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A SUCCESSFUL ATTEMPT TO ENHANCE SOLUBILITY OF BCS CLASS II DRUG USING LIQUISOLID COMPACT TECHNIQUE

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Keywords:

Flurbiprofen, Liquisolid technique, Carrier material, Coating material, Solubility enhancement

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ABSTRACT: The main purpose of the current research work is to enhance solubility and dissolution of BCS Class II drug, Flurbiprofen using liquid-solid compact technology. Flurbiprofen is a non-steroidal anti-inflammatory drug indicated for acute and chronic treatment of rheumatoid arthritis, osteoarthritis, and spondylytis. The rationale to select Flurbiprofen as the model drug is that it belongs to BCS Class II, having poor aqueous solubility of 10.45 ± 3.2µg/ml. Hence an attempt was made to enhance solubility, which may further increase the dissolution profile of the drug. In this regard, several liquisolid compact formulations were prepared for flurbiprofen and subjected to evaluation. They were prepared by using PEG 600 as a non-volatile solvent to dissolve the drug and further converted to freely flowing readily compressible powder using Avicel PH 102 as carrier material and Aerosil 200 as coating material. These liquisolid formulations were subjected to pre-compression rheological studies and post-compression evaluation parameters such as hardness, friability, weight variation, content uniformity, disintegration, and *in-vitro* dissolution. Results of dissolution profile of formulation TF3 showed a maximum release of 98% within 60 minutes, which was 2 folds higher than that of the directly compressed tablet (DCT). The probable reason for improved solubility may be due to improved wettability and greater surface area of drug-exposed to dissolution media. No drug-excipient incompatibility was observed, which was confirmed by FTIR and DSC studies. Finally, it can be concluded that liquisolid compact technique successfully enhanced solubility, which in turn enhanced the dissolution profile of BCS Class II drug Flurbiprofen.

INTRODUCTION: One of the major challenges faced by formulation scientists nowadays in pharmaceutical industries is solubility and dissolution enhancement of orally administered solid dosage forms of poorly water-soluble drugs. Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability [1].

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Earlier, several techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of poorly water-soluble drugs.

Flurbiprofen is a cyclooxygenase (COX-1 and COX-2) inhibitor that blocks the synthesis of prostaglandin E2 and is reported to have analgesic and anti-inflammatory effects [2]. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID), one of the most potent platelet aggregation inhibitors. It is used in the treatment of gout, rheumatoid arthritis, osteoarthritis, and sunburn. This drug is classified as a BCS class II drug and exhibits low aqueous solubility [3].

On the other hand, it also has poor bioavailability due to its poor aqueous solubility (10.45 ± 3.2µg/ml) [4]. Therefore, Flurbiprofen possesses problems during the formulation of oral solid dosage forms due to its poor absorption and bioavailability. But Flurbiprofen, being NSAID, should be rapidly absorbed for the treatment of pain and inflammation, and it is very important to enhance the solubility of the drug in those cases.

Earlier several attempts have been reported to enhance solubility and bioavailability of flurbiprofen like solid dispersions, microemulsions, complexation using cyclodextrin inclusion complexes, spray drying methods, nanosuspensions, micelle formulation, solid lipid nanoparticles, solid self-microemulsifying drug delivery system SMEDDS [5-8]. Recently, liquisolid technique has shown a promising approach for the dissolution enhancement [9]. Hence, in the present study, an attempt has been made to increase the solubility and dissolution profile of flurbiprofen using liqui-solid technique.

The liquisolid technique, also known as Powder solution technology, was first introduced by Spireas and considered a newer technique to improve the solubility and dissolution rate of the poorly water-soluble drugs. These liquisolid systems are considered as acceptably flowable and compressible powdered forms of liquid medications (that implies liquid lipophilic drugs or water-insoluble solid drugs dissolved in suitable water-miscible non-volatile solvent systems).

Such liquid medication can be converted into non-adherent, dry-looking, free-flowing and readily compressible powders by a simple admixture process with selected powder excipients referred to as carrier (having good absorption properties) and coating materials carrier (having good adsorption properties). However, the drug will be molecularly distributed in the liquisolid compact and enhance dissolution, and improves oral bioavailability [10].

Hence, due to their significant increase in wetting properties and available surface area of the drug for dissolution, liquisolid compacts of water-insoluble substances may be expected to display improved drug release properties, and consequently, enhanced bio-availability [11].

MATERIALS AND METHODS:

Materials: Flurbiprofen was purchased from Alfa Aesar, USA. Avicel PH 102, Aerosil 200, Propylene glycol, sodium starch glycolate (SSG), magnesium stearate, and talc were obtained from S.D Fine Chemicals Ltd, Mumbai. Polyethylene glycols such as PEG 200, PEG 400, PEG 600, Tween 20, Tween 80, Span 20, and Span 80 were purchased from Himedia, Mumbai. All other reagents and solvents used were of analytical grade.

Experimental Methods:

Saturation Solubility Studies: Saturation solubility studies for Flurbiprofen were carried out in distilled water, 7.4 pH phosphate buffer, and various other non-volatile solvents such as propylene glycol, PEG 600, PEG 400, PEG 200, Tween 20, Tween 80, Span 20, and Span 80. Saturated solutions of the drug in these solvents were prepared by adding an excess of the drug to 5ml of each selected solvent in screw-capped vials. The screw-capped vials were kept on a mechanical shaker (Remi, Mumbai) for 24 h and then centrifuged at 2500 rpm for 15 min. Finally, accurately measured quantities of the filtered supernatant solutions were further diluted and analyzed spectrophotometrically at 247 nm for the drug content [12].

Application of Mathematical Model for Designing the Liquisolid Systems: [11] A powder can only retain a limited amount of liquid medication while maintaining acceptable flow-ability and compressibility [13]. To calculate the required quantities of excipients (carrier & coating materials), a new mathematical approach is used for the formulation of liquid-solid systems. This approach is based on the flowable (Φ) and compressible (Ψ number) liquid retention potential which are constants for each powder material with the liquid vehicle.

The Φ-value of the powder system represents the maximum amount of a particular non-volatile liquid that can be retained inside its bulk (w/w) while maintaining an acceptable flowability.

The Ψ- number of powder system is defined as the maximum amount of the liquid that the powder can retain inside the bulk (w/w) while maintaining acceptable compatibility resulting in compacts of

sufficient hardness without liquid leaking out during the process of compression.

Depending upon the excipients ratio (R) or the ratio of the carrier: coating of the liquisolid powder system used, where

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

R represents the ratio between the weights of the carrier material (Q) and coating material (q) present in the formulation.

An acceptably flowing and compressible liquisolid system can be prepared only if a certain maximum amount of liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) to the weight of the carrier powder (Q) in the system, which should be possessed by an acceptable flowing and compressible liquisolid system *i.e*.

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

Spireas et al. used the flowable liquid retention potentials (Φ-values) of the powder excipients in order to calculate the required ingredient quantities. Hence the powder excipients ratio R and the liquid load factors Lf of the formulations are related as follows:

$$Lf = \Phi + \Phi\,(1/R) \quad ... (3)$$

So, in order to calculate the required weights of the excipients used, first, from equation (3), Φ and Φ are constants, where Φ is flowable liquid retention potential of the carrier material, and Φ is flowable liquid retention potential of coating material. Therefore, according to the ratio of the carrier to coating materials (R), Lf was calculated (where R is predetermined). Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution or liquid medication (W) will be used. So, by knowing both Lf and W, the appropriate quantities of the carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equations (1) and (2).

Preparation of Flurbiprofen Liquisolid Compacts: liquisolid compacts of Flurbiprofen were prepared by dissolving accurately weighed quantities of drug and PEG 600 in a 20 mL glass beaker and then mixed well. The resulting medication was mixed with calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first step, the liquisolid powder system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second step, the liquisolid powder system was evenly spread as a uniform layer on the surface of the mortar and left for about 5 min to allow the liquid medication to be absorbed inside powder particles. In the third step, the liquisloid powder was scraped off the mortar surface using an aluminum spatula. This final formulation was compressed into compacts using a 12 mm punch using a multi-station tablet press (Cadmach Ahmedabad, India) after the addition of sodium starch glycolate as a disintegrating agent. From the calculated Φ and Φ values, the liquid load factor (Lf) was calculated.

A conventional formulation of directly compressed Flurbiprofen tablet was also prepared to contain 50 mg of drug-drug, Avicel PH 102, Aerosil 200, and sodium starch glycolate. The composition of Flurbiprofen liquisolid compacts is shown in **Table 1**.

TABLE 1: FORMULATION OF FLURBIPROFEN LIQUISOLID COMPACTS

F code	Drug concentration (%)	R	Drug (mg)	Lf	PEG (mg)	Q (mg)	Q (mg)	SSG (mg)	Mg stearate (mg)	Talc (mg)	Final wt (mg)
TF1	33.33	5	50	0.382	100	392.67	78.53	15	5	2	643.20
TF2	33.33	7.5	50	0.333	100	450.45	60.060	15	5	2	682.51
TF3	33.33	10	50	0.309	100	485.44	48.54	15	5	2	705.98
TF4	40	5	50	0.382	75	327.22	65.45	15	5	2	539.67
TF5	40	7.5	50	0.333	75	375.38	50.05	15	5	2	572.42
TF6	40	10	50	0.309	75	404.53	40.45	15	5	2	591.98
TF7	50	5	50	0.382	50	261.78	52.36	15	5	2	436.13
TF8	50	7.5	50	0.333	50	300.3	40.04	15	5	2	462.34
TF9	50	10	50	0.309	50	323.62	32.36	15	5	2	477.98

Pre-compression Studies of the Flurbiprofen Liquisolid System:

Flow Properties of the Flurbiprofen Liquisolid System: The flow properties of the liquisolid powder systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel method. The bulk density and tapped density for liquisolid powder systems were also determined for the calculation of Hausner's ratio and Carr's index **Table 2**.

Post-compression Evaluation of Flurbiprofen Liquisolid Compacts: The prepared Flurbiprofen liquisolid compacts were evaluated for various parameters such as content uniformity, friability, weight variation, hardness, and disintegration. All the above-mentioned tests were carried out according to the United States Pharmacopeia (USP) compendia specifications **Table 3**.

***In-vitro* Dissolution Studies:** The *in-vitro* dissolution release profiles of Flurbiprofen drug from liquisolid compacts and directly compressed tablets were obtained using USP-II dissolution test apparatus (Electrolab Pvt. Ltd Mumbai, India). The dissolution study was carried out in 900 ml phosphate buffer pH 7.4 as the dissolution medium at 37 °C ± 0.5 °C and 50 rpm. Aliquots of 5 ml samples were collected for up to 60 min at specified time intervals.

The dissolution medium was further replaced with 5 ml of fresh dissolution medium to maintain sink conditions. The withdrawn samples were filtered and analyzed spectrophotometrically at 247 nm. The mean of three determinations was used to calculate the drug release from each of the formulations.

IR Spectra Analysis: FTIR spectra of Flurbiprofen, Avicel PH102, Aerosil 200, and optimized liquisolid compact formulation were obtained. KBr pellet method was used, taking about 5mg of sample mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12,000 psi for 3min. The resultant disc was mounted in a suitable holder in FTIR spectrophotometer (Shimadzu, Japan), and the sample was scanned from 4000 to 400 cm^{-1} [14].

Differential Scanning Calorimetry (DSC): Thermograms of the Flurbiprofen and optimized liquisolid formulation were recorded using Philips PW3710 X-ray diffractometer. The analysis was carried out by heating 2 to 3 mg of sample on an aluminum crimp pan at a rate of 10 °C/min in a nitrogen atmosphere.

Powder X-ray diffraction (PXRD): Powder X-ray diffraction (PXRD) spectra of Flurbiprofen and optimized sample were recorded using a high-power powder X-ray diffractometer (Ru-200B, Pune, India) with Cu as a target at a scan speed of 4°/min. The samples were analyzed at a 2θ angle range of 2-45° at a time of 0.5 sec. The operating voltage and current were 40 kV and 55 mA, respectively [15].

Scanning Electron Microscopy (SEM): Surface morphology and particle shape of pure drug Flurbiprofen and optimized liquisolid formulation samples were analyzed by scanning electron microscope (SEM) (Hitachi, Japan) studies. The samples were first adhered to the carbon-coated metallic stub using double-sided adhesive tape. This was sputter-coated with a platinum coating machine and mounted on SEM for surface analysis. Imaging was carried out at an acceleration voltage of 30 kV.

Stability Studies: The optimized formulation was subjected to accelerated stability studies according to ICH guidelines at 40 °C ± 2 °C/75% RH ± 5% RH for a period of three months in a stability chamber. The optimized formulations were placed in USP Type I flint vials, hermetically closed with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at period of 30, 60 and 90 days and evaluated for hardness, drug content, disintegration, and *in vitro* drug release.

RESULTS AND DISCUSSION:

Saturation Solubility Studies: Drug solubility in non-volatile vehicle is considered the most important aspect in liquisolid systems. The solubility of a drug in a non-volatile solvent contributes to molecular dispersion, which will further improve the dissolution rate. The solubility of the drug was performed in various non-solvents, and the results for saturation solubility studies of Flurbiprofen were given in **Fig. 1**.

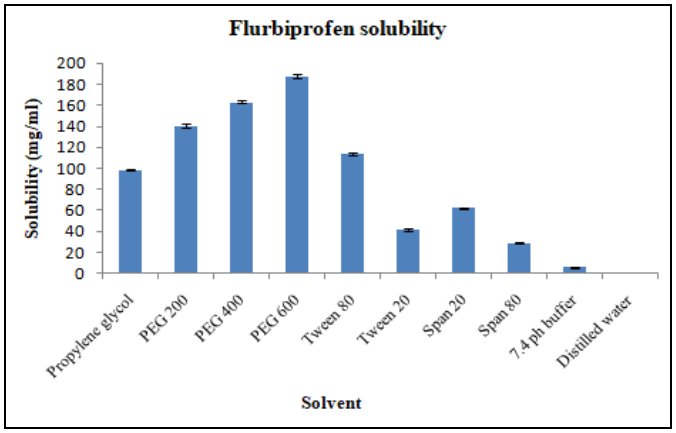

FIG. 1: SATURATED SOLUBILITY OF FLURBIPROFEN IN VARIOUS NON-VOLATILE SOLVENTS

Flurbiprofen has shown the highest solubility in PEG 600 (186.6 ± 2.93mg/ml). Based on the solubility data, PEG 600 was selected as the non-volatile liquid vehicle for the formulation of liquisolid compacts of Flurbiprofen.

Application of Mathematical Model for Designing the Liquisolid Systems: In order to determine the quantities of the ingredients of the compacts i.e., amount of carrier and coating materials, the flowable liquid-retention potentials (Φ-values) of both carrier and coating materials and liquid load factor (Lf value) have to be determined.

Determination of Flowable Liquid-Retention Potential (Φ-values): The flow properties of powder excipients (Avicel PH 102 and Aerosil 200 with PEG 600) are evaluated using the ‘‘Angle of slide” measurement. Several uniform non-volatile liquid vehicle/powder admixtures which contain 10g of the carrier or coating materials with increasing amounts of non-volatile liquid vehicle (PEG 600) were prepared. To measure the angle of slide, the prepared non-volatile liquid/powder admixtures were placed on polished metal plates, the plate was then tilted gradually until the non-volatile liquid/powder admixture was about to slide. The angle formed between the metal plate and the horizontal surface was defined as the angle of slide (h). The flow properties of excipients may be altered due to adsorption of the liquid vehicle.

The flowable liquid-retention potential (Φ values) of each non-volatile liquid/powder admixture (for both carrier and coating material) was calculated using the following equation.

$$\Phi \text{ value} = \text{weight of non-volatile liquid/weight of solid}$$

The Φ -values for Avicel PH102 and Φ -values Aerosil with PEG 600 were 0.236 and 0.731, respectively. R values selected were 5, 7.5 and 10.

Determination of Liquid Load Factor: Using the Φ –values, the liquid load factor, Lf, was calculated according to the equation

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

The Lf values were used to calculate the required quantities of excipients.

Pre-compression Studies of the Flurbiprofen Liquisolid System:

Flow Properties of the Flurbiprofen Liquisolid System: The flow properties of the Flurbiprofen liquisolid powder system were employed and results are depicted in **Table 2**. Batch TF3 showed good flow properties with angle of repose (θ) value of 28.02±1.28 and was considered as the liquisolid system with acceptable flowability. It also showed Carr’s index up to 17.86 was considered acceptable as a flow property. Hausner’s ratio was related mainly to the inter particle friction; hence powders with low interparticle friction had a ratio of approximately 1.217 indicating a good flow.

TABLE 2: FLOW PROPERTIES OF FLURBIPROFEN LIQUISOLID SYSTEM (*MEAN ± SD, N=3)

F code	Bulk Density* (mg/mL)	Tapped Density* (mg/mL)	Carr's compressibility Index	Hausner's Ratio	Angle of Repose(θ) *
TF1	0.427±0.03	0.507±0.05	15.779	1.187	30.14±1.44
TF2	0.442±0.07	0.532±0.02	16.917	1.204	29.14±1.13
TF3	0.446±0.02	0.543±0.11	17.864	1.217	28.02±1.28
TF4	0.411±0.04	0.486±0.03	15.432	1.182	32.10±1.30
TF5	0.421±0.01	0.507±0.02	16.963	1.204	31.66±1.25
TF6	0.436±0.02	0.527±0.03	17.268	1.209	31.94±1.33
TF7	0.379±0.03	0.465±0.02	18.495	1.227	33.77±1.21
TF8	0.586±0.02	0.472±0.04	18.220	1.223	32.85±1.31
TF9	0.392±0.01	0.487±0.02	19.507	1.242	30.49±1.43

Post-compression Evaluation of Flurbiprofen Liquisolid Compacts: The results of thickness, hardness, weight variation, friability, drug content and disintegration of the Flurbiprofen liquisolid compacts are mentioned in **Table 3**. All the Flurbiprofen compacts had acceptable friability as none of the tested formulae had percentage loss in tablet weights that exceed 0.5%. Also, none of the tablets was cracked, split or broken. The liquisolid tablet disintegrated in less than 5 min which is as per specifications given for the uncoated tablets in the IP. Uniform drug content was observed for all the formulations, around 98 to 100%.

TABLE 3: 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)	Thickness* (mm)
TF1	3.3±0.05	643.20	100±0.25	0.53±0.06	3.38±0.12	2.5±0.03
TF2	3.4±0.05	682.51	99±0.39	0.54±0.05	3.49±0.11	2.6±0.11
TF3	3.7±0.13	705.98	98±0.29	0.51±0.09	3.55±0.09	2.7±0.08
TF4	3.1±0.17	539.67	98±0.31	0.49±0.12	3.11±0.08	2.7±0.11
TF5	3.1±0.12	572.42	100±0.42	0.61±0.07	3.13±0.11	2.7±0.09
TF6	3.2±0.07	591.98	99±0.42	0.58±0.08	3.15±0.11	2.6±0.07
TF7	2.8±0.09	436.13	98±0.28	0.57±0.11	2.51±0.07	2.5±0.09
TF8	2.8±0.12	462.34	98±0.32	0.58±0.14	2.58±0.06	2.6±0.13
TF9	2.9±0.09	477.98	98±0.38	0.56±0.18	3.05±0.08	2.6±0.04

***In-vitro* Dissolution Studies:** The drug dissolution profile of all the prepared liquisolid compacts and the directly compressed tablet (DCT) of Flurbiprofen was studied. As observed in Figure 2, TF3 liquisolid compacts showed better *in-vitro* release than that of the DCT. In case of liquisolid compacts, due to the presence of the drug in the form of solution in PEG 600, facilitates the wetting of drug particle by decreasing the interfacial tension between compact and dissolution medium. Also, the drug surface available for dissolution is tremendously increased. After disintegration, in case of liquisolid compacts, the primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas in case of directly compressed compacts, they are just exposed micronized drug particles.

Hence, in the case of liquisolid compacts, the surface area of the drug available for dissolution is much greater when compared to that of the directly compressed compacts. According to the Noyes and Whitney equation, the rate of dissolution of the drug (DR) is directly proportional to the concentration gradient (Cs-C) of the drug in the stagnant diffusion layer and its surface area (S) available for dissolution, as well surface area of particle exposed to dissolution medium[16]. Thus, the significantly increased surface area of the molecularly dispersed Flurbiprofen in the liquisolid compacts may be principally responsible for their observed higher dissolution rates.

In the present study different drug concentrations in liquid medication were used such as 33.33%, 40% and 50%. Further, for each drug to non-volatile solvent R value was varied from 5 to 10 and its *in-vitro* drug release patterns were studied. The drug release observed the following pattern:

R10 > R7.5 > R5

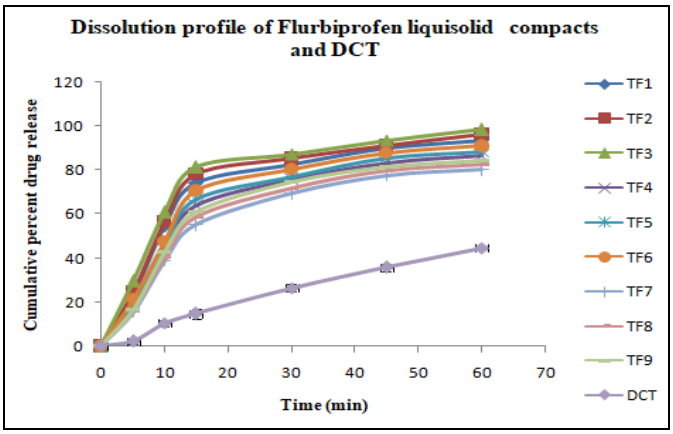

FIG. 2: DISSOLUTION PROFILE OF FLURBIPROFEN LIQUISOLID TABLETS AND DCT

IR Spectra Analysis: The IR spectrum showing percentage transmission (T%) versus wave number for the samples of Flurbiprofen, Avicel PH 102 and Aerosil 200 are shown in **Fig. 3**. The IR spectrum of Flurbiprofen **Fig. 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). From the figure, it was observed that the functional groups of Flurbiprofen was retained in liquisolid compact formulation, indicating the absence of chemical interaction with any of the excipients used in the preparation of liquisolid compacts.

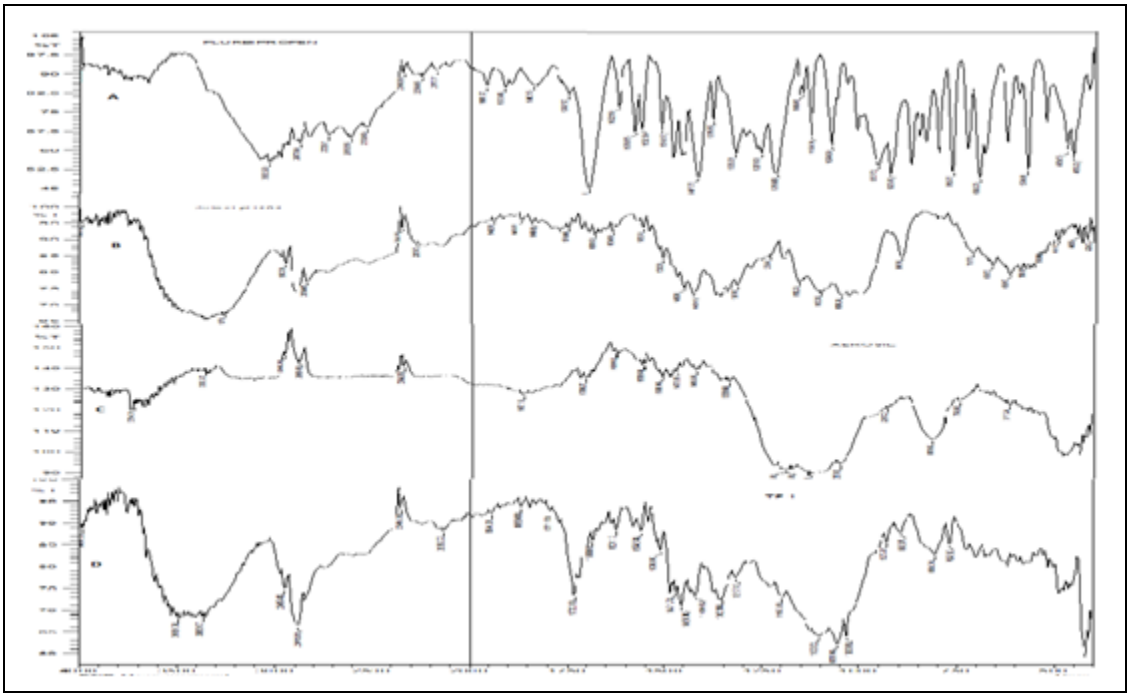

FIG. 3: FTIR OF A. FLURBIPROFEN B. AVICEL PH102 C. AEROSIL 200 D. TF3

Differential Scanning Calorimetry (DSC): One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation; it is very important to establish the existence of any incompatibilities to ensure the success of the subsequent stability studies [17]. Here, DSC is used to study the possible interactions between drug entities and excipients used in liquisolid compacts. **Fig. 4** shows the endothermic peaks of pure drug, Flurbiprofen, and optimized liquisolid system. The Flurbiprofen showed a sharp characteristic endothermic peak at 115.68 °C **Fig. 4A** corresponding to its melting temperature (Tm), and such sharp endothermic peak indicates that the drug used was in a pure crystalline state. On the other hand, the characteristic sharp endothermic peaks of Flurbiprofen had disappeared in the optimized liquisolid system **Fig. 4B**; this confirms that the drug was molecularly dispersed within the liquisolid matrix system by the formation of solid solution in the liquisolid powdered system.

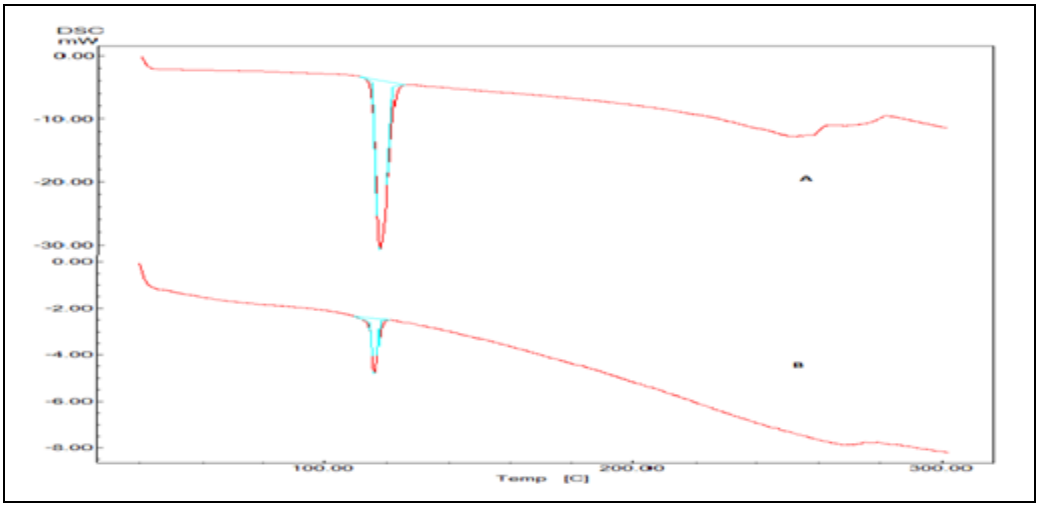

FIG. 4: DSC THERMOGRAM OF A. FLURBIPROFEN B. TF3

Powder X-ray Diffraction (PXRD): Powder X-RD is used to study the crystalline nature of compounds. The occurrence of polymorphic changes in the drug is an important factor that might affect the dissolution rate and in turn, bioavailability of the drug. The crystalline nature of the pure drug and the optimized liquisolid compacts samples was determined. The X-Ray Diffraction pattern **Fig. 5** of the pure drug (Flurbiprofen) showed sharp diffraction peaks. The absence of such sharp characteristics peak in optimized formulation indicated that the drug had probably converted from crystalline to amorphous form.

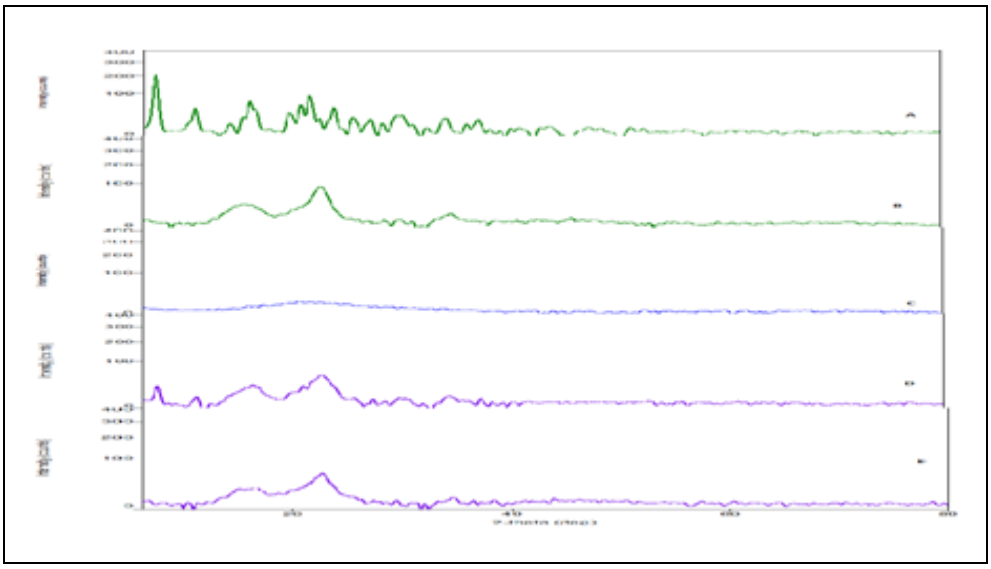

FIG. 5: X-RAY DIFFRACTOGRAMS OF A. FLURBIPROFEN B. AVICEL C. AEROSIL D. PHYSICAL MIXTURE E.TF3

Scanning Electron Microscopy (SEM): The surface morphology of the pure drug Flurbiprofen, Avicel, Aerosil and TF3 were examined by SEM and the images are represented in **Fig. 6**. The typical crystalline structure of Flurbiprofen as shown in **Fig. 6A** was completely disappeared in liquisolid formulation which indicates that the drug was totally solubilized in the liquisolid system. The complete transformation of a drug to an amorphous or molecular state supports the liquisolid formulation hypothesis that the drug, even in its solid dosage form, is held within the powder substrate in solution form or in an almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

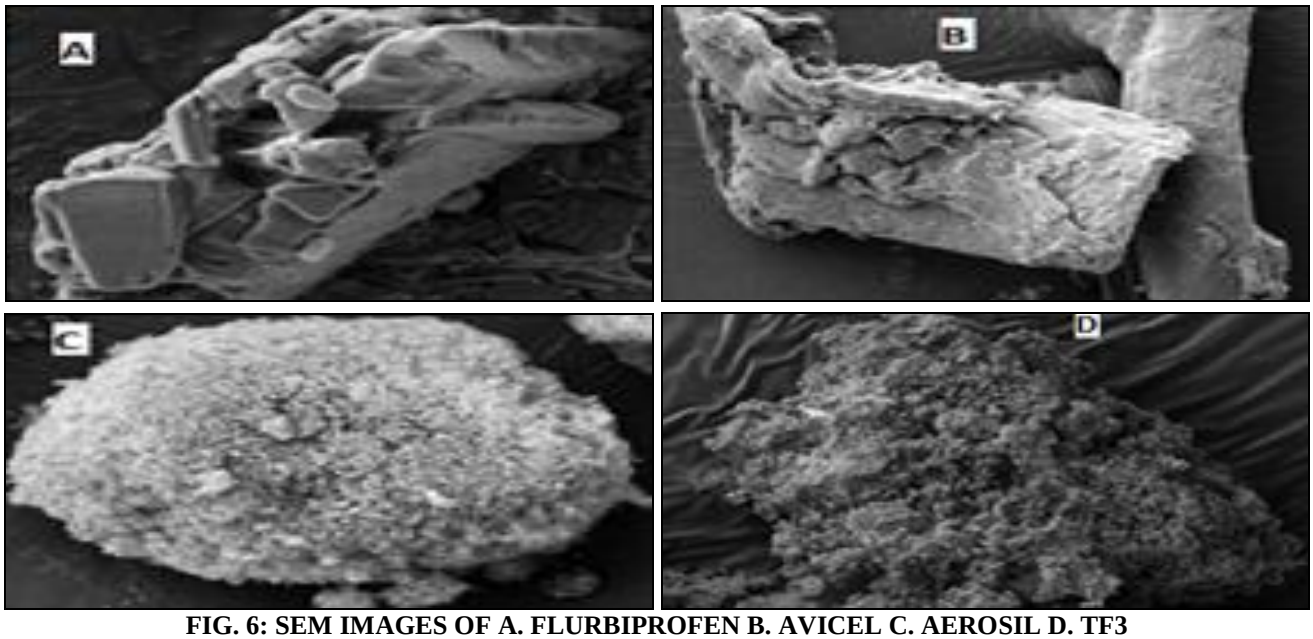

FIG. 6: SEM IMAGES OF A. FLURBIPROFEN B. AVICEL C. AEROSIL D. TF3

Stability Studies: The optimized liquisolid formulation was subjected to stability studies to evaluate any change in the formulation. Stability study of optimized liquisolid formulation was performed under accelerated stability conditions at 40 °C ± 2 °C/75% RH ± 5% RH for three months. Drug release profile was measured for the aged compacts. The results showed that there was no significant different between hardness of fresh (3.7 Kg/cm^2) and aged (3.6 Kg/cm^2) of TF3 liquisolid compacts. The results also showed that there was no significant different between the disintegration of fresh (3.55 min) and aged (3.53 min) as well content uniformity of fresh (98%) and aged (97.7%) TF3 liquisolid compacts. **Fig. 7** showed an almost similar dissolution profile for fresh and aged liquisolid formulation, which means that aging had no significant effect on the drug release profile of Flurbiprofen liquisolid tablets. This study concluded that the tested liquisolid formulations are found to be stable.

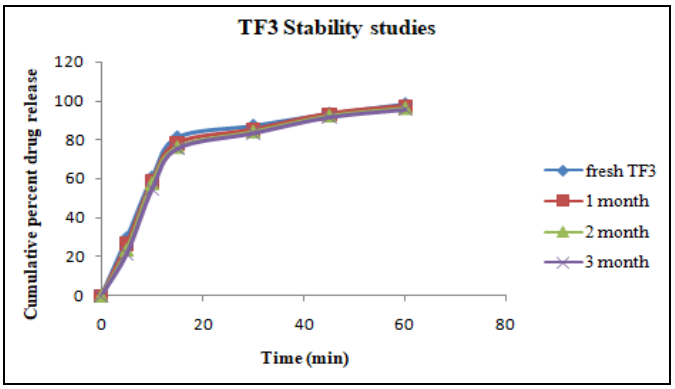

FIG. 7: DISOLUTION PROFILE OF TF3 LIQUISOLID COMPACTS DURING STABILITY STUDIES

CONCLUSION: Flurbiprofen exhibits high permeability through biological membranes, but its absorption after oral administration is limited by its low dissolution rate due to its very low aqueous solubility. Hence, the use of the liquisolid technique was chosen to enhance the dissolution properties of Flurbiprofen. The Flurbiprofen liquisolid compacts were prepared using Avicel PH 102 and Aerosil 200 as the carrier and coating material, respectively. The PXRD studies showed complete inhibition of crystallinity in the Flurbiprofen liquisolid compacts. The DSC study confirmed the absence of any interaction between the drug and excipients used in the preparation of Flurbiprofen liquisolid compacts. The hardness, friability, weight variation and disintegration tests were within acceptable limits. The *in-vitro* dissolution study confirmed enhanced drug release from liquisolid compacts compared to that of the directly compressed tablet. It was also observed that the prepared compacts are stable and had no significant effect on the hardness, disintegration time, and dissolution profile. Stability studies by means of dissolution testing showed that the liquisolid preparation produced was stable and not significantly affected by aging [18].

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