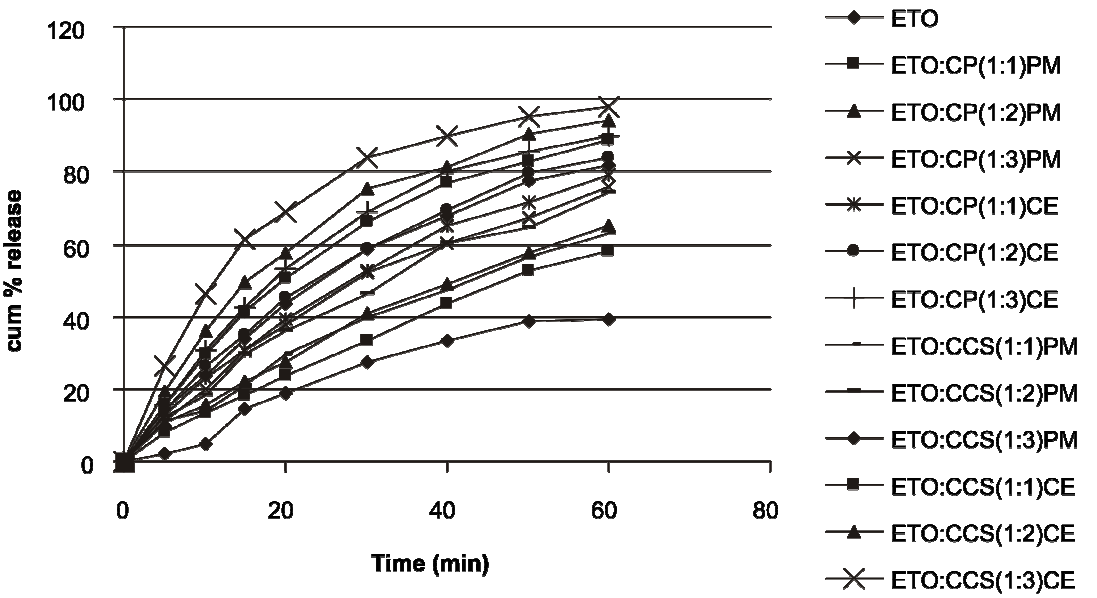

Fig. 4 : Dissolution profiles of ETO and its solid dispersions

The dissolution profiles of ETO as such and its solid dispersions in newer carriers prepared by physical mixing and co-evaporation method are shown in Fig. 4.

The dissolution of ETO as such and from the solid dispersion followed first order kinetics. The first order dissolution rates and the dissolution efficiency values were calculated and are shown in Tables 2 and 3.

Table 2. Dissolution parameters of ETO and its solid dispersions prepared by physical mixing

Solid dispersion	T_{10} (min)	T_{50} (min)	T_{90} (min)	% dissolved in 10 min	DE_{30}%	K_1 (min^{-1})	R value
Pure drug	8	>60	>60	5.08	14.26	0.0105	0.9957
ETO : CCS(1 : 1)	6	43	>60	14.18	22.5	0.0163	0.9975
ETO : CCS(1 : 2)	4	30	>60	18.48	28.33	0.021	0.9985
ETO : CCS(1 : 3)	3	28	>60	23.54	30.33	0.029	0.9987
ETO : CP(1 : 1)	6	47	>60	13.42	16.66	0.0145	0.9997
ETO : CP(1 : 2)	4	39	>60	15.57	21.66	0.0172	0.9976
ETO : CP(1 : 3)	3	28	>60	19.75	28.33	0.0232	0.997

Table 3. Dissolution parameters of ETO and its solid dispersions prepared by co-evaporation method

Solid dispersion	T_{10} (min)	T_{50} (min)	T_{90} (min)	% dissolved in 10 min	DE_{30}%	K_1 (min^{-1})	R value
Pure drug	8	>60	>60	5.08	14.26	0.0105	0.9957
ETO:CCS(1:1)	3	19	>60	29.75	39.16	0.0366	0.9958
ETO:CCS(1:2)	2	15	48	36.2	45.33	0.0465	0.995

Cont...

Solid dispersion	T_{10} (min)	T_{50} (min)	T_{90} (min)	% dissolved in 10 min	DE_{30}%	K_1 (min^{-1})	R value
ETO:CCS(1:3)	2	10	40	46.33	56.66	0.0628	0.995
ETO:CP(1:1)	4	27	>60	22.91	28.33	0.0257	0.999
ETO:CP(1:2)	3	22	>60	26.33	33.33	0.0308	0.999
ETO:CP(1:3)	2	17	60	30.63	40.00	0.0391	0.999

Solid dispersions of ETO-CCS/CP exhibited higher rates of dissolution and dissolution efficiency values than ETO as such. These are increased as the proportion of polymer (CCS/CP) was increased.

Solid dispersions prepared by co-evaporation method exhibited higher dissolution rates and dissolution efficiency values than those prepared by physical mixing method. This is due to better interaction of drug and polymer during co-evaporation process. Out of all dispersions described above, ETO-CCS (1 : 3) prepared by co-evaporation exhibited highest dissolution rate and dissolution efficiency values. A 5.98 fold and 3.97 fold increase in dissolution rate (K_1) and DE_{30}, respectively was observed with co-evaporates prepared at 1 : 3 ratio of drug : carrier. Thus, both solubility and dissolution rate of ETO were markedly enhanced by solid dispersion technique.

CONCLUSION

It was found that dissolution rate of poorly soluble drug ETO could be enhanced by solid dispersion technique using new carriers like CP and CCS. Solid dispersions demonstrated a higher dissolution rate than pure drug. The ETO : CCS (1 : 3) solid dispersion made by co-evaporation technique gave highest dissolution rate than the other dispersions. Hence the co-evaporation technique with CCS provides a promising way to increase the dissolution rate of poorly soluble drug i. e. ETO. A 5.98 fold and 3.97 fold increase in dissolution rate (K_1) and DE_{30}, respectively was observed with co-evaporates prepared at 1 : 3 ratio of drug : carrier. Thus, both solubility and dissolution rate of ETO were markedly enhanced by solid dispersion technique.

ACKNOWLEDGEMENTS

Authors are thankful to K. V. S. R. Siddhartha College of Pharmaceutical Sciences, Vijayawada for providing necessary facilities to carry out the work.

REFERENCES

1. J. L. Ford, Pharm. Acta Helv., **61**, 69 (1986).
2. M. Mayersohn and M. Gibaldi, J. Pharm. Sci., **55**, 1323 (1996).
3. K. Uekama, J. Pharm. Soc., (Japan), **100**, 903 (1980).
4. J. L. Ford, Pharm. Acta Helv., **61**, 58-101(1983).
5. T. S. Rawat, S. K. Jain and Y. B. Chawan, Pharmazine, **58(A)**, 639 (2003).
6. M. Vlachou and G. Papaidannou, J. Biomatter Appl., **17(3)**, 197-206 (2003).
7. T. Higuchi and K. A. Conners Adv. Anal. Hem. Instum., Reilley, C. N. (Ed) (1965) p. 117.

Accepted : 16.07.2008