ISSN: 0974-2115
Journal of Chemical and Pharmaceutical sciences

ENHANCEMENT OF DISSOLUTION RATE OF ETORICOXIB BY SOLID DISPERSION TECHNOLOGY

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ABSTRACT

The main aim of the present study is to improve the solubility of highly water insoluble drug Etoricoxib by using solid dispersion technology. Etoricoxib, the drug being studied is a Non steroidal anti-inflammatory drug belonging to "Specific COX-2 inhibitors" classification. It is a drug which is highly insoluble in water, hence dissolution is rate limiting. Therefore the aim is to increase its solubility by using polymers such as PEG4000, PEG6000 & Urea. This Solid dispersion technology can be used to improve the dissolution properties of poorly soluble drugs. Etoricoxib is one of the drugs which are practically insoluble in water. Solid dispersions of Etoricoxib in various carriers (PEG 4000, PEG 6000 & Urea) were prepared to enhance its dissolution rate of the drug.

KEY WORDS: Etoricoxib, Solid dispersion, Poly-ethylene glycol, Urea.

1. INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Bioavailability can be defined as the rate and extent at which the drug is delivered to the systemic circulation from dosage form and reaches the site of action to produce the desired effect (Yadav, 2009). Hence for drug whose aqueous solubility is less than 0.01 μg/ml will definitely create a bioavailability problem and thereby affecting the therapeutic efficiency. Once if we are able to increase the aqueous solubility of a drug, the disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved (Chiou and Rielman, 1971). Methods to increase aqueous solubility of a drug are Salt formation, solubilization, particle size reduction, complexation, solvent evaporation, solid solution and solvent formation (Dhirendra, 2009). They have been commonly used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs. There are practical limitations to these techniques (Tiwari, 2009). Practical methods where by many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome (Patel, 2008). This method which was later termed as 'Solid Dispersion', involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. The drug was present in a eutectic mixture in a microcrystalline state (Patel, 2007). The entire drug in solid dispersions might not be necessarily present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and carrier dissolved, the drug was released as very fine and colloidal particles (Muralidhar, 2010). Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high (Suhagia, 2006).

2. MATERIALS AND METHODS

2.1 Materials: Etoricoxib has been obtained as a gift sample from Glenmark & Burgeon Pharmaceutical**,** PEG 4000, PEG 6000, Urea and Methanol Colorcon Asia Pvt. Ltd., Goa. All other ingredients, reagents and solvents were of analytical grade.

2.2 Preparation of Etoricoxib solid dispersion by solvent evaporation method: The solvent used to prepare the solid dispersions by this method is methanol. Five different ratios of drug: Polymers were formulated for each polymer (1:1, 1:2, 1:3, 1:4 and 1:5). The calculated amount of polymer was dissolved in required amount of solvent methanol (usually 10ml) taken in a conical flask with a side tube. Then the calculated and weighed amount of etoricoxib was added to this solution carefully with constant stirring. Stirring was continued until the drug was completely incorporated in the solvent. Then the solvent was removed by evaporation at 40ºC under vacuum (Karekar, 2009). The mass obtained was then dried in a dessicator, crushed, pulverized and sifted through mesh No.80.

2.3 Evaluation of etoricoxib solid dispersion

2.3.1 *In-vitro* dissolution rate studies: Dissolution studies are the most important part in the evaluation of solid dispersions. In this test the rate and extent of dissolution of both pure drug and solid dispersions is calculated. Dissolution rate studies of various solid dispersions were carried out in pH7.4 phosphate buffer using USP Type II dissolution rate apparatus (Dangprasirt and Limwong, 2005). Solid dispersions equivalent to 50mg of etoricoxib was taken in a hard gelatin capsule. The paddle type stirrer was adjusted to 50 rpm and the temperature was maintained at 37º $\pm$ 1º C. The capsule was then dropped into the apparatus and time noted. 5ml aliquot dissolution medium was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution medium. The samples were analyzed for etoricoxib after suitable dilution by measuring absorbance at 232.4 nm using Shimadzu UV-vis. spectrophotometer. The percentage of etoricoxib dissolved at various time intervals was calculated and plotted against time (Chauhan, 2005).

3. RESULTS AND DISCUSSION

The *in-vitro* dissolution study of etoricoxib solid dispersion was found to be around 100% drug release using PEG 4000 as carried, for PEG 6000 it was found to be around 75% and for urea it was around 90% at the end of 90minutes.

3.1 IR Spectral Analysis: Studies of compatibility between Etoricoxib and carriers were performed using Perkin Elmer IR Spectrometer. It was observed that the IR spectrum of the solid dispersions matched with the IR spectrum of the pure drug and also, there was no appearance of any characteristic peaks. This confirms that any type of chemical interaction between the drug and the carriers used is absent.

3.2 X-Ray diffraction studies: Normally it is observed that materials which are crystalline have poor dissolution properties in water compared to amorphous materials. Usually a drug which is crystalline in nature can be converted to amorphous form by preparing its solid dispersions. This property of the drug and solid dispersion can be analyzed using X-Ray diffraction studies. In X-Ray diffraction graphs, materials which are crystalline show intensive peaks while materials which are amorphous show peaks which are less in intensity.

4. CONCLUSION

Despite of many disadvantages of solid dispersions, successful development of solid dispersion systems for preclinical and commercial use have been feasible in recent years due to the availability of surface active agents and self emulsifying carriers with relatively low melting points. The application of hot melt extrusion to the production of solid dispersions is a particularly important breakthrough for scale up for formulation.

Table no 1 Etoricoxib Drug and Carrier Ratios

Drug : Carrier Ratio	Drug (mg)	Carrier (mg)
1 : 1 (SD1)	100	100
1 : 2 (SD2)	100	200
1 : 3 (SD3)	100	300
1 : 4 (SD4)	100	400
1 : 5 (SD5)	100	500

Table no 2 Dissolution of etoricoxib

%drug release of Etoricoxib		Time (min)					
		10	20	30	40	60	90
Pure drug(50mg)		7.2	12.6	19.8	25.2	28.8	32.4
PEG4000	SD1	27	36	46	59.4	68.4	70.2
	SD2	27	36	46	48.6	63	72
	SD3	21.6	30.6	54	72	84	90
	SD4	10.8	32.4	46.8	57.6	81	99
	SD5	27	32.4	52	63	90	100
PEG6000	SD1	19.8	25.2	32.4	36	46.8	56
	SD2	16.2	27	41.4	41.4	52.2	59.4
	SD3	16.2	30	36	41.4	46.8	63
	SD4	14.4	30.6	41.4	46.8	54	64.8
	SD5	14.4	27	36	43.2	64.8	73.8
Urea	SD1	21.6	25.2	30.6	34.2	43.2	52.2
	SD2	25.2	28.8	34.2	45	48.6	52.2
	SD3	30.6	34.2	39.6	59.4	66.6	70.2
	SD4	41.4	50.4	63	70.2	73.8	82.8
	SD5	46.8	54	59.4	73.8	81	91.8

ISSN: 0974-2115
Journal of Chemical and Pharmaceutical sciences

Table no 3 Percentage of etoricoxib un-dissolved

% of Etoricoxib un-dissolved		Time (min)					
		10	20	30	40	60	90
Pure drug (50mg)		92.8(1.9675)	87.4(1.9415)	80.2(1.9042)	74.8(1.8739)	71.2(1.8525)	67.6(1.8299)
PEG4000	SD1	73(1.8633)	64(1.8062)	54(1.7324)	40.6(1.6085)	31.6(1.4997)	29.8(1.4742)
	SD2	73(1.8633)	64(1.8062)	54(1.7324)	51.4(1.7110)	37(1.5682)	28(1.4472)
	SD3	78.4(1.8943)	69.4(1.8414)	46(1.6628)	28(1.4472)	16(1.2041)	10(1.0000)
	SD4	89.2(1.9504)	67.6(1.8299)	53.2(1.7259)	42.4(1.6274)	19(1.2788)	10(1.0000)
	SD5	73(1.8633)	67.6(1.8299)	48(1.6812)	37(1.5682)	10(1.0000)	0
PEG6000	SD1	80.2(1.9042)	74.8(1.8739)	67.6(1.8299)	64(1.8062)	53.2(1.7259)	44(1.6435)
	SD2	83.8(1.9232)	73(1.8633)	58.6(1.7679)	58.6(1.7679)	47.8(1.6794)	40.6(1.6085)
	SD3	83.8(1.9232)	70(1.8451)	64(1.8062)	58.6(1.7679)	53.2(1.7259)	37(1.5682)
	SD4	85.6(1.9325)	69.4(1.8414)	58.6(1.7679)	53.2(1.7259)	46(1.6628)	35.2(1.5465)
	SD5	85.6(1.9325)	73(1.8633)	64(1.8062)	56.8(1.7543)	35.2(1.5465)	26.2(1.4183)
Urea	SD1	78.4(1.8943)	74.8(1.8739)	69.4(1.8414)	65.8(1.8182)	56.8(1.7543)	47.8(1.6794)
	SD2	74.8(1.8739)	71.8(1.8561)	65.8(1.8182)	55(1.7404)	51.4(1.7110)	47.8(1.6794)
	SD3	69.4(1.8414)	65.8(1.8182)	60.4(1.7810)	40.6(1.6085)	33.4(1.5237)	29.8(1.4742)
	SD4	58.6(1.7679)	49.6(1.6955)	37(1.5682)	29.8(1.4742)	26.2(1.4183)	17.2(1.2355)
	SD5	53.2(1.7259)	46(1.6628)	40.6(1.6085)	26.2(1.4183)	19(1.2788)	8.2(0.9138)

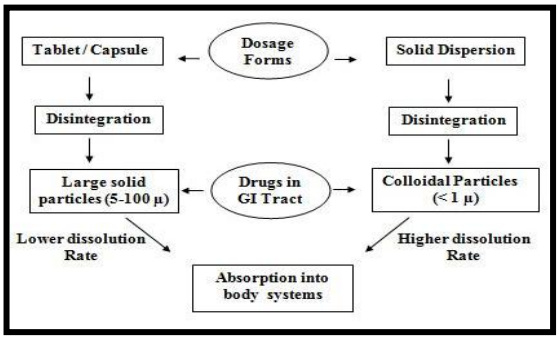


Figure no 1 Comparative absorption Mechanism of tablets and solid dispersion

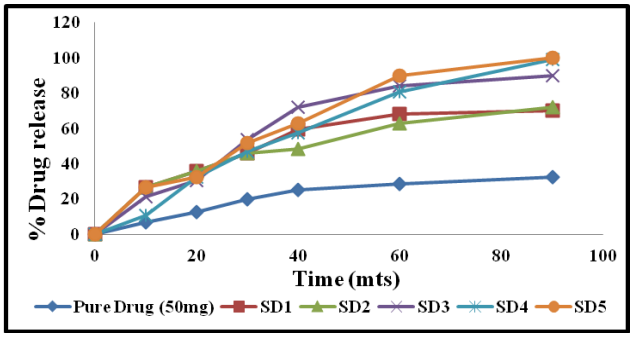


Figure no 2 Dissolution of etoricoxib from PEG 4000

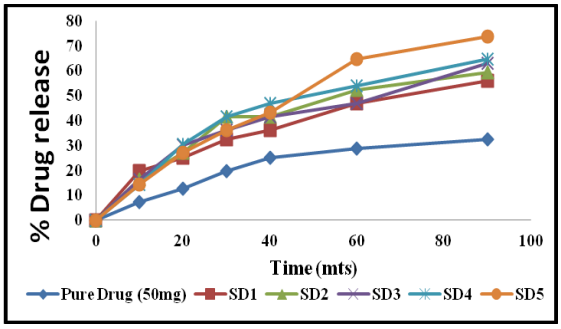


Figure no 3 Dissolution of etoricoxib from PEG 6000

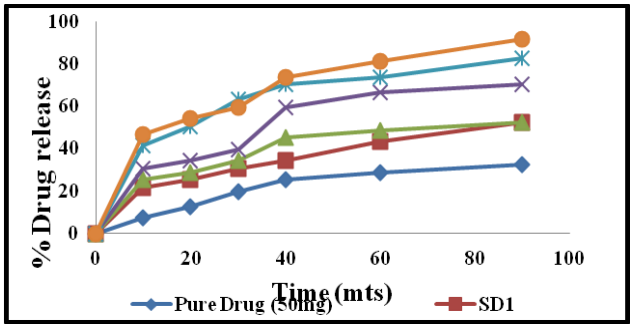


Figure no 4 Dissolution of etoricoxib from Urea

ISSN: 0974-2115
Journal of Chemical and Pharmaceutical sciences

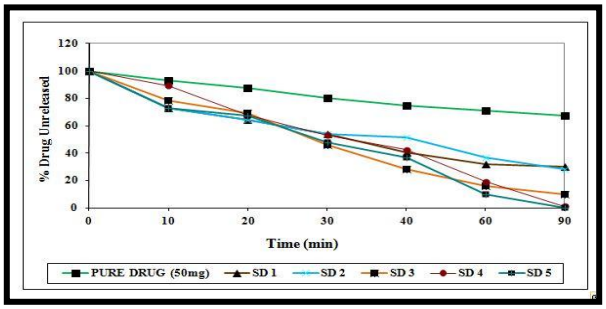


Figure no 5 Etoricoxib un-dissolved from PEG 4000

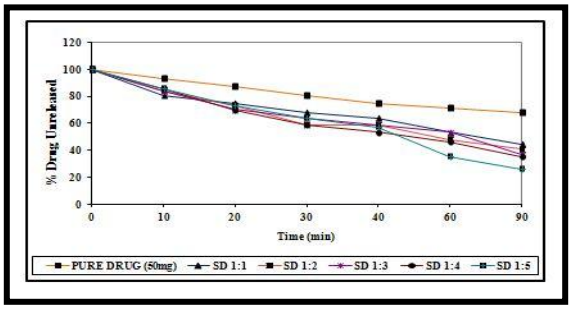


Figure no 6 Etoricoxib un-dissolved from PEG 6000

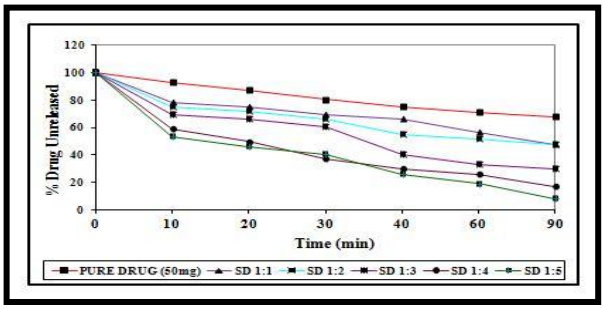


Figure no 7 Etoricoxib un-dissolved from Urea

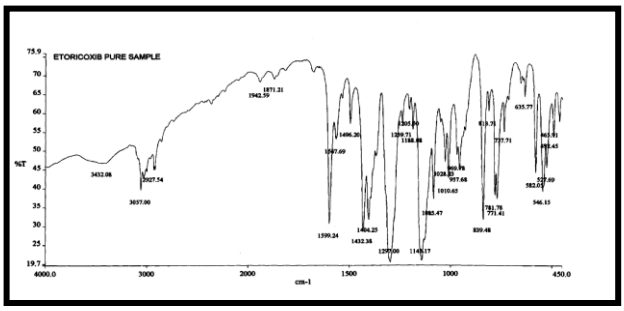


Figure no 8 FTIR of Pure drug (Etoricoxib)

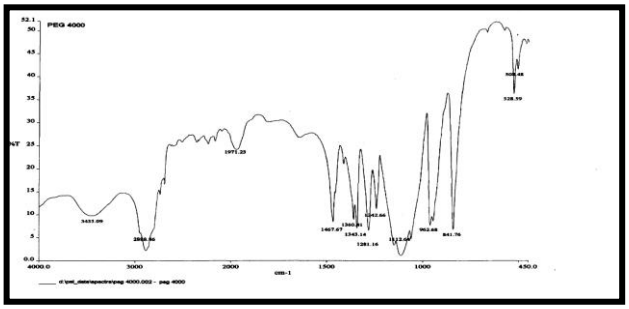


Figure no 9 FTIR of PEG 4000

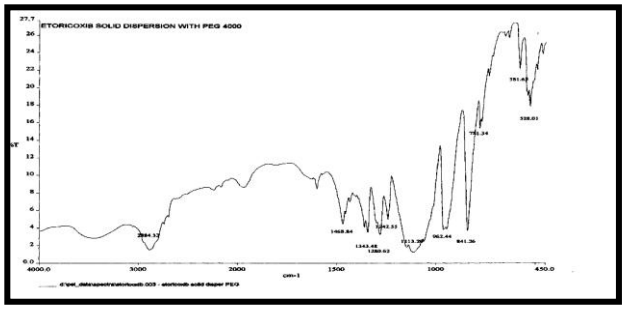
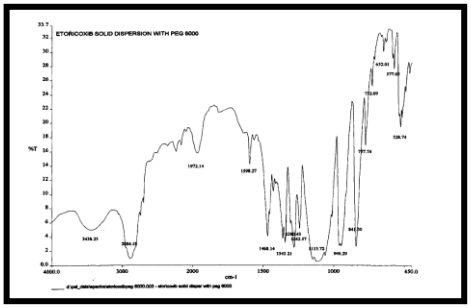
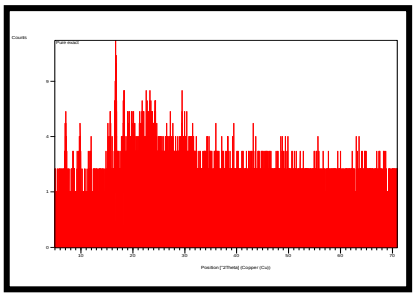


Figure no 10 FTIR of Etoricoxib solid dispersion with PEG 4000





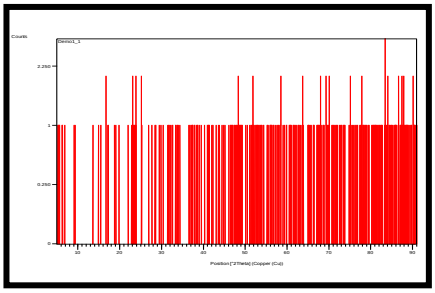


Figure no 11 FTIR of Etoricoxib solid dispersion with PEG 6000 Fig 12: X-ray studies of pure drug (Etoricoxib) Fig 13: X-ray study of solid dispersion of Etoricoxib: PEG 4000

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