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SOLUBILITY ENHANCEMENT OF ETODOLAC BY SOLID DISPERSION TECHNIQUES

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ABSTRACT
The aim of the present study was solubility and dissolution rate enhancement of etodolac by using different solid dispersion techniques. Solid dispersion of etodolac was prepared by kneading and solvent evaporation method. Solid dispersions of etodolac with PEG-600 and guar gum were prepared in different ratios as 1:1, 1:2, 1:3. FTIR, DSC and XRD were performed to study the interaction between drug and polymers. In solid dispersion formulations there was decrease in crystallinity of etodolac, which leads to increase in dissolution of etodolac from solid dispersions. All methods showed improvement in dissolution profile of etodolac as compare to pure drug. Solvent evaporation shows faster drug release as compared to physical mixture and kneading method (etodolac and guar gum) this might be due to the hydrophilic nature of the carrier, hydrodynamic microenvironment was changes and drug get dispersed in to polymer which prevents aggregation and/or reagglomeration phenomenon during dissolution. At time of dissolution, drug and carrier from mixtures comes in contact with dissolution fluid, passing of dissolution medium into drug carrier particles takes place, which initiates the formation of stagnant gel layer of carrier around the particles. The drug particles that are separate entities but disperse rapidly throughout dissolution medium and expose a greater surface area, resulting in rapid drug release.

KEYWORDS: Solubility enhancement, solid dispersion, kneading, solvent evaporation.

INTRODUCTION
The ultimate goal of drug product development is to design a system that maximizes therapeutic potential of the drug substance and facilitates its access to patients. Poorly water-soluble drug candidates often emerge from contemporary discovery programs and present formulation scientists with considerable technical challenges. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water-soluble compounds has dramatically increased.[1] In pharmaceutical industry recently developed more than 40% new chemical entities are practically insoluble in water. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. There are different approaches used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. Various techniques are used to increase the solubility of poorly soluble drugs are chemical modifications, physical modifications techniques like media milling/ nanocrystal technology, cryogenic technology, supercritical fluid process, modification of the crystal habit, complexation, micellar technologies, other techniques like co-crystallization, co-solvency, hydrotrophy, solid dispersion.[2]

Sekiguchi and Obi first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs in 1961.[3] Sekiguchi and Obi first time enhanced rate and extent of absorption of sulfathiazole using the solid dispersion technique.[4] It is defined as "dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method". Mayersohn and Gibaldi first used the solid dispersions may also be called solid-state dispersions.[5]

Etodolac is 1, 8-diethyl- 1, 3, 4, 8-tetrahydropyrano [3, 4-*b*] indole-1-acetic acid. For acute and long-term use in the management of Osteoarthritis and Rheumatoid arthritis.[6] It belongs to BCS class-II i.e. low solubility and high permeability. The solubility of etodolac, retards dissolution and results in poor bioavailability. So, enhancement of solubility useful to improve dissolution and ultimately bioavailability. The aim of the present study was to apply the principles of solid dispersions for solubility enhancement etodolac using different polymers

as PEG-6000 and guar gum by physical mixture, kneading method and solvent evaporation techniques.

MATERIALS AND METHODS

Materials: Etodolac (Ipca Laboratories, Mumbai), PEG-6000(Shreya Laboratories, Aurangabad), Guar gum (Research lab fine chem. industries). All other chemicals used were analytical grade.

Methods

Phase Solubility Study[7,8]

Phase solubility of etodolac with PEG-6000 and guar gum was determined by the method reported by Huguchi and Connor, by dissolving excess amount of etodolac in 20 ml of distilled water containing increasing concentration of the PEG-6000/Guar gum (i.e.1-5 %w/v) separately, Samples were shaken for 48 hrs at 37°C ± 0.5°C at constant speed and after 48 hrs samples were filtered using whatman filter paper no.41. Absorbance of filtrate was measured spectrophotometrically at 278 nm (phosphate buffer pH 7.5), 279 nm (distilled water), and 271 nm(0.1NHCl).

FORMULATION OF SOLID DISPERSION OF ETODOLAC

Solid dispersions of etodolac PEG-6000 and guar gum were prepared by following methods:

Formulation of solid dispersion of Etodolac

Physical Mixture

Physical mixtures were prepared by mixing weighed quantities of etodolac and polymer in various ratios (1:1, 1:2, 1:3) in a glass mortar for 15-20 min individually. These mixtures were then sifted through sieve no 80 for uniform size (table:1).

Kneading Method

Kneading mixtures of etodolac and polymers were prepared in different ratios (1:1, 1:2, 1:3), polymer was taken in mortar and wetted by adding small quantity of water till slurry like consistency formed. Then drug was slowly incorporated into slurry and triturated for one hour. The paste was dried at 40^0C in oven until dry, dried mass pulverized and sifted through sieve no 80 for uniform size (table :1).

Solvent Evaporation

Etodolac and polymers were accurately weighed in different ratios (1:1, 1:2, 1:3) separately. Etodolac was dissolved in ethanol to get a clear drug solution and polymer is added to it with continuous stirring. Solvent was evaporated at room temperature for 24 hours. After drying product was crushed, pulverized and passed through sieve no.80 (table :1).

Table 1: Formulations of solid dispersions of Etodolac + PEG-6000, Etodolac + Guar gum by different methods

Method	Formulations		Drug Polymer Ratio
	Etodolac + PEG 6000	Etodolac + Guar gum	
Physical Mixture	F-1	F-10	1:1
	F-2	F-11	1:2
	F-3	F-12	1:3
Solvent Evaporation	F-4	F-13	1:1
	F-5	F-14	1:2
	F-6	F-15	1:3
Kneading Method	F-7	F-16	1:1
	F-8	F-17	1:2
	F-9	F-18	1:3

Evaluation of Solid Dispersion

Prepared solid dispersions were evaluated for:

Drug Content

Solid dispersion equivalent to 200 mg of etodolac was taken in to 100 ml volumetric flask and dissolved in 25 ml of ethanol and volume was adjusted upto 100 ml using phosphate buffer pH 7.5. From this 1 ml solution was withdrawn and diluted to 10 ml using phosphate buffer pH7.5, filtered using whatman filter paper no.41 and absorbance was noted at 278 nm.

FTIR analysis[9]

Samples were prepared by grinding drug, excipients, physical mixture and solid dispersions with KBr and then, pressing powder in the sample holder and placed in IR chamber (Shimadzu-8400 S) and spectra of individual drug, excipients, their physical mixture and solid dispersions were obtained.

DSC Study[10]

Thermogram of etodolac, excipient, physical mixture and solid dispersions were obtained. Samples (1-10 mg) were sealed in flat bottomed aluminum pans and heated over a temperature range of 50-300°C at a rate of 10°C /min. in a nitrogen atmosphere using Shimadzu-60 DSC.

XRPD[11]

Polymorphic nature of drug, physical mixture and solid dispersion was determined by X-ray powder diffraction technique. XRD patterns of were obtained by using Brukar D-8 X-Ray Diffractometer at voltage of 40 kV and current of 40 mA and scanning rate of 1°/min at diffraction angle of 2 theta degree using Cu (as anode) and radiation of wavelength 1.540600 A°.

***In-vitro* drug release study of solid dispersion formulations[6]**

An accurately weighed quantity of solid dispersions equivalent to 200 mg of etodolac was filled in hard gelatin capsule shell. The dissolution studies of capsule were conducted by using dissolution test apparatus (Labindia) type II, IP (basket method). The dissolution test was performed using 900 ml, phosphate buffer pH7.5 as dissolution medium at 37°C ± 0.5°C and 100 rpm. Capsules were placed in basket and when temperature of dissolution medium reached, immersed in dissolution medium. Aliquots of 5 ml was withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, 45 minute time intervals, filtered using whatman filter paper no.41 and samples were replaced with fresh dissolution medium of same quantity to maintain volume of dissolution medium after each sampling and analyzed spectrophotometrically at 278 nm.

RESULTS AND DISCUSSION

Phase Solubility Study

Etodolac belongs to BCS class II drug category i.e. having low solubility and high permeability. Solubility of etodolac was found to be 0.145 mcg/ml, 1.867 mcg/ml, 20.4643 mcg/ml in distilled water, 0.1N HCl, phosphate buffer pH 7.5 respectively. Phase solubility was carried out using PEG-6000 and Guar gum as carriers in different concentration range (1-5% w/v) in distilled water, 0.1N HCl and phosphate buffer pH 7.5. It was found that solubility of etodolac increases with increase in concentrations of polymers as shown in table 2,3,4. The increase in solubility of etodolac was found due to effect of polymers in phases. Thus above polymers may be found to be promising tool to improve the solubility of etodolac.

The Gibb's free energy transfer (ΔGtr) gives information about whether the treatment is favorable or unfavorable for drug solubilization. Negative Gibb's free energy values indicate improved dissolution. Gibb's free energy transfer (ΔGtr) was calculated by using the following equation[12]:

$$\Delta G_{tr}^{\infty} = -20303\ RT\ Log\ S_O/S_S \ldots\ldots\ldots\ldots 1$$

Where

S_O/S_S = is the ratio of solubility of etodolac in solution polymer to that of pure solution without polymer in same medium.

R (gas constant) = 8.31 $J.K^{-1}.mmol^{-1}$

T = Temperature

Table 2,3,4 shows solubility and Gibb's free energy associated with the solubility of etodolac, guar gum and PEG-6000, in different media. The negative values of ΔG_{tr} was observed at all concentrations of polymers, indicated that the reaction becomes more favorable as the concentrations of polymers increased.

Table 2: Phase solubility (mcg/ml) and Gibb's free energy (kJ/mol at 37°C) of Etodolac in, Guar gum and PEG-6000 (Medium: Water).

Sr.No.	Concentration of Polymers (%w/v)	Guar gum		PEG-6000	
		Solubility	ΔG	Solubility	ΔG
1	0	0	0	0	0
2	1	2.199	-836.064	6.908	-1187.77
3	2	2.403	-863.96	7.776	-1225.21
4	3	3.433	-973.726	7.876	-1229.25
5	4	4.602	-1063.911	7.909	-1230.53
6	5	5.739	-1131.85	8.978	-1269.54

Table 3: Phase solubility (mcg/ml) and Gibb's free energy (kJ/mol at 37°C) of Etodolac in Guar gum and PEG-6000 (Medium: 0.1N HCl).

Sr. No.	Concentration of Polymers (%w/v)	Guar gum		PEG-6000	
		Solubility	ΔG	Solubility	ΔG
1	0	0	0	0	0
2	1	8.310	-459.38	4.043	-237.81
3	2	8.544	-480.87	5.104	-309.371
4	3	9.479	-499.94	6.507	-384.166
5	4	10.213	-522.88	10.413	-528.846
6	5	11.380	-556.76	10.514	-531.811

Table 4: Phase solubility (mcg/ml) and Gibb's free energy (kJ/mol at 37°C) of Etodolac in Guar gum and PEG-6000 (Medium: Phosphate Buffer pH 7.5).

Sr. No.	Concentration of Polymers (%w/v)	Guar gum		PEG-6000	
		Solubility	ΔG	Solubility	ΔG
1	0	0	0	0	0
2	1	24.070	-49.152	20.810	-5.156
3	2	28.978	-107.032	21.101	-9.423
4	3	29.145	-108.809	22.616	-30.751

5	4	30.848	-126.280	23.051	-36.625
6	5	32.351	-140.910	26.207	-76.105

Evaluation of Solid Dispersion

Drug Content

Drug content in solid dispersions of etodolac and polymers (PEG-6000 and guar gum) was found between 98.26 ± 0.378 to 100.40 ± 0.299 % w/w (Limit: 98-102% w/w).

FTIR analysis

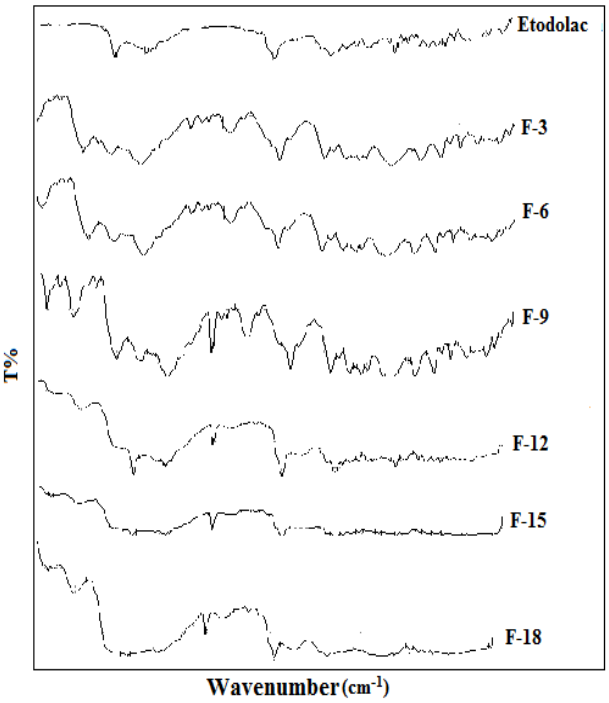

Fig.1: FTIR spectra of Etodolac and its solid dispersion formulations.

FTIR spectra of etodolac (Fig. 1), shows stretching vibration at 1033.88 cm^{-1} (C-O stretch), N-H wagging mode at 748.41cm^{-1}, 1180.87cm^{-1} (–C-O ether group), CH_2 deformation at 1319.35 cm^{-1},1411.94 cm^{-1} (CH_3 asymmetric deformation), 1743.71 cm^{-1} (C=O stretching vibration of the COOH group), 3340.82cm^{-1} (N-H stretching vibration of secondary amine group), 2970.48cm^{-1} (aromatic C-H group). FTIR spectra of etodolac and PEG-6000, physical mixture formulation F-3 (Fig.1) shows slight shifting of characteristic peaks of etodolac from 1033.88 cm^{-1}, 748.41 cm^{-1},1319.35 cm^{-1}, 1411.94 cm^{-1}, 1743.71 cm^{-1}, 3340.82 cm^{-1}, 2970.48 cm^{-1} to 1111.03 cm^{-1}, 740.69 cm^{-1}, 1350.22 cm^{-1}, 1465.95 cm^{-1}, 1705.13 cm^{-1}, 3201.94 cm^{-1}, 2885.6 cm^{-1} respectively which might be due to dilution effects of excipient. There were no new band are observed in above spectra indicating absence of chemical bond formation / interaction between drug and polymer. FTIR spectra of etodolac and PEG-6000, solvent evaporation formulation F-6 (Fig. 1) shows slight shifting of characteristic peaks of etodolac from 1033.88 cm^{-1}, 748.41 cm^{-1}, 1319.35 cm^{-1}, 1411.94 cm^{-1}, 1743.71 cm^{-1}, 3340.82 cm^{-1}, 2970.48 cm^{-1} to 1111.03 cm^{-1}, 740.69 cm^{-1}, 1342.5 cm^{-1}, 1465.95 cm^{-1}, 1705.13 cm^{-1}, 3201.94 cm^{-1}, 2885.6 cm^{-1} indicating strong physical interaction between drug and polymer in presence of ethanol. Also there is no formation of any new peaks indicating absence of chemical bond formation and chemical interaction between drug and polymer. FTIR spectra of etodolac and PEG-6000, kneading method formulation F-9 (Fig. 1) shows slight shifting of characteristic peaks of etodolac from 1033.88 cm^{-1}, 748.41 cm^{-1}, 1319.35 cm^{-1}, 1411.94 cm^{-1}, 1743.71 cm^{-1}, 3340.82 cm^{-1}, 2970.48 cm^{-1} to 1111.03 cm^{-1}, 740.69 cm^{-1}, 1342.5 cm^{-1}, 1465.95 cm^{-1},1705.13 cm^{-1}, 3201.31 cm^{-1}, 2885.6 cm^{-1} indicating physical interaction between etodolac and PEG-6000 due to kneading and solvent addition indicates formation of solid dispersion. Also there is no formation of any new peaks indicating absence of chemical bond formation and chemical interaction between drug and polymer.

FTIR spectra of etodolac and guar gum physical mixture F-12 (Fig. 1) shows slight shifting/change of intensity (1319.35 cm^{-1} to 1365.65 cm^{-1}, 3340.82 cm^{-1} to 3348.54 cm^{-1}) of some characteristic peaks of etodolac which might be due to higher concentration of polymer and dilution effect of polymer. There were no new band are observe in above spectra indicating absence of chemical bond formation/interaction between drug and polymer.

FTIR spectra of etodolac and gaur gum, solvent evaporation formulation F-15 (Fig.1) shows slight shifting of some characteristic peaks of etodolac indicating strong physical interaction between drug and polymer in presence of ethanol. Also there is no formation of any new peaks indicating absence of chemical bond formation and chemical interaction between drug and polymer. FTIR spectra of etodolac and guar gum by kneading method formulation F- 18 (Fig. 1) shows changes in frequencies of some peaks such as 748.41 cm^{-1}, 1743.71 cm^{-1}, 2970.48 cm^{-1}, 3340.82cm^{-1} to 895 cm^{-1}, 1743.71 cm^{-1}, 2360.95 cm^{-1}, 3348.54 cm^{-1}. The changes in frequencies and absence of some etodolac peaks are observed due to addition of water during kneading leads to formation of solid dispersion of drug with guar gum and hydrogen bonding with oxygen in drug. There is no new peaks observed, indicating absence of chemical bond formation in the binary system.

All solid dispersion systems shows shifting of characteristic peaks intensity and disappearance of characteristics IR band of either by drug or polymers indicating alteration in drug or polymer environment or may be due to surface absorption of polymer.

Differential Scanning Calorimetery

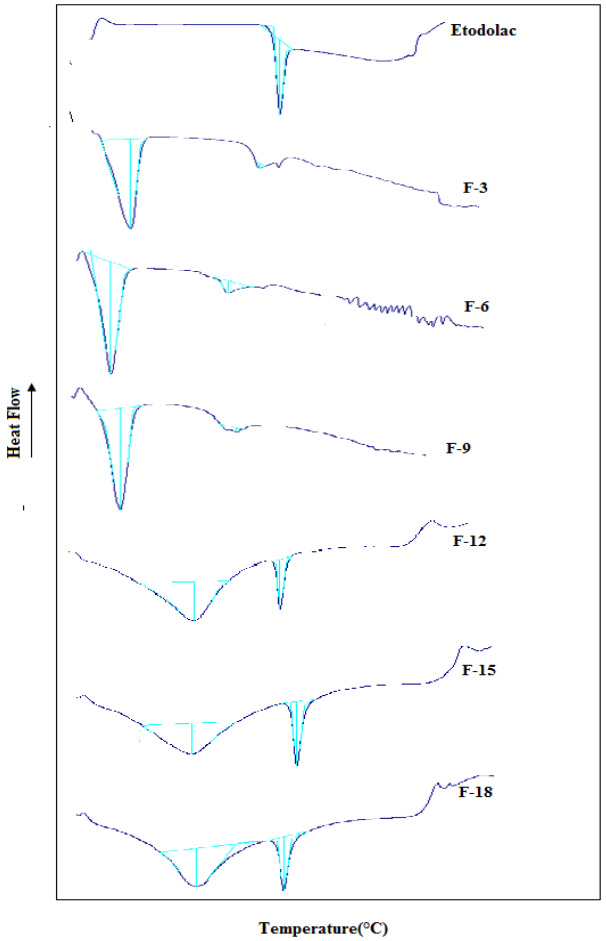

Fig. 2: FTIR spectra of Etodolac and its solid dispersion formulations.

Etodolac shows a sharp endothermic peak at 154.06 °C, ascribed to the melting of drug (Fig. 2). DSC thermogram of etodolac and PEG-6000 physical mixture F-3 (Fig. 2) shows a sharp melting endothermic peak at 60.80°C indicating presence of PEG-6000 in physical mixture. It also shows another small peak at 157.11°C, with peak height -0.84 mw, decrease in peak sharpness and height from -12.14 mw to - 0.84 mW is due to dilution effect of excipient (higher concentration of polymer). Also presence of polymer peak at 60.80°C indicated absence of any chemical reaction between etodolac and PEG-6000. Figure 2 shows DSC thermogram of etodolac, PEG-6000 and its solid dispersion formulation by solvent evaporation method (F-6). It shows a sharp endothermic peak at 57.92°C indicating presence of polymer and there is complete disappearance of endothermic peak at 154.06°C indicates formation of solid dispersion by solvent evaporation. DSC thermogram of etodolac, PEG-6000 and its solid dispersion formulation by kneading method formulation F-9 (Fig.2). It showed complete disappearance of endothermic peak at 154.06°C. This indicates interaction of etodolac with PEG-6000. Complete disappearance of endothermic peak of etodolac indicates formation of amorphous form of etodolac in solid dispersion with PEG-6000 by kneading method. Again this could be attributed to more uniform distribution of drug in crust of polymer and formation of solid dispersion.

DSC thermogram of etodolac and guar gum physical mixture, F-12 shows (Fig. 2) broad endothermic peak at 100.43°C of guar gum and endothermic peak of etodolac slightly shifted from 154.06 °C to 153.14°C, decrease in peak intensity and shifting of etodolac peak observed due to dilution effect of excipient. Presence of both peaks indicates there is no interaction between etodolac and guar gum. DSC thermogram of etodolac and guar gum solvent evaporation formulation, F- 15 (Fig.2) shows shifting of etodolac peak from 154.06°C to 153.10 °C. Also it shows decrease in peak height from -12.14 mJ to -10.14 mJ and decrease in peak intensity due interaction between etodolac and polymer indicates formation of amorphous solid dispersion of drug with polymer by solvent evaporation method. DSC thermogram of etodolac and guar gum by kneading method, F-18 (fig. 2) shows shifting of etodolac peak from 154.06°C to 153.27°C. It also shows decrease in peak height from -12.14 mJ to -9.16 mJ and decrease in peak intensity due interaction between etodolac and polymer indicates formation of amorphous solid dispersion of drug with polymer by kneading method.

Powder X-ray Diffraction Analysis (XRD)

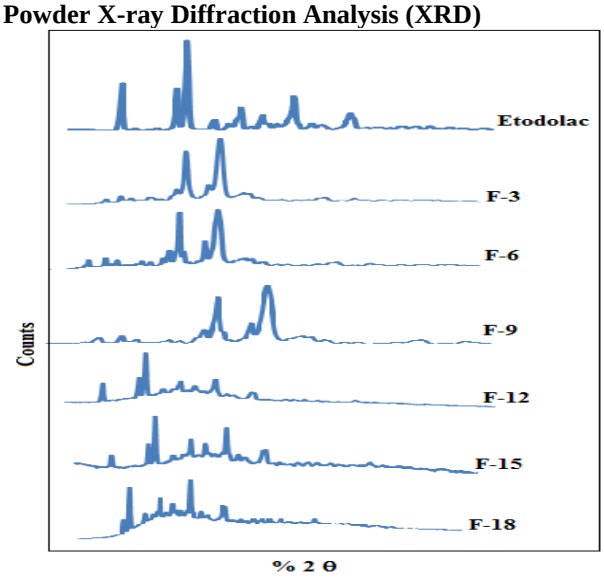

Fig. 3: XRD Spectra of Etodolac and its and its solid dispersion formulations.

Crystallanity of etodolac was determined by XRD. In XRD degree of crystallinity of any material can be determined from peak intensity in spectra, more the peak intensity more the crystalline. Figure 3 shows XRD spectra of etodolac and its solid dispersion formulations, pure etodolac shows major characteristic high intensity peaks at diffraction angle of % 2 θ at 9.3754, 13.7508, 14.5463, 18.8223, 22.9988, 27.4737 with peak intensity 50736, 46320, 96362, 26295, 38246, 19801 respectively indicating crystalline nature of etodolac. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary system

with those of reference. The relationship used for calculation of crystallinity is relative degree of crystallinity (RDC) was calculated from the ratio of highest peak intensity of formulation to highest peak intensity of drug. All formulations shows decrease in relative degree of crystallinity indicates decrease in crystalline nature of drug.

***In-vitro* drug release study of solid dispersion formulations**

Table 5: *In-vitro* drug release of Etodolac, Etodolac + PEG-6000 solid dispersion formulations (Physical Mixture: F: 1, F: 2, F: 3),(Solvent evaporation:F-4,F-5,F-6), (Kneading Method; F-7, F-8, F-9)

Time (Min.)	Etodolac	F-1 (1:1)	F-2 (1:2)	F-3 (1:3)	F-4 (1:1)	F-5 (1:2)	F-6 (1:3)	F-7 (1:1)	F-8 (1:2)	F-9 (1:3)
5	7.372±0.543	4.322±0.303	7.036±0.929	7.686 ±0.471	7.260 ±0.412	5.927±0.594	8.623±0.763	2.920±0.706	7.767±0.958	14.940±0.983
10	10.080±0.605	9.126±0.585	13.857±1.16	16.192±1.28	11.447±0.767	20.220±0.899	19.399±0.757	5.022±0.441	16.197±0.963	21.282±0.687
15	12.490±0.484	13.269±1.095	18.921±0.582	30.760±1.08	20.006±0.689	29.373±0.610	38.511±0.665	15.989±0.781	32.368±0.706	37.053±0.411
20	14.612±0.841	18.164±0.657	33.752±0.876	44.603±1.145	30.068±0.751	48.290±0.827	60.670±0.856	33.445±0.831	44.417±0.603	61.025±0.516
25	17.046±0.613	25.966±1.03	45.930±0.939	53.351±1.235	49.481±0.795	55.455±0.746	61.127±0.975	51.082±0.820	61.725±0.890	74.708±0.790
30	18.091±0.789	33.208±1.405	54.901±0.316	66.009±0.951	58.072±0.597	63.670±0.814	73.530±0.803	65.533±0.688	70.074±0.810	77.162±0.590
35	20.694±1.075	44.382±0.807	62.538±0.630	71.193±0.973	63.242±0.496	75.299±0.875	81.543±0.863	75.429±0.954	78.875±0.811	82.425±0.824
40	21.708±0.842	53.451±0.540	70.464±0.596	74.313±0.702	68.549±0.703	77.324±0.530	84.185±0.924	79.288±0.703	81.804±0.940	87.068±0.781
45	22.827±0.848	69.217±0.428	72.264±0.527	75.096±0.486	75.186±0.483	80.260±0.648	86.792±0.897	81.410±0.888	83.489±0.651	89.704±0.761

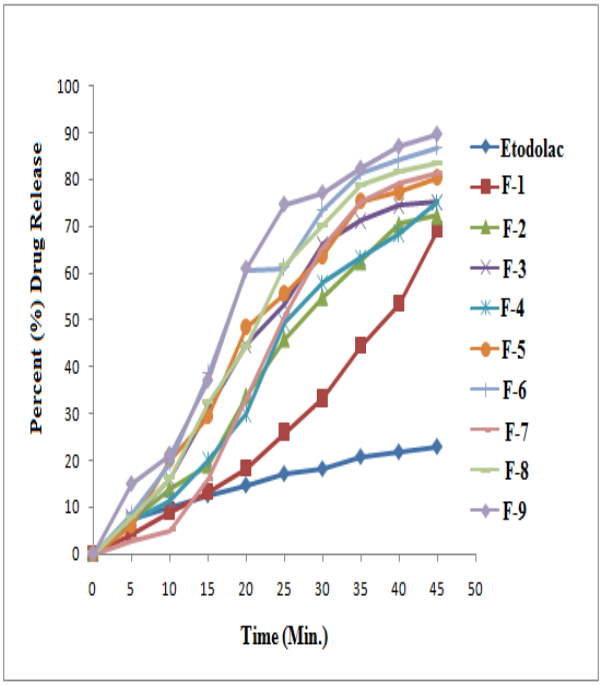

Fig. 4*: In-vitro* drug release of Etodolac, Etodolac + PEG-6000 solid dispersion formulations (Physical Mixture :F: 1, F: 2, F: 3),(Solvent evaporation:F-4,F-5,F-6), (Kneading Method; F-7, F-8, F-9).

Dissolution profile of etodolac is shown in table 5 and figure 4. Dissolution rate of etodolac at 5, 15, 30 and 45 minutes are 7.372 ± 0.543, 12.490 ± 0.484, 18.091 ± 0.789, 22.827 ± 0.848 respectively. The slowest dissolution rate of etodolac is due to its hydrophobicity that leads to floating of powder on the surface of dissolution medium and prevents its surface contacting the medium. It clears that drug having poor dissolution and needs to further dissolution enhancement. Physical mixture of etodolac and PEG-6000 (table 5 and fig. 4) shows increase in drug release as compared to pure etodolac. Physical mixture of etodolac and PEG-6000 in different ratio as 1:1, 1:2, 1:3 shows drug release of 69.217±0.428, 72.264 ± 0.527 and 75.096±0.486 percent respectively at 45 minutes, where as pure drug shows only 22.827±0.848 percent at 45 minutes. As the concentration of polymer in physical mixture increases it leads to increase in dissolution rate of drug and could be attributed due to the improved wettability of etodolac particles or the formation of soluble complex with PEG-6000, a hydrophilic polymer, that decreases interfacial tension between hydrophobic drug and dissolution medium, leads to increase in wetting and surface available for dissolution. Also it was found that pure drug float on the surface dissolution medium whereas drug carrier mixtures sink immediately in dissolution medium. Solid dispersion of etodolac and PEG-6000 prepared by solvent evaporation method in different ratio 1:1, 1:2, 1:3 shows drug release of 75.186±0.483, 80.260±0.648, and 86.792 ± 0.897 % at 45 minutes (table 5 and fig. 4). It shows better release as compared to physical mixture due to the formation of molecular dispersions with high surface free energy resulting in the pull of insoluble but discrete drug molecules into bulk of solvent as dissolved entity and additionally due to absence of aggregation and/or reagglomeration phenomenon during dissolution. Solid dispersion of etodolac and PGE-6000 prepared by kneading method shows faster dissolution as compared to physical mixture and solvent evaporation. Kneading method solid dispersion of different ratio as 1:1, 1:2, 1:3 shows 81.410 ± 0.888, 83.890 ± 0.651, 89.704 ± 0.761 percent respectively at 45 minutes (table 5 and fig. 4), this might be due to kneading results in uniform distribution of drug in the polymer and forms the molecular and colloidal dispersion of drug in hydrophilic a carrier. When such dispersion comes in contact with dissolution medium leads to dissolution of hydrophilic carrier and cause precipitation of drug into fine particles, leads to increase in surface available for dissolution. Other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction could be attributed to better dissolution. Physical mixture and solid dispersions of etodolac with PEG-6000 shows improvement in dissolution profile of drug as compared to pure drug. A PEG-6000 lead to improvement is dissolution of etodolac. Since PEG-6000 dissolve more of the drug leading to a greater percentage drug in the molecularly dispersed form and that the higher viscosity of the PEG -6000 hindered precipitation of the drug following dissolution of carrier. Also in this molecular weight (6000) the water solubility of PEG-6000 is still very high but hygroscopy is not problem. If low molecular weight PEG used leads to formation of sticky product.

Table 6: *In-vitro* drug release of Etodolac + Guar gum solid dispersion formulations (Physical Mixture;F-10,F-11,F-12), (Solvent Evaporation;F-13,F-14,F-15), (Kneading Method;F-16,F-17,F-18).

Time (Min.)	Etodolac	F-10 (1:1)	F-11 (1:2)	F-12 (1:3)	F-13 (1:1)	F-14 (1:2)	F-15 (1:3)	F-16 (1:1)	F-17 (1:2)	F-18 (1:3)
5	7.372±0.543	3.734±0.542	5.728±0.848	6.490±0.689	4.650±0.446	6.591±0.627	7.546±0.599	4.198±0.407	4.818±0.531	9.170±0.973
10	10.080±0.605	5.286±0.790	6.700±0.945	8.868±0.929	9.863±0.610	11.874±0.958	12.962±0.887	7.026±0.541	7.943±0.951	19.919±0.495
15	12.490±0.484	15.402±0.690	15.132±0.412	15.801±0.855	10.196±0.476	19.715±0.558	25.715±0.780	16.192±0.870	19.822±0.359	32.787±0.872
20	14.612±0.841	20.175±0.630	24.557±0.861	25.812±0.864	30.334±0.656	31.810±0.815	32.975±0.724	31.311±0.474	32.394±0.713	49.489±0.556
25	17.046±0.613	30.454±0.647	35.430±0.868	35.696±0.452	44.111±990	46.739±0.717	56.797±0.990	38.582±0.632	41.577±0.492	59.949±0.991
30	18.091±0.789	40.158±0.864	45.253±0.548	48.275±0.559	55.089±0.751	58.248±0.953	70.007±0.716	49.176±0.566	57.660±0.544	75.776±0.371
35	20.694±1.075	48.137±0.691	53.812±0.865	57.320±0.856	71.076±0.447	74.082±0.538	87.079±0.622	59.261±0.475	67.288±0.870	82.703±0.469
40	21.708±0.842	57.847±0.919	61.257±0.719	67.339±0.516	79.224±0.537	82.342±0.891	89.097±0.488	69.567±0.683	80.871±0.746	86.752±0.788
45	22.827±0.848	60.081±0.640	64.425±0.741	72.761±0.905	85.021±0.968	87.115±0.405	92.198±0.757	80.189±0.605	82.341±0.612	88.193±0.751

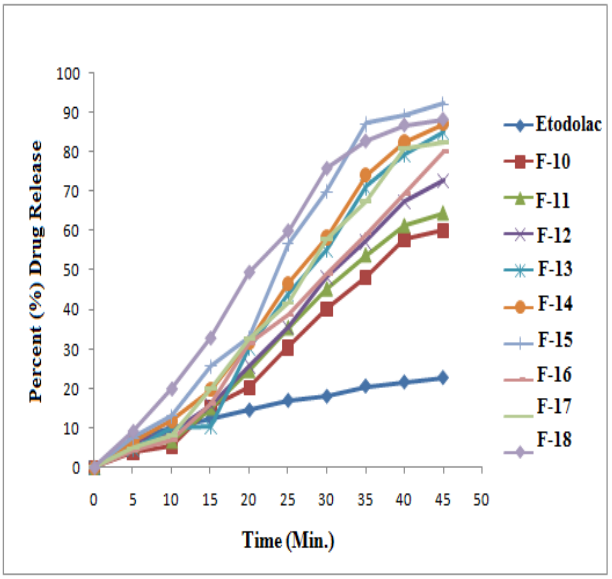

Fig. 5: *In-vitro* drug release of Etodolac + Guar gum solid dispersion formulations (Physical Mixture;F-10,F-11,F-12), (Solvent Evaporation;F-13,F-14,F-15), (Kneading Method;F-16,F-17,F-18).

Physical mixture of etodolac and guar gum (table 6 and fig. 5) shows increase in drug release as compared to pure etodolac. Physical mixture of etodolac and guar gum in different ratio as 1:1, 1:2, 1:3 shows drug release of 60.081±0.640, 64.425±0.741 and 72.761±0.905 percent respectively at 45 minutes, where as pure drug shows only 22.827 ± 0.848 percent at 45 minutes. It might be due to hydrophilic nature of polymer which helps to increase in wettability of drug and hence drug release. Solid dispersion of etodolac and guar gum prepared by kneading method (table 6 and fig. 5) in different ratio as 1:1, 1:2, 1:3 shows drug release of 80.189±0.605, 82.341±0.612 and 88.193±0.751 percent respectively at 45 minutes, this might be due to kneading results in uniform distribution of drug in the polymer and forms the molecular and colloidal dispersion of drug in hydrophilic a carrier. Solid dispersion of etodolac and guar gum prepared by solvent evaporation method in different ratio 1:1, 1:2, 1:3 shows drug release of 85.021±0.968, 87.115±0.405 and 92.198±0.757 percent at 45 minutes (table 6 and fig. 5). It shows better release as compared to physical mixture and kneading method due to the hydrophilic nature of the carrier, hydrodynamic microenvironment was changes and drug get dispersed in to polymer which prevents aggregation and/or reagglomeration phenomenon during dissolution. Guar gum is used in solid dosage form as binder and disintegrant. However due to swelling ability of the carrier profound influence on the improvement in dissolution of poorly water soluble drugs. Hydrophilic nature of the guar gum leads to change in hydrodynamic microenvironment around the particles. At time of dissolution, drug and carrier from mixtures comes in contact with dissolution fluid, passing of dissolution medium into drug carrier particles takes place, which initiates the formation of stagnant gel layer of carrier around the particles. The drug particles that are separate entities but disperse rapidly throughout dissolution medium and expose a greater surface area, resulting in rapid drug release.

CONCLUSION

From the study it was found that kneading and solvent evaporation methods for preparation of solid dispersion lead to improvement in dissolution profile of etodolac. Solid dispersion formulation containing guar gum prepared by solvent evaporation method shows better release as compare to others due to the hydrophilic nature of the carrier, hydrodynamic microenvironment was changes and drug get dispersed in to polymer which prevents aggregation and/or reagglomeration phenomenon during dissolution.

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