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Preparation and characterization of flurbiprofen capsules prepared by using liquisolid technique

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ABSTRACT

The current project is mainly focussed on the application of liquisolid (LS) technique in the enhancement of dissolution profile of flurbiprofen. Flurbiprofen is a NSAID indicated for acute and chronic osteoarthritis, rheumatoid arthritis and spondylitis. It is selected as model drug as it is a BCS Class II drug and has very poor aqueous solubility of 10.45 $\pm$ 3.2μg/ml. Hence, this study was designed to improve the dissolution rate of flurbiprofen using LS technique. Initially, saturation solubility studies were performed to select liquid vehicle showing higher solubility of drug to obtain liquid medication. PEG 600 was selected as non-volatile solvent, used at three different drug concentrations of 33.33, 40 and 50 % w/w to form LS formulations. Further, they were converted to powder by means of Avicel PH 102 and Aerosil 200 as carrier and coating materials to prepare LS formulations. Rheological tests were performed for the LS powder systems to study the flow properties. Later, several LS formulations were prepared, encapsulated in hard gelatin capsules. These capsules containing LS systems were subjected to evaluation tests and *in vitro* drug release studies. The results of dissolution profile of formulation CF3 showed maximum release of 98% within 30 minutes which was two folds higher than that of conventional capsule. FTIR studies revealed no drug-excipient interaction. DSC, SEM and PXRD studies revealed that drug in the system was completely soluble and available in molecularly dispersed state. Finally, it can be concluded that LS technique proved to enhance the dissolution profile of Flurbiprofen.

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INTRODUCTION

Enhancement of solubility has been an unending challenge for scientists since years due to the nature of poor solubility of drugs. These drugs show variable bioavailability because of low solubility and slow absorption in the GIT. Hence, researchers are immensely focussing on solubility enhancement for these drugs. Earlier many methods have been employed to increase the solubility of poorly water-soluble drugs like microemulsions, complexation using cyclodextrins (Muraoka *et al.*, 2004; Rudrangi *et al.*, 2016), solid dispersions (Patel *et al.*, 2011), nanosuspensions (Oktay *et al.*, 2018), solid lipid

nanoparticles (ud Din *et al.*, 2015), micelle formulation, SMEDDS (Vithani *et al.*, 2018), etc.

Liquisolid technique also termed as Powder solution technology first introduced by Spireas (Spireas, 2002); is employed to increase the solubility and further rate of dissolution for poorly aqueous soluble drugs. These LS systems refer to those obtained by converting liquid medications into flowable powders that can also be compressed by the addition of carrier and coating excipients. Liquid medication means drug is either dissolved or suspended in suitable hydrophilic solvent selected by saturation studies. The finally obtained LS systems are either compressed to compacts or encapsulated in hard gelatin capsules. It was postulated that, in case of liquisolid system, drug being present in a solid form, but actually it is present inside the powder either in solution form or dispersed in molecular state. Hence, due to enhancement in solubility, wetting property and drug surface area, this formulation proved to exhibit improved drug release profiles and subsequently enhanced bioavailability (Nokhodchi *et al.*, 2005; Javadzadeh *et al.*, 2005).

Flurbiprofen is a non-selective cyclooxygenase enzyme inhibitor which will block prostaglandins and exhibits analgesic, antipyretic and anti-inflammatory effects (Fukumoto *et al.*, 2018). It is indicated for gout, osteoarthritis and rheumatoid arthritis. It is selected as model drug because it is a BCS class II drug and has low aqueous solubility of $10.45 \pm 3.2\mu$g/ml (Dong *et al.*, 2010). Therefore, Flurbiprofen oral solid dosage forms faces difficulty during formulation owing to its poor absorption and bioavailability. Hence, in the present study effect of LS system was investigated to increase the solubility as well dissolution profile of flurbiprofen.

MATERIALS AND METHODS

Materials

Pure drug, Flurbiprofen was purchased from Alfa Aesar, USA. Aerosil 200, Avicel PH 102, Propylene glycol (PG), sodium starch glycolate (SSG) were obtained from S.D Fine Chemicals Ltd, Mumbai. Polyethylene glycols 200, 400 and 600), Tweens and Spans purchased from Himedia, Mumbai. All other reagents used were of analytical grade.

Methods

Solubility studies

Surplus amount of drug was added to 5 ml each of various non-volatile solvents, 7.4 pH phosphate buffer and distilled water kept in screw capped vials to obtain saturated solutions. These vials were later kept on mechanical shaker (Remi, Mumbai) for 24 hours and then subjected to centrifugation at 2500 rpm for 15 min. Later, the supernatant solutions were analyzed by using UV-VIS spectrophotometer after filtration and suitable dilution for the drug content at 247 nm (Vaskula *et al.*, 2012).

Mathematical Model for designing the LS systems

A new mathematical approach introduced by Spireas, is used for the formulation of liquid-solid systems (Spireas *et al.*, 1999, 1998). This approach is done by determining the values of flowable liquid retention potential (Φ) which is constant for each powder excipient with non-volatile liquid used in formulation. It is obtained by applying the equations as follows:

The ratio of excipients is determined by the Equation (1)

$$R = Q/q \tag{1}$$

where,

R is the ratio of carrier to coating material used in LS powder system,

Q is amount of carrier material and

q is amount of coating material.

The liquid load factor (Lf) is determined using Equation (2) which is defined as maximum amount of liquid held within the carrier material.

$$Lf = W/Q \tag{2}$$

Where,

W is the weight of liquid medication, and

Q is weight of the carrier material in the system

The Lf value is also determined by the Equation (3) using the flowable liquid retention potentials (Φ-values) of excipients used in the formulation. The Φ-values are constant for a particular excipient with a particular liquid vehicle.

$$Lf = \mathbf{\Phi} + \Phi\ (1/R) \tag{3}$$

where $\mathbf{\Phi}$ is the flowable liquid retention potential of carrier material, and

Φ is the flowable liquid retention potential of coating material.

From the Equation (3), Lf was calculated taking R value as predetermined. Next, using Equation (2), Q can be calculated where W is known which the combined weight of drug and liquid vehicle is used in formulation. Similarly, from Equation (1), q can be determined from the values of R and Q.

Preparation of Flurbiprofen LS capsules and conventional capsules

Flurbiprofen LS formulations were obtained taking three different drug concentration such as 40, 45 and 50% (w/w) in liquid vehicle PEG 600 that showed highest solubility for the drug. Avicel is used as carrier and Aerosil is used as coating material in the ratio of 5, 7.5 and 10. In order to prepare capsules, firstly, drug was accurately weighed (50mg/capsule) and mixed with PEG 600 taken into a beaker. This dispersion was further sonicated until a homogenous mixture was obtained. This liquid medication was combined with calculated quantity of the carrier material, Avicel, with mixing. This slurry was then blended with the calculated quantity of the coating material, Aerosil, using standard blending procedure according to Spireas (2002) to obtain LS formulation. Sodium starch glycolate was used as disintegrating agent. This final calculated unit formulation was encapsulated in hard empty gelatin capsule (size 0). The composition of each formulation is given in Table 1. The same procedure was followed to prepare Flurbiprofen conventional capsules.

Rheological properties of the Flurbiprofen LS system

The flow properties of the LS powder systems were measured by determining the angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index which are determined using bulk and tapped density (Zhao and Augsburger, 2005). The results are given in Table 2.

Evaluation of Flurbiprofen LS capsules

The prepared Flurbiprofen LS capsules were evaluated for content uniformity, weight variation, disintegration and *in vitro* dissolution (Chella *et al.*, 2012).

Drug content

In order to calculate the drug content, the LS powder formulation equivalent to 50mg of drug was dissolved in a 50 ml beaker containing 7.4pH phosphate buffer and then sonicated for 15 min and then filtered using whatman filter paper.

It was then diluted if necessary, with buffer and analysed for drug content by UV spectrophotometer at 247 nm.

Disintegration time

It was determined by disintegration apparatus using 7.4 pH phosphate buffer as disintegration medium according to IP.

The time was noted when all the six capsules completely disintegrated.

In vitro dissolution

The *in vitro* dissolution release profiles of Flurbiprofen drug from LS capsules and pure drug were obtained using USP-type I (rotating basket) dissolution apparatus (Electrolab Pvt. Ltd Mumbai, India). The dissolution study was performed in 900ml phosphate buffer pH 7.4 as the dissolution medium at 37 °C ± 0.5°C and 50 rpm for I hour to simulate the *in vivo* conditions. Aliquots of 5 ml samples were collected at specified time intervals. Similarly, at each time of sampling 5 ml of fresh dissolution medium was added to sustain sink conditions. The withdrawn samples were filtered, suitably diluted and analysed using UV-VIS spectrophotometer at 247 nm for the drug content (Hitesh *et al.*, 2014).

FTIR study

Fourier transform infrared spectra of Flurbiprofen, Avicel, Aerosil and optimized Flurbiprofen LS capsule were obtained. It is used to determine possible chemical interactions if any, present in the formulation. In the KBr pellet method, about 5mg of sample mixed with 100mg potassium bromide IR powder. It is compressed under vacuum at a pressure of about 12,000 psi for 3min. The final disc was mounted in a suitable holder in and the sample was scanned from 4000 to 400 cm^{-1} using FTIR spectrophotometer (Shimadzu, Japan) (Shavi *et al.*, 2010).

DSC study

Thermograms of the Flurbiprofen pure drug and optimized Flurbiprofen LS capsule were obtained using Philips X-ray diffractometer. It was determined by heating about 2 to 3 mg of sample in aluminium pans in nitrogen environment at a rate of 10°C/min.

PXRD study

Powder X-ray diffraction (PXRD) spectra of Flurbiprofen and optimized Flurbiprofen LS capsule was obtained using powder X-ray diffractometer with Cu as target at a scan speed of 4°/min. The samples were analysed at a 2θ angle range of 2-45° at time, current of 55 mA and operating voltage of 40 kV (Pavan *et al.*, 2014).

SEM analysis

The surface characteristics of Flurbiprofen and optimized Flurbiprofen LS capsule samples were obtained by SEM analysis (ZEISS scanning electron microscope). The samples were attached to a carbon-coated metallic stub using double sided tape. Imaging was performed at an acceleration voltage of 30 kV.

Table 1: Formulation of Flurbiprofen capsules prepared by using LS technique

F code	Drug concentration (%w/w)	R	Drug (mg)	Lf	PEG 600 (mg)	Avicel (mg)	Aerosil (mg)	Final wt (mg)
CF1	40	5	50	0.622	75	200.9646	40.19293	366.1576
CF2	40	7.5	50	0.465	75	268.8172	35.84229	429.6595
CF3	40	10	50	0.386	75	323.8342	32.38342	481.2176
CF4	45	5	50	0.622	61.11	178.6334	35.72669	325.4701
CF5	45	7.5	50	0.465	61.11	238.9462	31.8595	381.9157
CF6	45	10	50	0.386	61.11	287.8497	28.78497	427.7447
CF7	50	5	50	0.622	50	160.7717	32.15434	292.926
CF8	50	7.5	50	0.465	50	215.0538	28.67384	343.7276
CF9	50	10	50	0.386	50	259.0674	25.90674	384.9741
Conventional capsule		10	50			377.64	37.76	498.11

Table 2: Flow properties of Flurbiprofen LS system

F code	Bulk Density*	Tapped Density*	Carr's compressibility Index	Hausner's Ratio	Angle of Repose (θ)*
CF1	0.418±0.04	0.487±0.13	14.17	1.17	31.14±1.44
CF2	0.432±0.06	0.492±0.08	12.19	1.14	30.11±1.13
CF3	0.446±0.03	0.513±0.11	13.06	1.15	29.02±1.28
CF4	0.411±0.11	0.498±0.07	17.47	1.21	31.10±1.30
CF5	0.422±0.09	0.517±0.09	18.37	1.23	30.66±1.25
CF6	0.456±0.12	0.437±0.12	15.08	1.18	32.94±1.33
CF7	0.379±0.11	0.455±0.07	16.70	1.20	32.77±1.21
CF8	0.396±0.07	0.462±0.08	14.29	1.17	33.85±1.31
CF9	0.412±0.06	0.486±0.09	15.23	1.18	31.49±1.43

(*mean±SD, n=3)

Table 3: Evaluation of Flurbiprofen LS capsules

F code	Weight variation*(mg)	% Drug Content*	Disintegration (min)*
CF1	361.6±1.32	98±0.24	2.38±0.12
CF2	423.8±2.11	99±0.11	2.49±0.11
CF3	476.9±2.59	99±0.37	2.55±0.09
CF4	319.5±3.12	99±0.33	2.11±0.08
CF5	377.4±2.44	98±0.44	2.13±0.11
CF6	421.7±1.97	98±0.39	2.15±0.11
CF7	285.8±1.88	97±0.21	1.51±0.07
CF8	338.5±3.63	98±0.29	1.58±0.06
CF9	379.4±4.43	98±0.32	2.05±0.08

(*mean±SD, n=3)

RESULTS AND DISCUSSION

Solubility studies

Solubility of drug in selected non-volatile liquid vehicle is very significant in LS formulations because it promotes molecular dispersion and which further leads to enhanced dissolution rate. The results of saturation solubility studies of Flurbiprofen in different non-solvents were shown in Figure 1. As the drug showed highest solubility in PEG 600 (186.6±2.93mg/ml), it was selected as non-volatile liquid vehicle for formulation of LS capsules.

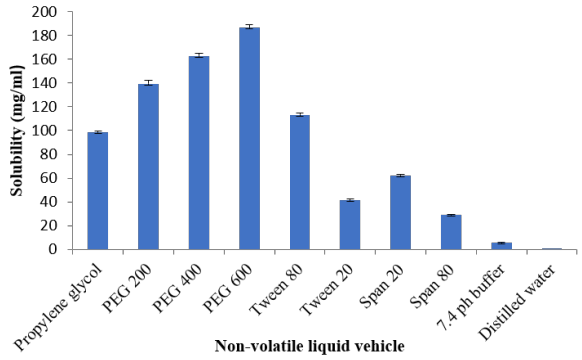

Figure 1: Saturated solubility of Flurbiprofen in various non-volatile solvents

Determination of flowable liquid-retention potential (Φ-values)

The flowable liquid retention potential values for excipients were determined using the "Angle of slide" method. In this method, around10g of excipient is mixed with increasing amount of liquid vehicle. These admixtures were kept on smooth metal plate and tilted until powder starts to slide. The angle formed between the metal plate and the horizontal surface was defined as the angle of slide (h) and the value equivalent to angle 33º was determined as flowable liquid-retention potential (Φ values) of each excipient. It is measure using the following equation.

$$\Phi\ value = \frac{weight\ of\ non{-}volatile\ liquid}{weight\ of\ excipient}$$

The Φ -value for Avicel and Φ –value for Aerosil with PEG 600 were 0.15 and 2.36 respectively. R values selected were 5, 7.5 and 10.

Depending on the R values of 5, 7.5 and 10, the Lf values calculated were 0.622, 0.465, 0.386 respectively using the Equation (3).

Rheological properties of the Flurbiprofen LS system

The rheological properties of powder are important in handling various pharmaceutical operations to obtain uniform final formulation. Hence, the study of flow properties of LS powders is significant to attain uniform filling from the hopper to the hard empty hard gelatin shells and hence analyzed prior to formulation. The results of flow properties of the Flurbiprofen LS powder system were given in Table 2. Batch CF3 showed good flow properties with angle of repose (θ) value of 29.02 and has acceptable flowability. It also showed Carr's index of 13.06 was considered acceptable as a flow property.

Evaluation of Flurbiprofen LS capsules

The evaluation results of the Flurbiprofen LS capsules are mentioned in Table 3. The disintegration time was less than 5 minutes which is as per the specifications given for capsules in IP. LS capsules also showed uniformity in drug content.

In vitro dissolution

The dissolution of Flurbiprofen LS capsules and flurbiprofen conventional capsules were shown in Figure 2. It was observed that CF3 LS capsules showed higher *in-vitro* release than that of conventional capsule. Presence of drug in solution form in PEG 600 attributes to increased wetting property of drug thereby decreasing the interfacial tension between LS system and dissolution medium. The surface area of drug exposed to the dissolution medium is also increased. Thus, increased surface area of the molecularly dispersed drug in the LS capsules is majorly responsible for higher dissolution rates. In the current study, the liquid medication were used in different concentrations such as 33.33, 40 and 50% and the ratio of excipients was 5 7.5 to 10. The results for drug release observed the following pattern of $R_{10} > R_{7.5} > R_{5.}$

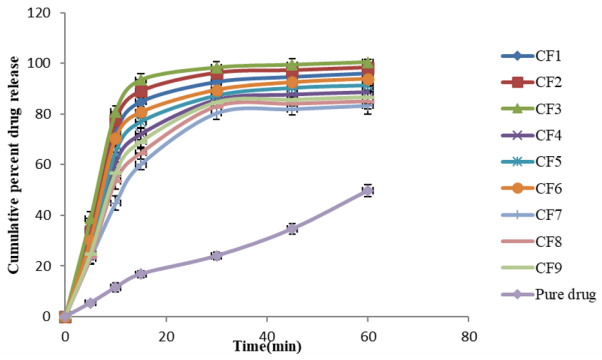

Figure 2: Dissolution profiles of Flurbiprofen LS capsules and conventional capsule

The cumulative percentage of drug released from CF3 was 98% after 30 min, while that of conventional dosage form the released drug content was 25% after 30 minutes. Therefore, it can be proved that the LS technique can be promising

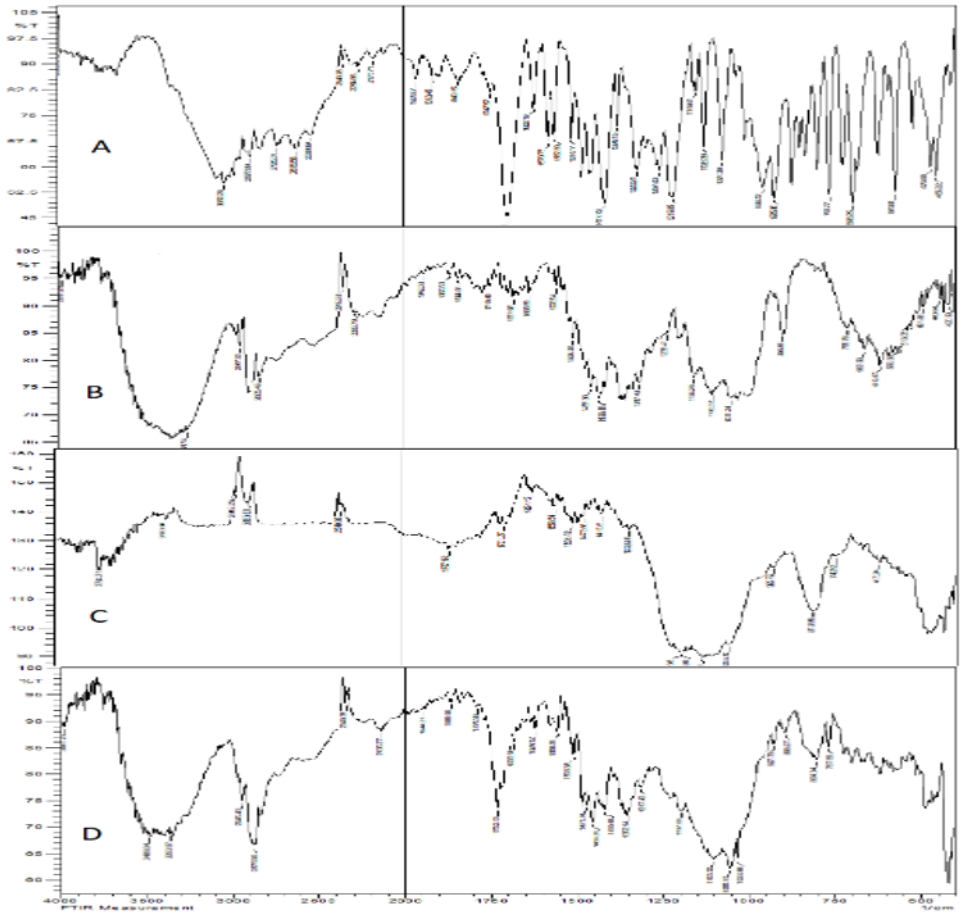

Figure 3: FTIR of A. Flurbiprofen B. Avicel C. Aerosil D. CF3

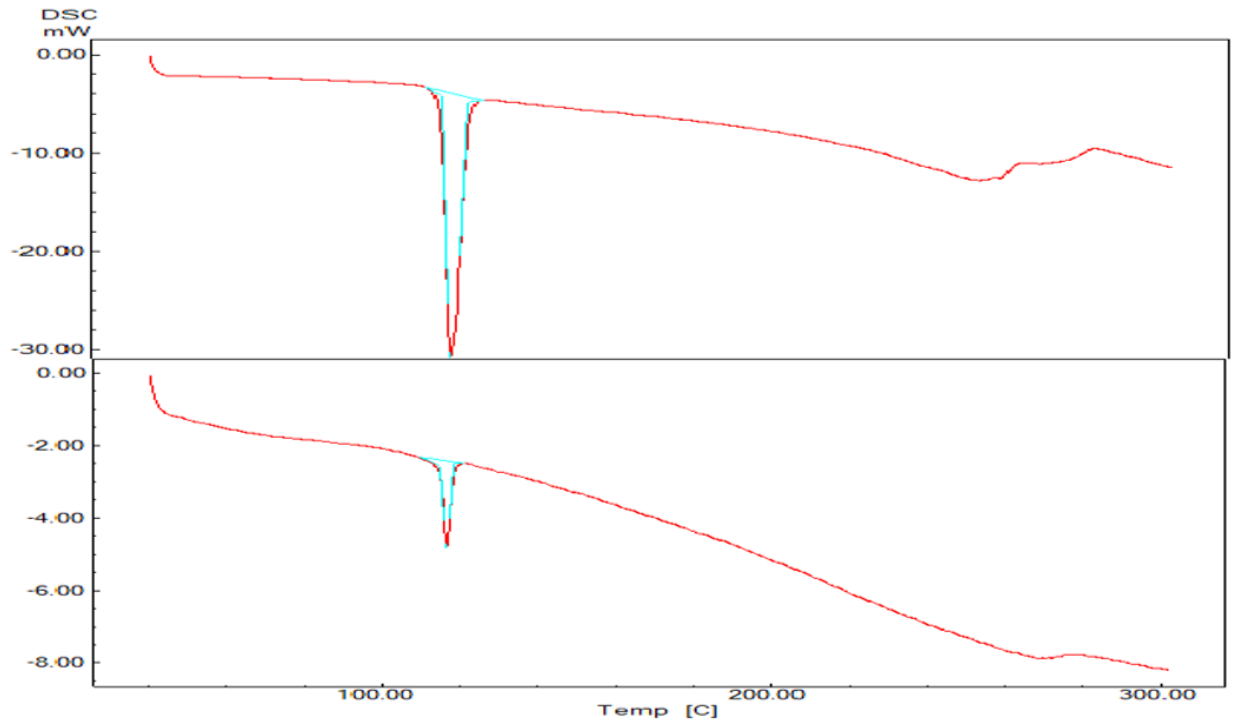

Figure 4: DSC thermogram of A. Flurbiprofen B. CF3

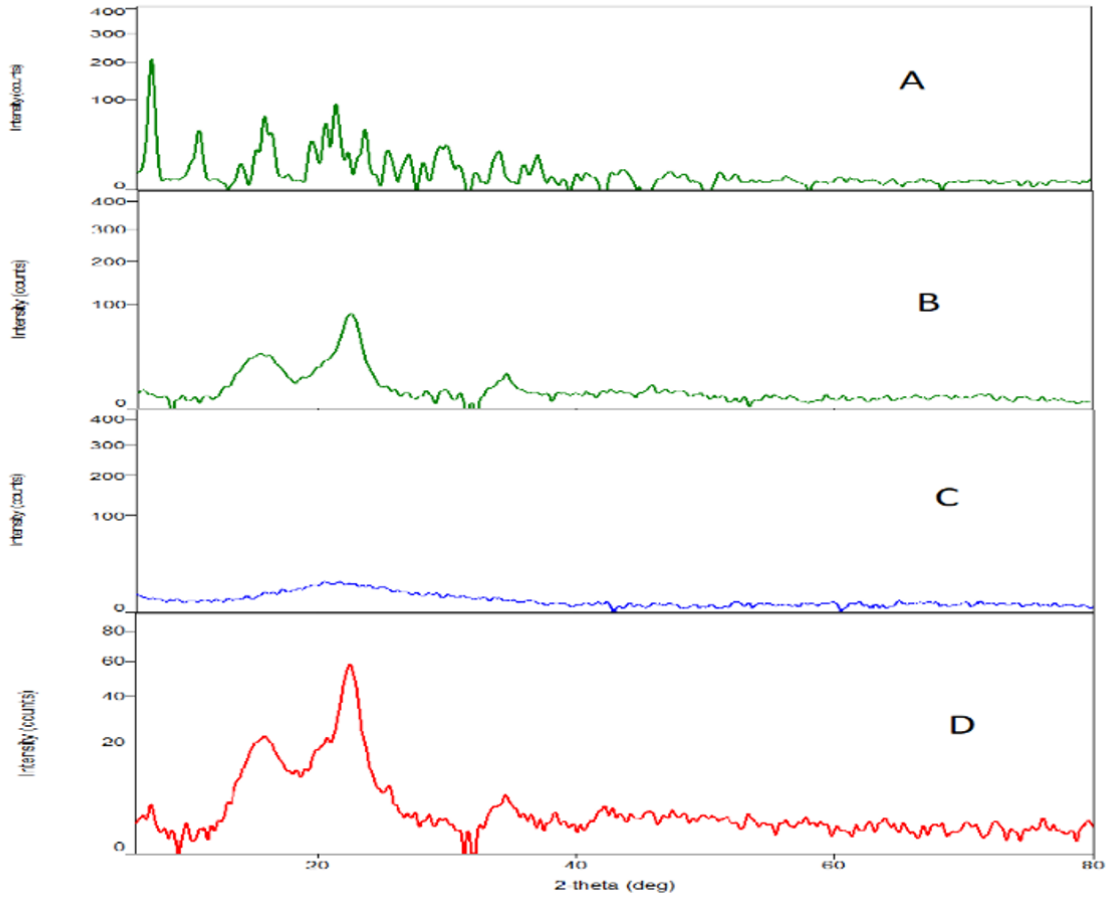

Figure 5: X-ray diffractograms of A. Flurbiprofen B. Avicel C. Aerosil D. CF3

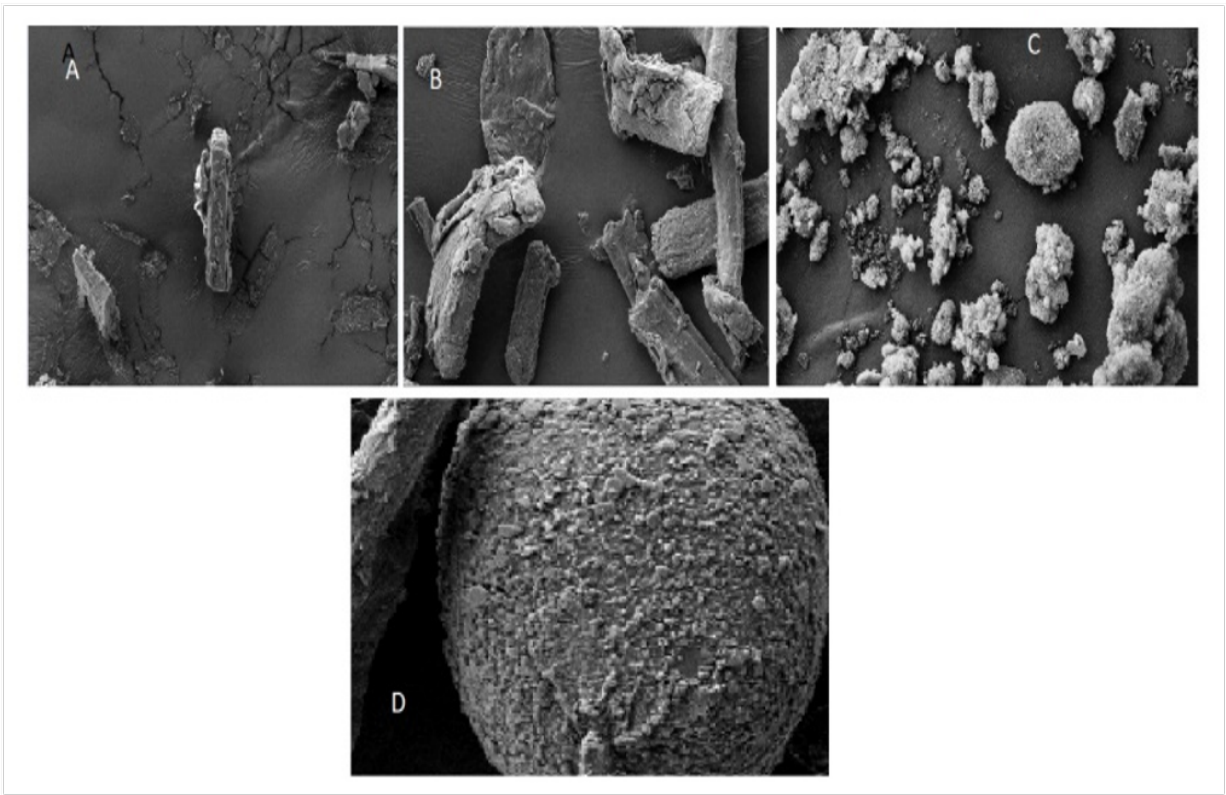

Figure 6: SEM images of A. Flurbiprofen B. Avicel C. Aerosil D. CF3

method for the formulation of poorly water soluble drugs. According to Spireas, the LS formulations possessing higher carrier to coating ratio is observed with increased water absorption, disintegration and enhanced drug release (Spireas *et al.*, 1999). However, high amounts of colloidal silica which is hydrophobic in nature may cause retardation of drug release. It was also proved earlier that LS systems showed enhanced dissolution rates compared to conventional capsules leads to increased oral bioavailability due to improved wetting nature of drug (Padmapreetha and Arulkumaran, 2016).

FTIR study

The FTIR spectrum for Flurbiprofen, Avicel and Aerosil and optimized Flurbiprofen LS capsule (CF3) are shown in Figure 3. The IR spectrum of Flurbiprofen (Figure 3A) exhibits characteristic peaks at 1700.01 cm-1 (Strong aldehyde C=O stretching vibration), 3032 cm-1 (carboxylic acid O-H stretching vibration), 1219.05 cm-1 (C-F strong, C-F stretching), 1579.75 cm-1 (C=C stretching vibration of aromatic ring). Figure 3 showed that the characteristic peaks of Flurbiprofen was retained in optimized Flurbiprofen LS capsule (CF3). The results suggest no chemical interaction between Flurbiprofen and excipients used in the LS capsules formulation.

DSC study

DSC is used to determine any interactions among the ingredients used in LS capsules. Figure 4 shows the endothermic peaks of pure drug, Flurbiprofen and optimized Flurbiprofen LS capsule (CF3). The Flurbiprofen showed a sharp endothermic peak at 115.68 °C (Figure 4A) conforming to its melting temperature. This shows the presence of pure crystalline form of drug However, the characteristic sharp endothermic peak of Flurbiprofen had disappeared in the optimized LS system (Figure 4B). This indicates that drug is present in molecularly dispersed form inside the LS system because of the formation of solid solution in the LS powdered formulation.

PXRD study

The PXRD studies are performed to study the solid-state characterization and crystal nature of compounds. In Figure 5, crystallinity of the pure drug Flurbiprofen and the optimized Flurbiprofen LS capsule (CF3) was determined. Figure 5A showed sharp characteristic peak for pure drug (Flurbiprofen) which was diffused in case of LS formulation (Figure 5D). Thus, the absence of sharp characteristic peaks in optimized formulation suggests that drug might had possibly attained amorphous nature from crystalline form.

SEM analysis

SEM analysis was performed for pure drug Flurbiprofen, Avicel, Aerosil and optimized Flurbiprofen LS capsule (CF3). Figure 6A showed crystal-like structure of Flurbiprofen and Figure 6D showed complete disappearance of crystalline structure in CF3 LS formulation CF3 which indicates the drug has been completely dissolved in the LS formulation. The transformation of drug to amorphous state supports the LS theory that the drug even in its solid dosage form, might be dispersed in molecular level or held inside the powder substrate in solution form, which triggered the enhanced drug dissolution properties.

CONCLUSION

Low aqueous solubility of flurbiprofen renders solubility and dissolution as the limiting step for the absorption of drug into systemic circulation. Hence, an attempt was made to apply liquisolid method to improve the rate of drug dissolution. The results of Flurbiprofen loaded LS capsules such as drug content and disintegration were within the limits as per IP. The cumulative drug release studies also confirmed improved dissolution profile from LS capsules compared to that of conventional capsule. The FTIR and DSC studies revealed no chemical incompatibility among excipients used in the formulation. Results of SEM and PXRD studies revealed physical change of crystalline to amorphous form of drug in the Flurbiprofen LS capsules. Finally, liquisolid method succeeded in the enhancement if dissolution profile of Flurbiprofen loaded LS capsules.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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