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Influence of Formulation Parameter on Dissolution Rate of Flurbiprofen Using Liquisolid Compact

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Attempts were made to improve solubility and the liquisolid technology dissolving of medication flurbiprofen. Liquisolid pill was developed utilizing transcutol-HP, polyethylene glycol 400, Avecil PH 102 carrier material and Aerosil 200 layer coating material. Suitable excipient amounts were determined to produce liquisolid powder using a mathematical model. On the other hand, flurbiprofen tablet with the identical composition, directly compressed, was manufactured for comparison without the addition of any unvolatile solvent. Both powder combination characterizations and after-compression tablets were evaluated. The pure drug and physical combination, and chosen liquisolid tablets were studied in order to exclude interacting with the differentional scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR).

The results showed that transcutol is the ideal solvent with a solubility of 260±3.9 mg/ml in flurbiprofen. All formula developed were determined to be flowable within the specified limitations. The transcutol-like liquidsolid tablet formula of 35 percent w/w flurbiprofen and carrier to coating ratio of 10 was the most acceptable for the disintegration time, the tablet weight and other approved tablet characteristics.

DSC thermographs demonstrated the development of a solid flurbiprofen amorphic solid solution for both the physical blend of the chosen liquisolid system and its tablets. The lack of chemicals interaction in medication and other components of the formula was demonstrated by the retention of all flurbiprofen characteristic peaks in all FTIR spectra. As an option to enhance solubility and dissolve flurbiprofen, which has a poor water solubility, liquisolid tablet has been evaluated.

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1. INTRODUCTION

Differentiate medicines into four classes based on their solubility and permeability by the Biopharmaceutical Classification System (BCS). The BCS Class II medicines display variable dose absorption because of their solubility restriction, which are classically referred to as high permeability and poor solubility.

Many new and possibly helpful chemical entities are accessible for medicinal purposes,however, because to their poor solubility and dissolution rate, these entities are not used.

Oral medicinal absorption is most often controlled by release and dissolvingin gastric fluid. The solution of the medicine can provide better bioavailability of the water-insoluble drug taken by mouth [1].

Various methods are used to enhance the solubility and dissolution of weakly aquatic drugs. The liquisolid technique is one such way. Liquisolid is a patented technology and a proven tool for improving the solubility and bioavailability of poorly soluble drugs [2].

It is characterized as dry, nonadhesive, free flowing and compressible powders combined by conversion of fluid drugs, suspenses or solution in non-volatile solvents with chosen carriers with coat materials.

Dispersed in a liquid vehicle, the medicine is integrated by the fluid technique into a carrier with a porous surface and firm matte fibers like cellulose that produce both adsorption and absorption. Liquid is initially absorbed by the particles and captures its inner structure. The fluid is adsorbed to the inner and outer surface of the porous carrier particles once this process has been saturated, then follows this procedure with strong adsorption characteristics on the coating substance. With the broad, specific surface area, the flow characteristics to designate it a liquisolid system are desirable. The medication is as solution in liquid vehicles in liquisolids system while it is also transported by powder [3].

Liquisolid systems have developed as a result of powder solutions, based on preparing a solution of medicine in solvent which its boiling point is high, the water-mixable or miscible solvent, which has been integrated into the structure of an inert carrier with a large surface (colloidal silica) [4]. However, these preparations were examined for their powder dispersion profiles since they were not appropriate for tablet compression. Compression enhancers such as microcristalline cellulose have been added to powder solution formulations to boost compression of the systems [5].

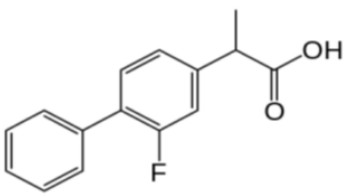
Spireas and Bolton devised a mathematical model for determining the number of supported and covered material for appropriate flow and compression [6].

The success of the appropriate flow rate and solid liquid compression system is determined by the liquid loadfactor (Lf) and the excipient relation (R). The Lf is a property of the volume of vehicles employed in the liquid medicines ratio (W) formula and the liquid carrier (Q). The powder excipient (R) ratio of the formula to the coating material (q) is determined by carrier weight (Q). The proportion of powder excipients is therefore related to the fluid load factor [7]:

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

Where $\boldsymbol{\varphi}$ and $\varphi$are flowable liquid-retention potential of carrier and coat material, respectively.

Flurbiprofen (FLB), a non-steroidal phenylalkanoic acid derivative often used to treat chronical rheumatic illnesses and classed as non-steroidal anti-inflammation medicinal products [8,9]. FLB is classed as a Class II medication which is not water-soluble and is primarily used to treat painful diseases requiring rapid release [10,11]. In order to enhance the bioavailability of a medication, the dissolution rate must be improved. Various methods have already been documented, such as superdisintegrants, solid dispersions. This work aims to improve the dissolution of FLB by use of liquid compaction techniques.



Scheme 1. Chemical structure of flurbiprofen

2. MATERIALS AND METHODS

2.1 Materials

FLB has been bought by (Hangzhou Hyper Chemicals Limited, Zhejiang, China). Microcrystalline cellulose PH 102 was supplied by (FMC, USA), Aerosil 200 (Wuhan Senwayer Century chemical Co., Ltd), sodium starch glycolate and PEC 400 was derived from (SD Fine Chem Ltd, Mumbai, india). Magnesium stearate from (Robert E. M. TILG, Germany). Transcutol HP from which was derived (International Labrotaroy, USA).

2.2 Methods

2.2.1 Solubility study

Three separate nonvolatile solvent systems have produced FLB solution: PEG 400, propylene glycol (PG) and transcutol, distilled water and 0.1N pH = 1.2 hydrochloric acid solution (HCL).

The saturated solution was created and shook for 48 hours in a water bath at 25±0.5°C by putting an excess medicine on the vehicle and after that period the UV-spectrophotometerλ max. 247 nm against the blank was filtered, diluted and assessed for this purpose For this (blank sample contained the same concentration of specific solvent used without drug) [12].

2.3 Calculation of Liquid Loading Factor L_F

PEG 400 and transcutol have been utilized as liquid vehicles in order to make compact Liquisolid based on the findings of the solubility research. As carrier and coating materials respectively microcrystalline cellulose P H 102(Avecil) and aerosil were utilized.

Equation (2) can determine the adequate amounts of powdered carrier materials (Q) and coating (q) necessary for converting a given quantity of liquid medicine (W) into an acceptable liquisolid system that can be compressed and flowed (3).

$$L_f = W/Q \quad (2)$$

$L_f$is the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system.

$$R = Q/q \quad (3)$$

R represents the ratio between the weights of the carrier (*Q*) and the coating (*q*) material present in the formulation [13].

For powder excipients, the flowable liquid retention potential of PEG 400(Φ- value) was used in calculating the needed amounts of ingredients. The Φ-value of Avicel PH 102 in PEG400 was determined to be 0,005 and the Aerosil 200 value of φ was found to be 3,26 [14].

Two excipient ratios(R) were applied which are 10 and 30 with different concentration of liquid medication (20, 35 and 50%).

2.4 Preparation of FLB liquisolid Compact

Dispersion in non-volatile solvent of 50 mg of FLB by utilizing PEG 400 in formats (F1-F6) and transcutol in formats (F7-F12), as indicated in Table 1 was made. A bindery combination (Avicel PH 102) and coating material (Aerosil 200) were then made by continuous mixing in the mortar at two ratios, 10:1 and 30:1, for a 10-minute period. The quantity of carrier and coating ingredients is sufficient for satisfactory flow and compression. To choose the optimum ratio with superior flow and compression qualities, two ratios have been applied. After that 5% of superdisintegrant crosscarmellose was added and stirred for 10 min.Finally 1% w/w of magnesium stearate was combined as lubricant the mixture are stirred for 2 minutes A single punch-tablet (Erweka/EKO, Germany) compacts the final mixture [15]. Because F4 and F10 are quite heavy in weight, they are difficult to be compacted with tablet machine.

2.5 Preparation of FLB Conventional Tablet

The standard FLB pill has been produced from 10 minutes mixing without the addition of a vehicle, of 50 mg FLB, 500 mg Avecil 102 and Aerosil 50 mg in the mortar. Thencrosscarmelose 25 mg has been mixed in the mortar for 2 minutes. Finally, 1% magnesium stearate was added, and 1 minute more mixed. A single, manual punch tablet (Erwika/EKO, Germany) compacted the mixture. This conventional direct tablet is known as DCT [16].

Table 1. Formulation of Flurbiprofen Liquisolid Tablets Using PEG-400 and Transcutol

Formula	FLB concentrationin liquidmedication %w/w	R [Q/q]	Loading Factor[w/Q]	PEG400 mg	Transcutl mg	FLB mg	Avecipl H102Q mg	Aerosil 200q mg	Crosscarmellose 5% (mg)	Magnesium stearate 1% (mg)	Weight of Tabletmg
F1	20	10	0.331	200		50	755	75.5	54	10.8	1145
F2	35	10	0.331	92.85		50	431	43	30.8	6.1	653.9
F3	50	10	0.331	50		50	302	30.2	21.6	4.3	458
F4	20	30	0.113	200		50	2212	74	126.8	25.3	2688
F5	35	30	0.113	92.85		50	1263	42	72.3	14.4	1491
F6	50	30	0.113	50		50	884	29	50.6	10.13	1073
F7	20	10	0.331		100	50	755	75.5	54	10.8	1145
F8	35	10	0.331		92.85	50	431	43	30.8	6.1	653.9
F9	50	10	0.331		50	50	302	30.2	21.6	4.3	458
F10	20	30	0.113		100	50	2212	74	126.8	25.3	2688
F11	35	30	0.113		92.85	50	1263	42	72.3	14.4	1491
F12	50	30	0.113		50	50	884	29	50.6	10.13	1073
DCT	-	-	-	-	-	50	500	50	30	6	636

Excipient ratio, R=Q/q, Q= Weight of carrier, q= Weight of coating material, Liquid load factor, Lf= W/Q, W= Weight of liquid medication, Q= Weight of carrier

2.6 Evaluation of Liquisolid System

2.6.1 Evaluation of powder mixture

2.6.1.1 Angle of repose

A loose powder's frictional force may be measured using the angle of repose (θ). To measure this angle, the fixed funnel method was utilized. At a certain height (h) a funnel was fixed with its tip, on the smooth horizontal surface above a petri plate. The mixture was poured through the funnel cautiously until the top of the conical stack only attacked to the tip of the funnel. The conical pile base's radius (r) was measured.

The angle of repose (θ) was calculated using the following formula:

$$\text{Tan } \theta = h/r \quad (4)$$

Where; θ = angle of repose, h = height of the cone in cm, r = radius of the cone base in cm [17].

2.6.2 Bulk and tapped density

The liquisolid powder (w) in the graduated cylinders has been properly weighed and the volume (vo) measured. Tapping the graduated cylinders 100 times, the volume (vf) was then measured after that. Using the following formula, thebulk density and tapped density were found:

$$\text{Bulk density} = \frac{w}{vo} \quad (5)$$

$$\text{Tapped density} = \frac{w}{vf} \quad (6)$$

Where w is the powder weight, vo is the first volume, vf is the last volume. Compression index was computed from the findings of bulk density and tapped density [18].

$$\text{Compressibility index} = \frac{Tapped\ density - Bulk\ density\ x100}{Tappeed\ Density} \quad (7)$$

Compressibility index below 15% suggest acceptable powder flow properties, whereas values above 25% reveal poor flow qualities.

2.6.3 Hausner's ratio

The indirect measurement of flow pattern of powders is given by:

$$\text{Hausner Ratio} = \frac{tpped\ Density}{Bulk\ ensity} \quad (8)$$

A number lower than < 1,25 suggests good performance, whereas> 1,5 indicates bad performance. The ratio of Hausner can vary depending on the determination technique, therefore this is not a crucial flow behavior parameter.

2.7 Differential Scanning Calorimetry (DSC)

DSC tests may be used to evaluate the thermal behavior of pure FLB, liquisolid physical mixture and liquisolid compact. The vacuum packed into aluminum pans using about 3–5 mg of the sample exposed to an invariable heating rate of 10°C/min at a temperature range of 30-300°C. The complete thermal behavior is examined by means of vacant aluminum pans as reference, and by purging nitrogen. The lack of a distinctive peak in the presence of excipients suggests the incompatibility of the medicament with excipients as well as changes in the crystalline pattern of the medication [19].

2.8 Fourier-transform Infrared Spectroscopy (FTIR)

The infrared spectrophotometer was conducted using (Lambda 7600, Australia). Samples of 2-3 mg were compacted into clear disks with around 100 mg of dry bromide powder, then scanned across a wave range of 4000-400 cm^{-1} in FTIR. The IR spectrum was conducted on pure drugs, a physical liquisolid system combination and a chosen liquidsolid tablet [2].

2.9 Evaluation of Liquisolid Compact

2.9.1 Hardness

Hardness tester (Monsanto) has been used to assess the hardness of the pill. From each recipe, three pills have been randomly picked and the hardness was estimated. The average value has been determined.

2.9.2 Friability testing

Roche friabilator was used to establish the friability of the tablets. A number of tablets have been added to the fribilator (equivalent to 6.5 g or more) and spun for a 4 minute time at 25 rpm. The friability was determined with the following formula:

Percentage Friability= $\frac{w1-w2}{w1} x100$ (9)

Where W1= initial weight of tablets, W2= weight of the tablets after testing.

2.9.3 Content uniformity

Ten tablets were smashed to estimate the medication content and the powder aliquot corresponding to 50 mg of medication was dissolved with an appropriate quantity of methanol/0.1N HCL buffer solution (pH=1.2). The solution has been filtered and diluted and the UV-Visible spectrophotometer measured drug concentration has been at 247 nm. Medication concentration from the calibration curve was determined [21].

2.9.4 Weight variation

Twenty separate pills and all together were weighed. Total weight of all pills was derived from the average. The weight was compared to the average weight. The weight differential should be within the acceptable limits indicated in USP, with not more than two tablets differentiated by more than the average weight of the tablets specified in USP. No pill cannot be more than double the proportion [22].

2.9.5 Disintegration test

The disintegration time in water kept at 37±2 °C was found. The disintegration time device with a basket rack mounting comprising six tubes and a 10 mm bottom screen was utilized. A tablet has been put in each basket tube and the total disassembly time has been recorded for the six tablets [23].

2.10 *In –vitro* Dissolution Studies

For in vitro dissolution experiments, the USP paddle technique was utilized. The stirring rates were 50± 2 rpm. In 900mL 0.1N HCL with the pH = 1.2 and 37 ± 0.1°C the prepared pills were put. 5 mL of the samples were selected and filtered using a 0,45 mm milliporic filter at suitable intervals (10, 20, 30 and 60 min). A 5 mL fresh dissolution fluid was substituted to maintain a consistent volume for this dissolution medium. Then, samples at 247 nm were examined. In order to estimate the medicament release from each formulation, the mean 3 determinations were employed [21].

2.11 Dissolution Data Evaluation

The effects of the fluid medication concentration, the type of nonvolatile solvents used and of the carrier ratio (R) to coating material on drug release have been determined by the use of DD solver software at the end of 60 min by calculation of the mean dissolution time (MDT) and the dissolution efficiency (DE).

The model-independent method incorporates the differencefactor (*f1*) and the similarity factor *f2*to compare the dissolving profile of the optimized formula to DCT.

The factor f1 quantifies the percentage inaccuracy of two curves at all time points:

$$f1 = \frac{\sum_t^n = 1|Rt - Tt|}{\sum_t^n = 1Rt} \times 100 \quad (10)$$

n is the number of times points and Tt and Rt are the test and reference product percentages dissolved. If tests and drugs are the same profile,the percentage error is non-existent and it is increases proportionally with the dissimilarity between the two profile [24].

The similarity factor (*f2*) is a logarithmic transformation of the sum-squared error of differences of drug percentage dissolved between the test and the reference products over all time points:

$$f_2 = 50 \log \{[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2)] - 0.5 \times 100\} \quad 11)$$

Where n is the number of times points the dissolved percentage has been established, Rt is the percentage dissolved of medicine at time point and Tt is thepercentage dissolved of the medicine to be compared at the same time point. The value between 0 and 100 is the factor of similarity. It is 100 when the profile are the same and approach 0 as the dissimilarity increases. A*f2* above 50 shows the two profiles being comparable [25].

3. RESULTS AND DISCUSSION

3.1 Solubility Study

The pattern of medicine solubility on diverse media was assessed for FLB in several nonvolatile solvents (PG, PEG 400, transcutol, distilled water and 0.1N HCL) (Table 2).

Table 2. Solubility of FLB in Various Solvents (±SD)

Solvent	Solubility mg/ml
Distilled water	0.68±0.01
0.1 N HCL	0.042±0.34
PEG 400	20±1.2
PG	15±2.6
Transcutol	260±3.9

Results were expressed in mean±SD (n=3), SD standard deviation

Table 2 showed that transcutol had the maximum solubility of the medicinal substance (260±3.9 mg ml^{-1}), with its substantial percentage in molecular form. The order of solubility in these solvents was in transcutol > PEG 400 > PG >distiled water > 0.1N HCL. Transcutol and PEG 400 were used as non-volatile solvents to make a compact liquisolid and compare the findings obtained to choose the most suitable formula.

3.2 Flowable Liquid Retention Potential (Φ value) and Liquid Load Factor (Lf)

Phi(φ) levels of PEG400 as a liquid vehicle for Avecil PH102 and Aerosil 200 respectively were 0.005 and 3.26. In order to make transcutol containing formulations like liquid vehicles, the same (φ) value of PEG 400 was used. PEG 400 and transcutol have been absorbed by Avecil PH 102 and Aerosil and their flow characteristics have altered. Lf has been utilized to select the best amount of carrier and layer materials necessary to provide a free, dry and compactable powder system.

Lf was calculated by using R value of 10 and 30 using equation (1) as follows:

$$Lf=0.005+3.26(1/R)$$

So, Lf=0.33, 0.113 for R =10 and 30 respectively.

3.3 Evaluation of liquisolid system

3.3.1 Evaluation of powder mixture

3.3.1.1 Angle of repose

The repose angle is indicative of the particles' internal frictional forces. If the particles are cohesive, the angle of repose is high. The angle values equal or less than 30 digits imply free flow whereas angles ~40 or more digits indicate low flow [26].

Powder flow is an important criterion for tablet formulation. Different activities such as hopper flow of powder, mixing and compression are impacted by tabular formulation. Poor powder flow from hopper to tablet compression machine might have effects on consistent weight and medication content of tablets.

It may be deduced from the results presented in Table 3 that the rise of the Lf value (i.e. the decrease in R value) leads to an increase in the repose angle and a reduction in formula flowability. It was observed that Lf has a connection with the flow characteristics of powder mixtures. Low Lf value provide superior flow characteristics. This may be explained by the fact that the high LF liquisolid systems have large liquid and low powder excipient quantities according to the equation (Lf=W/Q).

The liquisolid systems, by comparison, have significant volumes of carrier material (Avicel PH-102) and modest liquid vehicle volumes. The R value of 30:1 was optimal from the data presented.

The results also suggest that an increase in the vehicle drug concentration (20%, 35% and 50%, respectively) causes decrease in repose angle and rise in the formula's flow property in the F1, F2 and F3. The angle of repose of formula F1 (26.7^0) compared to F3 which is (22.4^0) because of the quantity of the fluid vehicle that was extremely soft and sticky compact produces [27].

The results of angle of repose ,compressibility index and Hausner's ratio are given in Table 3.

The compression index of Carr and the Hausner ratio are metrics to detect a tendency to compress particles. As the value attribute up to 21, the Carr index is acceptable as flow property. Hausner's ratio describe interparticle friction; powder with a minimum friction have a ratio of 1.25 which indicates a good flow [28].

Table 3. Flow properties of FLB liquisolid tablets and DCT

Formula	Angle of repose	Type of flow	Compressibility index	Type of flow	Hausner ratio
F1	26.7±1.3	Excellent	29.9±0.8	Poor	1.14±0.3
F2	25.5±1.3	Excellent	24.3±2.1	Passable	0.863±0.11
F3	22.4±0.9	Excellent	23.1±0.99	Passable	0.853±0.87
F4	19.9±0.82	Excellent	25.7±0.32	Poor	0.943±0.9
F5	17.9±0.76	Excellent	19.14±0.88	Fair	0.808±0.6
F6	17.1±0.7	Excellent	15.6±0.2	Fair	0.754±0.6
F7	18.1±0.4	Excellent	25±0.72	passable	0.919±0.1
F8	16.7±1.2	Excellent	23.6±0.63	Fair	0.873±0.2
F9	15.4±.5	Excellent	19.0±0.89	Good	0.819±0.11
F10	16.6±.7	Excellent	22±04	passable	0.760±0.34
F11	15.4±0.33	Excellent	19.3±0.4	Fair	0.806±0.39
F12	15.0±0.9	Excellent	18.9±0.6	Fair	0.803±0.4
DCT	31.1±0.3	Excellent	23±0.43	Passable	0.750±0.5

**Results were expressed in mean±SD (n=3)*

It was observed that, there was indirect relationship between powder excipient ratio (R value) and Carr's index and Hausner's ratio of the liquisolid powders i.e., when the powder excipient ratio (R) raised, theCarr's index and Hausner's ratio of the liquisolid powders dropped.

This finding was exhibited from the following results: formulas F1 and F4 were having the same drug concentration in liquid medication of 20% w/w and R value of 10,30 respectively.

Also formula F2 and F5 with 35% drug concentration in liquid medication and F3 and F6 with 50% one.The same results were observed when PEG 400 or transcutol was utilized as liquid vehicle.

This can be explained by the fact that, increasing R-value of the formula leads to increase in the amount of the carrier powder to be used (Avicel PH-102) and decrease in the amount of the non-volatile solvent available to the total carrier hence the powder admixture results in dry, free flowing powder and thus subsequently lead to the decrease in the Carr's index and Hausner's ratio of the powder and vice-versa.

The results also showed that although the same flowability value of Avecil 102 and Aerosil 200 in PEG 400 was applied to all formulas, excellent flow properties and acceptable compressibility is clearly apparent for the formulas that prepared with transcutol (F7-F12) as shown in Table 3 so they are subjected to further study and evaluation.

3.4 Evaluation of Liquisolid Compact

3.4.1 Hardness test

The hardness of all formulas' produced tablets is within an acceptable level. Tablet hardness produced with direct compression was determined in Table 4, between 3 and 7 kg/cm^2. The optimal tablet hardness should generally be created without excessive compression strength and with appropriate resistance to rupture during typical handling at the same time quick tablet breakup and drug release are maintained simultaneously.

3.4.2 Friability test

All FLB tablets were acceptable since none of the formulations tested surpassed a 1% decrease in tablet weight as indicated in Tablet 4; neither tablet was cracked, split or broken. Since all the formulae produced meet conventional friability standards, good durability and abrasion resistance are predicted. Formulation with a highly volatile solvent might indicate increased interparticular bonding between particles, resulting in a small percentage of friction [29].

3.4.3 Drug content

The medical content varies from 96.6-99.6 percent for tablet of all formulations (Table 3). The results show that all formulations' tablet contents are consistent and contain a therapeutic dosage of the active components.

3.4.4 Disintegration time

Table 4 showed the time for disintegration of the ready FLB liquisolid tablets. The period of disintegration for PEG 400 (F1-F6) included tablets was observed to be within (4.5-6 min) which was larger compared to transcutol (F7-F12) produced tablets with a disintegration time range (35sec -2 min) These results are consistent with the results of the transcutol liquid vehicle's period of disintegration [30].

3.4.5 Weight variation

Weight variation test was performed on the tablets of each formula, weight difference and percent difference for each tablet was determined. As stated in Table 4, test findings indicated that the tablet weights were within pharmacopeia.

3.5 *In vitro* Dissolution Study

For dissolving patterns, the findings of the in vitro drug released at different periods were compiled throughout time, as shown in Figs. 1, 2, 3 ,4 and 5 and Table 5 shows the finding of the dissolution data analyzes .

The findings from DE widely used to compare the dissolving profiles show that DE is reduced by the increased concentration of liquid medicines. The results indicated in Table 5, given the consistent preservation of all formulatory factors, the lower medicine concentration (20%) is significantly greater ($P<0.05$) than the other two levels of DE (35 percent and 50 percent).

Table 4. Hardness, friability, disintegration time, drug content and weight variation of FLB liquisolid tablets and DCT

Formula	Hardness (Kg /cm^2)	Friability %	Disintegration time	Drug content %±(SD)	Weight variation (mg) ±(SD)
F1	4.25±0,1	0.15	6 min±0.08	99.5±0.9	1145±2.3
F2	3.5±0.43	0.33	5 min±0.17	98.7±0.6	640.9±1.8
F3	3±0.22	0.6	4 min±0.05	94.2±0.4	450±2.4
F5	3.5±0.17	0.23	5 min±0.11	93.7±03	1480±2
F6	4.5±0.22	0.41	4.5 min±.13	99.6±0.9	1070±1.9
F7	5±0.31	0.71	2 min±0.24	98.4±1	1140±3.5
F8	5.4±0.2	0.41	55 sec±0.45	93.7±1	645.9±0.9
F9	5.6±0.6	0.29	40 sec±0.71	97.1±0.88	449±0.88
F11	5±0.1	0.11	47 sec ±0.32	98.3±0.76	1481±0.99
F12	4.5±0.37	0.12	35 sec±0.74	96.2±0.55	1099±1.2
DCT	7.1±0.9	0.38	2 min±0.23	96.6±0.91	640±0.32

Results were expressed in mean±SD (n=3), SD standard deviation, DCT: direct conventional tablet, min: minute, s: second

Table 5. Dissolution parameters of FLB liquisolid compact and CT

Formula	Q 30 min	MDT	DE%
F1	93±0.9	11.4	81.2
F2	68±0.3	21.33	70
F3	63±.68	22.81	51
F5	75±0.33	14.28	72
F6	68±0.54	17.72	62
F7	100±1.2	5.6	90.6
F8	86±0.31	12.15	79.8
F9	70±0.8	21.61	57.5
F11	88±0.98	11.4	81
F12	73±0.7	15.68	67.2
DCT	50±0.65	14.86	41.2

(Reading represent the mean ±SD,n=3)

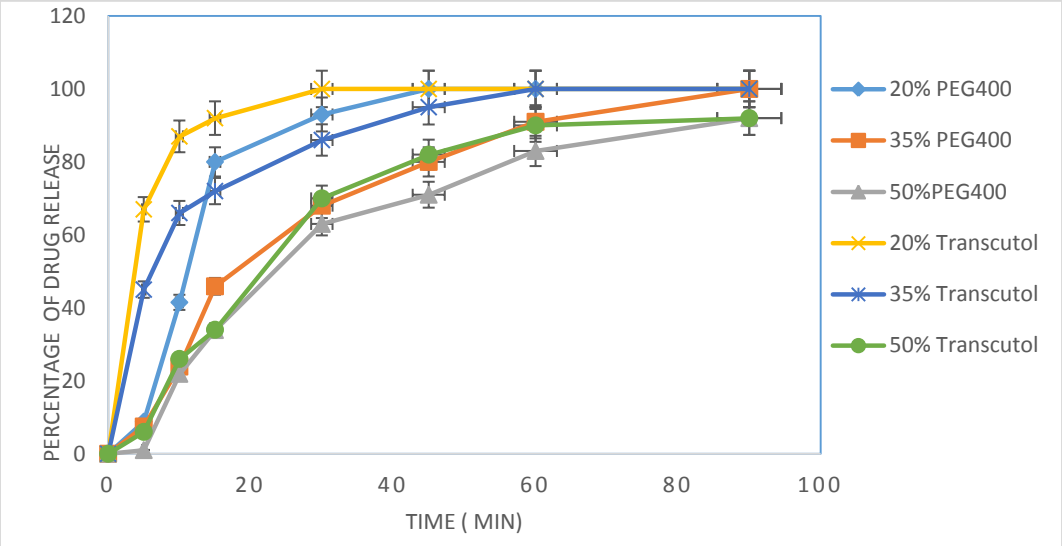


Fig. 1. Dissolution profile of FLB at different drug concentration, R=10 at 37°C
Results are expressed as mean±SD, n=3

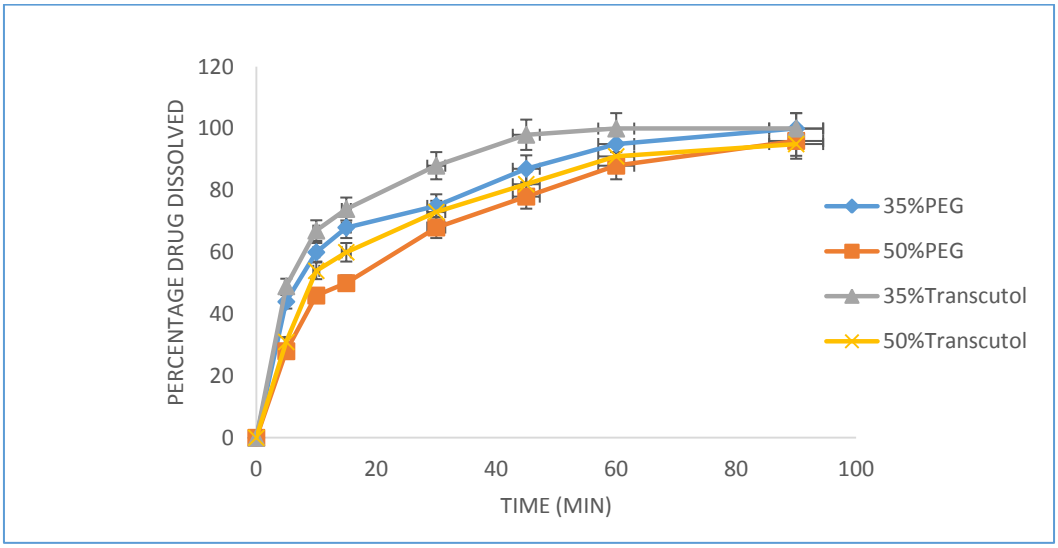


Fig. 2. Dissolution profile of FLB at different drug concentration ,R=30 at 37°C
Results are expressed as mean±SD, n=3

This can be explained by the dissolved condition of the medicine in the fluid medication.

$$FM = CL/Cd \quad (12)$$

Where FM is the molecular dispersed or dissolved drug fraction in the liquid medication of the liquisolid formula, CL is the saturation solubility of FLB in the liquid vehicle and Cd is the drug concentration in the liquid medication [31].

So as Cddecrease, the fraction of drug dissolved or dispersed is increase and viseversa.This also explain that liquisolids prepared with transcutol have higher DE and drug release profiles compared with those prepared with PEG 400 due to higher saturation solubility of FLB in transcutol compared with PEG 400.

The slow release can be explained by the fact that at high concentration of drug in liquid medication, only a small fraction of the drug will be in the molecular state which decreases drug release according to the Noyes– Whitney equation, i.e. the higher the drug concentration in a liquisolid formulation, the smaller the amount of liquid vehicle was added, thereby reduced

the amount of drug solubilized in the liquid vehicle.

It was proven that FM is directlyproportional to the drug dissolution rate [32].

The dissolving parameter and dissolution profile of FLB compact Fig. 4 findings have shown a substantial influence on drug release of increased carrier/coating ratio from 10 to 30 ($P < 0.05$). The R value is an essential parameter and represents the ratio of the carrier weights to the material for the coating optimization [33].

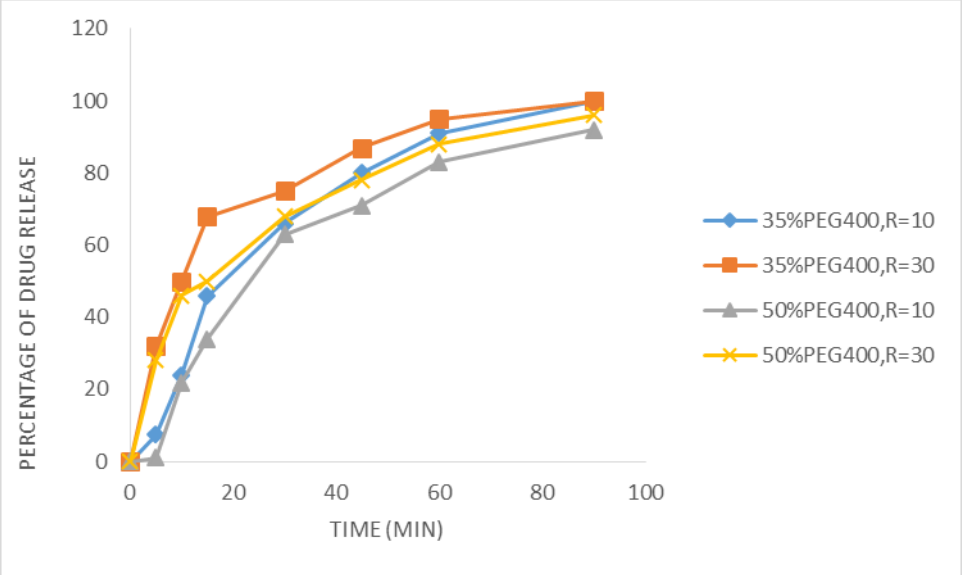


Fig. 3. The dissolution profile of FLB at different ratio using PEG 400 at 37°C
Results are expressed as mean±SD, n=3

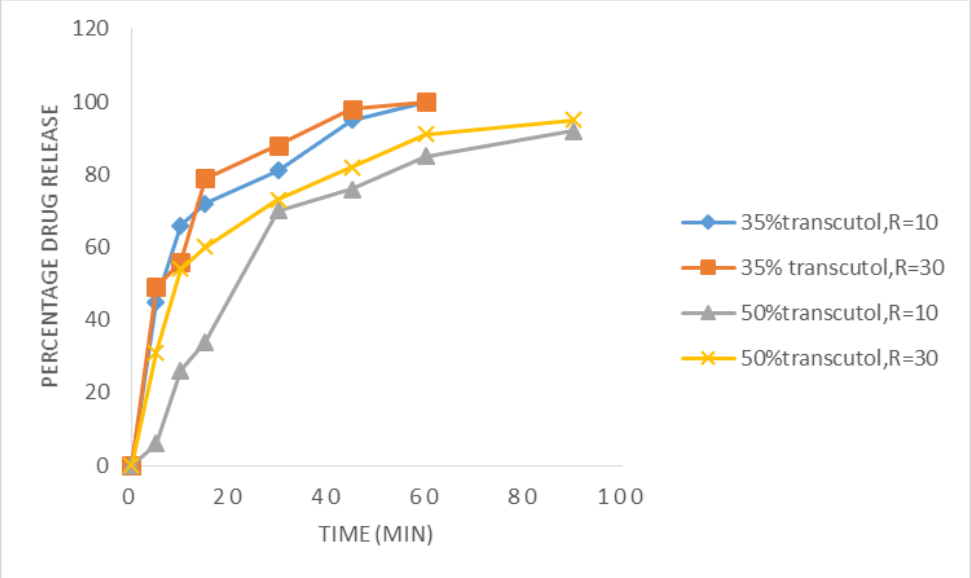


Fig. 4. The dissolution profile of FLB at different ratio using Transcutol at 37°C
Results are expressed as mean±SD, n=3

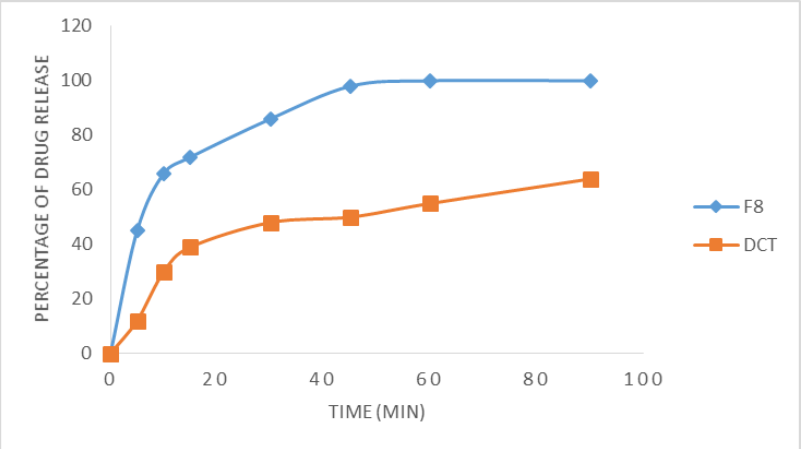


Fig. 5. The dissolution profile of FLB from F8 and DCT at 37°C
Results are expressed as mean ±SD, n=3, DCT: Direct conventional tablet

As the dissolving results in Table 5 indicate, liquisolid systems with lower R values include relatively small amounts of carrier (Avecil PH-102) and large amounts of Aerosil 200 particles loaded with tiny medications, and their ratios of fluid medications are comparatively greater per powder substrate. Low liquid-powder ratios, high levels of cellulose and low levels of Aerosil 200 are the main compact liquids with a high R-value [34].

This may be directly linked to improved characteristics of wicking, disinegration and deggregation [35].

The liquisolid pills demonstrate a comparatively low dissolving with low R values.

Using ratio of carrier to coating material of 30:1 with 20% w/w concentration of liquid medication represented by F4 and F10 resulted in large tablet weight as shown in Table 1.

Increasing the R-value and decreasing concentration of drug in the nonvolatile liquid will lead to increase in tablet weight due to higher amount of Avecil PH 102 used this explain why we exclude these formulas from further studies.

Table 5 data show that the maximum percentage 100% of medicament releases for liquisolid tablet F7 is within 30 minutes compared to 50% for CT. DE is often used to determine the better recipe to compare the dissolving profile.The values of DE can be arranged as follows F7>F1>F11>F8 .The DE for DCT was 41.2% indicating that liquisolid formulation significantly enhance the dissolution rate ($P<0.05$).

Lower MDT value indicate faster release of the drug from liquisolid formulation ,MDT of DCT was found to be 14.8 min while F7,F1,F11,and F8 has MDT of (5.6,11.4,11.4 and 12,6) respectively. All these formulas completely 100% release the medicine within less than 60 min.

The formula F8 was selected as best formula which has the lowest tablet weight 653mg compared to formulas F7,F1,F11 with tablet weight more than 1000 mg. The other parameter of F8 are within the pharmacopeia limit regarding hardness, friability, tablet weight dissolution rate and others.

Pairwise procedure such as dissimilarity (f1)and similarity (f2) factor provide a simple way to compare dissolution data .The FDA guideline proposes an equivalency in dissolution profile for f2 values of 50-100 and f1 between 0 and 15.

In comparison between optimized tablet F8 and DCT, f1, value was 99 >15 and f2 value was 22 <50 indicate non equivalence in the dissolution profile explained by increase in the wettability and surface availability to the dissolution media Fig. 5 [36].

3.6 Differntial Scanning Calorimetery (DSC)

Fig. 6 of the drug's DSC thermogram indicates that the FLB melting point is a prominent endothermic peak, at 118°C. This significant endothermic peak means that only crystalline medicines are used [37].

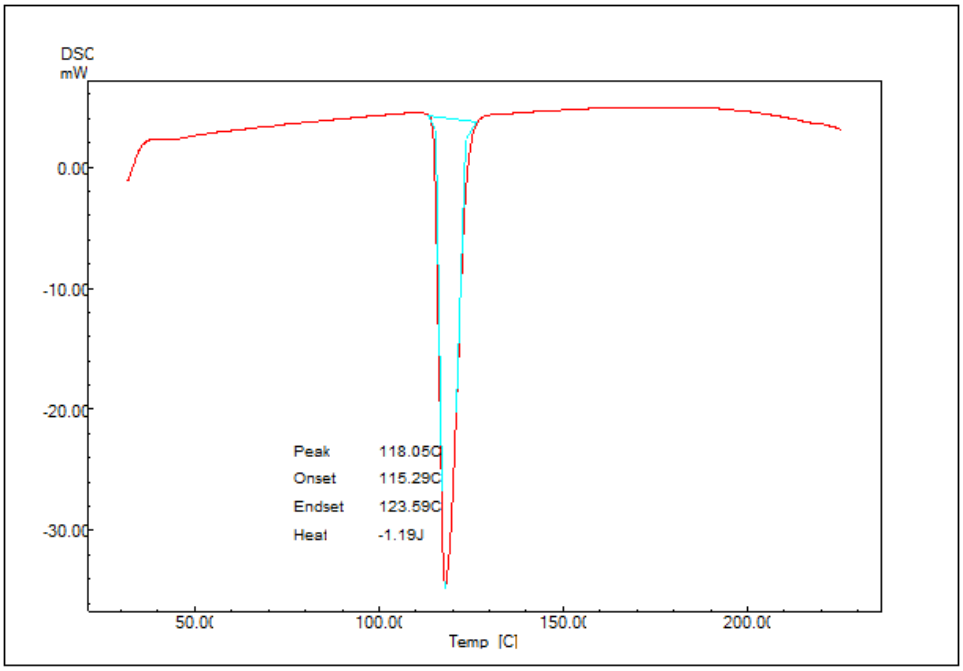


Fig. 6. DSC Thermogram of FLB

The optimized liquisolid system F8 and its physical blend as shown in Figs. 7 and 8 show that the drug melting peak has disappeared completely and the drug solution has developed accurately within the liquisolid powdered system, i.e. that the drug was molecularly distributed into the liquisolid matrix [38].

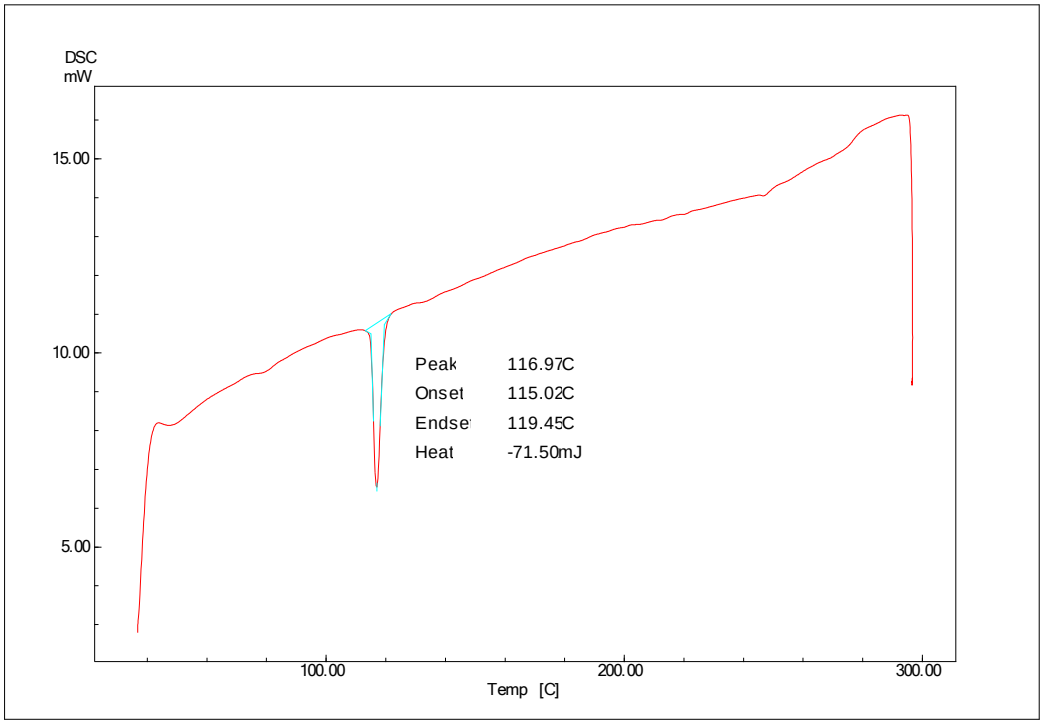


Fig. 7. DSC Thermogram of a Physical Mixture of F8 Liquisolid System

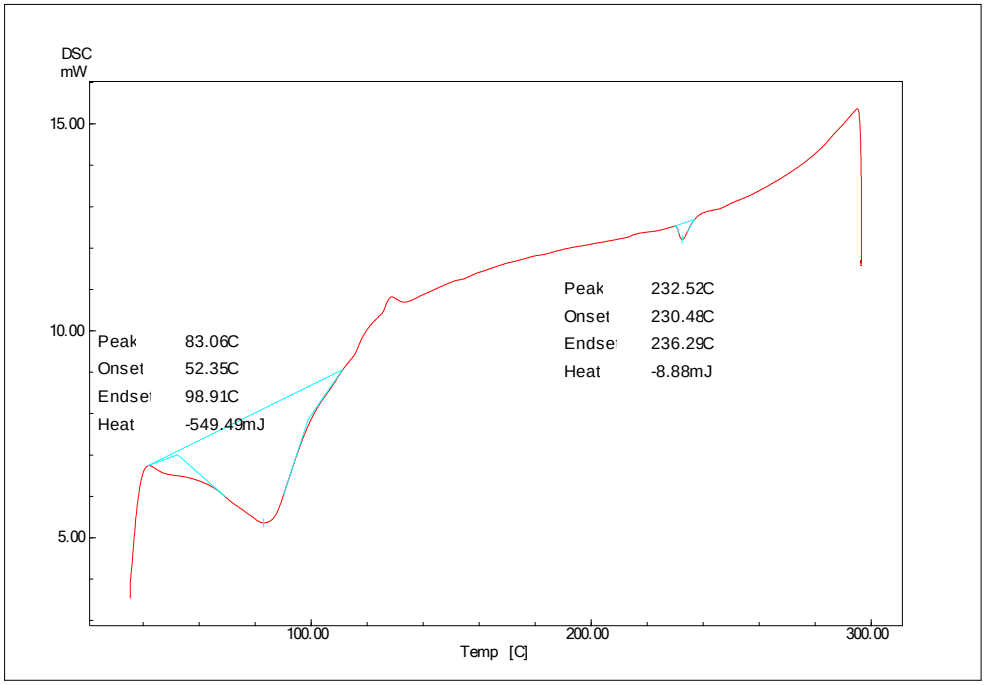


Fig. 8. DSC Thermogram of Optimized Formula 8

3.7 Fourier-transform Infrared Spectroscopy (FTIR)

The FTIR spectrum of FLB, physical mixture and liquisolid tablet of F8 was illustrated in Figs. 9, 10 and 11 respectively. The characteristic absorption peaks of FLB appeared at 3576.34, 3454.85 to 3283, 1701 to 1698, 1578.45 and 1455.03 cm^{-1}, denoting stretching vibration of OH group,-C=O and -C=C functional groups respectively [20]. Characteristic peaks of FLB and carriers were shown by the improved liquisolid system. These studies showed that when produced as a liquisolid system there is no chemical interaction between medicines and carriers. As illustrated in Figs. 10 and 11, the intensity of the drug's distinctive absorption band is reduced in liquisolid formulations due to the interaction between the drug and the hydrophilic polymer [33,39].

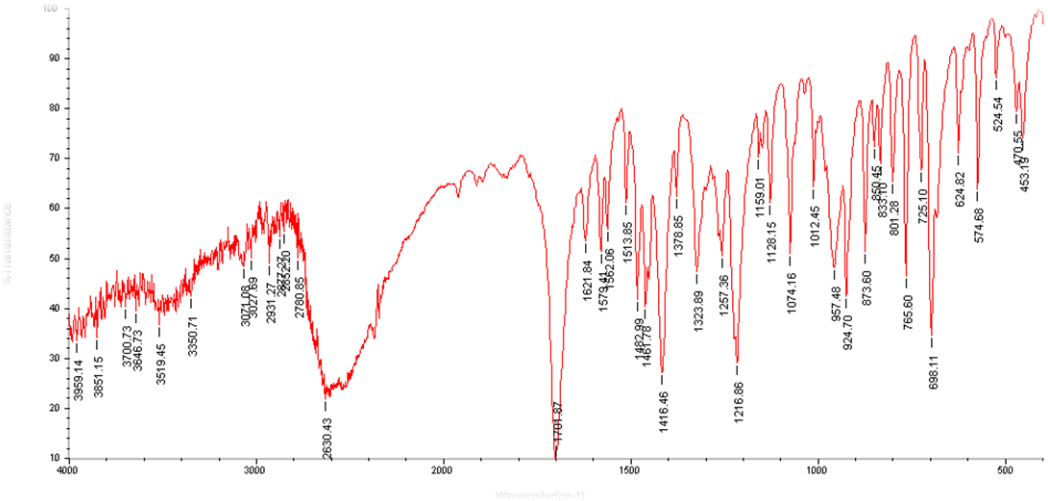


Fig. 9. FTIR Spectra of FLB

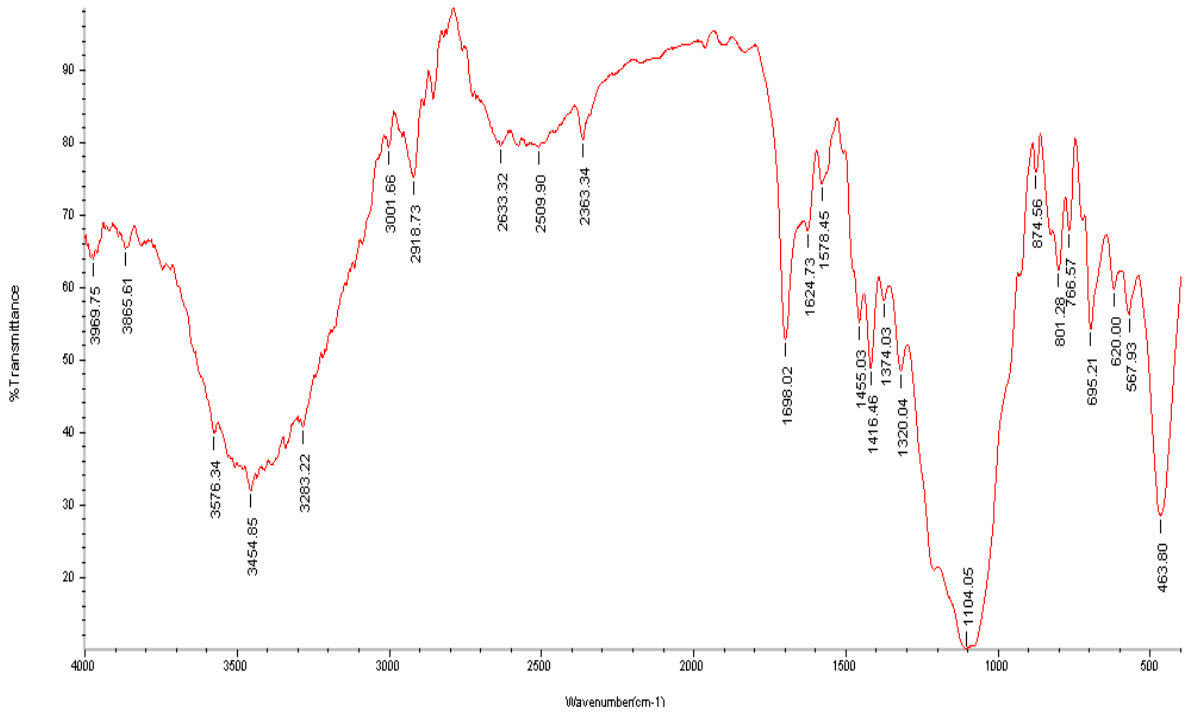


Fig. 10. The FTIR Spectra of Physical Mixture of F8

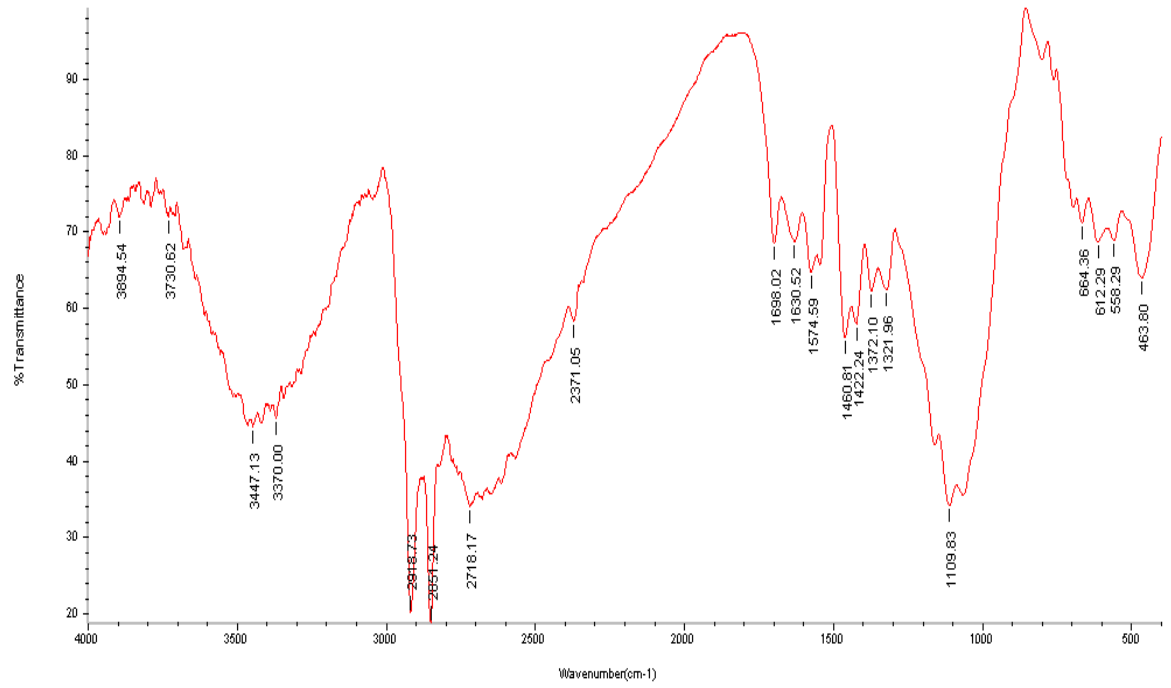


Fig. 11. The FTIR Spectra of Optimized Formula 8

4. CONCLUSION

A potential strategy to enhancing the dissolving of an insoluble medication such as flurbiprofen was discovered to be the liquisolid technique. In liquisolid compared with the straight traditional tablet, flurbiprofen solubility has risen substantially. F8 is the optimum formula for excellent flow and dissolving behavior with an acceptable tablet weight. F8 was selected. The

DSC and FTIR spectra suggest no change in the drug's crystalline form, and no drug/excipient interactions. The higher dissolving rate is possible because of increasing wettabilitity and increased particle surface.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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