IJBPAS, October, Special Issue, 2021, 10(10): 457-469
ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PREPARATION AND CHARACTERIZATION LIQUISOLID COMPACTS OF BCS CLASS II DRUG FLURBIPROFEN

MADHAVI KASTURI[*1] AND NEELESH MALVIYA[2]

1: Research Scholar, Mandsaur University, Department of Pharmacy, Rewas Dewda Road, Mandsaur, M.P- 458001

2: Faculty of Pharmacy, Smriti College of Pharmaceutical Education, Indore, M.P – 452010

***Corresponding Author: E Mail:** madhavi2386@gmail.com

Received 27th April 2021; Revised 25th June 2021; Accepted 1st Aug. 2021; Available online 1st Oct. 2021

https://doi.org/10.31032/IJBPAS/2021/10.10.1042

ABSTRACT

The current research work is mainly focused to improve the solubility and dissolution rate of BCS Class II drug flurbiprofen with the application of liquisolid technology. Flurbiprofen is selected as the model drug as it belongs to BCS Class II, and has extremely low water solubility of 10.45 3.2 g/ml. It is a non-steroidal anti-inflammatory drug andused to treat of rheumatoid arthritis, osteoarthritis and spondylitis. The Flurbiprofen liquisolid compacts were prepared and subjected to evaluation. After screening various solvents, PEG 400 was chosen as non-volatile liquid vehicle as it showed maximum solubility for drug.Theliquid medication was prepared containing drug in vehicle of various concentration of 33.33%, 40% and 50%. This is further converted to dry powder by admixing with suitable carrier (Avicel PH 102) and coating agent (Cab-O-Sil M5). These powdered liquisolid formulations were subjected to pre-compression rheological studies to determine their flow property. They are further compressed to obtain various liquisolid compacts ranging from TF1 to TF9. They are further subjected to post-compression evaluation parameters such as weight variation, content uniformity, hardness, friability, disintegration and *in vitro* dissolution. The dissolution efficiency at 21 minutes (DE_{21}) for optimized TF7 liquisolid compact was found to be 24.41 and that of directly compressed tablet was found to be 2.44 in pH 7.4 phosphate buffer solution. The most likely reason for improved solubility may be due to improved wettability and greater surface area of drug exposed to dissolution media. FTIR and DSC studies

confirmed no drug- excipient incompatibility. SEM and PXRD studies revealed the transformation of crystalline to amorphous nature of drug. Finally, it can be concluded that enhanced solubility of drug which in turn enhanced dissolution profile Flurbiprofen was successfully achieved using liquisolid compact technique.

Keywords: Liquisolid technique, Flurbiprofen, solubility enhancement, carrier material, coating material

INTRODUCTION

Solubility and dissolution enhancement of poorly aqueous soluble drugs has always been a challenge for the researchers to develop oral dosage forms having good bioavailability. Low water-soluble drugs contain dissolution as the rate limiting step which causes slow drug absorption, thus results in erratic bioavailability **[1]**. Previously, manytechniques have been applied to improve the solubility, dissolution rate and bioavailability of poorly aqueous soluble drugs.

Flurbiprofen is a non-steroidal anti-inflammatory drug containing analgesic and anti-inflammatory effects **[2]**. It acts against cyclooxygenase (COX-1 andCOX-2) that blocks the synthesis of prostaglandin E2 (pain inducer). It treats ailments such as osteoarthritis, gout and rheumatoid arthritis. It was selected as model drug in this study, because it belongs to BCS class II **[3]**. The poor aqueous solubility of drug (10.45 ± 3.2µg/ml) leads to poor bioavailability **[4]**. Hence, development of Flurbiprofen oral solid dosage forms possess problem due to its erratic absorption and bioavailability. Several attempts to improve flurbiprofen solubility and bioavailability have been reported in the past, including solid dispersions, microemulsions, complexation using cyclodextrin inclusion complexes, spray drying methods, nanosuspensions, micelle formulation, solid lipid nanoparticles, self-microemulsifying drug delivery system **[5-8]**. Recently, the liquisolid technique has proven to be a promising approach to improve the solubility of poorly aqueous soluble drug **[9]**. As a result, the current work employed the liquisolid approach to improve the solubility and dissolution profile of flurbiprofen.

Spireas was the first scientist to introduce the Liquisolid technique, as a novel method for improving the solubility and dissolving profiles of poorly aqueous soluble drugs using mathematical approach. These liquisolid systems are powdered forms of liquid medication (drugs) that are flowable and compressible. Liquid medication indicates lipophilic drug dissolved in suitable solvent system. This liquid medication into non-adherent, dry-looking, free-flowing, and readily compressible

powders A simple mixing technique with selected powder excipients referred to as carrier powders (having good absorption properties)and coating powders (having good adsorption properties) that can transform However, the drug will be distributed molecularly in the liquisolid compact, which will improve its dissolution and oral bioavailability **[10]**. As a result, liquisolid compacts of water-insoluble drugs may be expected to have improved drug release qualities and increased bioavailability due to their significant improvement in wetting properties and increase in available surface area of drug for dissolution **[11]**.

MATERIALS AND METHODS

Materials

Flurbiprofen was obtained in its purest form from Alfa Aesar, U.S.A. S.D Fine Chemicals Ltd, Mumbai, provided excipients such as Avicel PH 102, Propylene glycol, Cab-O-Sil M5, sodium starch glycolate, magnesium stearate, and talc. Polyethylene glycols such as PEG 200, PEG 400, PEG 600, Tween 20, Tween 80, Span 20 and Span 80, as well as Tween 20, Tween 80, Span 20 and Span 80, were obtained from Himedia in Mumbai. Analytical gradechemicals were used in the current research work.

Experimental methods

Saturation solubility studies

Saturation solubility studies for Flurbiprofen was performedin various solventsas shown in **Table 1**. Initially, drug solutions were prepared till saturation is achieved by adding excess of drug to 5ml of each selected solvent in screw capped vials. These vials were kept on orbital shaker (Remi, Mumbai) for 24 hours and then centrifuged for 15 min at 2500 rpm. From the above, accurately measured amounts of filtered supernatant solutions were obtained. They were further diluted and analysed spectrophotometrically using UV VIS spectrophotometer (Shimadzu 1800) at 247nm to determine thedrug content **[12]**.

Application of Spireas Mathematical Model for designing the liquisolid systems:

Generally, powder systems can withhold only certain amount of liquid medication and maintain acceptable flow property and compression property **[13]**. A new mathematical approach is used to calculate the required amounts of excipients such as carrier agent and coating agent in liquid-solid systems.

The flowable liquid retention potential (Φ-number) of powder system relates to the maximum quantity of solvent that can be retained inside its bulk (w/w) and also maintain acceptable flow behavior.The ratio of carrier to coating material, represented by R, in the liquisolid powder

system can be obtained from the below equation

$$R = Q/q \quad ... (1)$$

where, Qand q indicates weight of carrier material and coating material respectively.

During the development of liquisolid powder system, an acceptable flow and compressible nature of powder can be achieved only if liquid present in the carrier material donot exceed the limit that is termed as liquid load factor (Lf).It is determined using the equation below and is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier powder (Q) in the liquisolid system.

$$Lf = W/Q \quad ... (2)$$

Using the flowable liquid retention potentials (Φ-values) of the powder excipients, Spireas assessed the required quantities of powder excipients. As a result, the following relationship exists between the powder excipients ratio R and the liquid load factors Lf of the formulations:

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

where **Φ** is flowable liquid retention potential of carrier material and Φ is flowable liquid retention potential of coating material. They are constant values.

So, in order to calculate the required weights of the excipients used, firstly, from the equation (3), Lf can be calculated (where R is predetermined). Next, weight of the liquid drug solution or liquid medication (W) is known from the selected concentration of drug loaded solvent. Hence, from equation (2). after knowing both Lf and W values, the appropriate amounts of carrier material (Q) can be determined. Similarly, from equations (1) amount of coating (q) powder required can be calculated. Finally, using Spireas mathematical model, the amounts of carrier and coating agents required to convert a particular amount of liquid medication (W) into a flowable and compressible liquisolid system is estimated.

Preparation of Flurbiprofen Liquisolid Compacts:

Flurbiprofen liquisolid compacts were made by dissolving precisely weighed amounts of drug and selected liquid vehiclein a 20 mL glass beaker.Further, to the above solution predetermined amounts of carrier and coating ingredients were added.Mixing process involved three step procedures. Initially, to equally distribute liquid medication in the powder, the liquisolid powder system was mixed for about one minute at speed of one rotation per second. Later, the powder was spread evenly as a uniform coating on the mortar surface for 5 minutes to allow the liquid medication to be absorbed insidiously. Finally, the liquisloid powder was scraped from the mortar surface with an aluminium spatula in the third phase. After adding disintegrating agent, the final formulation was compacted into liquisolid compacts

using rotary tablet press (Cadmach Ahmedabad, India). A standard directly compressed Flurbiprofen tablet comprising 50 mg of drug, Avicel PH 102, Cab-O-Sil M5, and sodium starch glycolate was also made.The composition of Flurbiprofen liquisolid compacts were shown in **Table 2**.

Pre-compression studies of the Flurbiprofen liquisolid system

Flow properties of the Flurbiprofen liquisolid system

The angle of repose, Carr's index, and Hausner's ratio were used to determine the flow parameters of the liquisolid particle systems. The angle of repose was calculated applying the fixed funnel method.For the calculation of Hausner's ratio and Carr's index, the bulk density and tapped density of liquisolid powder systems were also calculated **(Table 3)**.

Post compression evaluation of Flurbiprofen liquisolid compacts

The prepared Flurbiprofen liquisolid compacts were tested for content homogeneity, friability, weight variation, hardness, disintegration and cumulative drug release. All of the preceding tests were performed in accordance with the United States Pharmacopeia (USP) compendia's guidelines **(Table 4)**.

***In vitro* dissolution studies**

The *in vitro* dissolution release patterns of Flurbiprofen drug from the formulated liquisolid compacts and the directly compressed tablets were determined using the USP-II dissolution test instrument (Electrolab Pvt. Ltd Mumbai, India).The dissolution investigation was conducted at 37°C ± 0.5 °C and 50 rpm in 900 mL phosphate buffer pH 7.4 as the dissolution medium. The samples were filtered and spectrophotometrically examined at 247 nm to estimate drug release. The results were shown in **Figure 1A and 1B**.

IR spectra analysis

The IR spectra of pure drug Flurbiprofen, Cab-O-Sil M5, Avicel PH102 and liquisolid compactTF7 formulation were determined **(Figure 2)**. Using the KBr pellet method, approximately 5mg of sample was well mixed with 100 mg KBr IR powder and compressed under vacuum for 3 minutes at a pressure of about 12,000 psi. The sample was scanned from 4000 to 400 cm^{-1} using an FTIR spectrophotometer (Shimadzu, Japan) with the disc fixed in an appropriate holder **[14]**.

Differential scanning calorimetry

Using a Philips PW3710 X-ray diffractometer, thermograms of Flurbiprofen and the optimized liquisolid formulation TF7 were recorded **(Figure 3)**. In a nitrogen atmosphere, 2 to 3 mg of sample was heated on an aluminium crimp pan at a rate of 10 °C/min for the analysis.

Powder X-ray diffraction

Flurbiprofen and optimized liquisolid TF7 formulation powder X-ray diffraction

(PXRD) spectra were acquired **(Figure 4)** using a high-power powder X-ray diffractometer (Ru-200B, Pune, India) with Cu as target at a scan speed of 4°/min. At a time of 0.5 seconds, the samples were evaluated at two angles ranging from 2 to 45 degrees. 40 kV and 55 mA were the operational voltage and current, respectively **[15]**.

Scanning electron microscopy

Scanning electron microscope (Hitachi, Japan) was used to examine the surface morphology and particle shape of pure drug Flurbiprofen and the optimisedliquisolidTF7 formulation **(Figure 5)**. The samples were first adhered to the carbon-coated metallic stubusing double sided adhesive tape. This was sputter coated with platinum coating machine and mounted on SEM for surface analysis. Imaging was carried out at acceleration voltage of 30 kV.

RESULTS AND DISCUSSION

Saturation solubility studies

The most significant component in developing liquisolid systems is drug solubility in various non-volatile vehicles. The drug's solubility improves molecular dispersion, which furtherenhances the dissolution rate. The results for Flurbiprofen saturation solubility are listed in **Table 1**.

PEG 400 has the maximum solubility of flurbiprofen (63.81 ± 2.18mg/ml) and hence chosen as the non-volatile liquid vehicle for the formulation of Flurbiprofen liquisolid compacts based on solubility data.

Application of Mathematical Model to develop liquisolid systems

The flowable liquid-retention potentials (Φ-values) of both carrier and coating materials, as well as the liquid load factor (Lf value), must be established in order to determine the amounts of the ingredients used in liquisolid compacts.

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

The Φ-values for Avicel PH102 and Φ -values Cab-O-Sil M5 with PEG 400 were 0.242 and 0.653 respectively. The ratio of excipients (R values) chosen were 5,7.5 and 10.

Determination of liquid load factor

The liquid load factor, Lf, was derived, substituting the Φ –values in below equation

$Lf = \Phi + \Phi (1/R)$

The required quantities of excipients were calculated using the Lf values.

Based on the R values of 5, 7.5 and 10, the Lf values calculated are 0.373, 0.329, and 0.307 respectively.

Preparation of flurbiprofen liquisolid compacts

Pre-compression studies of the Flurbiprofen liquisolid system

Flow properties of the Flurbiprofen liquisolid system

The flow characteristics of the Flurbiprofen liquisolid powder system were shown in **Table 3**. All the formulations showed good flow characteristics comprising adequate flow ability.

Post compression evaluation of Flurbiprofen liquisolid compacts

The results of the Flurbiprofen liquisolid compacts test results such as thickness, hardness, weight variation, friability, drug content, and disintegration are listed in **Table 4**. All of the Flurbiprofen compacts tested demonstrated adequate friability, with no percentage loss in tablet weights exceeding 0.5 percent. They also disintegrated in less than 5 minutes, which is consistent with the IP's criteria for uncoated tablets. All of the formulations had similar drug content, ranging from 98 to 100 percent.

***In vitro* dissolution studies**

The dissolution patterns of all the prepared Flurbiprofen liquisolid compacts were shown in **Figure 1A** and comparison withdirectly compressed tablet (DCT) were shown in **Figure 1B**. It was observed that TF7 liquisolid compacts showed higher *invitro*drug release when compared to that of the DCT. The presence of drug in the form of either solution or molecular dispersion in PEG 400, promotes the wetting of drug particles in liquisolid compacts by lowering the interfacial tension between the compact and the dissolution medium. In addition, the amount of drug surface available for disintegration also increased tremendously.As a result, the surface area of drug available for dissolution in liquisolid compacts is substantially higher than in directly compressed compacts.

Different drug concentrations in liquid medication were used in this trial, including 33.33 percent, 40 percent, and 50 percent. In addition, the R value for each drug to non volatile solvent was altered from 5 to 10, and the *in vitro* drug release patterns were investigated. The following pattern was observed during the medication release: R10 > R7.5 > R5.

The cumulative release of flurbiprofen in 10 minutes (Q10) for optimized liquisolidcompact TF7 formulation was found to be 48.55 ± 3.33% and that of DCT was 4.21 ± 1.43% in pH 7.4 phosphate buffer. The dissolution efficiency at 21 minutes (DE_{21}) for TF7 formulation was found to be 24.41 and that of DCT was found to be 2.44 in pH 7.4 phosphate buffer.

IR spectra analysis

Figure 2 shows the IR spectrum for Flurbiprofen, Avicel PH 102, and Cab-O-Sil M5 samples. Flurbiprofen's infrared spectra **(Figure 2A)** shows distinct 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 vibration), and 1579.75 cm-1 (C=C stretching vibration of aromatic ring). The functional groups of Flurbiprofen were preserved in the liquisolid compact formulation, showing that there was no chemical interaction with any of the excipients employed in the manufacturing of liquisolid compacts.

Differential scanning calorimetry

Figure 3 shows the endothermic peaks of pure drug, Flurbiprofen and optimized TF7 liquisolidcompact. The Flurbiprofen showed a sharp characteristic endothermic peak at 115.68 °C **(Figure 3A)** corresponding to its melting temperature (Tm) and such sharp endothermic peak indicates that the drug used was in a pure crystalline state. However, the characteristic sharp peak of Flurbiprofen had vanished in the optimised liquisolid system **(Figure 3B)**; this confirms that the drug was molecularly dispersed within the liquisolid matrix system by the formation of solid solution in the liquisolid powdered system.

Powder X-ray diffraction

The crystalline nature of substances is studied using powder XRD. The pure drug (Flurbiprofen) exhibited prominent diffraction peaks in the X-Ray Diffraction pattern **(Figure 4)**. However, lack of a prominent distinctive peak in the optimised formulation showed that the drug had most likely changed from crystalline to amorphous form.

Scanning Electron microscopy

SEM was used to study the surface morphology of the pure drugs Flurbiprofen, Avicel, Cab-O-Sil M5 and TF7, and the results are shown in **Figure 5**. The usual crystalline structure of Flurbiprofen, as illustrated in **Figure 5A**, was completely lost in the liquisolid formulation, indicating that the drug was completely dissolved. The entire change of the drug to an amorphous or molecular state supports the liquisolid formulation concept that the drug is held in solution form, or in an almost molecularly distributed state, within the powder substrate, contributing to improved drug dissolving capabilities.

Table 1: Saturation solubility studies of flurbiprofen in various non-volatile solvents (*mean ± SD, n=3)

Solvent	Solubility* (mg/mL)
Propylene glycol	50.35± 3.02
PEG 200	56.33± 1.12
PEG 400	63.81±2.18
PEG 600	58.16± 3.93
Tween 80	43.21±1.56
Tween 20	36.33± 1.88
Span 80	29.38± 2.67
Span 20	12.89± 2.35

Table 2: Formulation of flurbiprofen liquisolid compacts

F code	Drug (mg)	PEG 400 (mg)	R	L_f	Q (mg)	q (mg)	SSG (mg)	Mg stearate (mg)	Talc (mg)	Final weight (mg)
TF1	50	100	5	0.373	402.15	80.43	15	5	2	654.58
TF2	50	100	7.5	0.329	455.93	60.79	15	5	2	688.72
TF3	50	100	10	0.307	488.59	48.85	15	5	2	709.44
TF4	50	75	5	0.373	335.12	67.02	15	5	2	549.14
TF5	50	75	7.5	0.329	379.94	50.66	15	5	2	577.60
TF6	50	75	10	0.307	407.17	40.72	15	5	2	594.89
TF7	50	50	5	0.373	268.09	53.62	15	5	2	443.71
TF8	50	50	7.5	0.329	303.95	40.53	15	5	2	466.48
TF9	50	50	10	0.307	325.73	32.57	15	5	2	480.30
DCT	50	-	-	-	450	-	15	5	2	522.00

where, Drug – flurbiprofen, PEG 400 =Polyethylene glycol 400, Q = Avicel PH 102, q = Cab-O-Sil M5, R = ratio of carrier to coating material, L_f = load factor

Table 3: Flow properties of flurbiprofen liquisolid powder system (*mean ± SD, n=3)

F code	Bulk Density* (gm/ml)	Tapped Density* (gm/ml)	Carr's compressibility Index	Hausner's Ratio	Angle of Repose(θ) *
TF1	0.436±0.012	0.527±0.013	17.267	1.209	30.14±1.45
TF2	0.442±0.017	0.532±0.012	16.918	1.204	29.14±1.14
TF3	0.446±0.022	0.543±0.011	17.863	1.217	28.02±1.27
TF4	0.411±0.014	0.487±0.019	15.605	1.185	32.10±1.31
TF5	0.421±0.008	0.507±0.012	16.962	1.204	31.66±1.27
TF6	0.432±0.012	0.517±0.013	16.441	1.197	31.94±1.32
TF7	0.379±0.043	0.465±0.023	18.496	1.227	33.77±1.22
TF8	0.386±0.002	0.472±0.014	18.221	1.223	32.85±1.32
TF9	0.392±0.011	0.486±0.013	19.341	1.239	30.49±1.44

Table 4: Post compression evaluation of flurbiprofen liquisolid compacts (*mean ± SD, n=3)

F code	Hardness* (Kg/cm^2)	Weight variation* (mg)	% Drug Content*	% Friability*	Disintegration time* (min)
TF1	3.2 ± 0.3	652.19 ± 0.87	100 ± 0.25	0.53 ± 0.06	3.2 ± 0.54
TF2	3.5 ± 0.1	686.48 ± 0.85	99 ± 0.39	0.54 ± 0.05	3.4 ± 0.29
TF3	3.9 ± 0.5	708.97 ± 0.93	98 ± 0.29	0.51 ± 0.09	3.6 ± 0.48
TF4	3.1 ± 0.4	547.66 ± 0.79	98 ± 0.31	0.49 ± 0.12	3.1 ± 0.36
TF5	3.4 ± 0.6	576.41 ± 0.72	100 ± 0.42	0.61 ± 0.07	3.2 ± 0.47
TF6	3.8 ± 0.3	593.95 ± 0.95	99 ± 0.42	0.58 ± 0.08	3.4 ± 0.51
TF7	3.0 ± 0.2	442.11 ± 0.84	98 ± 0.28	0.57 ± 0.11	2.7 ± 0.33
TF8	3.3 ± 0.4	465.31 ± 0.32	98 ± 0.32	0.58 ± 0.14	3.0 ± 0.55
TF9	3.6 ± 0.1	478.93 ± 0.93	98 ± 0.38	0.56 ± 0.18	3.3± 0.49

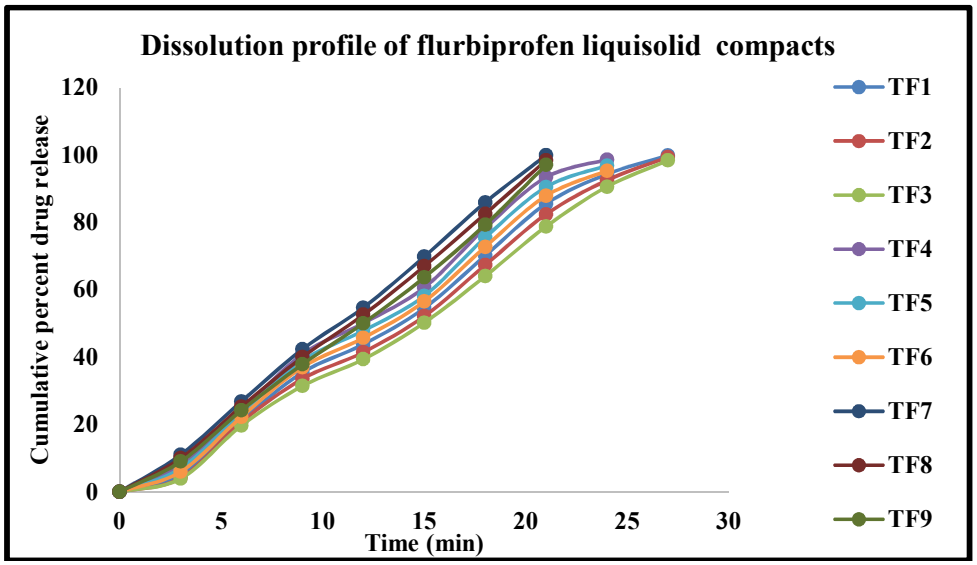

Figure 1A: *In vitro* dissolution profile for flurbiprofen liquisolid compacts TF1 to TF9 in pH 7.4 buffer at 247 nm

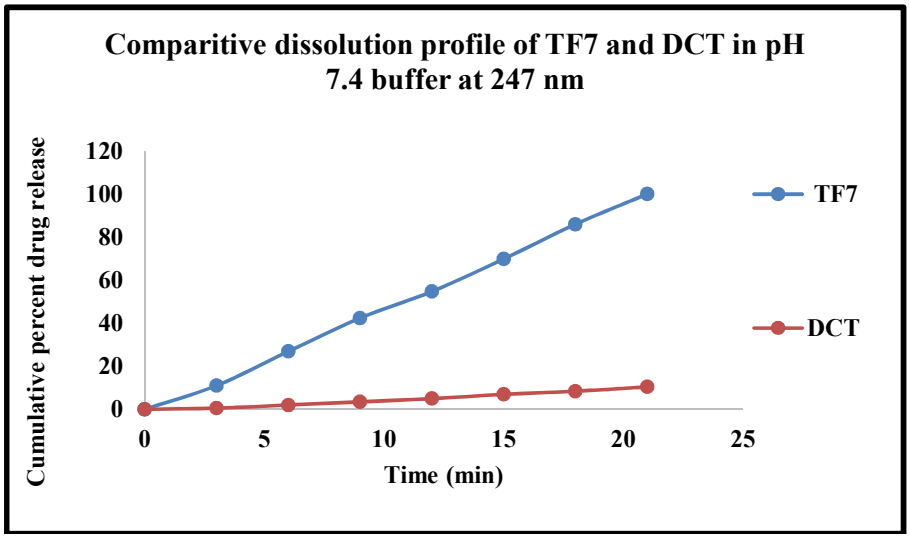

Figure 1B: *In vitro* dissolution profile for TF7 liquisolid compact and DCT in pH 7.4 buffer

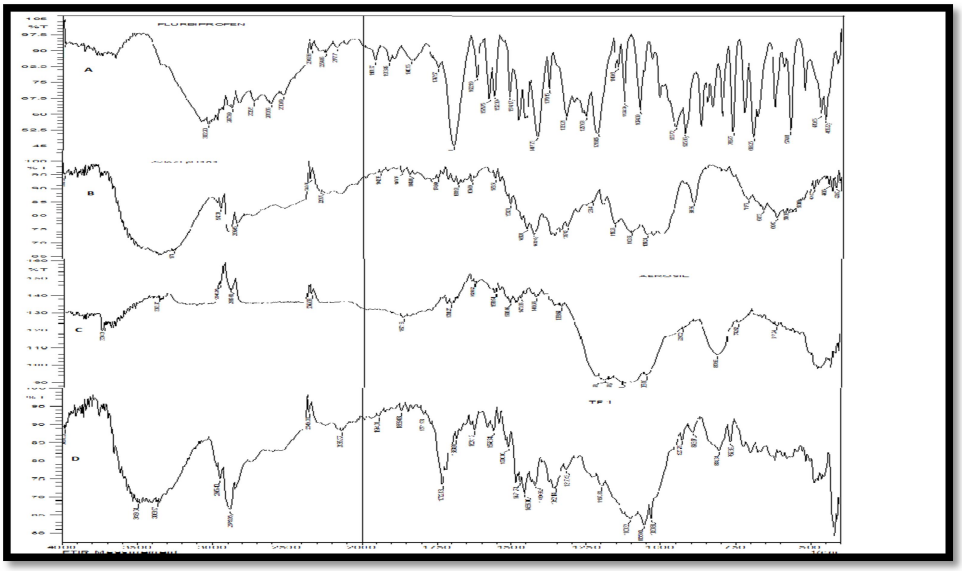

Figure 2: FTIR OF A. FLURBIPROFEN B. AVICEL PH102 C. Cab-O-Sil M5 D. TF7

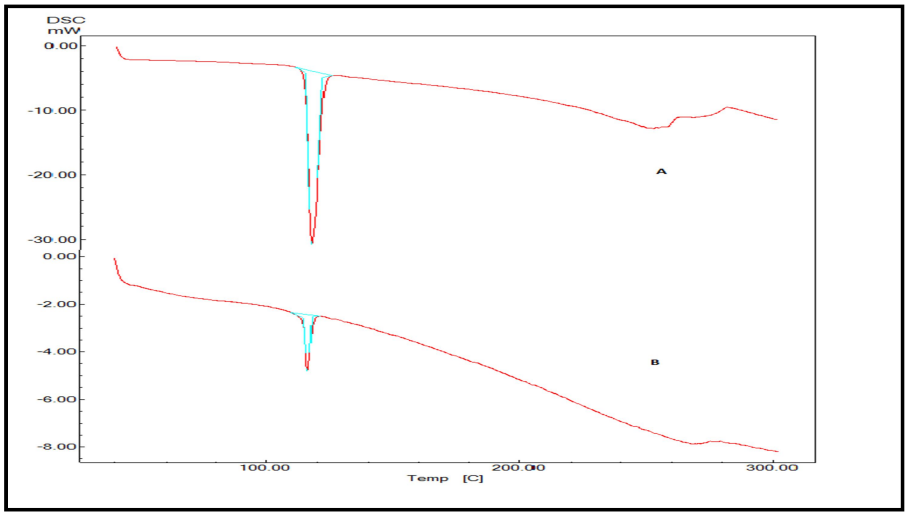

Figure 3: DSC THERMOGRAM OF A. FLURBIPROFEN B. TF7

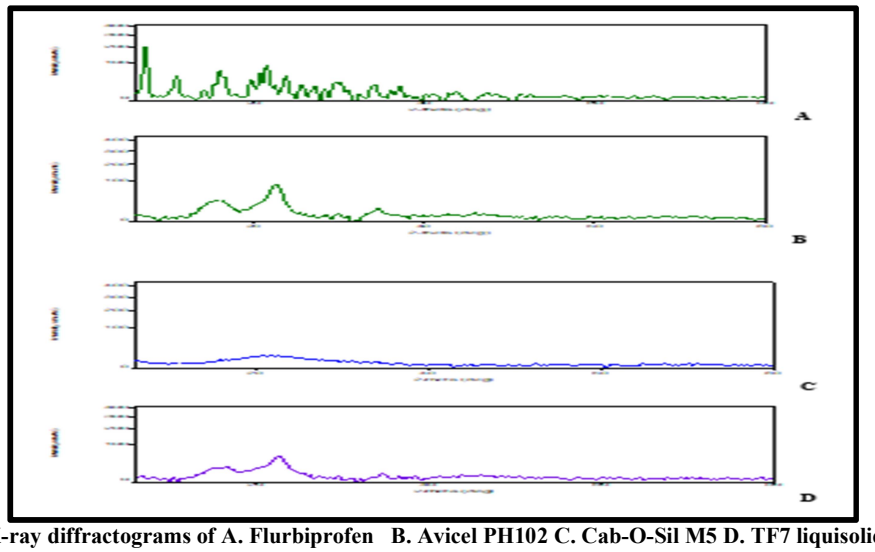

Figure 4: X-ray diffractograms of A. Flurbiprofen B. Avicel PH102 C. Cab-O-Sil M5 D. TF7 liquisolid compact

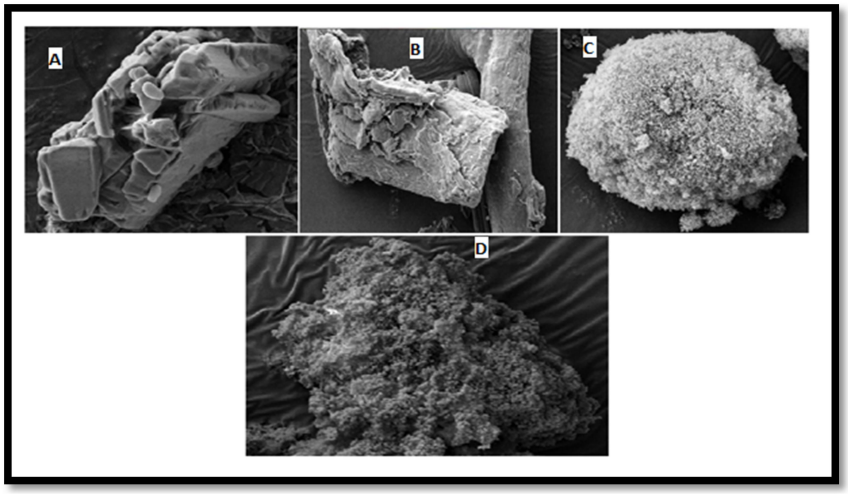

Figure 5: SEM IMAGES OF A. FLURBIPROFEN B. AVICEL C. Cab-O-Sil M5 D. TF7

CONCLUSION

The liquisolid approach was adopted to improve the dissolving characteristicsof Flurbiprofen. The Flurbiprofen liquisolid compacts showed full suppression of crystallinity in PXRD and SEM experiments. All the formulations passed the evaluation tests such as weight variation, hardness, friability and disintegration with the readings obtained within acceptable limits. The *in vitro* dissolving testing demonstrated that liquisolid compacts released more drugwhen compared with directly compressed tablets.The DSC and FTIR investigation confirmed that the drug and excipients utilised in the production of Flurbiprofen liquisolid compacts have no interaction.

Acknowledgements

Smriti College of Pharmaceutical Education provided the required facilities for the analysis, for which the authors are very grateful.

Conflict of Interest

There are no conflicts of interest stated by the authors.

REFERENCES

[1] Srikanth MV, Murali Mohan Babu GV, Sreenivasa Rao, Sunil SA and Ramanamurthy KV: Dissolution rate enhancement of poorly soluble bicalutamide using β- cyclodextrin inclusion complexation. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(1): 191-8.

[2] Fukumoto A, Tajima K, Hori M, Toda Y, Kaku S and Matsumoto H: Analgesic effect of S (+)-flurbiprofen plaster in a rat model of knee arthritis: Analysis of gait and synovial fluid prostaglandin E2 levels. Journal of Pharmacy and Pharmacology 2018; 70: 929–36.

[3] Junaid D, Ahmad K, Jallat K, Amjad K and Majid GK: Studies on self-nanoemulsifying drug delivery system of flurbiprofen employing long, medium and short chain triglycerides. Pakistan Journal of Pharmaceutical Science 2017;30: 601–6.

[4] Dong XL, Myo JH, Prabagar B, Yi Dong Y, Doon HO, Jung HJ, Seo Y, Kim JO, Park SM, Yong CS and Choi HG: Enhanced oral bioavailability of flurbiprofen by combined use of micelle solution and inclusion compound. Archives of Pharmacal Research 2010; 33(1):95-101.

[5] Oktay AN, Karakucuk A, Ilbasmis TS and Celebi N: Dermal flurbiprofen nanosuspensions: Optimization with design of experiment approach and in vitro evaluation. European Journal of Pharmaceutical Sciences 2018; 122: 254–63.

[6] Din FU, Mustapha O, Kim DW, Rashid R, Park JH, Choi JY, Ku SK, Yong CS, Kim JO and Choi HG: Novel dual-reverse thermosensitive solid lipid nanoparticle-loaded hydrogel for rectal administration of flurbiprofen with improved bioavailability and reduced initial burst effect. European Journal of Pharmaceutics and Biopharmaceutics 2015; 94:64–72.

[7] Rudrangi SR, Kaialy W, Ghori MU, Trivedi V, Snowden MJ and Alexander BD: Solid-state flurbiprofen and methyl-b-cyclodextrin inclusion complexes prepared using a single-step, organic solvent-free supercritical fluid process. European Journal of Pharmaceutics and Biopharmaceutics 2016; 104:164–70.

[8] Vithani K, Hawley A, Jannin V, Pouton C and Boyd BJ: Solubilisation behavior of poorly water-soluble drugs during digestion of solid SMEDDS.European Journal of Pharmaceutics and Biopharmaceutics 2018;130: 236–46.

[9] Aparna TN andRao AS:Liquisolid compacts: an approach to enhance the dissolution rate of domperidone. World

Journal of Pharmacy and Pharmaceutical Sciences 2017;6(7):1219-32.

[10] Bhattacharyya S, Pasha I, Verma A, Kothapalli R, Jafar F and HR K: Formulation and evaluation of liquisolid compact of azithromycin dihydrate.Journal of Research in Pharmacy 2019; 23(6): 1022-32.

[11] Spireas S, Wang T and Grover R: Effect of powder substrate on the dissolution properties of methylchlothiazideliquisolid compacts. Drug Development and Industrial Pharmacy 1999; 25 (2): 163–8.

[12] Rajab NA: Preparation and in-vitro evaluation of lacidipine oral liquid solid tablet as an approach of solubility and dissolution rate enhancement. International Journal of Applied Pharmaceutics 2018;10(1): 145-53.

[13] Padmapreetha Jand Arulkumaran KSG: Improvement of dissolution rate of diacerein using liquisolid technique. Journal of Chemical and Pharmaceutical Research 2016; 8(7): 209-19.

[14] Naveena C, Shastria N and RamaRao T: Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharmaceutica Sinica B 2012;2(5): 502–8.

[15] Hitesh J, Pasha TY, Bais CS and Anil B:Formulation and characterization of liquisolid tablets of valsartan for improvement of dissolution rate.Asian Journal of Pharmaceutical and Clinical Research 2014;7(4):21-6.

[16] Pavan RK, Sameer KS and Pravin DC: Application of liquisolid technology for enhancing solubility and dissolution of rosuvastatin.Advanced Pharmaceutical Bulletin2014; 4(2): 197-204.

[17] El-Sayyad NM, Badawi A, Abdullah ME and Abdelmalak NS: Dissolution enhancement of leflunomide incorporating self emulsifying drug delivery systems and liquisolid concepts. Bulletin of Faculty of Pharmacy 2017; 55(1):53-62.

[18] Asma AM and Snehalata lG: Formulation and evaluation of liquisolid compacts of lornoxicam. International Journal of Pharmacy and Pharmaceutical Sciences 2019; 11(6): 33-7.