ORIGINAL ARTICLE

Formulation and Evaluation of Flurbiprofen Solid Dispersions using Novel Carriers for Enhancement of Solubility

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Abstract

Introduction: The main objective of the current study is to enhance the solubility and dissolution of poorly water-soluble drug flurbiprofen, a propionic acid derivative, used as non-steroidal anti-inflammatory drug by formulating into solid dispersion (SD) employing various hydrophilic polymers as carriers in the formulation. **Materials and Methods:** The solubility of drug in various polymers such as AQOAT AS, PVP-K30, hydroxypropryl methyl cellulose, Soluplus, and Kollidon VA 64 was studied. Total 15 SD formulations were prepared by solvent evaporation technique with different polymers and were evaluated for particle size analysis, % practical yield, drug content determination, and *in vitro* dissolution studies. **Results:** Based on the evaluation parameters and dissolution studies, SD6 was found to be optimized formulation. The SD6 prepared using flurbiprofen:AQOAT AS:sodium lauryl sulfate as drug:polymer:surfactant in 1:5:2 ratios showed maximum drug release of 99.86 in 15 min when compared with other formulation and the solubility of the formulation SD6 was enhanced 44 folds when compared to that of pure drug. Drug excipient compatibility studies were conducted using FTIR and XRD and scanning electron microscope (SEM) studies were also conducted. FTIR studies showed the compatibility between drug and polymers. XRD and SEM studies showed that the optimized formulation was in amorphous form which fetched in better dissolution of the drug from the SD formulation when compared to the pure drug. **Conclusion:** This indicates the formulation technology employed with a potential of enhancing bioavailability of poorly water-soluble drug by improving its dissolution rate.

Key words: AQOAT AS, flurbiprofen, rheumatoid arthritis, solid dispersion, solvent evaporation method

INTRODUCTION

Solubility enhancement of poorly water-soluble drugs is the main focus of research nowadays. For this reason, numbers of different formulation mechanisms were developed and one of them includes solid dispersion (SD) technique,[1] many of the drugs now commercially available formulated using SD technique resulted in enhanced bioavailability. SD technology is one of the most budding and abundantly performed proposals to enhance the dissolution rate of low soluble or insoluble drug compounds. Ease of scalability, and conversion to conventional dosage forms such as tablets, capsules, taste masking strips, and implants are some of the favorable conditions met by formulating drug by SD technology.[2] Flurbiprofen is a non-steroidal anti-inflammatory drug with antipyretic and analgesic activities, it is mainly prescribed in the treatment for acute or symptomatic rheumatoid arthritis, osteoarthritis, and also pain caused due to dysmenorrhea. Flurbiprofen belongs to Class II drug of biopharmaceutical system with low bioavailability and high permeability.as the drug has low aqueous solubility and extensive first-pass metabolism it is a drug of choice for SD formulation which can enhance the solubility, dissolution, and finally bioavailability.

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of flurbiprofen by preparing SDs with various suitable polymers and the prepared SDs were evaluated for solubility study, drug content, and *in vitro* dissolution rate studies.

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MATERIALS AND METHODS

Materials

Flurbiprofen gifted by Hetero Labs Limited, Hyderabad. AQOAT AS, hydroxypropryl methyl cellulose (HPMC), and Kollidon VA 64, PEG 6000, Labrafac CC, Kolliphor ELP, Soluplus, Kleptose HPB, and Kolliphor P188 were obtained from Gattefosse, Mumbai. All other chemicals and reagents used were of analytical grade.

Methods

Preliminary solubility studies of flurbiprofen

Solubility measurements of flurbiprofen were done by adding an excess amount of flurbiprofen to 25 ml of aqueous solution of hydrophilic carriers such as AQOAT AS, HPMC, and Kollidon VA 64, PEG 6000, Labrafac CC, Kolliphor ELP, Soluplus, Kleptose HPB, Kolliphor P188, PEG 400, Span 40, Tween 80, and polyvinyl pyrrolidone k30 (PVP-k30) in screw capped bottles. The bottles were kept in orbital shaker for the 24 h at room temperature. Eventually, the suspensions were filtered using a 0.45 μm filter and the filtered solution was diluted with methanol. This diluted solution was analyzed by UV visible spectrophotometer at 247 nm [Table 1].[3-5]

Preparation of SDs

SDs were prepared by solvent evaporation method. The composition of all formulations is presented in Table 2. Five polymers were selected with maximum solubility of the drug which were screened after checking the preliminary solubility of the drug are dissolved individually in ethanol with continuous stirring until clear solution is obtained. To this solution drug, flurbiprofen was then added with continuous thorough stirring for 45 min. The solvent was evaporated under reduced pressure and the resulting SDs were kept at room temperature in a dessicator, which is then subjected to size reduction and sieving.[6]

Table 1: Preliminary solubility studies of flurbiprofen pure drug and physical mixtures in 1:1 ratio

Physical mixture (1:1)	Solubility (mg/ml)*
Flurbiprofen (pure drug)	0.013±0.04
Drug+AQOAT AS	0.265±0.73
Drug+ HPMC	0.175±0.014
Drug+Kollidon VA 64	0.180±0.82
Drug+PEG 6000	0.148±0.017
Drug+Labrafac CC	0.157±0.34
Drug+Kolliphor ELP	0.128±0.025
Drug+Soluplus	0.183±0.79
Drug+Kleptose HPB	0.147±0.35
Drug+ PVP-k30	0.168±0.32
Drug+Kolliphor P188	0.136±0.092
Drug+PEG 400	0.158±0.17
Drug+Span 40	0.168±0.01
Drug+Tween 80	0.136±0.62
Drug+sodium lauryl sulfate	0.234±0.25

*n=SD±3

Characterization of flurbiprofen SDs

Solubility studies

Solubility studies were carried out for pure flurbiprofen and all the formulations by placing them in medium of pH 7.2. All the samples were shaken for 48 h in an orbital shaker by keeping temperature at 37°C. This solution is then filtered by Whatman filter paper and filtrate was further diluted and measured using spectrophotometrically at 247 nm.[7,8]

Particle size determination

Particle size analysis was carried out by laser diffraction size analyzer (LS 13 320, Beckman Coulter, CA). For this purpose, the samples were ultrasonicated for a minute after suspending in silicone oil. Then, these samples were analyzed by laser diffraction analyzer.[7]

Drug content

All the samples of various formulations were placed in 25 ml volumetric flask (equivalent to 50 mg of drug). 10 ml methanol was added to the each sample mixture and sonicated for 10 min. Methanol was used to make the final volume. This solution is then diluted by methanol up to certain extent so that it can easily be analyzed spectrophotometrically at λ = 247 nm.[7]

Percentage practical yield (PY)

Percentage PY was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine PY from the following equation.[8]

$$\%\ \text{Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer + Surfactant)}} \times 100$$

Dissolution studies

Dissolution studies were performed using Type II paddle apparatus. The dissolution medium consisted of 900 ml phosphate-buffered solution with pH 7.2 containing

Table 2: Composition of flurbiprofen solid dispersions

Formulation code	Ingredients (units in mg)							
	Flurbiprofen	Soluplus	AQOAT AS	HPMC	Kollidon VA64	PVP k-30	Sodium lauryl sulfate	Methanol
SD1 (1:1:1)	50	50	-	-	-	-	50	qs
SD2 (1:3:1.5)	50	150	-	-	-	-	75	qs
SD3 (1:5:2)	50	250	-	-	-	-	100	qs
SD4(1:1:1)	50	-	50	-	-	-	50	qs
SD5 (1:3:1.5)	50	-	150	-	-	-	75	qs
SD6 (1:5:2)	50	-	250	-	-	-	100	qs
SD7 (1:1:1)	50	-	-	50	-	-	50	qs
SD8 (1:3:1.5)	50	-	-	150	-	-	75	qs
SD9 (1:5:2)	50	-	-	250	-	-	100	qs
SD10 (1:1:1)	50	-	-	-	50	-	50	qs
SD11(1:3:1.5)	50	-	-	-	150	-	75	qs
SD12 (1:5:2)	50	-	-	-	250	-	100	qs
SD13 (1:1:1)	50	-	-	-	-	50	50	qs
SD14 (1:3:1.5)	50	-	-	-	-	150	75	qs
SD15 (1:5:2)	50	-	-	-	-	250	100	qs

1% sodium lauryl sulfate (SLS). The temperature was maintained at 37 ± 0.5°C and stirring speed of 50 rpm. The samples were spread on the surface of dissolution medium and 5 ml of aliquots were withdrawn at specific intervals and measured spectrophotometrically for flurbiprofen content at wavelength 247 nm. The volume of dissolution medium was kept constant by adding same amount of fresh medium.[9]

FTIR spectroscopy

The FTIR spectra for all the formulations were studied on FTIR spectrometer Pristige-21 (Shimadzu- Japan). KBr disks were prepared by mixing the samples with potassium bromide before analysis. The samples were analyzed over the range of 4000–400 cm-1 at the resolution of 2 cm^{-1}.[10]

X-ray powder diffraction (XRD)

X-ray diffraction of flurbiprofen and the formulations was carried out by diffractometer. This was done to determine the polymorphic state of flurbiprofen. Recording was made from 3 to 1500 in Si (Li) PSD detector with scanning speed of 30/min. All the process was operated at 40 kV and35 mA.[11]

Scanning electron microscope (SEM) studies

The surface morphology of the layered sample was examined by using SEM (Hitachi, Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer (30 Å) of gold by employing POLARON-E 3000 sputter coater. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.[11]

Stability studies

Prepared SDs were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75% ± 5% RH and temperature of 40 ± 2°C for stability studies. The samples were removed after 1, 2, and 3 months and evaluated for % drug content and *in vitro* dissolution studies.[12]

RESULTS AND DISCUSSION

Preparation of SD

In the current study, 15 formulations of SDs of flurbiprofen were prepared using varying ratios of polymers, and their complete composition is shown in Table 2. All the SDs prepared were found to be fine and free flowing powders.

Solubility studies

From these studies, the solubility of pure flurbiprofen was found to be 0.013 mg/ml and the solubility of SD complex of flurbiprofen was increased to be many folds when compared with pure drug and the results are summarized in Table 3 and Figures 1 and 2.

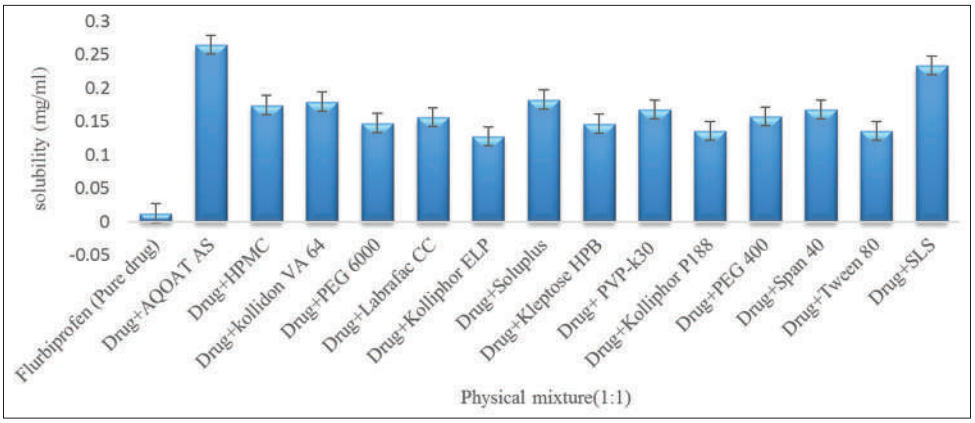

Figure 1: Preliminary solubility studies of flurbiprofen physical mixture

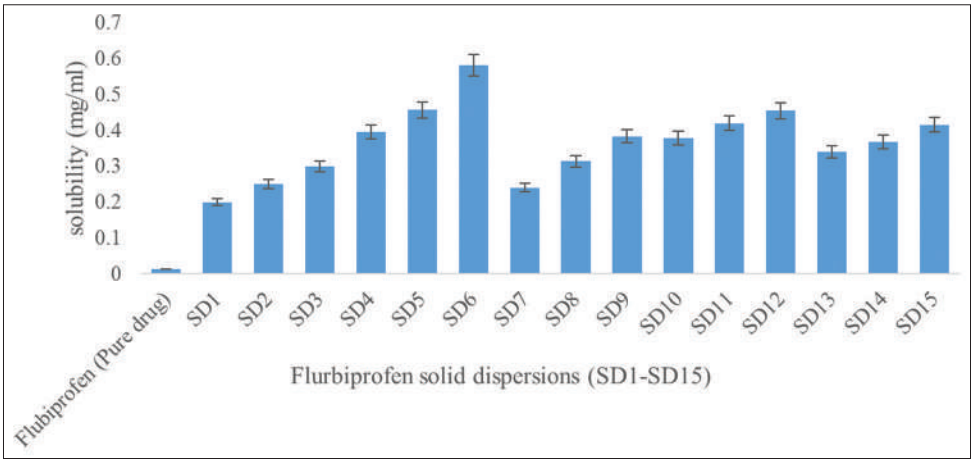

Figure 2: Solubility studies of flurbiprofen solid dispersion

Table 3: Solubility profile of flurbiprofen pure drug and SDs

Formulation code	Solubility (mg /ml)*
Flurbiprofen (pure drug)	0.013±0.04
SD1	0.202±0.24
SD2	0.255±0.50
SD3	0.300±0.06
SD4	0.396±0.13
SD5	0.457±0.47
SD6	0.582±0.08
SD7	0.248±0.02
SD8	0.314±0.47
SD9	0.384±0.37
SD10	0.379±0.41
SD11	0.421±0.24
SD12	0.455±0.37
SD13	0.342±0.06
SD14	0.368±0.28
SD15	0.416±0.38

*n=SD±3

Particle size determination

Particle size was determined using sieving method and found to be in between 52.84 ± 2.36 and 78.82 ± 2.01. Particles size analysis was carried out for all the SD formulations as it plays an important role in drug release. Optimum particle size is needed for good drug release, general assumption is smaller the size of the particle the more will be the release and it is observed that the optimized final formulation SD6 with optimum particle size 52.84 ± 2.36 showed good drug release, as shown in Table 4.

Particle size, % PY, and drug content determination

Particle size was determined using sieving method and found to be in between 52.84 ± 2.36 and 78.82 ± 2.01 and particles size analysis was carried out for all the SD formulations as it plays an important role in drug release. Optimum particle size is needed for good drug release, general assumption is smaller the size of the particle the more will be the release and it is observed that the optimized final formulation SD6 with optimum particle size 52.84 ± 2.36. The results of % PY for all formulations of SDs found to be 91.38 ± 0.41–98.48 ± 0.32%. Maximum yield was found to be 98.48 ± 0.32% in formulation SD6. Drug content

determination was carried out for control of drug quality and effectiveness of process for preparation of formulation. The drug content of various formulations was in range of 92.28–99.82% and SD6 was showing maximum drug content of 99.82%. The results confirmed the homogeneous distribution of drug within complexes and all the results are summarized in Table 4.

Table 4: Particle size, % practical yield, and drug content of flurbiprofen solid dispersions

Formulation code	Particle size in µm	% Practical yield	% Drug content
SD1	57.73±1.2	91.38±0.41	92.28±0.16
SD2	63.82±4.78	92.87±0.02	93.57±0.31
SD3	58.82±0.25	94.83±0.24	95.27±0.41
SD4	60.84±2.36	94.73±0.12	95.26±0.5
SD5	78.82±2.01	96.52±0.49	97.42±0.41
SD6	52.84±2.36	98.48±0.32	99.82±0.43
SD7	74.73±3.86	91.83±0.09	92.53±0.25
SD8	69.37±4.01	93.82±0.18	94.51±0.33
SD9	59.82±3.82	95.72±0.28	96.42±0.40
SD10	69.71±2.76	91.83±0.19	92.41±0.21
SD11	60.82±1.37	93.28±0.28	94.59±0.48
SD12	74.92±2.69	95.99±0.5	96.42±0.46
SD13	65.71±2.76	92.84±0.07	93.72±0.03
SD14	57.82±1.37	94.82±0.49	95.62±0.49
SD15	67.28±3.78	97.62±0.32	98.62±0.19

n=SD±3

In vitro dissolution studies

Dissolution studies of all 15 flurbiprofen SD from SD1-SD15 were carried out to determine the release properties of drug from the SD formulations. The dissolution profile of pure flurbiprofen, SD prepared using AQOAT AS in 1:5:2 ratio of drug:polymer:surfactant showed maximum drug release of 99.86 in 15 min. Increased dissolution rates of SDs are attributed to more polymer concentration used for formulating SDs, it is clearly observed that as the polymer carrier concentration was increased in the formulation the drug release increased accordingly and also increased surface area of drug due to decrease in particle size enhanced solubility of drug when it comes in contact with dissolution medium as carrier dissolves resulting in enhanced wettability of drug [Figures 3-5].

FTIR spectroscopy

FTIR spectroscopy was carried out for the determination of any polymorphic alteration in complexes and to check interaction between drug and polymers. FTIR spectrum of pure drug flurbiprofen [Figure 6] gives characteristic sharp peak at 1732.13 representing the presence of (C=O) carbonyl compound, peak at 1225.6 represents stretching of

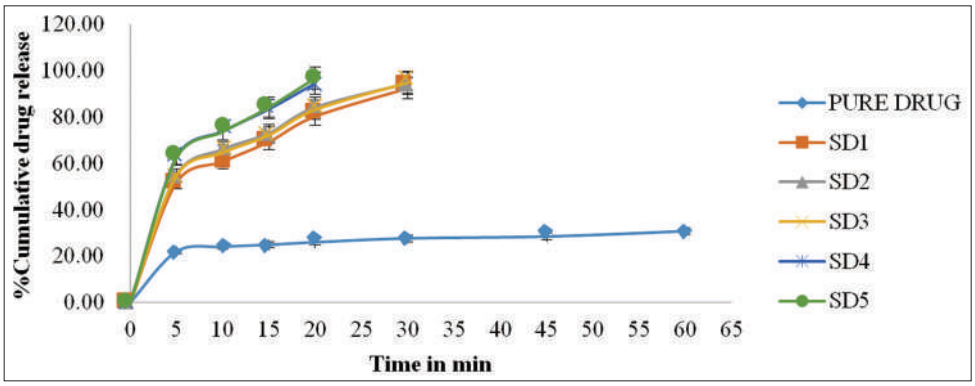

Figure 3: Dissolution profile of flurbiprofen pure drug and solid dispersions of Flurbiprofen (SD1 to SD5)

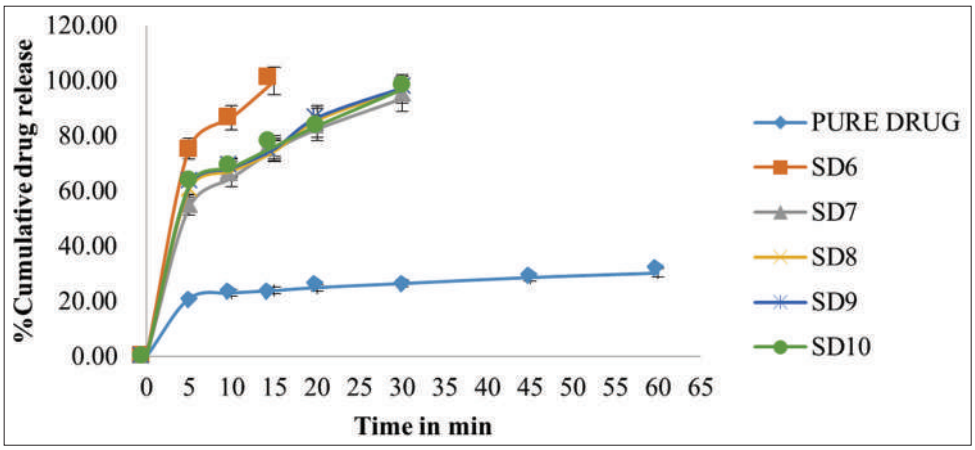

Figure 4: Dissolution profile of flurbiprofen pure drug and solid dispersions of flurbiprofen (SD6 to SD10)

C-F and a characteristic broad peak of flurbiprofen in the range of 2500–3300 cm^{-1} due to hydrogen bonding. Spectra of formulation SD6 [Figure 7] showed the same absorbance pattern as the combination of drug and polymers.

XRD

The flurbiprofen SDs were carried out to find out whether the SDs of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure flurbiprofen indicates that it was present as a crystalline material [Figure 8]. On the other hand, the spectrum of optimized formulation SD6 of SD was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound [Figure 9]. The enhancement in the dissolution rate of the drug from the drug-AQOAT AS SD is ascribed to the marked reduction in the crystallinity of the drug.

SEM studies

SEM photographs for pure drug and optimized formulation SD6 are shown in Figures 10 and 11. The drug crystals seemed

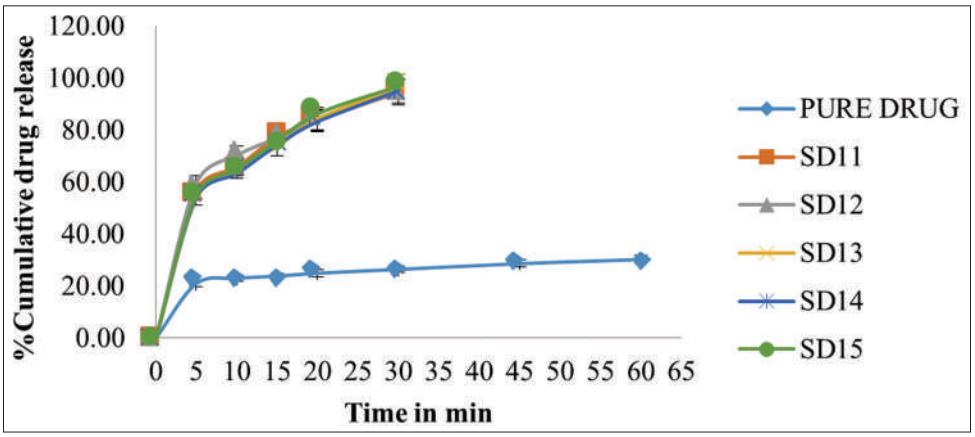

Figure 5: Dissolution profile of flurbiprofen pure drug and solid dispersions of flurbiprofen (SD11 to SD15)

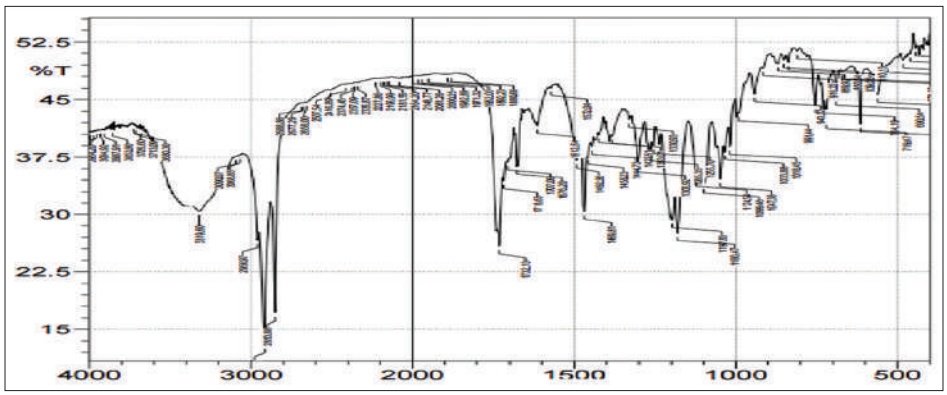

Figure 6: FTIR spectrum of flurbiprofen pure drug

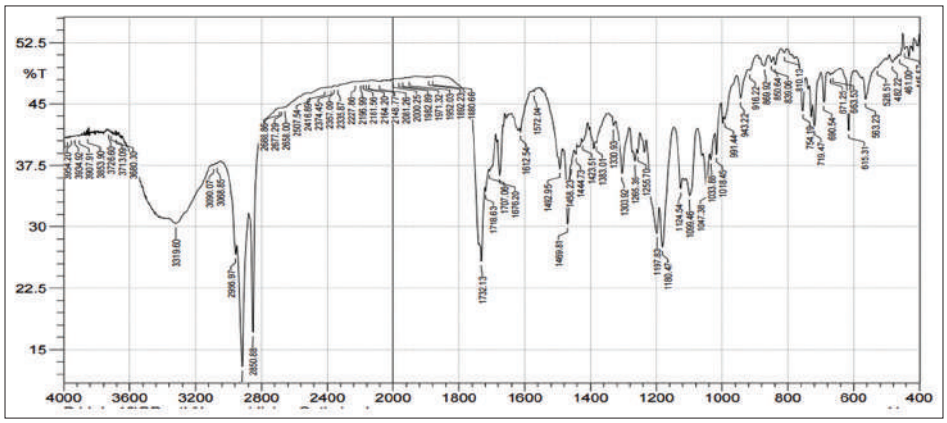

Figure 7: FTIR spectrum of flurbiprofen solid dispersions optimized formulation SD6

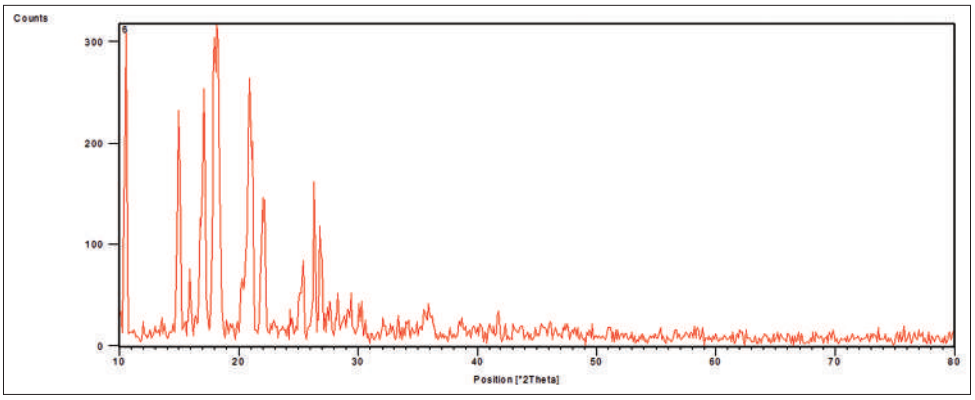

Figure 8: XRD of flurbiprofen pure drug

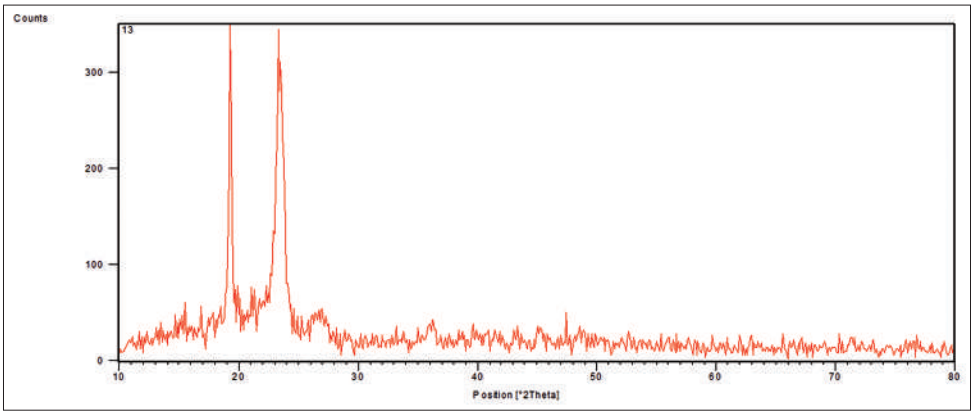

Figure 9: XRD of Flurbiprofen optimized formulation SD6

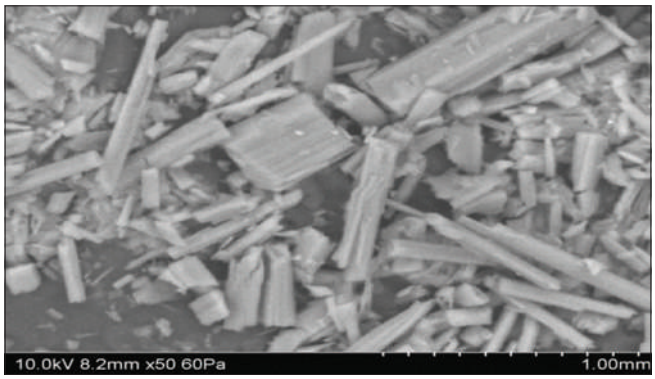

Figure 10: Pure drug of flurbiprofen

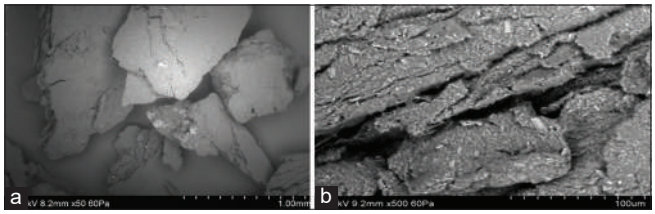

Figure11: (a and b) Flurbiprofen optimized formulation SD6

to be smooth-surfaced, irregular in shape and size and in case of SDs, it was difficult to distinguish the presence of drug crystals. The drug surface in SD seems to be more porous in nature. SDs appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The SD looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

Table 5: Evaluation data of formulations subjected to stability studies at 40°C±2°C/75% RH±5%

Retest time for optimized formulation	% Drug content	*In vitro* drug release (%)
0	99.82±0.43	99.86±3.87
30	98.36±0.25	98.59±0.39
60	97.62±0.37	97.89±0.40
90	96.67±0.48	97.52±0.39

Stability studies

Optimized formulation SD6 was loaded for stability studies at 40°C±2°C/75% RH±5% to evaluate and formulation was found to be stable. There was no significant change in %drug content and *in vitro* drug release was observed, as shown in Table 5.

CONCLUSION

SDs of flurbiprofen were prepared by solvent evaporation method, a simple, and easily reproducible method. A total of

15 formulations were prepared using different hydrophilic carrier polymers and all the formulations showed better drug release when compared to pure drug. The solubility of flurbiprofen was found to be highest in polymer AQOAT AS which was almost 20 folds and the same reflected in the formulation SD6 which showed highest release of 99.86 in 15 min containing 1:5:2 ratio of flurbiprofen drug:AQOAT AS:SLS and found to be the best optimized formulation. Solubility of flurbiprofen was also increased by 44 folds in SD formulation SD6 when compared to pure drug. For all the formulations evaluation was carried and found to be adequate and FTIR studies disclosed the compatibility between drug and polymers. XRD and SEM studies manifest that the optimized formulation was in amorphous form which achieved in better dissolution of the drug from the SD formulation when compared to the pure drug. Therefore, it can be assessed that SDs can result in enhancement of solubility thereby improvement in drug release of poorly water-soluble drugs like flurbiprofen.

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