Original Article

Formulation Development And Evaluation Of Liquisolid Compacts For Ibuprofen Liquisolid Tablets

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Abstract

Poor aqueous solubility and slow dissolution rate adversely affect the bioavailability of ibuprofen. The purpose of the investigation was to develop and evaluate liquisolid compact to improve the dissolution rate of the poorly soluble drug ibuprofen. Mathematical models were used to develop different liquisolid compacts. The calculated required quantities of microcrystalline (carrier), aerosil 200 (coating material), sodium starch glycolate (disintegrant) and cremophor RH 40, and kolliphor p 188 (non-volatile liquid vehicle) were used to produce acceptably flowable and compressible admixture. FTIR and DSC studies showed the compatibility among the excipients and drug. The tablets were developed by the direct compression method. The formulated liquisolid tablets were evaluated for weight variation, hardness, friability, disintegration time, drug content, and in vitro release characteristics of the ibuprofen. The tableting properties of the liquisolid compacts were within acceptable limits. The formulation (LS6) showed complete drug release within 60 min. Dissolution data treatments (Q_{15}, IDR, RDR, DE) showed better drug release (LS6) than pure drug and marketed formulation. The t-test indicated a statistically significant difference in the dissolution profiles between LS6 and marketed formulation. The liquisolid technique proved the success of improving the dissolution of a poorly soluble drug like ibuprofen.

KEYWORDS: Ibuprofen, poorly soluble drug ,liquisolid compact, mathematical model.

INTRODUCTION

The development of the oral drug delivery system principally depends on drug solubility, thereby its oral bioavailability.[1] Over 90 % of active pharmaceutical ingredients under development and 50 % of presently marketed dosage forms have solubility problems.[2] Ibuprofen is most commonly used for the treatment of rheumatoid arthritis, osteoarthritis, and mild-to-moderate pain.[3]The poor aqueous solubility of ibuprofen is a significant hurdle in its bioavailability and therapeutic application.[4] Efforts to increase the solubility of ibuprofen have focused on co-spray drying, [5] co-milling,[6] wet granulation with β-cyclodextrin,[7] ionic and non-ionic micellar systems,[8] co-processed superdisintegrants,[9]solid dispersion (SD).[10]However, these attempts have received a varying degree of success, and there is enough scope for improvement.

The liquisolid compact technique is a promising and novel technique to enhance poorly water-soluble drugs' solubility and dissolution rate.[11] In this technique, the liquid form of a drug in a non-volatile solvent is converted into dry-looking, non-adherent, and freely flowing powder by using carrier and coating materials. [11, 12] The primary mechanism behind liquisolid formulations is increased wettability and surface area available for drug release.[11-14] So, using the liquisolid technique, we can achieve better bioavailability of poorly soluble drugs.

With these considerations, it is essential to understand the solubility behavior of ibuprofen in SDs and the influence of carrier and coating material on the stability of the product to improve its solubility and bioavailability. Hence, the work aimed to formulate the liquisolid compacts foribuprofen to improve the solubility and dissolution rate. This approach can help to minimize the oral dosage required to achieve the same effect.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Yarrow ChemPvt. Ltd., Mumbai, India. Kolliphor HS 15, kolliphor p 188, and cremophor RH 40 were obtained from Yarrow ChemPvt. Ltd., Mumbai, India. Microcrystalline cellulose and aerosil 200 were purchased from Cabot Sanmarm Limited, Mumbai, India, sodium starch glycolate and crospovidone were received as gift samples from Merck Specialities Pvt. Ltd., Mumbai, India. Talc and magnesium stearate were obtained from LobaChemiePvt. Ltd., Mumbai, India. All other chemicals, reagents, and solvents were of analytical grade obtained from Lotus Enterprises, Andhra Pradesh, India.

Selection of non-volatile solvent

Solubility studies were conducted to select the non-volatile solvent. Solvents such as propylene glycol, polyethylene glycol 200, cremophor RH 40, tween 80, and kolliphor HS 15 (each 2 ml) were taken in screw cap vials for the solubility study. These vials are kept on a water bath shaker at 37±2 ºC for 72 h. Then, each test tube was centrifuged at 6000 rpm for 20 min after equilibrium. The supernatant was filtered using 0.45 µm pore size filter papers, and absorbance was measured using a UV visible spectrophotometer (Model- cary 60, Agilent Technologies, USA) at 220 nm.

Preparation and characterization of Binary system of solid dispersions of drug

To select the liquid form of the drug, 13 formulations were developed by the kneading technique. These formulations were developed by taking different ratios of ibuprofen and non-volatile solvent with varying kneading times (5, 10, 15 min). The composition of the drug, non-volatile solvent ratios, and kneading times was shown in Table S1. In vitro dissolution studies were performed for 13 formulations to optimize the binary system to develop the ternary system.

Preparation and characterization of ternary system of solid dispersions of drug

Ternary system (ibuprofen, cremophor RH 40, and kolliphor p 188) was adopted to prepare the liquid form of the drug. Different ratios (ICK1 to ICK3) of the ternary system were developed by constant weight of ibuprofen, cremophor RH 40, and three different ratios of kolliphor p 188 in a glass mortar and pestle and kneaded for 15 min. The formulation design of the ternary system is shown in Table S2.

In vitro dissolution studies

USP dissolution test apparatus type I (USP basket type apparatus) was used to conduct dissolution studies. The dissolution was performed at 50 rpm using 900 ml of 0.1 N HCl as dissolution medium at 37 ± 0.5 ºC temperature. The percentage drug release values obtained from the dissolution studies were plotted against time.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of drug, polymers and developed formulations were obtained by FTIR spectrophotometer (Model: cary 630, Agilent Technologies, Germany). Samples (2-5 mg) were directly placed into the diamond ATR and scanned over a scanning range of 4,500-500 cm^{-1}.

Differential scanning calorimetry (DSC)

Thermograms of the ibuprofen, polymers, and formulations were recorded by a DSC apparatus (Pyris Diamond Thermogravimetry (TG) /Differential thermal analysis (DTA), PerkinElmer, Singapore). The powdered sample (3-5 mg) was hermetically sealed in aluminum pans, and lids were crimped using a TA crimper and heated at a constant rate of 10ºC/min over a temperature range of 20-350 ºC, using nitrogen as purge gas at a flow rate of 150 ml/min. Platinum crucible with alpha alumina powder was used as a reference.

X-ray powder diffraction (XRD)

Diffraction of the ibuprofen, polymers, and formulations was recorded at room temperature by an X-ray diffractometer (Ultima-III, Rigaku, Japan). The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 3-40º using a step size of 0.02º at a scan speed of 1sec/step.

Stability of drug in the ternary system

The ternary system and tablets was packaged (triplicate) in a clear glass bottle with a screw cap and subjected to stability testing at 40 ± 2 ºC and 75 % R.H. for 3 months. The drug content, color, odor, and dissolution (tablet formulation) were evaluated during the specified period (1, 2, and 3 months).

A mathematical model for the preparation of liquisolid systems

Mathematical models were adopted to calculate the required quantities of carrier and coating materials for the formulation and development of liquisolid compacts.[15, 16]The required quantities of carrier and coating materials were calculated by using the following formulas:

$$L_f = \frac{W}{Q}$$

$$Q_0 = {}^{W}/_{L_0}$$

$$q_0 = {}^{Q_0}/_{R}$$

Where: W is the weight of the liquid medication and
Q is the weight of the carrier material.

Flow properties of liquisolid powder

After converting the liquid form of a drug into a powder form, the flow properties of powders were determined by using an angle of repose, Carr's index (CI), and Hausner's ratio (HR).

Preparation of liquisolid tablets

Liquisolid tablets were prepared by taking ibuprofen, cremophor RH 40, and kolliphor p 188 in a mortar and kneaded for 15 min to form a homogenous mixture. Calculated quantities of microcrystalline cellulose and aerosil 200 were added and triturated. The liquid/powder admixture was spread as a uniform layer on the mortar surface and left for 5 min to allow the drug solution to be absorbed in the interior of the powder particles. Then the powder was scraped off the powder surface with the help of an aluminum spatula. In this work, two types of super disintegrants (sodium starch glycolate, crospovidone) were used and compared in the ratios of 1, 2.5, and 5% (w/w). A typical design of liquisolid formulations is given in Table 1.

Compression of ibuprofen liquisolid tablets

After pre-compression evaluation of ibuprofen liquisolid powders, all six formulations were compressed into tablets. Tablets were compressed using 12 mm round punches concave on a 10 station rotary tablet punching machine (Rimek MINI PRESS 1, Karnavathi Engineering Pvt. Ltd., Gujarat, India). Sufficientcompression force was applied to produce acceptable hardness. The developed liquisolid tablets were subjected to evaluation tests.

RESULTS AND DISCUSSION

Screening of non-volatile solvents

Solubility studies

Screening of suitable non-volatile solvents was required for the preparation of the liquid form of a drug. The non-volatile solvents were screened based on the solubility of ibuprofen. The highest solubility was taken into consideration. Fig. 1 shows the solubility of ibuprofen in different non-volatile solvents. Ibuprofen showed the highest solubility (96.87 mg/ml) in cremophor RH 40. It showed 22 folds increased solubility compared with the aqueous solubility of ibuprofen (3.61 mg/ml). The solubility of ibuprofen was in the order of cremophor RH 40 >kolliphor HS 15 >propylene glycol>PEG 200 > tween 80 (Figure S1). Therefore, cremophor RH 40 was selected as a non-volatile solvent to prepare the liquid form of a drug.

Preparation of binary system of solid dispersions

Different weight ratios of ibuprofen and cremophor RH 40 (1:0.5, 1:1, and 1:1.5) were kneaded for 5, 10, and 15 min (IC1 to IC9). Then 1:3, 1:5, 1:7, and 1:9 ratios (IC10, IC11, IC12, and IC13) of ibuprofen and cremophor RH 40 were kneaded for 15 min.

In vitro dissolution studies of solid dispersions prepared from a binary system

The in vitro dissolution studies were performed for ibuprofen and binary system (Figure S2). The pure drug ibuprofen, IC1, IC2, and IC3 formulations showed incomplete drug release (17.08 %) within 90 min. In comparison with the above three formulations, IC3 showed higher drug release. It showed two-fold increases in drug release as compared to pure drugs. IC4, IC5, and IC6 showed a slight improvement in the drug release as compared to IC1, IC2. When compared to a pure drug, IC9 showed 3.5 folds increase in drug release. Formulation IC11 showed 5 folds increase in drug release than pure drug. The IC12 and IC13 showed approximately 98.50 % ibuprofen release. Formulation (IC12) contains less concentration of cremophor RH 40 than IC13 formulation. Therefore, IC12 formulation was selected for further development. After preparation, the total weight of the liquisolid system was more than 3.2 g because of a large amount of cremophor RH 40 for the preparation of liquid form of drug, and it required a high amount of carrier and coating materials to obtain free-flowing liquisolid powder. Therefore, it was not easy to prepare good-shaped liquisolid tablets for drugs like ibuprofen. To overcome this problem, a ternary system was proposed.

Preparation and characterization of ternary system of solid dispersions

The ternary system was prepared by taking the minimum quantity of non-volatile solvent to reduce the quantities of carrier and coating materials and thereby reducing the overall weight of liquisolid tablets. IC1-IC3 formulations contain the minimum quantities of cremophor RH 40 as comparison IC3 showed a higher drug release profile. Therefore, in IC3 formulation, kolliphor p 188 was included to prepare the ternary system. Kolliphor p 188 acts as a dissolution rate enhancer, solubilizer and it also improves stability. In the ternary system, three formulations were prepared by taking IC3 (1:0.5 ratio) formulation and varying amounts of kolliphor p 188 (0.5, 1, and 1.5) and knead for 15 min.

In vitro dissolution studies

In vitro dissolution profiles of different ratios of the ternary mixture are shown in Figure 1. Within 45 min of dissolution formulation, ICK3 showed the highest percentage of drug release (93.53 ± 2.13) than ICK1 and ICK2. ICK3 formulation showed complete drug release within 90 min. ICK3 formulation showed a ~ 6 folds increase in drug release than pure drug. This might be due to the kolliphor p188.

FTIR

FTIR spectrum of the ibuprofen, polymers, and formulations was displayed in Figure S3. FTIR spectrum of pure drug ibuprofen exhibits carboxylic acid O-H stretch (2953.9cm^{-1}), O-H stretching motion (2870.1cm^{-1}), carbonyl C=O stretch (1697.8 cm^{-1}), C-H bending (779.0cm^{-1}), aromatic C=C bond bending (1418.3 cm^{-1}). Similar FTIR

values were reported by Mohsinet al.[15]. FTIR spectrum of pure cremophor RH 40 showed the absorption band of the OH group at 3450 cm^{-1}. The ether C-O stretch at 1100cm^{-1}, carbonyl C=O stretch at 1733.2 cm^{-1}. The alkane C-H stretch was observed at 2850 and 2950cm^{-1}. Similar results were supported by Gamal et al. [16].The FTIR spectrum of kolliphor p 188 exhibits carboxylic acids O-H stretch (2710 cm^{-1}), (C-O stretch 1100cm^{-1} and alkane C-H stretch (2870.1 cm^{-1}). Similar results were supported by Yan et al.[17]. The ternary mixture displayed similar characteristic bands of ibuprofen. There was no significant shift, and no new peaks indicate the ibuprofen and excipients were chemically compatible. Microcrystalline cellulose showed O-H stretch (3328.5 cm^{-1}), alkane C-H stretch (2894.3cm^{-1}). The FTIR spectra of the tableting mixture (Figure S3F) exhibited identical peaks of the drug and excipients and no significant shift in the peak values. This indicates the chemical compatibility between ibuprofen and excipients.

DSC studies

The DSC thermograms of the ibuprofen, polymers, and formulations were displayed in Figure S4. Ibuprofen showed a sharp characteristic endothermic peak at 80.78 ºC, corresponding to its melting temperature. The sharp endothermic peak signifies the crystalline nature of ibuprofen. The thermogram of cremophor RH 40 and kolliphor p 188 displayed an endothermic peak at 37.5 ºC and 60.80 ºC, respectively. The melting peak of ibuprofen disappeared in the ternary system, indicating the conversion of the crystalline form of ibuprofen into amorphous. This was further supported by XRD studies.

XRD analysis

An XRD pattern of pure drug ibuprofen, polymer, and formulations are shown in Figure 2. The crystalline nature of the drug was demonstrated by the characteristic XRD pattern with peaks appearing at 2θ equivalent to 6º, 12º, 17º, 19º, and 22º. The XRD results were in good agreement with the thermal analysis data, where the X-ray diffraction pattern revealed that pure drug ibuprofen was clearly in a crystalline state. The XRD pattern of cremophor RH 40 did not show any sharp peaks indicating the liquid nature of cremophor RH 40. The pure kolliphor p 188, the characteristic peaks were observed at 19º and 23º. The disappearance of ibuprofen peaks in the ternary system indicates conversion to an amorphous state or solubilized form.

Stability of drug in the ternary system

Drug stability in the ternary system (ICK3) was studied at 40 ± 2 ºC and 75 ± 5% R.H. The drug content remained the same after 3 months of stability study (Table 2). The physical appearance and odor were not affected after 3 months of study at stress condition. It indicates the physical and chemical stable nature of the formulation.

Mathematical approaches for the calculation of optimum quantities of carrier and coating material to formulate liquisolid tablets

The liquid form of a drug is converted into powder form by a mathematical approach. Spireaset al.[18, 19] suggested that particles with high absorption properties should be used as carrier materials, such as cellulose, starch, and lactose. The coating material should be fine excellent, and highly absorptive silica powder. Based on these criteria, in the present study, microcrystalline cellulose and aerosil 200 were taken as carrier and coating materials, respectively.

The liquid load factor was calculated using the selected ratio of liquid medicament (ternary mixture). Selected carrier and coating materials were added and measured the angle of repose, CI, and HR. This procedure was repeated until the acceptable values of angle of repose, CI, and HR were achieved. Then the liquid load factor can be calculated from the given equation.

$$L_f = \frac{W}{Q} = \frac{600}{600} = 1$$

Where Lf is the liquid load factor; W is the liquid medication (ternary system) weight; Q is the carrier material weight.

In the present study, the liquid load factor of all the formulations was found to be 1. According to Kamelet al.[20] the best carrier has a higher liquid load factor and good flow properties.

The required quantities of the carrier (Q) and coating (q) materials were calculated using the following equation.

$$Q = \frac{W}{L_f} = \frac{600}{1} = 600$$

The excipients ratio (R) was calculated from the equation.

$$R = \frac{Q}{q} = \frac{600}{60} = 10$$

Where Q is the weight of carrier material; q is the weight of coating material.

An increase in the R-value will lead to higher quantities of carrier and coating materials. An optimum value of R is recommended to be 20. Hence, in the present study excipients ratio (R) was kept at a constant value of 10. The quantity of coating material was calculated from the equation.

$$q = \frac{Q}{R} = \frac{600}{10} = 60$$

From the above calculations, the quantities of carrier and coating materials were found to be 600 and 60, respectively.

Ibuprofen liquisolid powder systems were developed using the required quantities of coating and carrier material. Further, super disintegrants, sodium starch glycolate, and crospovidone (1%, 2.5%, and 5% (w/w) were added and subjected for the pre-compression parameters.

Pre and post compression parameters of ibuprofen liquisolid compact

Precompression parameters were evaluated, and the results are shown in Table S3. Flow properties were determined for prepared liquisolid powder before compression into a tablet. The angle of repose is characteristic of the internal frictional force of the particles. The angle of repose is high if the particles are cohesive. Values for the angle of repose ≤30º indicate free flow, and angles ≥40º indicate poor flow[21]. For all the formulations (LS1 to LS6), the angle of repose was in the range of 23º - 31º, indicating excellent to good flow properties compared to pure drug ibuprofen (48.36º). CI of all liquisolid formulations was found to be 12.89%- 23.61% indicating good to acceptable flow properties. HR of all liquisolid formulations confirmed good to acceptable flow properties, and values are found in 1.15 to 1.31 with satisfactory compressible characteristics as shown in (Table S3). The pre-compression parameters were in the acceptable range and subjected for the compression into tablets. The liquisolid tablets were developed and subjected to post compression evaluation.

Thickness

Thickness evaluates the uniformity in the hardness of prepared tablets. There was not much variation (8.54 ± 0.13 to 8.45 ± 0.75) in the thickness of tablets in each formulation which showed that the powder blends were consistent in particle size and had uniform behavior during the compression process.

Hardness

Generally, the tablets should be sufficiently hard to resist breaking during normal handling and soft enough to disintegrate appropriately after swallowing. All the prepared liquisolid formulations showed acceptable hardness ranging from 3.16 ± 0.28 to 4.33 ± 0.57 kg/cm^2. The inclusion of liquid medication in tablets improved the mechanical strength of tablets prepared by the liquisolid technique.

Friability

All the prepared liquisolid tablets passed the friability test and showed friability in the range 0.086 ± 0.05 to 0.771 ± 0.06. The results indicating that friability was>1 % by weight, and no tablet showed cracking, splitting, or broken pieces.

Weight variation

The lowest weight variation confirms the uniform flow of the material during compression. All the prepared liquisolid tablets passed the weight variation test and were within the limits of Indian Pharmacopeia. The weight variation of all liquisolid tablets ranges from 1269.6 ± 2.14 to 1320 ± 1.15 mg.

Drug content

The drug content of all the formulations was in the range of 85.42 ± 5.51 to 101.91 ± 2.58 % and the values were within the IP limits of 85-115 %. Uniform drug content confirms proper mixing of the drug with the rest of the excipients.

In vitro disintegration time

Disintegration times of all the prepared liquisolid formulations were within limits. Liquisolid formulations (LS1 to LS2) showed higher disintegration time (4.2 ± 0.17 to 4.2 ± 0.17 min) compared to formulations prepared with crospovidone (1.88 ± 0.61 to 4.16 ± 0.52 min). The low disintegration time of LS6 indicates rapid drug release. The longer disintegration time may retard the release of the drug from the dosage form.

Different post-compression parameters like thickness, hardness, weight variation, friability, drug content, and disintegration time were reported in Table 3.

In vitro dissolution studies of ibuprofen liquisolid tablets

The in vitro dissolution studies were performed on all the liquisolid formulations, pure drug ibuprofen, and marketed tablets (Ibutas 200 mg tablet, Intas Pharmaceuticals Ltd.) as showed in Figure 3. Dissolution studies were performed in USP dissolution apparatus-I at 50 rpm using 0.1N HCl as a dissolution medium. All the prepared ibuprofen liquisolid formulations (LS1 – LS6) showed the highest drug release compared to pure drug ibuprofen and marketed tablet. The liquisolid formulations (LS4 to LS6) prepared with 1%, 2.5%, and 5% w/w of crospovidone showed the highest percentage of drug release within 90 minutes. Compared to all the prepared liquisolid formulations, LS6 showed the highest drug release (91.07 %) within 30 minutes. The pure drug ibuprofen and marketed tablet sowed incomplete drug release within 90 min. This might be due to the increased surface area of the drug available for release, where the liquisolid tablet contains a solution of ibuprofen in non-volatile solvent (cremophor RH 40) absorbed on the powder carrier. Hence the drug is available in a solubilized, molecularly dispersed state, increasing the surface of the drug available for dissolution[22].Also, in the diffusion layer at the solid/liquid interface, the liquid vehicle may diffuse with the drug particles away from the primary liquisolid particles. In this case, the small amount of liquid vehicle may be sufficient to increase the solubility of drug particles by acting as a co-solvent with the dissolution medium. As a result, the concentration gradients of the drug and dissolution rate were increased[23].

Dissolution data treatment

The improved dissolution was further confirmed by comparing the various dissolution parameters calculated from the dissolution of ibuprofen, marketed tablet, and liquisolid formulation LS6. The formulation LS6 showed the highest $Q_{15\ min}$ (60%) as compared to the marketed tablet and pure drug. The dissolution results were further supported by significantly high dissolution efficiency (DE) values of LS6 compared to marketed tablets and pure drugs (Table 4). The initial dissolution rate (IDR, 4.20) and relative dissolution rate (RDR, 53.65) of LS6 indicated the improvement or enhancement of solubility and dissolution rate.

Stability studies of ibuprofen liquisolid tablet

The ibuprofen liquisolid tablets (LS6) showed a similar dissolution profile after 3 months of storage period as showed in Figure 4. The similarity factor (f_2) of release profiles against fresh tablets was 75.44 after three months. This indicated the stable nature of the developed ibuprofen liquisolid tablets. This signifies the enhancement of the solubility and dissolution enhancement with suitable methods and selected excipients.

Table 1: Formulation design for the preparation of ibuprofen liquisolid tablets

Formulations (mg)	Ibuprofen	Crem-ophor RH 40	Kolli-phor p-188	Loading factor (Lf)	MCC (Q)	Aerosil 200 (q)	SSG	Crospovidone
F1	200	100	300	0.33	900	90	15.9 (1%)	-
F2	200	100	300	0.33	900	90	39.7	-

							(2.5%)	
F3	200	100	300	0.33	900	90	79.5 (5%)	-
F4	200	100	300	0.33	900	90	-	15.9 (1%)
F5	200	100	300	0.33	900	90	-	39.7 (2.5%)
F6	200	100	300	0.33	900	90	-	79.5 (5%)

Each batch contains 70 tablets; Excipients ratio (R) value is 10 for all formulations; L_f: liquid load factorQ and q are quantities of carrier and coating materials respectively.

Table 2. Stability of ibuprofen in ternary system

Sampling time (Month)	Drug content (%)*	Physical appearance	Odour
1	94.24 ± 4.67	Unaffected	Unaffected
2	93.88 ± 3.82	Unaffected	Unaffected
3	92.35 ± 3.21	Unaffected	Unaffected

*Values are expressed as mean ± SD, n=3

Table 3: Post compression parameters of ibuprofen liquisolid tablets

Formulation code	**Weight variation[a] (mg)**	**Hardness[b] (kg/cm^2)**	**Thickness[c] (mm)**	**Friability[d]**	**Drug content[e] (%)**	**Disintegration time[f] (min)**
LS1	1269.6±2.14	3.46±0.95	8.54±0.13	0.633	94.77±2.8	6.29±0.20
LS2	1287.5±1.06	3.33±0.28	8.32±0.45	0.465	94.24±4.0	4.2±0.17
LS3	1318±1.46	3.33±0.28	8.67±0.27	0.69	85.42±5.5	4.2±0.17
LS4	1271.6±1.55	3.16±0.28	8.76±0.72	0.771	97.87±2.3	4.16±0.52
LS5	1290.5±1.30	3.66±0.57	8.77±0.49	0.086	101.91±2.5	3.14±0.09
LS6	1320±1.15	4.33±0.57	8.45±0.75	0.174	97.86±1.5	1.88±0.61

a: Avg±% deviation, n=20; b: mean±SD, n=6; c: mean±SD, n=5; d: n=6.5 g; e: mean±SD, n=20; f: mean±SD, n=6

Table 4: Dissolution parameters of pure drug, LS6 liquisolid formulation and marketed tablet

Dissolution parameters	**Pure drug**	**LS6 liquisolid formulation**	**Marketed formulation**
$DE_{15\ min}$ (%)	3.2	43.10	28.00
$DE_{30\ min}$ (%)	7.95	60.23	48.11
$Q_{15\ min}$ (%)	1.17	63.10	15.45
IDR (%/min)	0.07	4.20	1.03
RDR	-	53.65	4.08

DE: dissolution efficiency, IDR: initial dissolution rate, RDR: relative dissolution rate

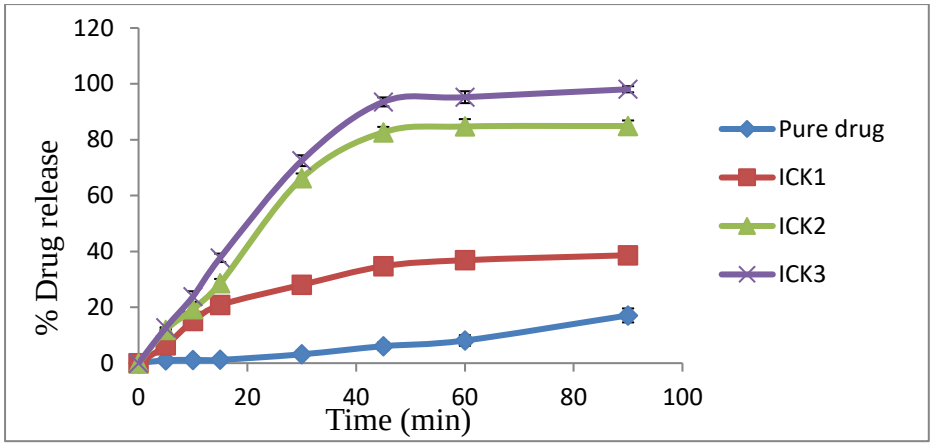

Fig.1: In vitro release profiles of ternary system

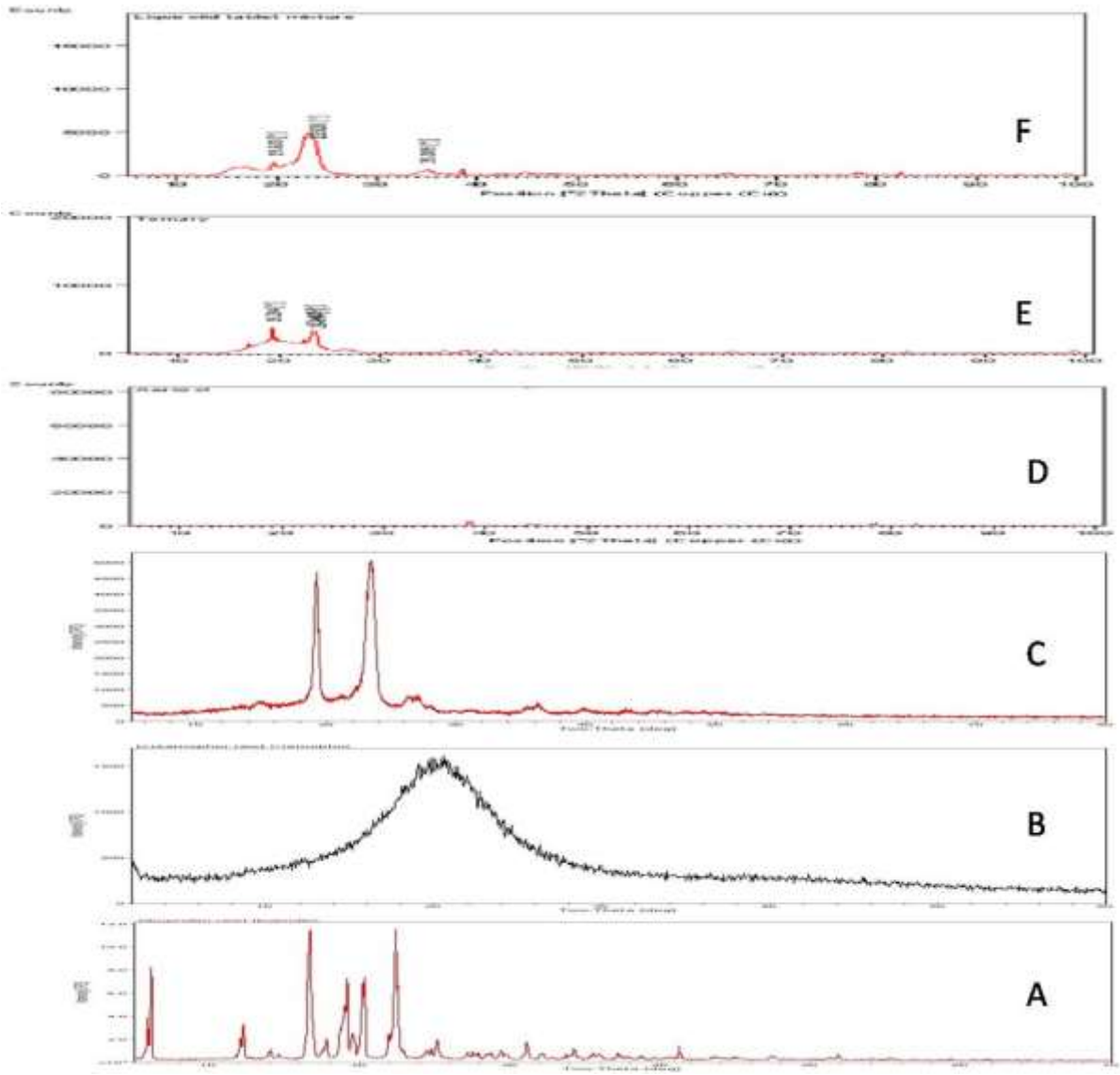

Fig. 2: XRD pattern of (A) pure drug ibuprofen, (B) cremophor RH 40,(C) kolliphor p 188, (D) aerosil 200, (E) ternary system (ICK3) and (F) tableting mixture

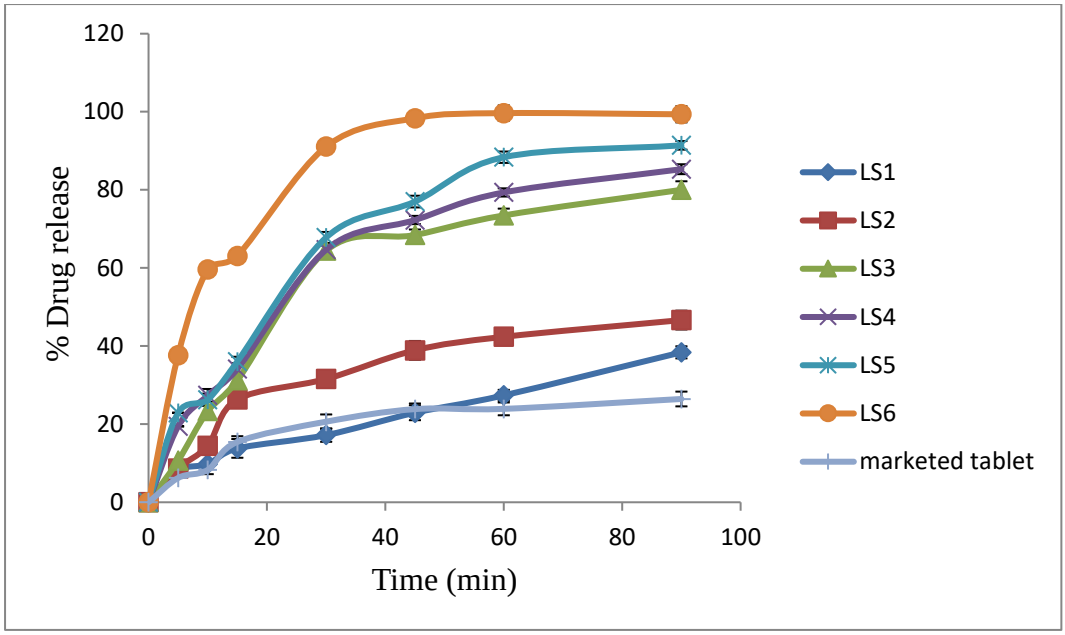

Fig. 3: In vitro dissolution profiles of liquisolid formulations

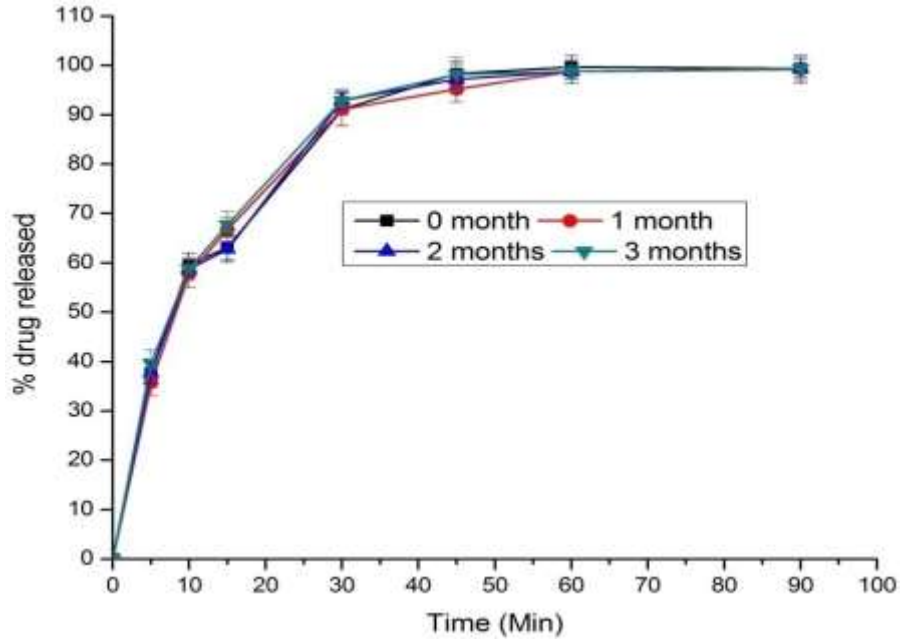

Fig.4: Stability study: In vitro drug release profiles of LS6 after 0, 1, 2 and 3 months of storage period

Table S1. Formulation design of binary system (ibuprofen and Cremophor RH 40)

Formulations	Drug : Non-volatile solvent	Kneading time (min)
IC1	1:0.5	5
IC2		10
IC3		15
IC4	1:1	5
IC5		10
IC6		15
IC7	1:1.5	5
IC8		10
IC9		15
IC10	1:3	15

IC11	1:5	15
IC12	1:7	15
IC13	1:9	15

Table S2. Formulation design of ternary system (ibuprofen, cremophor RH 40 and kolliphor p 188)

Formulations	Ibuprofen	Cremophor RH 40	Kolliphor p 188
ICK1	1	0.5	0.5
ICK2	1	0.5	1
ICK3	1	0.5	1.5

Table S3. Flow properties of pure drug ibuprofen and developed liquisolid formulations

Formulation code	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	CI (%)	HR
Ibuprofen	48.36±1.67	0.26±0.01	0.40±0.03	33.33±2.65	1.5±0.05
LS1	27.55±0.71	0.38±0.03	0.48±0.04	15.48±1.66	1.18±0.02
LS2	27.37±1.15	0.38±0.03	0.51±0.06	15.37±1.54	1.18±0.02
LS3	23.84±0.13	0.33±0.91	0.37±0.11	12.89±0.26	1.15±0.03
LS4	30.37±1.71	0.34±0.02	0.39±0.39	23.61±1.96	1.30±0.03
LS5	31.35±1.44	0.34±0.03	0.46±0.05	21.78±2.52	1.31±0.04
LS6	24.27±0.47	0.34±0.03	0.39±0.04	13.37±1.24	1.15±0.01

Values are expressed as mean ± SD, n=3

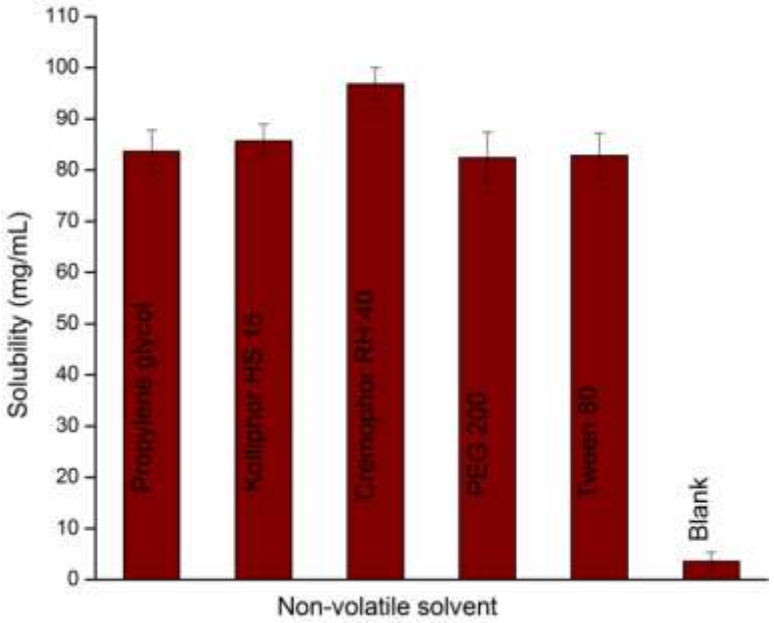

Fig. S1: Solubility of ibuprofen in different non-volatile solvents

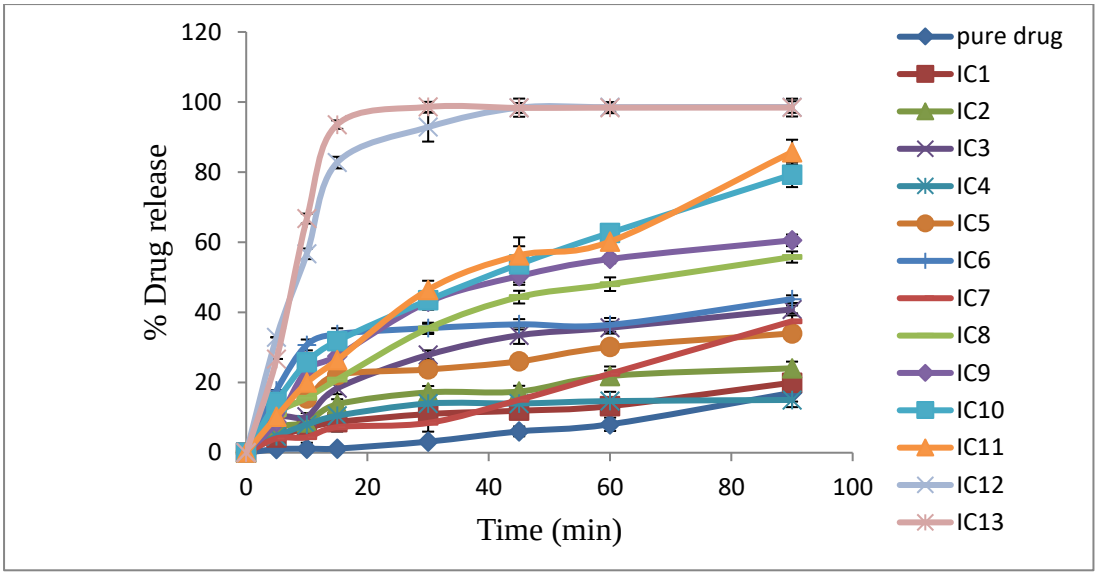

Fig. S2:In vitro dissolution of the binary system of the ibuprofen

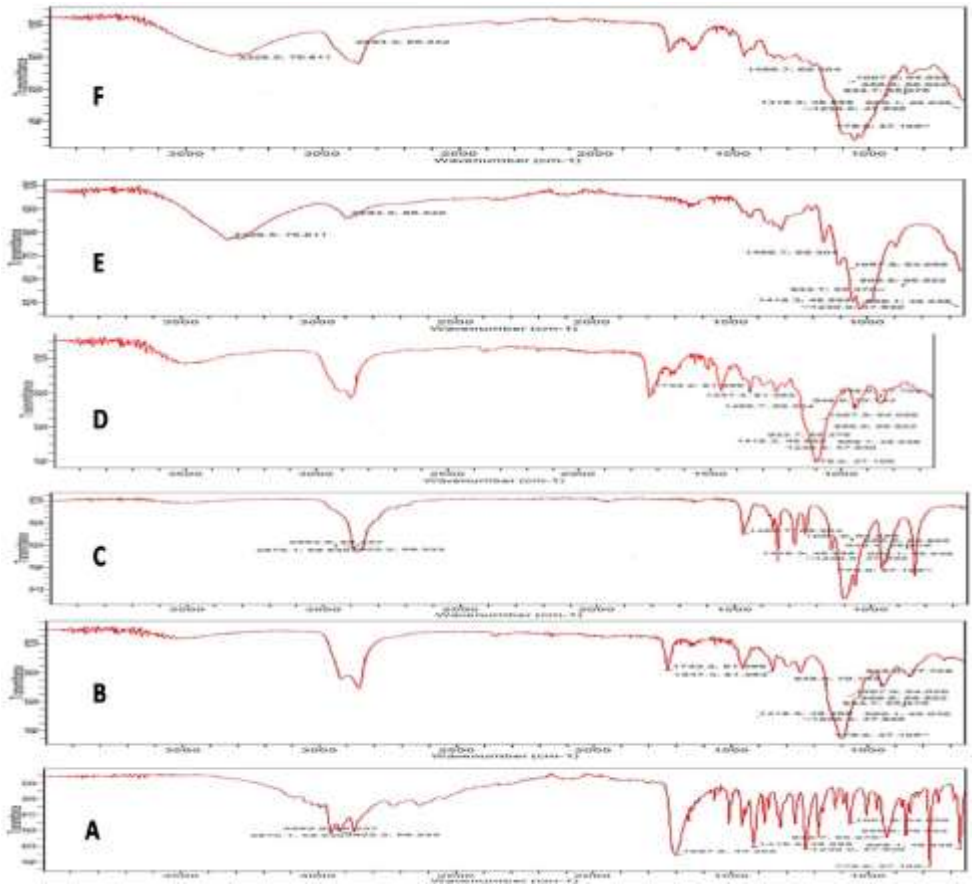

Fig.S3: FTIR spectrum of (A) pure drug ibuprofen, (B) cremophor RH 40, (C) kolliphor p 188, (D) ternary system (ICK3), (E) microcrystalline cellulose and (F) tableting mixture

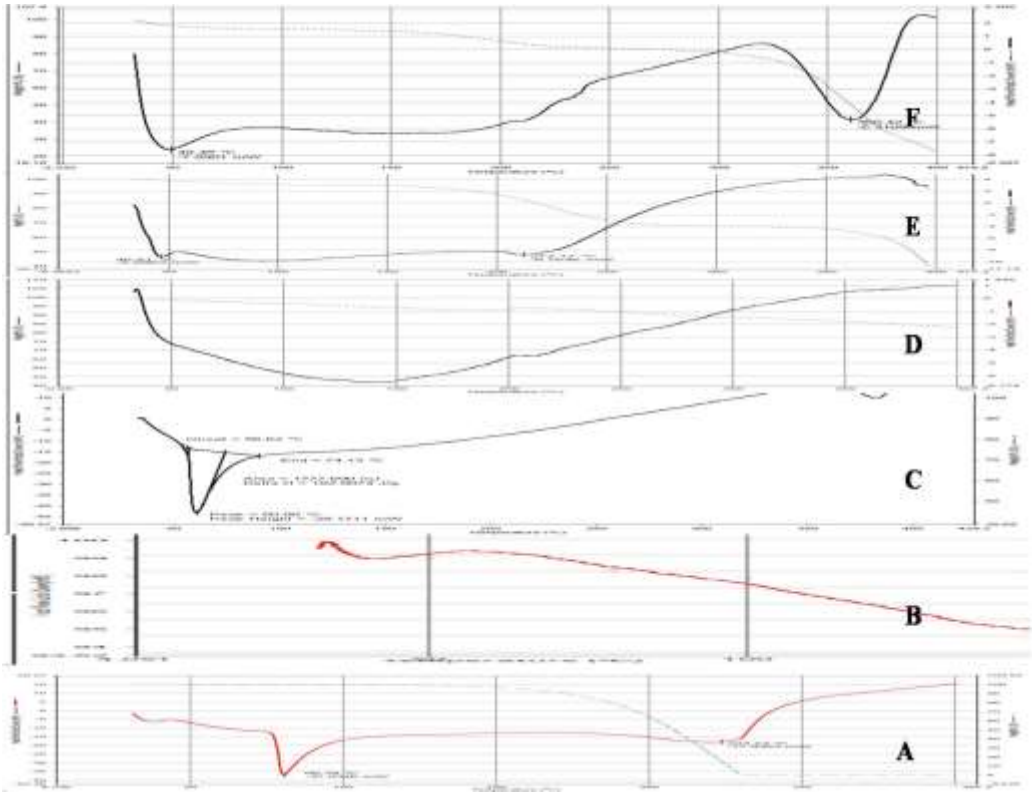

Fig. S4: DSC thermogram of (A) pure drug ibuprofen, (B) cremophor RH 40,(C) kolliphor p 188, (D) aerosil 200, (E) ternary system (ICK3) and (F) tableting mixture

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

CONCLUSION

This study concluded that the liquisolid technique is a promising approach to enhance the dissolution characteristics of the poorly water-soluble drug ibuprofen. The formulation in liquisolid tablets facilitated the molecular dispersion of poorly soluble drugs in the hydrophilic carrier matrix that was amenable to pharmaceutical manufacturing.

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