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# DISSOLUTION RATE ENHANCEMENT, IN VITRO EVALUATION AND INVESTIGATION OF DRUG RELEASE KINETICS OF FLURBIPROFEN SOLID DISPERSION

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ABSTRACT
In the present research work dissolution rate enhancement efficiency, solid dispersion formation ability of hydrophilic polymers and investigation of drug release kinetics of Flurbiprofen was studied. The hybrid method of fusion-solvent and solvent evaporation was employed to prepare solid dispersion. PEG 6000 and PVP K-30 was used as hydrophilic polymers to improve the solubility, dissolution of Flurbiprofen, and evaluated for flow properties. Physicochemical characterizations of solid dispersions were carried out by FT-IR, XRD and DSC. FTIR study did not show any chemical modification or complexation in solid dispersion. This indicates that there is a physical interaction between the drug and carriers, and increase in the solubility is due to surface modification. Diffuse XRD pattern shows that the drug remains in the amorphous form in solid dispersion. The solubility and dissolution study shows marked increase in solid dispersion than the physical mixtures. The reason for increase in solubility and dissolution rate is increased surface area due to reduction in crystallinity and increased wetting of drug molecules. It may be concluded from the DSC, XRD and FT-IR study that the drug is dispersed homogenously in carrier in amorphous form and does not interact chemically with the carrier. Hydrophilic polymers were found to increase the solubility of Flurbiprofen.

Keywords: *Flurbiprofen; PEG 6000; PVP K-30; Saturation solubility; and Solid dispersion.*

## INTRODUCTION

Improving the dissolution characteristics of poorly water soluble drugs is important to achieve better bioavailability and reduced side effects. The poor water solubility behaviour of the drug remains a major problem limiting its dissolution in the biological fluid and thus affects its bioavailability after its administration[1]. In the case of improvement of solubility and dissolution a poorly water-soluble drug that dissolves into the gastrointestinal tract; it is not possible to modify neither the drug molecules nor the dissolution environment (solvent and system conditions)[2-4]. In order to improve the oral bioavailability of the poor water soluble drugs (BCS class II), solid dispersion is one of the best methods for the enhancement of solubility and dissolution profile of the poor water soluble drugs because of its advantages, reliability and simplicity [5-9]. In solid dispersion technique drug can be dispersed molecularly, in amorphous particles or in crystalline particles should preferably be designated according to their molecular arrangement. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class and belongs to BCS Class II category. It is a white or almost white, crystalline powder practically insoluble in water, freely soluble in alcohol and in methylene chloride[10].

The objective of this work was to study dissolution enhancement efficiency, solid dispersion formation ability of hydrophilic polymers and investigation of drug release kinetics. The solid dispersions of Flurbiprofen prepared by using various hydrophilic polymers were further used for preparing tablets.

## MATERIALS AND METHODS

### Materials

Flurbiprofen was a generous gift from Torrent Pharma, Ahmadabad (India). Polyethylene glycol 6000 and Polyvinylpyrrolidone K-30 were obtained from Alkem Pharmaceutical, (India). Ethanol was purchased from Rankem, (India); all other reagents were of analytical grade.

### Methods

Preparation of Solid Dispersions and Physical Mixtures [11,12]

Solid Dispersion of Flurbiprofen and PVP K-30

Solid dispersions of Flurbiprofen and PVP K-30 by solvent evaporation method in four different weight ratios (1:1, 1:2, 1:3, 1:4) and denoted as SDPVP1/1, SDPVP1/2, SDPVP1/3 and SDPVP1/4, respectively (Table 1); weighed amount of PVP K-30 was dissolved in ethanol followed by the drug. The resulting solution

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was then homogenized thoroughly and then the solvent was evaporated under rotary evaporator. The dried mass obtained was kept in oven at 40ºC for 24 h for complete removal of solvent. Solid dispersion was then ground, sieved, and kept for further analysis.

Table 1: *Different Ratios of Solid Dispersions and Physical Mixtures*

| Drug | PEG 6000 | PVP K30 |
|---|---|---|
| 1 | 1 | - |
| 1 | 2 | - |
| 1 | 3 | - |
| 1 | 4 | - |
| 1 | - | 1 |
| 1 | - | 2 |
| 1 | - | 3 |
| 1 | - | 4 |

Solid Dispersion of Flurbiprofen and PEG 6000

Solid dispersions of Flurbiprofen and PEG 6000 prepared by melting method in four different weight ratios (1:1, 1:2, 1:3, and 1:4) and denoted as SDPEG1/1, SDPEG1/2, SDPEG1/3, and SDPEG1/4, respectively (Table 1). Flurbiprofen drug was added to molten PEG at 72 °C with constant stirring and resulting homogenous dispersion rapidly cooled in ice bath, and store in desiccators for 24h. The solid dispersion formed was ground in mortar and sieved to get uniform particle size dispersion.

Physical Mixtures

Physical mixtures (PM) of Flurbiprofen with PEG 6000 and PVP K30 containing four different weight ratios (1:1, 1:2, 1:3,1:4) were obtained by blending the components in a mortar. They are denoted as PMPEG1/2, PMPEG1/2, PMPEG1/3, PMPEG1/4, PMPVP1/1, PMPVP1/2, PMPVP1/3, and PMPVP1/4 respectively (Table 1). Polymers and drug were accurately weighed and passed through a #60 sieve, mixed well in the mortar, shifted through the same sieve and stored in desiccators.

Evaluation and Characterization of Solid Dispersion and Physical Mixtures

Saturation Solubility S tudies

The known excess of solid dispersion from each batch equivalent to approximately 20 mg of Flurbiprofen was added to 1 mL of distilled water in a screw cap bottles. Samples were sonicated for 30 min and kept in a water bath (37±0.5ºC) for 48 h. The samples were then filtered, suitably diluted, and analyzed by UV spectrophotometer at 247.5 nm[13]. The results of solubility studies are shown in Table 2.

Table 2: *Drug content and solubility of flurbiprofen in physical mixture and solid dispersion*

| Sample | Solubility of Flurbiprofen (mg/mL) | | | | Drug content (%) | Percent Yield |
|---|---|---|---|---|---|---|
| | pH 1.2 buffer | Water | pH 6.8 buffer | pH 7.2 buffer | | |
| Drug | 0.003 | 0.114 | 1.616 | 2.99 | 97.11 | - |
| PMPEG 1/1 | 0.0015 | 0.111 | 1.747 | 3.610 | 97.92 | 98.23 |
| PMPEG 1/2 | 0.008 | 0.113 | 1.817 | 3.699 | 99.18 | 99.43 |
| PMPEG 1/3 | 0.011 | 0.115 | 1.916 | 3.709 | 98.32 | 98.78 |
| PMPEG 1/4 | 0.0124 | 0.133 | 1.986 | 3.849 | 96.42 | 98.33 |
| SDPEG 1/1 | 0.0124 | 0.155 | 1.867 | 4.526 | 99.31 | 97.89 |
| SDPEG 1/2 | 0.0134 | 0.171 | 2.2046 | 4.775 | 95.51 | 98.07 |
| SDPEG 1/3 | 0.019 | 0.177 | 2.205 | 5.014 | 97.46 | 98.18 |
| SDPEG 1/4 | 0.032 | 0.187 | 2.212 | 5.021 | 96.91 | 97.56 |
| PMPVP 1/1 | 0.006 | 0.115 | 2.673 | 3.988 | 98.84 | 99.24 |
| PMPVP 1/2 | 0.015 | 0.116 | 2.683 | 4.178 | 100.1 | 98.89 |
| PMPVP 1/3 | 0.022 | 0.128 | 2.793 | 4.307 | 96.9111 | 99.13 |
| PMPVP 1/4 | 0.024 | 0.130 | 2.893 | 4.307 | 98.84 | 98.22 |
| SDPVP 1/1 | 0.08 | 0.115 | 2.982 | 4.337 | 98.06 | 98.11 |
| SDPVP 1/2 | 0.061 | 0.120 | 3.062 | 6.149 | 96.911 | 98.01 |
| SDPVP 1/3 | 0.078 | 0.148 | 3.142 | 6.887 | 98.26 | 97.69 |
| SDPVP 1/4 | 0.096 | 0.191 | 3.20 | 6.896 | 97.11 | 98.15 |

Infrared (FT -IR) Analysis

The FT-IR spectra were obtained using FT-IR spectrophotometer (Shimadzu-8101A, Japan). The samples were previously triturated and mixed thoroughly with potassium bromide in 1:5 (sample : KBr) ratio, KBr discs were prepared by compressing the powder at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 $cm^{-1}$ from 4500 to 400 $cm^{-1}$.

DSC Analysis

The differential scanning calorimeter study was performed on a DSC-61000 (Seiko Instruments, Japan) with thermal analyzer. All accurately weighed samples (about 5 mg of sample) were placed in a sealed aluminum pan, and the samples were heated under nitrogen flow (20 mL/min) at a scanning rate of 10 °C/min from 25 to 300 °C. An empty aluminum pan was used as reference.

X-ray dif fraction study

X-ray diffraction patterns of the powdered samples of the drug, the carrier and the solid dispersion were recorded using Philips XPERT PRO powder diffractometer operated at 45 kV and 40 mA (Goniometer PW3050/60) with monochromatic Cu-K (=1.5406 Aº) radiation. The samples were scanned continuously over the range of 10 to 60; 2è with the sampling interval of 0.017 2è.

Dissolution studies

Solid dispersion equivalent to 50 mg of drug was taken for the dissolution study using USP type II dissolution apparatus in 900 mL of pH 7.2 phosphate buffer at 50 rpm and temperature 37±0.5 °C. The sample volume

of 5 mL was withdrawn at the interval of 10 min and the volume was replaced with the fresh dissolution media to maintain sink condition. The samples were analyzed spectrophotometrically under UV at wavelength 247.5 nm[14,15].

### Drug Release Kinetic S tudies from Solid dispersions and Physical Mixtures

To describe the kinetics of drug released from Solid dispersions and Physical mixtures, mathematical models such as zero-order, first-order, Higuchi square root of time model, Hixson-Crowell, and Korsmeyer-peppas model were used. The criteria for selecting the most appropriate model were based on goodness of fit test[16]. The results of release kinetic studies of Flurbiprofen from solid dispersions and physical mixtures are shown in Table 3.

Table 3: *R value of various release models for solid dispersion of Flurbiprofen*

| Sample | Solubility of Flurbiprofen (mg/mL) | | | | Drug content (%) | Percent Yield |
|---|---|---|---|---|---|---|
| | pH 1.2 buffer | Water | pH 6.8 buffer | pH 7.2 buffer | | |
| Drug | 0.003 | 0.114 | 1.616 | 2.99 | 97.11 | - |
| PMPEG 1/1 | 0.0015 | 0.111 | 1.747 | 3.610 | 97.92 | 98.23 |
| PMPEG 1/2 | 0.008 | 0.113 | 1.817 | 3.699 | 99.18 | 99.43 |
| PMPEG 1/3 | 0.011 | 0.115 | 1.916 | 3.709 | 98.32 | 98.78 |
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| SDPVP 1/3 | 0.078 | 0.148 | 3.142 | 6.887 | 98.26 | 97.69 |
| SDPVP 1/4 | 0.096 | 0.191 | 3.20 | 6.896 | 97.11 | 98.15 |

### Formulation of T ablet of Flurbiprofen Solid Dispersion

Formulation composition for the Flurbiprofen solid dispersion tablet is given in Table 4.

### Evaluation of Pre-Compression Properties of Formulation Batches

The tablet blends were evaluated for their bulk density, tapped density, carr's index (% compressibility) and flow properties according to the methods proposed in the literatures[17,18] . The results of pre-compression evaluation are shown in Table 5.

### Evaluation of Post-compression properties of Tablets [19]

The thickness, diameter, hardness, friability and disintegration time of the tablets were determined using

Table 4: *Formulation Composition of Flurbiprofen Solid Dispersion Tablets*

| Formulation batch | Drug (mg) | SDPEG 1/4 (%) | SDPVP 1/4 (%) | MCC (%) | Lactose (%) | DCP (%) | PVP K30 (%) | Mg Stearate (%) | Talc (%) |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 50 | 40 | - | 35 | - | 19 | 5 | 0.5 | 0.5 |
| F2 | 50 | 40 | - | 35 | 19 | - | 5 | 0.5 | 0.5 |
| F3 | 50 | - | 40 | 35 | - | 24 | - | 0.5 | 0.5 |
| F4 | 50 | - | 40 | 35 | 24 | - | - | 0.5 | 0.5 |
| F5 | 50 | 60 | - | 25 | - | 10 | 5 | 1 | 1 |
| F6 | 50 | 60 | - | 25 | 10 | - | 5 | 1 | 1 |
| F7 | 50 | - | 60 | 30 | - | 10 | - | 1 | 1 |
| F8 | 50 | - | 60 | 30 | 10 | - | - | 1 | 1 |

Table 5: *Pre-compression evaluation studies*

| Formulation batch | Angle of repose | Bulk density (g/mL) | Tapped density (g/mL) | Compressibility (%) | Hausner ratio |
|---|---|---|---|---|---|
| F1 | 33.66 | 0.66 | 0.64 | 3.00 | 1.03 |
| F2 | 34.215 | 0.66 | 0.634 | 3.9 | 1.04 |
| F3 | 35.37 | 0.655 | 0.625 | 4.5 | 1.049 |
| F4 | 34.95 | 0.66 | 0.634 | 3.0 | 1.04 |
| F5 | 28.36 | 0.645 | 0.606 | 6.04 | 1.064 |
| F6 | 29.68 | 0.645 | 0.615 | 4.65 | 1.048 |
| F7 | 31.38 | 0.677 | 0.625 | 7.6 | 1.08 |
| F8 | 31.38 | 0.625 | 0.66 | 5.20 | 1.056 |

Digital Vernier Callipers, Monsanto hardness tester, friabilator and disintegration test apparatus, respectively. Weight variation test was carried out by weighing 20 tablets individually and then calculating the average weight. The results are shown in Table 6.

Table 6: *Evaluation of Post-compression parameters of tablets*

| Formulation batch | Weight Uniformity | Hardness (kg/cm²) | (%) Friability | Disintegration time (min) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 251.4 | 2 | 0.4 | 4 | 98.21 |
| F2 | 248.9 | 2 | 0.48 | 5 | 99.01 |
| F3 | 251.2 | 4 | 0.52 | 8 | 99.48 |
| F4 | 258.1 | 4 | 0.15 | 11 | 97.94 |
| F5 | 249.1 | 3 | 0.99 | 5 | 98.21 |
| F6 | 247.9 | 2 | 0.62 | 3 | 97.69 |
| F7 | 252.1 | 4 | 0.62 | 9 | 96.97 |
| F8 | 249.8 | 3 | 0.31 | 8 | 99.28 |

### Dissolution of T ablet

Dissolution was carried out using USP apparatus II taking 900 mL of pH 7.2 phosphate buffer as dissolution media at 50 rpm and temperature 37±0.5 °C. The sample volume of 5 mL was withdrawn at the interval of 10 min and the volume was replaced with the fresh dissolution media to maintain sink condition. The samples were filtered, by passing through 0.45 µm membrane filters (Millipore, USA). The samples were analyzed spectrophotometrically under UV at wavelength 247.5 nm[14].

Drug Release Kinetic S tudies from T ablet s [16]

To describe the kinetics of drug released from tablets, mathematical models such as zero-order, first-order, Higuchi square root of time model, Hixson-Crowell, and Korsmeyer-peppas model were used. The criteria for selecting the most appropriate model were based on goodness of fit test. The results of release kinetic studies of Flurbiprofen from formulated solid dispersion tablets are shown in Table 7.

Table 7: *R value of various release model for formulation batches*

| Solid dispersion | Zero order | First order | Higuchi Matrix | Korsmeyer - Peppas | Hixson - Crowell |
|---|---|---|---|---|---|
| F1 | 0.9627 | 0.9839 | 0.9656 | 0.9888 | 0.9970 |
| F2 | 0.9634 | 0.9751 | 0.9620 | 0.9832 | 0.9952 |
| F3 | 0.9597 | 0.9789 | 0.9673 | 0.9855 | 0.9855 |
| F4 | 0.9536 | 0.9811 | 0.9708 | 0.9848 | 0.9984 |
| F5 | 0.9283 | 0.9518 | 0.9654 | 0.9622 | 0.9746 |
| F6 | 0.9696 | 0.9761 | 0.9694 | 0.9939 | 0.9976 |
| F7 | 0.9496 | 0.9749 | 0.9828 | 0.9855 | 0.9952 |
| F8 | 0.9577 | 0.9744 | 0.9788 | 0.9872 | 0.9970 |

## RESULTS AND DISCUSSION

Solid dispersion prepared by melting method was very sticky and difficult for processing of formulation of dosage form development. But solid dispersion prepared by solvent evaporation method was found to be suitable for processing in formulation.

### Drug content and percent yield

The percentage drug content of solid dispersions and physical mixtures was found in the range of 95.51 to 100.1% as shown in Table 2. This indicated that Flurbiprofen was uniformly distributed in all of these prepared solid dispersions and physical mixtures.

### Saturation solubility study

The drug in solid dispersion and physical mixtures showed greater solubility in pH 7.2 buffer as compared to the solubility of the drug alone. The order of solubility (Table 2) is solid dispersion > physical mixture > drug. The solid dispersion batch no. SDPVP1/4 and SDPEG1/4 showed higher solubility in the ratio of 1:4 as compared to other ratios and batches (Table 2). The increase in the solubility is due to the amorphous form of the drug in the dispersion.

### FT-IR Spectroscopy

Comparing the spectra of solid dispersion of Flurbiprofen and PEG 6000 and physical mixture, no significance difference was seen in the position of the absorption bands and the spectra can be simply regarded as the super position of those of Flurbiprofen and PEG 6000. The entire characteristic peaks were retained in the spectrum of solid dispersions (Figure 1). This indicates that there is no structural modification. The intensity of the peaks was changed due to the surface adsorption of the polymer.

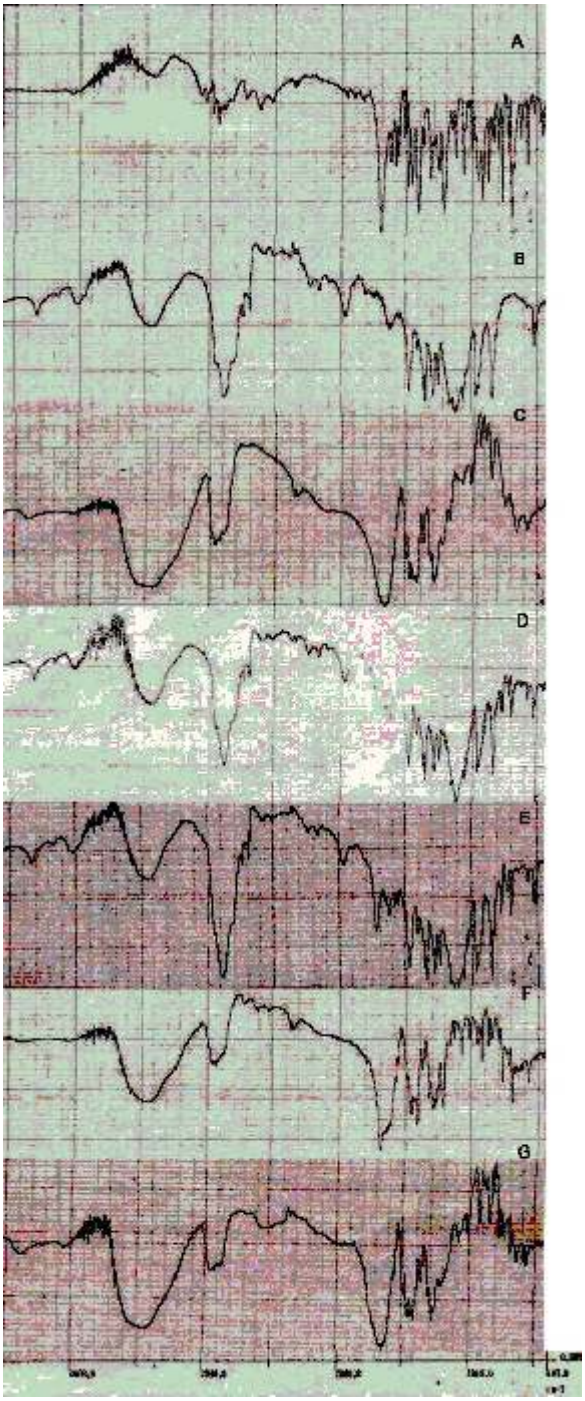


Fig. 1: *FT-IR spectra of (A) flurbiprofen, (B) PEG 6000, (C) PVP K-30, (D) PEG 6000 + flurbiprofen (PM), (E) PEG 6000 + flurbiprofen (SD), (F) PVP K-30 + flurbiprofen (PM), (G) PVP K-30 + flurbiprofen (SD)*

Differential Scanning Calorimetry

It was found that the sharp melting point of pure Flurbiprofen appeared at 116.54 °C where as no such peak was observed in solid dispersion and physical mixture prepared with PEG 6000 and PVP K-30, suggesting that Flurbiprofen was molecularly dispersed and is in amorphous form (Figure 2).

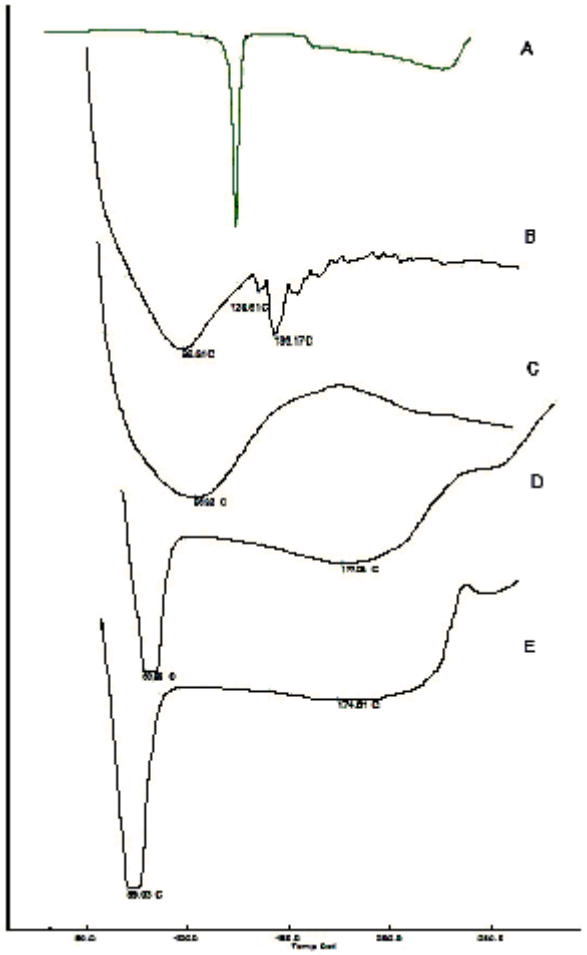


Fig. 2: *DSC Thermograms of (A) Flurbiprofen, (B) PEG 6000+ Flurbiprofen (PH), (C) PEG 6000+ Flurbiprofen (SD), (D) PEG K-30 6000+ Flurbiprofen (PH), (E) PEG K-30 6000+ Flurbiprofen (SD)*

XRD study

The presence of numerous distinct peaks on the XRD spectrum indicated that drug is in crystalline form in physical mixtures due to presence of free drug (Figure 3). The diffraction patterns of all the samples of solid dispersions show absence of major diffraction peaks corresponding to physical mixture; hence drug is as amorphous material inside the PEG 6000 and PVP K-30 matrix.

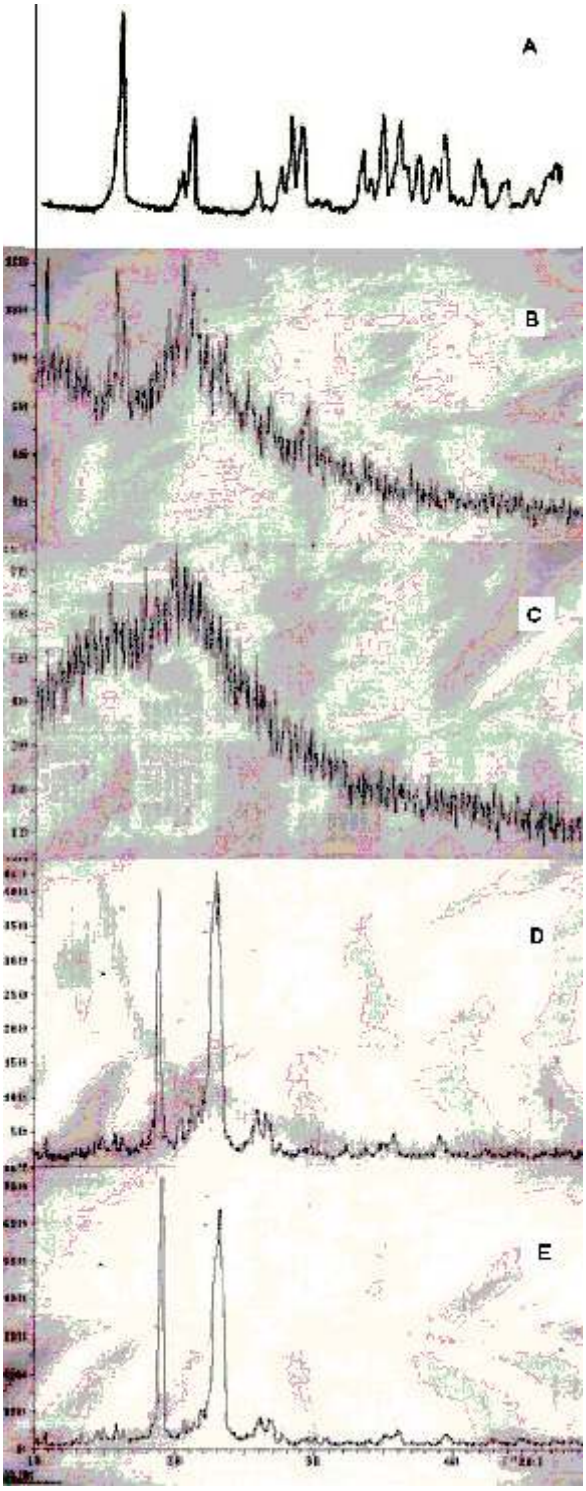


Fig. 3: *X-ray Diffractograms of (A) Flurbiprofen pure, (B) PVP K-30 + Flurbiprofen (SD), (C) PVP K-30 + Flurbiprofen (PH), (D) PEG 6000+ Flurbiprofen (SD), (E) PEG 6000+ Flurbiprofen (PH)*

Dissolution studies

Solid dispersion shows better performance over corresponding physical mixtures and pure drug. The hydrophilic polymer PEG 6000 and PVP K-30 increase the rate of dissolution of drug by increasing the wettability of drug particles and also the amorphous form of drug favours enhancement of dissolution rate of Flurbiprofen in solid dispersion. This may be due to an improved wettability of drug particle, a significant reduction in particle size during the formation of solid dispersion, and the intrinsically higher rate of dissolution of the soluble polymer component of the solid dispersion. When the dissolution data of all batches were compared with the drug alone it was found that the solid dispersion of the drug improves the dissolution rate of the drug (Figure 4). The solid dispersion batch SDPEG1/4 and SDPVP1/4 shows higher dissolution rate and these batches were further considered for preparation of solid dispersion tablets.

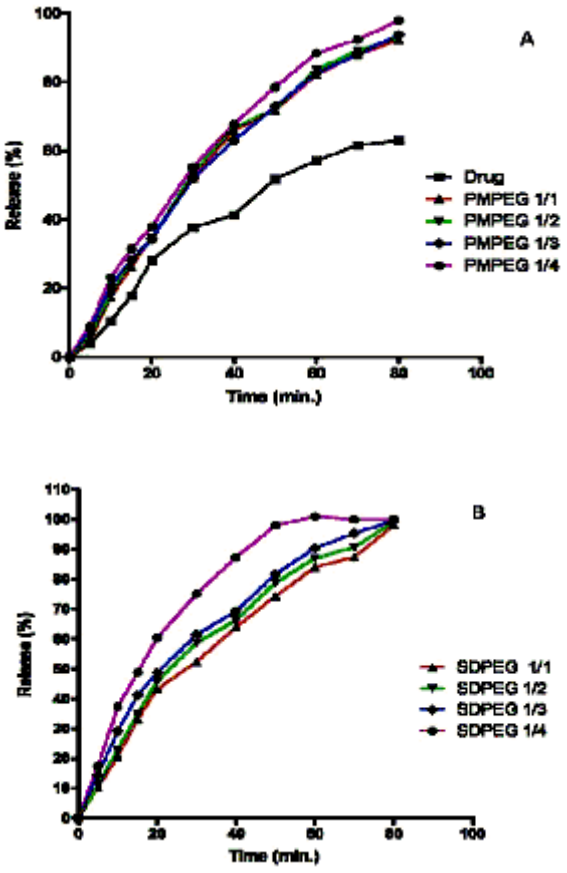


Fig. 4: *In-vitro dissolution profiles of pure Flurbiprofen, physical mixture, and solid dispersions in pH 7.2 buffer*

Release kinetics study

The release mechanism of Flurbiprofen from solid dispersion was obtained by fitting the data of *in-vitro* release studies into zero order, first order, Higuchi Matrix, Korsmeyer-Peppas and Hixson-Crowell kinetic models. The value of correlation co-efficient is shown in Table 3. The Hixson-Crowell model was found to be the best fit model for all batches except SDPVP1/3 and SDPVP1/4 (Table 3).

Evaluation of Pre-Compression Properties of Formulation Batches

Based on solubility and dissolution rate studies, two batches of solid dispersion SDPEG1/4 and SDPVP1/4 were selected for the preparation of tablet formulation. Before preparation of solid dispersion tablets, the formulation batches were subjected for the analysis of flow properties and compressibility (Table 5).

The result of angle of repose values for all the formulations prepared indicated the good and free flowing characteristics. All formulations also showed good compressibility except the formulation F7. The formulation batches of tablets were prepared by directly compressing

the optimized solid dispersions of Flurbiprofen with MCC, lactose and dicalcium phosphate as diluents and PVP K30 used as a binder as shown in the Table 2. PVP was only used in the formulation of PEG based solid dispersion tablets.

### Evaluation of Post-Compression Properties of Flurbiprofen T ablets

The hardness values were found to be in the range of 2 to 4 kg/cm². The hardness, friability and drug content was found to be within IP limits. All formulated tablets were evaluated for disintegration test and it was found that tablets containing dicalcium phosphate as a diluent requires less time to disintegrate as compared to lactose (Table 6).

### Dissolution S tudy of Solid Dispersion T ablets

*In-vitro* releases of all formulated tablets were in the range of 94.13% to 96.24% (Figure 5). The formulation batch F4 shows higher release up to 96.24% in 90 minutes and it requires less time to disintegrate. The ratio of drug and hydrophilic polymer in solid dispersion to prepare all the tablets were 1:4 and it was observed that Flurbiprofen dissolved rapidly due to its amorphous nature in the dispersion.

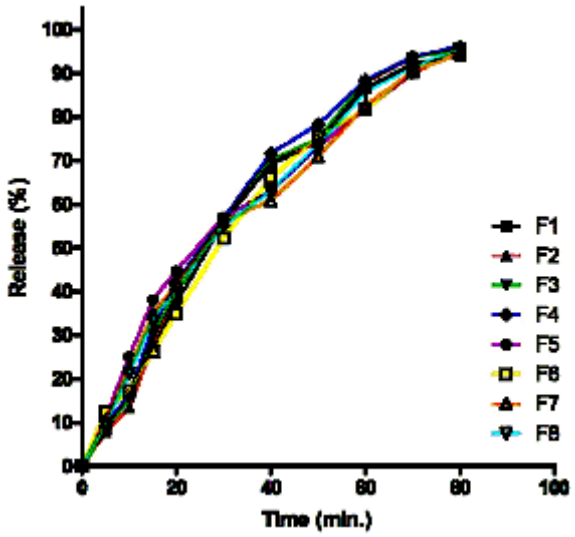


Fig. 5: *In-vitro dissolution profile of tablet formulation batches in pH 7.2buffer*

### Release Kinetic S tudy

The release mechanism of Flurbiprofen from tablet studies by fitting the data obtained from in-vitro release studies into zero order, first order, Higuchi Matrix, Korsmeyer-Peppas and Hixson-Crowell. The value of correlation coefficient is shown in Table 7. The Hixson-Crowell model was found to be the best fit model for formulation (Table 7).

## CONCLUSION

The solid dispersion prepared by solvent evaporation method in the ratio of 1:4 of the drug to polymer shows higher saturation solubility and hence enhances the dissolution rate. The formulation batches for the tablets also show good flowing properties and good compressibility index. All tablet formulation batches show rapid disintegration within 2-4 minutes and improving dissolution rates. The kinetic mechanism for the release of flurbiprofen from the prepared solid dispersion tablets was found to be Hixson-Crowell model.

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