

Development, Characterization and *In Vitro* Evaluation of Flurbiprofen Solid Dispersions using Polyethylene Glycols as Carrier

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ABSTRACT

The purpose of the present investigation was to increase the solubility and dissolution rate of flurbiprofen (FLB) by the preparation of its solid dispersion with polyethylene glycol 4000 and 6000 as carriers using solvent evaporation method (SM) and kneading method (KM). Drug polymer interactions were investigated using Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), x-ray diffraction (XRD). The prepared solid dispersions were characterized by IR spectroscopy, which suggests no interaction of drug with carriers. XRD and DSC study indicates reduction in drug crystallinity. Drug solubility was more and also the dissolution was rapid for Flurbiprofen solid dispersions compared to pure drug.

INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate-determining step for the onset of therapeutic activity. Therefore, poorly aqueous soluble drugs are usually characterized by a low bioavailability due to less absorption, which is a major concern of pharmaceutical industries worldwide (Hasnain and Nayak, 2012). Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general include micronization, the use of surfactant, and the formation of solid dispersions (Sammour *et al.*, 2006). Solid dispersion is one of the techniques that can potentially enhance the dissolution rate of hydrophobic drugs with pharmacologically inert, polymeric materials (Shin and Kim, 2003). The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability (Craig, 2002). The improvement of solubility and dissolution rate of drugs from solid dispersions is based on mainly three different mechanisms includes; increased wettability of drug due to direct contact with hydrophilic carrier, the reduction in particle size results increased surface area, and the conversion of crystalline state to more soluble amorphous state (De Waard *et al.*, 2008).

Propionic acid derivatives, like Flurbiprofen (FLB), are considered to be the first line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. They are safe and effective analgesic and by inhibiting the prostaglandin synthesis they can interrupt the normal paracrine signaling necessary for the elaboration of inflammatory response (Brooks and Day, 1991; Qiu and Bae, 2006). Flurbiprofen has been found to be one of the most potent members of a series of phenylalkanoic acids in various animal species in anti-inflammatory, analgesic and antipyretic tests (Van Miert and Van Duin, 1977). It is highly effective and safe in the treatment of rheumatoid arthritis. Flurbiprofen also causes a dose dependent inhibition of collagen induced platelet aggregation in platelet rich plasma from human, rats and rabbit's *in-vitro* (Nishizawa *et al.*, 1973). Area under the plasma drug concentration versus time curve increases with increasing dose administration (Kaiser *et al.*, 1986). It has a short elimination half- life of 3.9 hr. and is slightly soluble in water (Verma and Murthy, 1997). Since the rate of Flurbiprofen absorption is controlled by the release of drug from its dosage form into the gastrointestinal tract. The major drawback in the therapeutic use and efficacy of Flurbiprofen as oral dosage form is its very low aqueous solubility because of its hydrophobic nature. Poor aqueous solubility and slow dissolution rate of the drug leads to low oral bioavailability consequently irreproducible. Therefore a better oral formulation was developed by increasing the water solubility of drug.

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The literature survey reveals that the solubility of poorly water soluble drugs can be enhanced by solid dispersion using polyethylene glycols (Perng *et al.*, 1998; Khan, and Zhu., 1998; Dubois, and Ford, 1985; Betageri, and Makarla, 1995). Hence in the present study, solubility of Flurbiprofen (FLB) will be improved by solid dispersion methods' using different water soluble carries.

MATERIAL AND METHODS

Materials

Flurbiprofen (FLB) was received as a gift sample from Sun Pharma (Ahmednagar), PEG 6000 and PEG 4000 was purchased from CDH, New Delhi. Double distilled water is used throughout the study and other chemicals were of analytical or pharmaceutical grade.

Development of Solid Dispersions (SDs)

Physical Mixture

The physical mixtures (1:1) were prepared by weighing the calculated amounts of Flurbiprofen and carriers. Then mix them in a glass mortar by triturating. The resultant physical mixtures were passed through 60-mesh sieve and stored in desiccators until used for further studies.

Kneading Method (KM)

The calculated amounts of drug and polymer were weighed and mixed in the different ratios 1:1, 1:3, 1:5. The mixtures were kneaded with small volume of water for 30 min in a glass mortar to produce a homogeneous dispersion. The paste formed was dried in oven at 45 °C under vacuum until the solid dispersion was dry. The dispersions after drying were passed through 60 # sieve. The granules obtained were stored in desiccators until used for further studies (Table no 1 and 2).

Table 1: Composition of Various Solid Dispersions of FLB with PEG 4000.

Formulation Code	Carrier	Drug : Carrier Ratio	Method
PM ₁₁₄	PEG 4000	1 : 1	Physical Mixture
KM ₁₅₄	PEG 4000	1 : 5	Kneading Method
SM ₁₅₄	PEG 4000	1 : 5	Solvent Evaporation Method

Table 2: Composition of Various Solid Dispersions of FLB with PEG 6000.

Formulation Code	Carrier	Drug : Carrier Ratio	Method
PM ₁₁₆	PEG 6000	1 : 1	Physical Mixture
KM ₁₅₆	PEG 6000	1 : 5	Kneading Method
SM ₁₅₆	PEG 6000	1 : 5	Solvent Evaporation Method

Solvent Evaporation Method (SM)

The required amount of drug and polymer was dissolved in acetone in 1:1 proportions and transferred to a petri dish; the solvent was allowed to evaporate at room temperature, until a major portion of the solvent used was volatilized. Further for

complete removal of solvent it is dried in oven at 45 °C until dryness. The dried mass was pulverized, passed through a 60 # sieve and stored in desiccators at room temperature until further evaluation (Table 1 and 2).

Solubility Study

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (Higuchi and Connors, 1965). In brief, an excess amount (equivalent to 40 mg of drug) of samples (pure Flurbiprofen, physical mixtures and Flurbiprofen solid dispersions) were added to 25 ml distilled water in a stopper conical flask and the mixtures were rotated for 24 hrs in a rotary flask shaker (37±0.5 °C).

The mixtures were filtered through a 0.45µm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 247 nm using a UV-VIS spectrophotometer (Varian USA. Model: Carry 50).

EVALUATION OF FLUBIPOFEN SOLID DISPERSION SYSTEMS

Drug-Content

SDs was weighed accurately (equivalent to 10 mg of flurbiprofen) and dissolved in 10 ml of methanol. The drug content was analyzed at 247 nm spectrophotometrically after suitable dilutions. (Perkin Elmer, USA). Each sample was analyzed in triplicate.

In Vitro Dissolution

The dissolution study was carried out using USP XXII apparatus type II (Electrolab TDT-06T). The dissolution medium was 900 ml of distilled water kept at 37 ± 0.5 °C, with rotational speed of 50 rpm. 5 ml of test fluid were withdrawn at specified time intervals and filtered through a membrane filter (0.45µ). The same volume of fresh medium was added to the dissolution medium. The samples were analyzed spectrophotometrically at 247 nm. Each preparation was tested in triplicate and the mean values were calculated.

Statistical Comparisons

The dissolution profiles were compared using two parameters DP30 (percentage of Flurbiprofen dissolved at 30 min) and DP60 (percentage of Flurbiprofen dissolved at 60 min). The comparisons were made between the methods and carriers by analysis of variance (ANOVA). The dissolution release kinetics and the results of best-fit model among the preparations were also compared.

FTIR Study

The Infrared spectra (IR) of Flurbiprofen and some selected preparations were obtained using FTIR (Perkin Elmer 1600 Series). The IR spectroscopy was carried out by KBr pellet method and scanned at wavenumbers 4000 cm⁻¹ to 400 cm⁻¹.

Differential Scanning Calorimetry (DSC)

The DSC thermograms were recorded using a differential scanning calorimeter (DSC 8000 Perkin Elmer, USA). Approximately 3-5 mg of each samples was accurately heated from 20 to 150 °C at a scanning rate of 10⁰ / min., purge gas nitrogen 20 ml/min.

X-Ray Diffractometry (XRD)

Powder X-ray diffraction patterns were recorded using X-ray diffractometer (Phillips X-Ray Diffractometer PW 1710) under the following conditions. Ni - filter Cu-K α radiation, 40 KV voltages: 30 mA current, scan speed 2⁰ min in turns of 2 θ .

RESULT AND DISCUSSION

Drug Content

The drug content in all the tested combinations was found to be in the range of 95.91 \pm 0.70 to 99.89 \pm 0.04 % for Physical mixture and solid dispersion respectively. Table no 3 indicates the applications of the present method for the preparation of SDs with high content uniformity.

Table 3: % Drug Content, Solubility Data of Physical Mixture & Solid Dispersions.

Formulations Code	PEG 4000		PEG 6000	
	Percentage Drug Content	Solubility in Water(mg/ml)	Percentage Drug Content	Solubility in Water(mg/ml)
PM 1:1	98.04 \pm 0.12	0.117 \pm 0.09	96.80 \pm 0.35	0.139 \pm 0.01
KM 1:5	98.12 \pm 0.62	0.279 \pm 0.12	99.06 \pm 0.42	0.285 \pm 0.12
SM 1:5	99.78 \pm 0.42	0.296 \pm 0.07	98.62 \pm 0.61	0.349 \pm 0.04

Saturation Solubility of FLB Solid Dispersions

Among all the PMs and SDs the carrier PEG 6000 containing formulations showed enhanced solubility results (Fig.1). The 1:5 ratios SD showed high solubility may be due to higher proportion of hydrophilic carriers present in SDs (Table no 3). On applying t-test there is no significant difference found in physical mixtures and drug solubility. But there is significant difference present in solubility of drug and SDs prepared both by kneading method and solvent evaporation method (1:5). These results are in accordance with the established formation of soluble complex between water-soluble polymeric carriers and poorly soluble drug (Mura *et al.*, 1996, Zerrouk *et al.*, 2002).

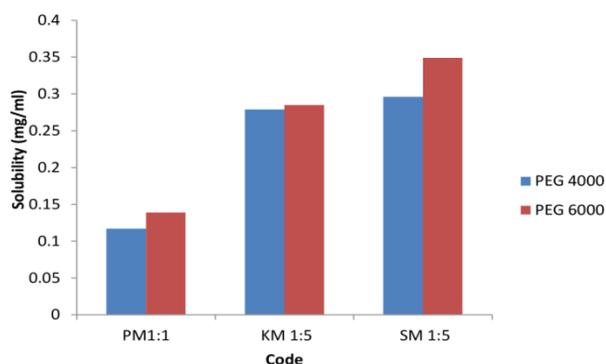


Fig. 1: Solubility of FLB Solid dispersions in Distilled Water 25 \pm 0.5 °C.

FTIR Spectroscopy Studies

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The IR spectra of SDs were compared with the standard spectrum of Flurbiprofen and PEG alone. The FTIR spectrum of pure FLB demonstrated peaks at 1701 cm⁻¹ (C=O stretching), 1217 cm⁻¹ (C-F stretching), 2980.03 cm⁻¹ (C-H stretching), 3031.89 cm⁻¹ (C-H stretching) and 3647.14 cm⁻¹ (O-H stretching). The FTIR spectrum of PM shows the characteristic peaks of drugs but with small decrease in intensity of peaks. FTIR spectra of solid dispersions KM_{1:5}, SM_{1:5}, KM_{1:5} and SM_{1:5} (Fig 2 and 3) show no substantial shifting of the position of the functional groups. The peaks are only broadened, indicating no major interaction between Flurbiprofen and hydrophilic carriers (Ahuja *et al.*, 2007).

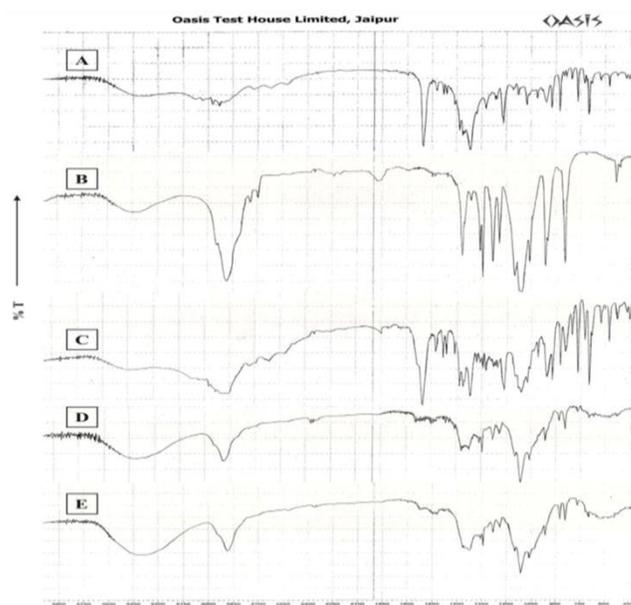


Fig. 2: FTIR Spectra of: (A) FLB, (B) PEG 4000, (C) PM, (D) KM 1:5, (E) SM 1:5.

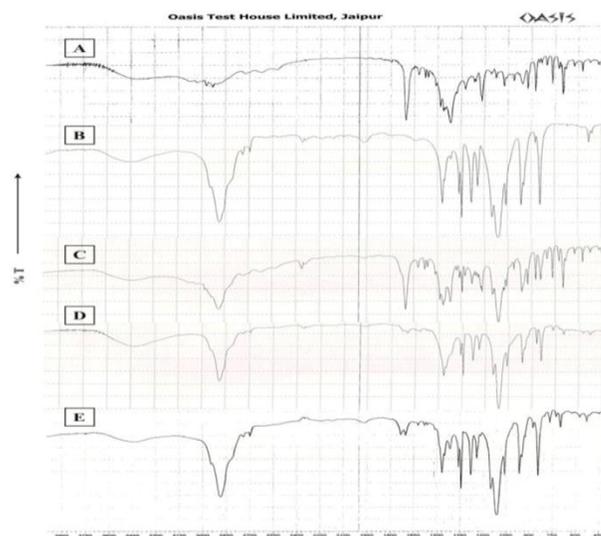


Fig. 3: FTIR Spectra of: (A) FLB, (B) PEG 6000, (C) PM, (D) KM 1:5, (E) SM 1:5.

Differential Scanning Calorimetry (DSC)

The thermograms of the pure drug (FLB), polymer, SDs and PMs are illustrated in fig.4 and 5. DSC thermogram of Flurbiprofen (Figure 4a) show an endothermic peak at 116.80 °C corresponding to the melting point of Flurbiprofen (ΔH 112.17 J/g), indicating it's crystalline nature (Soliman *et al.*, 2005). The thermal behavior of PEG 4000 and PEG 6000 exhibited a sharp but slightly broad endothermic peak at 58.58 °C, 61.94 °C respectively.

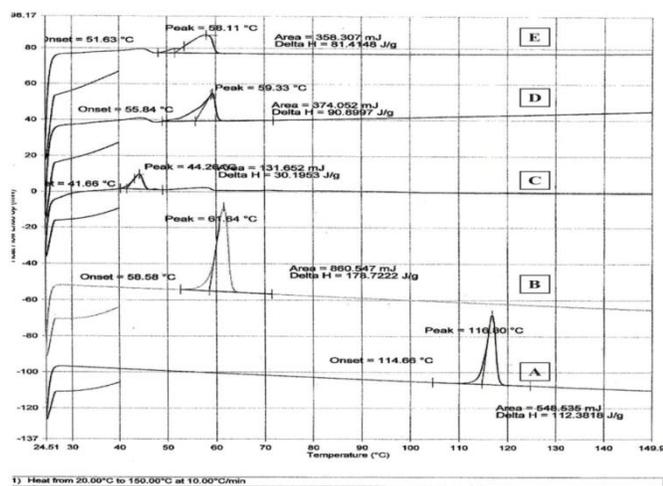


Fig. 4: DSC thermograms of: (A) FLB (B) PEG 4000 (C) PM (D) KM 1:5 (E) SM 1:5.

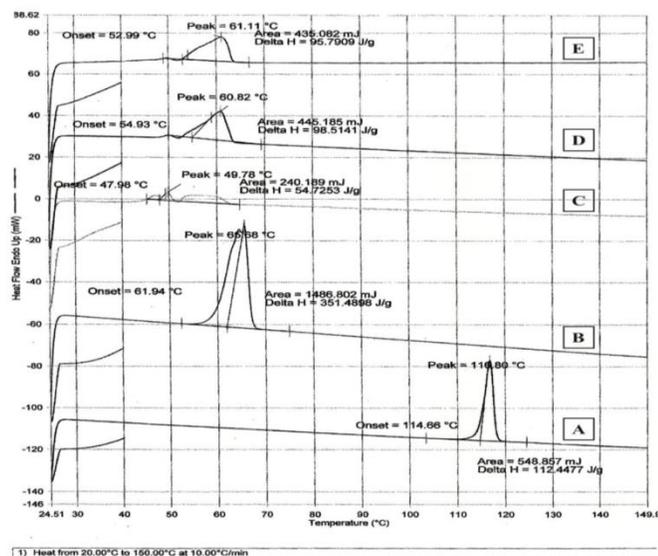


Fig. 5: DSC thermograms of (A) FLB (B) PEG 6000 (C) PM (D) KM 1:5 (E) SM 1:5.

DSC curves of physical mixtures of carriers demonstrated a broadening or almost complete disappearance of FLB peaks together with a shift to a lower temperature than pure FLB and enthalpy of fusion of FLB was decreased. The DSC curves of PEG 4000 and PEG 6000 sharp FLB peaks were lost in all the SDs. In KM_{154} and KM_{156} PEG 4000, PEG 6000 the onset was 59.33 °C, and 60.82 °C, respectively. In SM_{154} and SM_{156} PEG

4000, PEG 6000 the broad reduced endotherm was observed with onset was 58.11 °C and 61.11 °C respectively. Complete disappearance of the flurbiprofen melting peak observed in both PM and SD was attributable to complete miscibility of the drug in the melted carrier. The enthalpy of drug melting in solid dispersion was gradually decreased as compared to the drug. This phenomenon could be attributed to the amorphous form of the drug in solid dispersion (Damian *et al.*, 2000, Lin CW and Cham, 1996).

X-Ray Diffractometry (XRD)

The powder XRD patterns of various Flurbiprofen, PEG 4000, PEG 6000 and its solid dispersions were compared in fig. 6 and 7. The diffraction pattern of pure drug showed, it's highly crystalline nature as indicated by numerous distinctive peaks at 2θ were 6.97, 10.60, 15.65, 16.17, 20.41, 21.22, 23.49. PEG 4000 and 6000 exhibited two high intensity peaks at 19.07, 23.26.

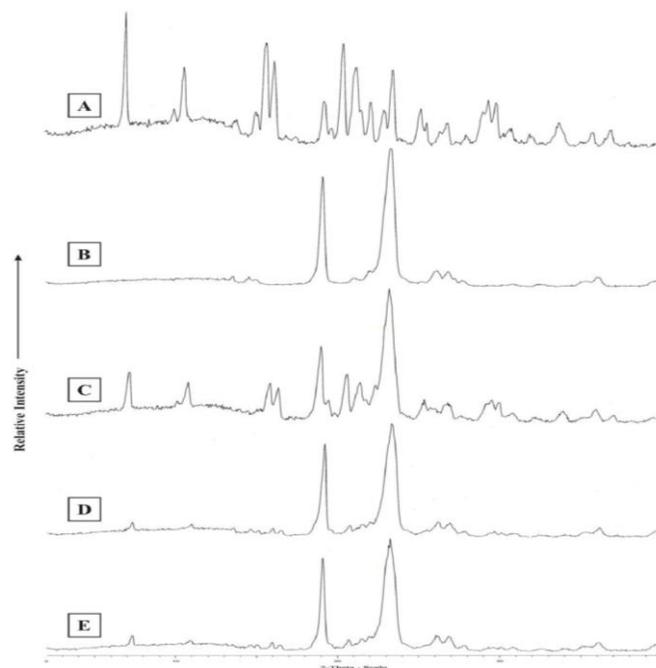


Fig. 6 : X-ray Diffraction Patterns of Pure FLB (A), PEG 4000 (B), Physical Mixture (PM) (C) and SD using PEG 4000 Combination Carrier - KM (D) SM (E)

Diffraction patterns of SDs display the characteristic peaks of both FLB and polymers but the intensity and number of drug peaks are reduced suggesting there is a decrease in drug crystallinity (Parmar *et al.*, 2011). Thus less intense peak in SD as compared to pure drug indicates amorphous nature results in higher solubility and dissolution rate as compared to pure drug (Reza *et al.*, 2014). Thus with increasing polymer concentration, the crystallinity of the drug reduces further conversion to completely amorphous state, this explains that greater miscibility of FLB in the polymer at (1:5) ratio and decreased crystalline peaks which are obtained.

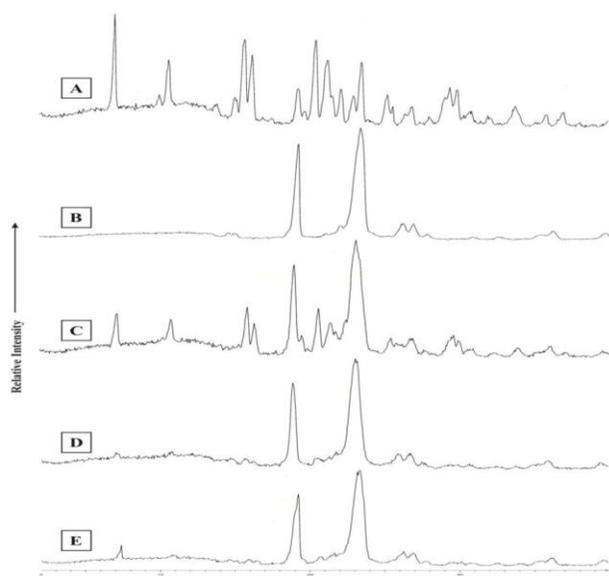


Fig. 7: X-Ray Diffraction Patterns of Pure FLB (A), PEG 6000 (B), Physical Mixture (PM) C, and SD using PEG 6000 Combination Carrier- KM (D), SM (E).

Dissolution Study

The solid dispersions of Flurbiprofen with PEG 4000 and 6000 showed improved dissolution when compared with physical mixtures and pure drug (Fig 8 and 9). The trend observed for percent dissolution of Flurbiprofen from solid dispersions containing PEG 6000 and 4000 prepared by physical mixing, kneading method and solvent evaporation methods, was an increase in dissolution rate with an increase in PEG percentage.

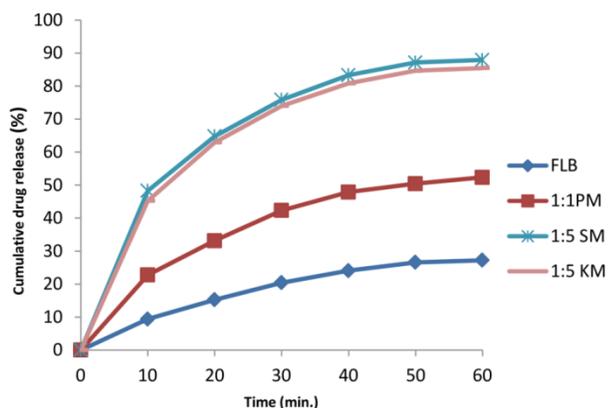


Fig. 8: Dissolution Profile of FLB from Physical Mixtures and SDs with PEG 4000 (Distilled water)

The dissolution of pure drug was only about 27.23 % in distilled water at the end of 60 min. The release of drug from formulation of PEG 4000 containing SD (SM 1:5) were 80.54 % and PEG 6000 containing SD (SM 1:5) reached a maximum of about 85.45 % at the end of 60 min. in distilled water. Results in table no 4 suggest that all solid dispersions increased dissolution efficiency as compared to that of FLB in powder form. On applying ANOVA there is significant difference found in % DE and % DR of all the formulations. As the concentration of polymer

increased the DE increased significantly ($P < 0.05$) due to enhanced wetting of FLB particles in the presence of hydrophilic groups of polymers (1:5). Tuckey's test revealed that all pairs differ significantly and highest mean was found for 1:5 SM. SDs prepared by solvent evaporation method showed a higher dissolution of FLB than those prepared by physical mixture and kneading, while SDs prepared by kneading technique showed a rather variable dissolution. This may be attributed to the fact that SDs prepared by solvent evaporation method result in a more uniform dispersion of drug in the hydrophilic carrier matrix as compared to those prepared by the kneading method (Dhingra *et al.*, 2010).

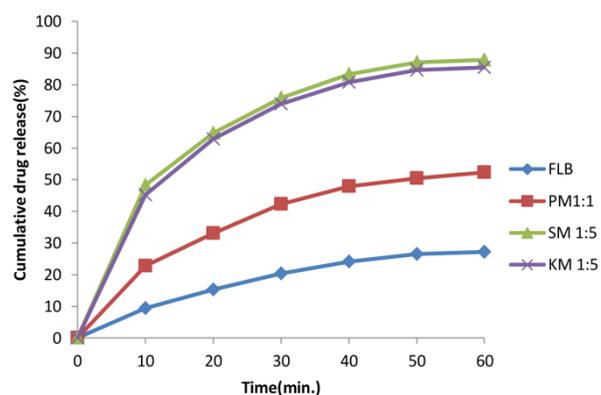


Fig. 9: Dissolution Profile of FLB from Physical Mixtures and SDs with PEG 6000 (Distilled water).

Table 4: % Dissolution Efficiency and % Drug Released of SDs in Distilled Water.

Formulation Code	% Drug Dissolved (Q_{60})	Dissolution Efficiency (%DE ₃₀)	Dissolution Efficiency (%DE ₆₀)
FLB	27.23±0.73	11.63±0.35	18.23±0.25
PM ₁₁₄	51.73±0.33	25.59±0.56	36.37±0.25
PM ₁₁₆	52.34±0.64	25.79±0.48	37.31±0.27
SM ₁₅₄	83.60±0.48	46.05±0.23	63.08±0.27
SM ₁₅₆	87.92±0.15	50.32±0.97	67.21±0.33
KM ₁₅₄	80.54±0.22	47.89±0.26	62.85±0.17
KM ₁₅₆	85.85±0.11	48.39±0.17	65.06±0.22

Physical mixture of PEG also improves the dissolution profile of Flurbiprofen due to its hydrophilic nature but not such an extent as by kneading method and solvent evaporation method. As the proportion of PEG increased, Flurbiprofen dissolution rates increased up to an extent after that decreased; may be due to the localization of higher amounts of carrier itself. The improvement of dissolution may be due to reducing particle size of Flurbiprofen and hence improving drug wettability and significantly improved dissolution.

Table 5 lists the regression parameters obtained after fitting various release kinetics models to in vitro dissolution data. The goodness of fit for various models investigated for binary systems ranks in the order of Korsmeyer-Peppas > Higuchi > first-order > zero-order. Results were based on the r^2 and residual sum of squares (SSR) values. The Korsmeyer-Peppas model describes drug release kinetics in the most fitting manner.

Table 5: Kinetics of Drug Release from SDs.

Formulation Code	Zero-order		First-order		Higuchi model		Korsmeyer-Peppas model		“n” value
	R ²	SSR	R ²	SSR	R ²	SSR	R ²	SSR	
FLB	0.9257	87	0.9475	55	0.9931	8	0.9918	8	0.6148
PM ₁₁₄	0.8505	549	0.9259	256	0.9952	19	0.9964	7	.04401
PM ₁₁₆	0.8578	564	0.9275	244	0.9938	27	0.9897	22	0.4790
SM ₁₅₄	0.7756	2186	0.7526	329	0.9815	201	0.9849	58	0.3837
SM ₁₅₆	0.7380	2716	0.9594	348	0.9451	293	0.9870	43	0.3463
KM ₁₅₄	0.7882	1943	0.9464	341	0.9833	170	0.9843	62	0.3974
KM ₁₅₆	0.7511	2479	0.9519	363	0.9816	256	0.9825	56	0.3644

R²- Regression Coefficient SSR- Sum of Residuals Squares, n- Diffusion Coefficient

The value of diffusional exponent “n” was obtained from the slopes of the fitted Korsmeyer-Peppas model (Aggarwal *et al.*, 2010). The solid dispersion tablets tended to exhibit Fickian diffusional characteristics, as the corresponding values of n were lower than the standard value from declaring Fickian release behavior, the results point out the prevalence of diffusional mechanistic phenomena.

CONCLUSION

Solid dispersion provides a simple and effective method of increasing solubility and oral bioavailability of poorly water-soluble drugs. The present study demonstrated the suitability of PEG 4000 and PEG 6000 as a carrier for the preparation of SDs of FLB. FTIR, XRD and DSC studies, offered an explanation of better dissolution rate from its SDs. The solubilization effect of PEG 6000 results in the reduction of aggregation of the drug particles, reduction of crystallinity, increased wettability and dispersibility and alteration of the surface properties of the drug particles. The Korsmeyer-Peppas model properly describes the dissolution data, possibly suggesting Fickian diffusion as the mechanism of drug release from SDs. Flurbiprofen-PEG 6000 combination provides a promising approach to enhance the solubility and dissolution rate of the drug.

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