Formulation and Evaluation of Liquisolid Compacts of BCS Class II Drug Ketoprofen

Madhavi Kasturi* and Neelesh Malviya

1Department of Pharmacy, Mandsaur University, Rewas Dewda Road, Mandsaur, M.P- 458001, India.
2Department of Pharmacy, Smriti College of Pharmaceutical Education, Indore, M.P – 452010, India.

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

ABSTRACT
Aims: The main objective of the current research work is to develop liquisolid compacts of BCS Class II drug ketoprofen with an intention to enhance the solubility of drug by applying liquisolid technique.

Place and Duration of Study: Smriti College of Pharmaceutical Education between June 2018 June 2019.

Methodology: Initially liquid medication was obtained by dissolving drug in suitable solvent. Saturation solubility studies were performed in various hydrophilic non-volatile solvents to select the solvent showing highest solubility for drug. This liquid medication was admixed with calculated amounts of carrier material (Avicel PH 102) and coating material (Cab-O-Sil) using Spireas mathematical model in order to obtain liquisolid formulations. Further, this powder mass of liquisolid system was compressed to form Ketoprofen liquisolid compact formulations ranging from TK1 to TK9. They were further subjected to post compression evaluation tests such as weight variation, hardness, friability, content uniformity, disintegration and in vitro dissolution studies.

Results: Based on the solubility studies, PEG 400 was selected as solvent for ketoprofen drug. Rheological properties for the prepared liquisolid powder system were performed for all the formulations and they showed acceptable flow properties. The results obtained for the post compression evaluation tests of all the prepared liquisolid compacts were present within the acceptable limits. The disintegration time observed for all formulations were within 5 minutes. The results of in vitro release of all the liquisolid compacts showed enhanced release rates compared to
that of directly compressed tablet. Liquisolid compact formulation TK7 showed maximum release of 97.62% of drug within 12 minutes in pH 7.4 phosphate buffer which was much higher when compared to that of directly compressed tablet. The SEM and PXRD studies for TK7 revealed conversion of crystalline to molecularly dispersed form of drug in the obtained liquisolid formulation. DSC and FTIR studies also revealed that there was no presence of any significant interaction between drug and excipients involved in the formulation.

**Conclusion:** Finally, it could be concluded that Liquisolid technique was successful in enhancing the solubility and further dissolution profile of BCS Class II drug Ketoprofen.

**Keywords:** Carrier material; coating material; ketoprofen; liquisolid technique; solubility enhancement; dissolution profile.

1. **INTRODUCTION**

Solubility is an important criterion to achieve desired concentration of drug in systemic circulation and show its therapeutic efficacy. Solubility enhancement of poorly aqueous soluble drugs promotes drastic increase in rate and extent of drug absorption rate in human body which leads to reduced side effects upon oral administration. The Biopharmaceutical Classification System (BCS) classified drugs into four major classes based on the solubility and permeability nature of drugs wherein BCS Class II drugs exhibit low solubility and high permeability nature. Most of the non-steroidal anti-inflammatory drugs (NSAIDs) belong to the BCS Class II, due to which they are highly permeable through biological membrane but have limitation due to poor aqueous solubility. The absorption rates of these drugs are controlled by dissolution in the gastrointestinal fluids. Henceforth, enhanced solubility promotes enhanced dissolution of the drugs. Earlier various methods have been developed by the researchers to challenge the formulation of poorly soluble BCS Class II drugs in solid dosage form [1]. The most commonly used methods for improving the solubility include salt formation, solid dispersions [2,3,4], inclusion complexation with cyclodextrin [5,6], microemulsion and micellar solubilization [7], nanosuspension formation [8, 9], surface adsorption on inert carriers, micronization[10], lipid nano particles [11]. Nowadays, one of the most prominent approach developed to face this challenge is liquisolid technique developed by Spireas [12].

Ketoprofen, a propionic acid derivative, is a potent NSAID with good analgesic properties widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gouty arthritis. It is poorly aqueous soluble (0.5 μg/ml) belonging to BCS Class II drug. It has poor dissolution rate and reduced gastrointestinal absorption [13]. This poor aqueous solubility of the drug limits its therapeutic action which further leads to low or erratic bioavailability. Due to its acidic nature its oral administration causes severe complication in the GIT. Therefore, enhancing the solubility and dissolution profile of the drug may reduce the side effects on the stomach due to rapid absorption and reduction in contact with the stomach wall [14]. The current research article is mainly aimed at enhancing solubility and dissolution profile of ketoprofen using liquisolid technique.

Liquisolid technique is considered a newer, safer, economic method employed to enhance solubility of poorly aqueous soluble drugs. Initially liquid medication is prepared by dissolving drug in selected non-volatile hydrophilic solvent by saturation solubility studies. It is further admixed with calculated quantities of carrier material with good absorption properties and coating material with good adsorption properties by applying Spireas mathematical expression. Finally, dry looking, free flowing, non-adherent, readily compressible powder is obtained which is termed as liquisolid system. This can be further compressed using compression machine to obtain liquisolid compacts. From the earlier studies it was observed that the liquisolid systems showed improved solubility and dissolution profiles. The postulated mechanism for improved solubility may be due to increased surface area of the drug exposed to dissolution medium, or enhanced solubility of the drug in the microenvironment or increased wettability of the drug due to reduced interfacial tension between solid/liquid interface [15].

2. **MATERIALS AND METHODS**

2.1 Materials

Ketoprofen was purchased from TCI, Tokyo Chemical Industry, Japan. Excipients and
chemicals such as Avicel pH 102, Cab-O-Sil, Polyethylene glycol (PEG 200, PEG 400 and PEG 600), propylene glycol (PG), Tween 20, Tween 80, Span 20, span 80, sodium hydroxide, potassium dihydrogen orthophosphate was purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All the chemicals belong to analytical grade.

2.2 Methods

2.2.1 Saturation solubility studies

Saturation solubility studies for ketoprofen were carried out in various non-volatile solvents such as propylene glycol, PEG 600, PEG 400, PEG 200, Tween 20, Tween 80, Span 20 and Span 80. Excess amount of drug was added to each 5 ml of selected solvent in screw capped vials to obtain saturated solutions. These vials were kept on mechanical shaker for 48 hours at 25ºC under constant vibration. Later the solutions were filtered 0.45μm Millipore filter, diluted and then analyzed spectrophotometrically at 260 nm for the drug content [16]. The solubility results for drug in various solvents were shown in Table 1.

2.2.2 Application of Mathematical Model for designing the liquisolid systems

In this study, PEG 400 was used as liquid vehicle, Avicel 102 was selected as carrier material and Cab-O-Sil was selected as coating material. In order to achieve acceptable flowability and compressibility of liquisolid compacts, a new mathematical model developed by Spireas for liquisolid systems was applied to calculate the quantities of excipients in the formulation of liquisolid systems [17,18]. This model was based on new fundamental features of powders which are constants for each excipient material with the liquid vehicle called as flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-value).

In most cases, carrier and coating agents can only withstand a small amount of solvent while maintaining adequate flow and compression properties.

It can be achieved depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used in formulation and given by formula:

\[ R = \frac{Q}{q} \cdots (1) \]

where R denotes the weight ratio of the carrier (Q) and coating (q) materials.

An acceptably flowing and compressible liquisolid system can be prepared only if maximum liquid on the carrier material is not exceeded. The liquid load factor (Lf) is the ratio of the weight of the liquid medication (W) to the weight of the carrier powder (Q) in the system, and it is defined as the weight of the liquid medication (W) divided by the weight of the carrier powder (Q). It is calculated using a formula:

\[ Lf = \frac{W}{Q} \cdots (2) \]

The following is a relationship between the powder excipients ratios R and the liquid load factors Lf of the formulations:

\[ Lf = \Phi + \Phi \left( \frac{1}{R} \right) \cdots (3) \]

where Φ and Φ are flowable liquid retention potentials for carrier and coating materials.

So, in order to calculate the required quantities of excipients used, first, from equation (3), Lf was calculated using Φ and Φ which are constants and predetermined R values. Secondly, depending on concentration of liquid vehicle used, weights of the liquid drug solution (W) will be obtained. So, by knowing both Lf and W, the appropriate quantity of carrier material (Q) can be calculated from equation (2). Finally, the quantity of coating material (q) can be calculated from equation (1).

2.2.3 Preparation of liquisolid compacts and conventional tablet

For the formulation of Ketoprofen liquisolid compacts, accurately weighed quantity of drug and selected liquid vehicle was taken in beaker and then stirred constantly, until a homogenous drug solution or liquid medication was obtained. Lastly, calculated and weighed quantities of carrier material were added to resultant liquid medication and incorporated into a mortar.

The mixing procedure was carried out three stages. In the first stage, the liquisolid powder system was mixed at a rate of one rotation/sec for about one minute so that liquid medication is uniformly distributed into the powder. In the second mixing stage, this powder was spread as a uniform layer evenly on the surface of the mortar and allowed to stand for 5 min to make the drug solution absorbed into the interior of powder particles. In the third stage, aluminum spatula was utilized to scrap off the powder from mortar.
surface. This is further added with disintegrant and mixed for another thirty seconds in similar manner as that of first stage. Later, the obtained liquisolid powder system was compressed to form liquisolid compacts using rotary compression machine. The directly compressed tablet (DCT) is also prepared containing the same ingredients with the exception of liquid vehicle.

2.2.4 Pre-compression studies for ketoprofen liquisolid compacts

The prepared Ketoprofen liquisolid powder systems of different formulations were evaluated for their flow properties such as angle of repose, bulk density, tapped density, compressibility index and Hausner’s ratio.

Angle of repose (θ) was measured by fixed funnel method and calculated using the following formula:

\[ \tan \theta = \frac{h}{r} \]

where, θ is angle of repose, h represents height of cone and r represents radius of cone base of powder. The angle less than 30° indicates free flowing powder.

The compressibility index or Carr’s Index is a measure of propensity of powder to be compressed. It is calculated using the following formula based on the bulk and tapped densities:

\[ \text{Carr’s Index} = \frac{(\text{Tapped density}-\text{Bulk density})}{\text{Tapped density}} \times 100 \]

Hausner’s ratio is an indirect index for determining the ease of powder flow and calculated using the following formula:

\[ \text{Hausner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

The value less than 1.25 indicates good flow and more than 1.5 indicates very poor flow properties.

2.2.5 Post compression characterization of Ketoprofen liquisolid compacts

Several post-compression test parameters, such as hardness, weight variation, friability, and drug content homogeneity, were estimated for ketoprofen liquisolid compacts. An electronic weighing balance (Shimadzu, Japan) was used to weigh 20 compacts of each liquisolid formulation to determine the weight variation parameter. The crushing strength of six liquisolid compacts of each formulation was measured using Monsanto hardness and expressed in kg/cm². The friability of ten compacts was tested in a Roche friabilator (Mumbai, India) for 4 minutes at a speed of 25 rpm.

2.2.5.1 Determination of drug content

For estimation of drug content, ten compacts were crushed, and the powder equivalent to 50 mg of drug was dissolved in suitable quantity of 7.4 pH phosphate buffer solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer (Analytical Technologies, India) at 260 nm.

2.2.5.2 In vitro dissolution studies

The USP Type II Rotating paddle apparatus (Electrolab, Mumbai) was used for the in vitro dissolution studies taking 7.4 pH phosphate buffer as dissolution media. Each formulation of liquisolid compact was placed in dissolution jar containing 900ml phosphate buffer maintained at a temperature 37±0.1⁰C and rotating speed at 100±2 rpm. At appropriate time intervals, 5ml of the sample was taken and filtered through a 0.45 μm Millipore filter. The dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume and sink condition. After suitable dilution, the samples were then analyzed at 260 nm by UV-VIS spectrophotometer. The mean of three determinations was used to calculate the release of drug from each formulation.

2.2.6. Analysis of optimized formulations

2.2.6.1 Fourier transform infrared spectroscopy

FTIR spectra were obtained for pure drug Ketoprofen, Avicel PH 102, Cab-O-Sil and optimized liquisolid compact TK7 formulation. The KBr pellet method was used in this experiment, in which 5mg of sample was well combined with 100mg potassium bromide powder. This is compressed for 3 minutes under vacuum at a pressure of roughly 12,000 psi. On FTIR (Shimadzu, Japan), the produced disc was mounted in a suitable holder, and the sample was scanned from a range of 4000 to 400 cm⁻¹ [19].

2.2.6.2 Differential scanning calorimetry

Thermograms of the Ketoprofen and optimized liquisolid compact TK7 formulation were
recorded using Philips PW3710 X-ray diffractometer. In a nitrogen atmosphere, 2 to 3 mg of sample were heated on an aluminum crimp pan at a rate of 10 °C/min for the analysis.

2.2.6.3 Powder X-ray diffraction

Powder X-ray diffraction spectra for Ketoprofen, Avicel PH102, Cab-O-Sil, physical mixture and optimized liquisolid compact TK7 formulation was recorded using a high-power powder X-ray diffractometer (Ru-200B, Pune, India) using copper as target at a scan speed of 4°/min. The samples were analysed at an angle 2θ range of 2 to 45° for 0.5 sec and the operating voltage and current were 40 kV and 55 mA, respectively [20].

2.2.6.4 Scanning electron microscopy

Surface morphology and the solid state characterization is performed using SEM analysis. Microscopic images for Ketoprofen, Avicel PH 102, Cab-O-Sil and optimized liquisolid compact TK7 formulation were obtained using scanning electron microscope (ZEISS scanning electron microscope) studies. The samples were initially adhered to carbon-coated metallic stub using double sided adhesive tape and mounted on SEM for surface analysis. The imaging was recorded at an acceleration voltage of 30 kV.

3. RESULTS AND DISCUSSION

3.1 Saturation Solubility Studies

The solubility of Ketoprofen in various non-volatile solvents and the results were determined. From the results it was observed that PEG 400 showed highest solubility for drug. Hence, PEG 400 was selected as non-volatile hydrophilic solvent for the formulation of Ketoprofen liquisolid compacts.

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

| Solvent       | Solubility*(mg/mL) |
|---------------|--------------------|
| Propylene glycol | 58.76 ± 1.76       |
| PEG 200       | 62.49 ± 2.09       |
| PEG 400       | 70.18 ± 3.76       |
| PEG 600       | 66.04 ± 3.22       |
| Tween 80      | 45.48 ± 1.99       |
| Tween 20      | 39.44 ± 0.86       |
| Span 80       | 32.39 ± 0.36       |
| Span 20       | 21.19 ± 0.74       |

* Mean values of three determinations

3.1.1 Application of mathematical model and preparation of liquisolid systems

For the preparation of liquisolid compacts of Ketoprofen, initially a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies, liquisolid systems were prepared using PEG 400 as it showed highest solubility for drug. Moreover, Avicel PH 102 and Cab-O-Sil were selected as carrier and coating materials respectively for formulation of liquisolid systems. Various ratios of carrier to coating materials were selected and the formulations were shown in Table 2.

In order to determine the quantities 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.

The flowable liquid-retention potential (Φ-values) properties of powder excipients (Avicel PH 102 and Cab-O-Sil with PEG 400) are evaluated using the “Angle of slide” method. In this method increasing amounts of PEG 400 was added to 10 g of excipient and allowed to slide on smooth metal plate. The angle made by the metal plate and the horizontal surface was calculated as the angle of slide (θ). That angle equivalent to 33° was chosen as angle of slide value. The following equation was used to compute the flowable liquid-retention potential (values) of each non-volatile liquid/powder admixture, including the carrier and coating material.

\[ \Phi = \text{weight of non-volatile liquid/weight of solid} \]

The compressible liquid retention potential value for Avicel PH102 (Ψ -value) with PEG 400 and Cab-O-Sil (Ψ-value): with PEG400 were reported to be 0.242 and 0.653, respectively. The predetermined R values selected here were 5, 7.5 and 10.

The liquid load factor (Lf) was calculated according to equation (3) using the \( \Phi \) –values.

\[ \text{Lf} = \frac{\text{Lf value}}{\Phi} \]

Depending on the R values of 5, 7.5 and 10, the Lf values calculated were 0.382, 0.333 and 0.309 respectively.

3.1.2 Pre-compression studies for Ketoprofen liquisolid compacts

The liquisolid powder systems of different formulations were evaluated for angle of repose,
bulk density, tapped density, compressibility index and Hausner’s ratio and the results were shown in Table 3. The bulk density and tapped density values ranged from 0.389 to 0.462 and 0.475 to 0.563 respectively. The results of angle of repose(θ) and Carr’s index (%) ranged from 29.12±1.28 to 33.49±1.43 and 15.77 to 19.01 respectively. The results indicated acceptable flow properties for the prepared liquisolid formulations.

3.2 Post Compression Parameters

The post compression evaluation tests were performed for all the prepared liquisolid compacts and the results were shown in Table 4. The liquisolid compacts were found to have hardness ranging from 2.9±0.08 to 3.6±0.12 kg/cm². The loss in weight during friability test was found below 1% of their weight and is considered as acceptable. The compacts were found to contain 98±0.21 to 100±0.33% of the labelled amount indicating uniformity of drug content. The results showed acceptable post compression properties for all the prepared liquisolid compact formulations.

3.3 In-vitro Dissolution Study

The dissolution profile of all the prepared liquisolid compacts (TK1 to TK9) were studied and depicted in Fig. 1 and 2, and comparison of dissolution profile of TK7 with that of directly compressed tablet (DCT) of Ketoprofen was shown in Fig. 3. From the dissolution graph it was clear that liquisolid compact formulation TK7 showed maximum release compared to all other formulations and the directly compressed tablet (DCT).

The cumulative release of ketoprofen in 10 minutes (Q10) for optimized LSC TK7 formulation was found to be 82.98 ± 2.31% and that of DCT 8.07 ± 1.24 % in pH 7.4 phosphate buffer. The dissolution efficiency at 12 minutes (DE12) for optimized liquisolid compact TK7 formula was found to be 34.17 and that of DCT was found to be 3.51 in pH 7.4 phosphate buffer. The relative dissolution rate for LSC TK7 was observed 9.74 folds compared to that of DCT in pH 7.4 phosphate buffer. Finally, the liquisolid compacts showing highest dissolution profile was selected as optimized liquisolid compact (TK7).

The estimated reason for improved dissolution profile of drug may be improved wettability of drug due to reduction in solid/liquid interface and also increase in surface area of the molecularly dispersed drug that is available for dissolution medium.

In the current study different concentrations of drug used were 33.33%, 40% and 50% and the excipients ratio used were 5, 7.5 and 10 for each drug concentration. The results of drug release patterns were observed as R10 > R7.5 > R5 along with 33.33% > 40% >50%.

![Dissolution profile of ketoprofen liquisolid compacts in pH 7.4 buffer at 260 nm](image-url)
### Table 2. Formulation of ketoprofen liquisolid compacts

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

*Where, Drug is ketoprofen, PEG 400 = Polyethylene glycol 400, Q = Avicel PH 102, Q = Cab-O-Sil M5, R = ratio of carrier to coating material, Lf = load factor

### Table 3. Flow properties of ketoprofen liquisolid system (*mean ± SD, n=3)*

| F code | Bulk Density* | Tapped Density* | Carr’s compressibility Index | Hausner’s Ratio | Angle of Repose(θ) * |
|--------|---------------|-----------------|-------------------------------|------------------|----------------------|
| TK1    | 0.447±0.12    | 0.547 ± 0.12    | 18.281                        | 1.224            | 31.14 ± 1.44         |
| TK2    | 0.456 ± 0.03  | 0.552 ± 0.08    | 17.391                        | 1.211            | 29.14 ± 1.13         |
| TK3    | 0.462 ± 0.06  | 0.563 ± 0.11    | 17.939                        | 1.219            | 29.12 ± 1.28         |
| TK4    | 0.411 ± 0.09  | 0.496 ± 0.07    | 17.137                        | 1.207            | 32.10 ± 1.30         |
| TK5    | 0.422 ± 0.06  | 0.507 ± 0.09    | 16.765                        | 1.201            | 29.66 ± 1.25         |
| TK6    | 0.437 ± 0.04  | 0.527 ± 0.13    | 17.077                        | 1.206            | 31.94 ± 1.33         |
| TK7    | 0.389 ± 0.11  | 0.466 ± 0.09    | 16.523                        | 1.198            | 32.77 ± 1.21         |
| TK8    | 0.401 ± 0.11  | 0.475 ± 0.07    | 15.578                        | 1.185            | 32.85 ± 1.31         |
| TK9    | 0.416 ± 0.07  | 0.482 ± 0.08    | 13.692                        | 1.157            | 33.49 ± 1.43         |

*Mean values of three determinations
Table 4. Post compression evaluation of ketoprofen liquisolid compacts (*mean ± SD, n=3)

| F code | Hardness* (Kg/cm²) | Weight variation* (mg) | % Drug Content* | % Friability* | Disintegration time* (min) |
|--------|--------------------|------------------------|-----------------|--------------|--------------------------|
| TK1    | 3.3 ± 0.4          | 651.19 ± 1.27          | 99 ± 0.24       | 0.51 ± 0.05  | 3.1 ± 0.51               |
| TK2    | 3.6 ± 0.3          | 685.48 ± 1.81          | 98 ± 0.37       | 0.55 ± 0.04  | 3.5 ± 0.33               |
| TK3    | 3.8 ± 0.5          | 707.97 ± 0.93          | 100 ± 0.23      | 0.54 ± 0.07  | 3.7 ± 0.15               |
| TK4    | 3.2 ± 0.2          | 546.66 ± 1.49          | 100 ± 0.33      | 0.53 ± 0.11  | 3.0 ± 0.46               |
| TK5    | 3.5 ± 0.6          | 575.41 ± 1.62          | 99 ± 0.44       | 0.55 ± 0.08  | 3.4 ± 0.53               |
| TK6    | 3.7 ± 0.3          | 591.95 ± 1.35          | 99 ± 0.39       | 0.56 ± 0.07  | 3.6 ± 0.46               |
| TK7    | 3.1 ± 0.5          | 441.11 ± 1.24          | 98 ± 0.21       | 0.59 ± 0.09  | 2.9 ± 0.38               |
| TK8    | 3.4 ± 0.7          | 464.31 ± 1.62          | 98 ± 0.29       | 0.61 ± 0.12  | 3.4 ± 0.23               |
| TK9    | 3.6 ± 0.4          | 477.93 ± 1.63          | 99 ± 0.32       | 0.55 ± 0.13  | 3.5 ± 0.39               |

*Mean values of three determinations

Fig. 2. *In vitro* dissolution profile of ketoprofen liquisolid compacts TK7 to TK9 in pH 7.4 buffer at 260 nm
**3.4 Analysis of Optimized Formulations**

**3.4.1 Fourier transform infrared spectroscopy**

The IR spectrum for the samples of Ketoprofen, Avicel PH 102, Cab-O-Sil and optimized liquisolid formulation TK7 were shown in Fig. 4.1 & 4.2. The IR spectrum of Ketoprofen (Fig. 4.1) exhibits characteristic peaks at 1697.41 cm\(^{-1}\) (strong aldehyde C=O stretching vibration), 2980.12 cm\(^{-1}\) (carboxylic acid O-H stretching vibration), 1517.82 cm\(^{-1}\) (C=C stretching vibration of aromatic ring), 3053.42 cm\(^{-1}\) (C-H stretching vibration of aromatic ring), 1419.66 cm\(^{-1}\) (C-H bending vibration). From the Fig. 4.2, it was observed that the functional groups of Ketoprofen was retained in liquisolid compact formulation, TK7 representing that there was no chemical interaction between the drug and the excipients used in the preparation of liquisolid compacts.

**3.4.2 Differential scanning calorimetry**

DSC study is used to understand the presence of interactions between drug and excipients used in the formulation. The endothermic peaks of pure drug Ketoprofen and optimized liquisolid system TK7 are shown in Fig. 5. The Ketoprofen showed a sharp characteristic endothermic peak at 97.62°C (Fig. 5A) and such sharp endothermic peak indicates that the drug is present in a pure crystalline state. On the other hand, absence of sharp endothermic peak of in the optimized liquisolid system TK7 (Fig. 5B) confirms that the drug was molecularly dispersed due to the formation of solid solution within the liquisolid system.

![Comparative dissolution profile of TK7 and DCT in pH 7.4 buffer at 260 nm](image)

**Fig. 3. In vitro dissolution profile of TK7 and DCT in pH 7.4 buffer at 260 nm**

![FTIR of ketoprofen](image)

**Fig. 4.1. FTIR of ketoprofen**
3.4.3 Powder X-ray diffraction

Powder X-Ray diffractometer is used to study the crystalline nature of substances. The results for X-Ray diffraction patterns for pure drug Ketoprofen, Avicel PH 102, Cab-O-Sil, physical mixture and the optimized liquisolid compact formulation TK7 were shown in Fig. 6. The Fig. 6A showed sharp diffraction peaks for pure drug Ketoprofen and the absence of such sharp characteristics peak in optimized formulation TK7 indicated that drug had probably converted from crystalline to amorphous form. This might be due to the presence of drug in molecularly dispersed state upon formation of solid solution in liquisolid formulation.

3.4.4 Scanning electron microscopy

The surface morphology of the pure drug Ketoprofen, Avicel PH102, Cab-O-Sil and optimized liquisolid compact formulation TK7 were examined by SEM and the images were depicted in Fig. 7. The Fig. 7A showed typical crystalline structure of Ketoprofen and it was completely disappeared in optimized liquisolid formulation as shown in Fig. 7D. Hence, transformation of drug occurred from crystalline to amorphous state. This supports the liquisolid formulation theory, that the drug is held in solution form, or in a nearly molecularly distributed state, within the powder substrate, contributing to improved drug dissolving capabilities.
4. CONCLUSION

Finally, it can be concluded that an attempt was made to develop the liquisolid compacts of Ketoprofen to achieve improved solubility and dissolution profile. Similarly, from the in-vitro drug release studies the optimized liquisolid compact formulation TK7 showed highest drug release, showing almost three times the dissolution efficiency compared to that of conventional tablet. FTIR and DSC studies revealed that there is no interaction between the drug and excipients. PXRD and SEM studies also revealed molecularly dispersed form of drug in the liquisolid systems. Hence, it can be concluded that liquisolid technique proved to be a promising method to enhance solubility and dissolution profile of water-insoluble drugs belonging to BCS Class II. The faster dissolving rates of liquisolid compacts could indicate improved oral...
bioavailability. Increased solubility, wetting characteristics, and drug surface area accessible for dissolution in the liquisolid formulation were the suggested reasons for improved dissolution profile of ketoprofen.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

ACKNOWLEDGEMENTS
The authors are thankful to Smriti College of Pharmaceutical Education for providing the necessary facilities to carry out the study.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES
1. Chowdary KP, Kumar AP. Recent research on formulation development of BCS class II drugs—A Review. Int Res J Pharm Appl Sci. 2013;3(1):173-81.
2. Kovačič B, Vrečer F, Planinšek O. Solid dispersions of carvedilol with porous silica. Chem Pharm Bull. 2011;59(4):427-33.
3. Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharm Lett. 2012;4(5):1574-86.
4. Bobe KR, Subrahmanyia CR, Suresh S, Gaikwd DT, Patil MD, Khade TS, et al. Formulation and evaluation of solid dispersion of atorvastatin with various carriers. Int J Compr Pharm. 2011;2(1):1.
5. Alsarra IA, Alanazi FK, Ahmed SM, Bosela AA, Alhamed SS, Mowafy HA, Neau SH. Comparative study of itraconazole-cyclodextrin inclusion complex and its commercial product. Arch Pharm Res. 2010;33(7):1009-17.
6. Singh R, Bharti N, Madan J, Hiremath SN. Characterization of cyclodextrin inclusion complexes—A Review. J Pharm Sci Technol. 2010;2(3):171-83.
7. Bhagwat DA, Souza JI. Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier. Int Curr Pharm J. 2012;1(12):414-9.
8. El-Feky GS, Zayed GA, Farrag AR. Optimization of an ocular nanosuspension formulation for Acyclovir using factorial design. Int J Pharm Pharm Sci. 2013;5(SUPPL 1):213-9.
9. Amin MA, Elbakry A, Zayed G, Zaky A. Preparation and Evaluation of Nanosuspension for Poorly Soluble Drug to Improve the In Vitro and In Vivo Efficacy. J Med Life. 2013;1(3):99-107.
10. Rasenack N, Müller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm Res. 2002;19(12):1894-900.
11. Kheradmandnia S, Vasheghani-Farahani E, Nosrati M, Atyabi F. Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. Nanomed Nanotechnol Biol Med. 2010;6(6):753-9.
12. Kaur MA. Enhancement of Dissolution Properties of Amlodipine Besylate Using Liquisolid Technique. Int J Pharm Pharm Sci. 2013;5(3):394-400.
13. Patwekar SL. Solubility and dissolution enhancement of poorly water-soluble Ketoprofen by microwave-assisted Bionanocomposites: in vitro and in vivo study. Asian J Pharm. 2016;10(04): S601-S611.
14. Khaleel NY, Abdulrasool AA, Ghareeb MM, Hussain SA. Solubility and dissolution improvement of ketoprofen by solid dispersion in polymer and surfactant using solvent evaporation method. Int J Pharm Pharm Sci. 2011;3(4):431-5.
15. Spireas SS, Jarowski CI, Rohera BD. Powdered solution technology: principles and mechanism. Pharm Res. 1992;9(10):1351-8.
16. Vaskula S, Vemula SK, Bontha VK, Garrepally P. Liquisolid compacts: An approach to enhance the dissolution rate of nimesulide. J Appl Pharm Sci. 2012;2(5):115-21.
17. Spireas S, Wang T, Grover R. Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid compacts. Drug Dev Ind Pharm. 1999;25(2):163-8.
18. Spireas S. Liquisolid systems and methods of preparing same. United States patent US 6,423,339;2002.
19. Chella N, Shastri N, Tadikonda RR. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharm Sin B. 2012;2(5):502-8.

20. Jain HI, Pasha TY, Bais CS, Bhandari AN. Formulation and characterization of liquisolid tablets of valsartan for improvement of dissolution rate. Asian J Pharm Clin Res. 2014;7(4):21-6.

© 2021 Kasturi and Malviya; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.