ABSTRACT

Objective: The purpose of this study was to enhance the dissolution pattern of the practically water-insoluble diuretic drug, furosemide through its formulation into liquisolid tablets.

Methods: A mathematical model was used to formulate four liquisolid powder systems using polyethylene glycol 400 as a non-volatile water miscible liquid vehicle. The liquid loading factors of the vehicle were used to calculate the optimum quantities of carrier (Avicel PH 102) and coating materials (Aerosil 200) needed to prepare acceptably flowing and compatible powder mixtures and (R) ratio used was 25. The liquisolid tablets were evaluated for weight variation, percent friability, hardness, content uniformity, disintegration time and in vitro drug release profile. Drug and the prepared systems were characterized by fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder x-ray diffraction (PXRD) studies.

Results: The enhanced dissolution rate due to the increased wetting properties and the large available surface areas for dissolution were obtained in case of the liquisolid tablets. The selected optimal formulation (F2) of 50% drug concentration released 90% of its content during the first 10 min in vitro. DSC and PXRD studies revealed that there was no interaction between drug and polymers. FTIR studies revealed that there was no interaction between drug and polymers. DSC and PXRD indicated conversion of crystalline to amorphous form of furosemide in case of the liquisolid tablets. The selected optimal formulation (F2) of 50% drug concentration released 90% of its content during the first 10 min in vitro.

Conclusion: The dissolution rate of furosemide can be enhanced to a great extent by liquisolid technique.

Keywords: Furosemide, Liquisolid compact, PEG 400, Co-processed super disintegrant, Solvent evaporation method

INTRODUCTION

The poor dissolution rate of water-insoluble drugs confronts a major obstacle in the development of pharmaceutical dosage forms. The drugs which are poorly water soluble will be released at a slow rate owing to their limited solubility within gastrointestinal tract [1]. In general drugs with low aqueous solubility (lower than 100µg/ml) show dissolution-limited and incomplete absorption from the gastrointestinal tract of animals and humans [2].

The various properties of drug-like solubility, particle size, polymorphism, salt form, complexity, wettability affect drug dissolution and its rate and can be targeted to enhance dissolution of poorly water-soluble drugs [3]. Some commonly used physical modifications to enhance the dissolution of API include: (a) Reducing particle size to increase surface area, thus increasing dissolution rate of drug, (b) solubilization in surfactant systems, (c) formation of water-soluble complexes, (d) drug derivatization such as a strong electrolyte salt form that usually has higher dissolution rate, and (e) manipulation of solid state of drug substance to improve drug dissolution, i.e., by decreasing crystallinity of drug substance through formation of solid solutions [4].

The most promising and new technique for promoting dissolution is the formation of liquisolid tablets among the various novel techniques. Liquisolid compacts promote dissolution rate of water-insoluble drugs to a greater extent and also enhance the drug flow property [5].

The liquisolid technique is a novel and most promising technique for improving the dissolution rate of poorly water-soluble drugs. With the liquisolid technology, a liquid may be transformed into a free-flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material [5, 6].

Furosemide is 5-([Aminosulfonyl]yl)–4–chloro–2–[(2–furyl methyl) amino] benzoic acid (fig. 1), the empirical formula is C₁₈H₁₈ClN₂O₇S corresponds to the molecular weight of 330.77. Furosemide is a white to slightly yellow, odourless, almost tasteless crystalline powder, slightly soluble in water, chloroform and ether, soluble in acetone, methanol, dimethyl formamide and in solutions of alkali hydroxides. Its melting point is 206 °C [7].

Fig. 1: Chemical structure of furosemide [8]

Furosemide is a loop diuretic act primarily by inhibiting chloride and sodium reabsorption over the entire length of the thick ascending limb of the loop of Henle, it is widely used for the symptomatic treatment of heart failure and fluid retention in chronic kidney disease [9].

The present research work was aimed to prepare furosemide liquisolid compact and to enhance the solubility and dissolution rate of furosemide by liquisolid technique.

MATERIALS AND METHODS

The following gift samples were received: furosemide from (Awa medica, Erbil), microcrystalline cellulose PH 102 (FMC, USA), Aerosil 200 and crospovidone (Wuhan Senwayer Century chemical Co., Ltd), PEG 400, and sodium starch glycolate (were obtained from SD Fine Chem Ltd., Mumbai, India), magnesium stearate (Robert E. M. TILG, Germany). All reagents used were of analytical grade.

Methods

Solubility studies

Solubility studies of furosemide were carried out in water, phosphate buffer pH 5.8 and polyethylene glycol (PEG 400). Saturated solutions were prepared by adding an excess drug to the vehicle and shaking in a water bath with a shaker for 48h at 25±0.5 °C under
constant vibration. After this period the solutions were filtered, diluted and analyzed by UV spectrophotometer (Cary, Australia) at 277 nm. Three determinations were carried out for each sample to calculate the solubility of furosemide.

Application of the mathematical model for designing the liquisolid systems

The formulation design of liquisolid systems was done in accordance with new mathematical model described by Spireas et al.

In this study, PEG 400, microcrystalline cellulose (Avicel® PH 102-MCC), and Aerosil® 200 were used as a liquid vehicle, carrier and coating materials respectively. The concentration of the drug in liquid vehicle was varied and the carrier: coating ratio was kept constant in all formulations (R=25:1).

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed "liquid load factor Lf" and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

\[ Lf = \frac{W}{Q} \]  \hspace{2cm} (1)

\[ R = \frac{Q}{q} \]  \hspace{2cm} (2)

The liquid load factor that ensures acceptable flowability (Lf) can be determined by:

\[ Lf = \Phi + \varphi \left( \frac{1}{R} \right) \]  \hspace{2cm} (3)

Where \( \varphi \) and \( \Phi \) are the Ф-values of the carrier and coating material, respectively [10].

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Ф-values) of powder excipients were utilized. In polyethylene glycol 400, the Ф-value of Avicel PH 102 was found to be 0.005 and the \( \Phi \)-value for Aerosil 200 was 3.26 [11].

So, by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equation (1) and (2).

Preparation of co-processed superdisintegrant

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and sodium starch glycolate (in the ratio 1:1) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued until most of the ethanol evaporated. The wet coherent mass was granulated through #44 mesh sieve.

The wet granules were dried in a hot air oven at 60°C for 20 min. The dried granules were sifted through #44 mesh sieve and stored in an airtight container until further use [12, 13].

The co-processed superdisintegrants at a ratio (1:1) was used in the preparation of liquisolid compacts to study the effect of co-processed superdisintegrants on the disintegration and dissolution rate of furosemide liquisolid compacts.

Preparation of furosemide liquisolid compact

Four liquisolid tablets denoted (F1 to F4) containing 40 mg of furosemide were prepared by dispersing in the non-volatile vehicle (PEG 400). Then a bindery mixture of the carrier (Avicel PH 102) and coating material (Aerosil 200) was prepared at a ratio of 25:1, by continuous mixing for a period of 10 min in a mortar. The amount of carrier and coating materials are enough to maintain acceptable flow and compression properties. R 25 was used in all formulations since it gave the optimal flow property.

Finally, a 5 %w/w of co-processed superdisintegrant (crospovidone and sodium starch glycolate at ratio 1:1) was added and mixed for 10 min then 1% w/w of magnesium stearate as a lubricant was added into the mixture and mixed for 2 min. The final mixture was compacted using a single punch tablet machine (Korsch EKO, Germany) [14]. The composition of liquisolid tablets is shown in table 1.

Preparation of direct conventional tablet of furosemide

Furosemide conventional tablets were prepared by mixing the drug with Avicel PH 102 and aerosil 200 (ratio of microcrystalline cellulose: aerocil was 25:1) for a period of 10 min in a mortar without the addition of the vehicle. The mixture then was mixed with (5%) of co-processed super-disintegrant (1:1) for 10 min, and then (1%) of magnesium stearate was mixed for 2 min. The mixture was compressed using a single punch tablet machine (Korsch, Germany). This formulation was denoted as DCT [15].

<table>
<thead>
<tr>
<th>Formulas</th>
<th>Furosemide concentration in liquid medication (%w/w)</th>
<th>Loading factor (Lf) W/Q</th>
<th>PEG 400 (mg)</th>
<th>Furosemide (mg)</th>
<th>MCC PH 102 (mg)</th>
<th>Aerosil® 200 (mg)</th>
<th>Co-processed superdisintegrant (1:1) 5% (mg)</th>
<th>Magnesium stearate 1% (mg)</th>
<th>Unit dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>40</td>
<td>25</td>
<td>0.1354</td>
<td>60</td>
<td>40</td>
<td>738.6</td>
<td>30</td>
<td>43</td>
<td>91.0</td>
</tr>
<tr>
<td>F2</td>
<td>50</td>
<td>25</td>
<td>0.1354</td>
<td>40</td>
<td>40</td>
<td>591</td>
<td>24</td>
<td>35</td>
<td>7.3</td>
</tr>
<tr>
<td>F3</td>
<td>60</td>
<td>25</td>
<td>0.1354</td>
<td>27</td>
<td>40</td>
<td>495</td>
<td>20</td>
<td>29</td>
<td>6.11</td>
</tr>
<tr>
<td>F4</td>
<td>70</td>
<td>25</td>
<td>0.1354</td>
<td>17</td>
<td>40</td>
<td>421</td>
<td>17</td>
<td>25</td>
<td>5.2</td>
</tr>
</tbody>
</table>

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

Pre-compression studies

Characterization of powder mixture

Angle of repose

The frictional force of a loose powder can be measured by the angle of repose (θ). The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a Petri dish is placed on a flat horizontal surface. The blend carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

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

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

Where; \( \theta \) = angle of repose, h = height of the cone in cm, r = radius of the cone base in cm [16].

Bulk and tapped density

An accurately weighed quantity of the liquisolid powder (w) was carefully poured into the graduated cylinder and the volume (vo) was measured. The graduated measuring cylinder was tapped for 1000 times and after that, the volume (vf) was measured. The bulk density and tapped density were calculated using the formulas below:

\[ \text{Bulk density} = \frac{w}{vo} \]

\[ \text{Tapped density} = \frac{w}{vf} \]
Tapped density=$\frac{W}{V}\times100$

Where $w$ is the weight of powder, $v_o$ is the initial volume and $v_f$ is the final volume.

From the results of bulk density and tapped density, carr’s index was calculated [17]

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Post-compression studies

Hardness

The hardness of the tablet was determined using Monsanto hardness tester. Three tablets were randomly selected from each formulation and hardness of the same was determined. The average value was calculated [14].

Friability testing

Friability of the tablets was determined by using Roche friabilator. A number of tablets (equal to 6.5g or more in weight) were placed in the friabilator and rotated at 25rpm for a period of 4 min. The friability was determined using the following formula:

$$\text{Percentage friability}=\frac{W_1-W_2}{W_1}\times100$$

Where $W_1=$ initial weight of tablets, $W_2=$ weight of the tablets after testing [15, 18].

Content uniformity

The drug content of the tablets was measured according to united state pharmacopoeia USP. Ten tablets were selected randomly from each formula; each tablet was crushed in a mortar and transferred it into a 100 ml volumetric flask and sonicated for 10 min. Then volume made up to 100 ml with phosphate buffer pH 5.8. Then 1 ml into a 100 ml volumetric flask and sonicated for 10 min. The dissolution rates of all formulations were measured by using tablet dissolution apparatus USP Type II. Dissolution studies were carried out using 900 ml of phosphate buffer pH 5.8, at 50 rpm and at a temperature of 37±2°C. The disintegration time was determined in water maintained at 37±2°C. The disintegration apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded [21-23].

In vitro dissolution test

The dissolution rates of all formulations were measured by using tablet dissolution apparatus USP Type II. Dissolution studies were carried out using 900 ml of phosphate buffer pH 5.8, at 50 rpm and at a temperature of 37±0.5 °C. 10 ml of the medium was withdrawn at a suitable time interval, filtered and diluted with phosphate buffer pH 5.8. Sink conditions were maintained throughout the study. The samples were then analyzed at 277 nm by UV/visible spectrophotometer. The study was carried out in triplicate [15,24].

Dissolution data evaluation

For the comparison of dissolution data for each formulation, percentages of drug dissolved at 10 min (Q10 min), mean dissolution time (MDT) and percentage of dissolution efficiency (%DE) at the end of 60 min were calculated using DDSolver software in order to select the optimized formula.

The model-independent approach includes the difference factor ($f_1$) and the similarity factor ($f_2$) was used to compare between the dissolution profile of optimized formula and the DCT. The $f_1$ factor measures the percentage error between two curves over all time points:

$$f_1 = \frac{\sum^n_{t=1} | R_t - T_t |}{\sum^n_{t=1} R_t} \times 100$$

Where $n$ is the number of time points and $R_t$ and $T_t$ are the percentages of the reference and test product dissolved, respectively, at each time point. The percentage error is zero when the test and drug reference profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles [25].

The similarity factor ($f_2$) 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:

$$f_2 = 50 \log \left( 1 + \frac{1}{n} \sum^n_{t=1} \left( R_t - T_t \right) \right)^{-0.5} \times 100$$

Where $n$ is the number of time points at which % dissolved was determined, $R_t$ is the % dissolved of one formulation at a given time point, and $T_t$ is the % dissolved of the formulation to be compared at the same time point [26].

Differential scanning calorimetry (DSC)

Samples (3-5 mg) were placed in an aluminum pan and heated in the DSC 60-plus (Shimadzu, Japan) at a constant rate of 10 °C/min, in an atmosphere of nitrogen over a temperature range of 25-300 °C. The DSC studies were performed on the pure drug, a physical mixture of the optimized liquisolid system, and on the liquisolid tablet [27].

Fourier-transform infrared spectroscopy (FTIR)

It was performed using the infrared spectrophotometer (Lambda 7600, Australia). Samples of 2-3 mg were mixed with about 100 mg of dry potassium bromide powder and compressed into transparent discs then scanned over a wave range of 4000-400 cm⁻¹ in FTIR instrument. FTIR spectra were performed on the pure drug, sodium starch glycolate, crospovidone, co-processed superdisintegrant at a ratio (1:1), a physical mixture of the optimized liquisolid system and on the liquisolid tablet [28].

X-ray powder diffraction (XRPD)

X-ray diffractograms of pure furosemide, physical mixture of liquisolid and liquisolid tablet were obtained using analytical XRD instrument. The scanning range was from 5 to 60° at 2 theta scale and 5 degree/min. The voltage and strength of the electric current were 40 KV and 30 mA, respectively [29].

Statistical analysis

All the results were expressed as the mean value±standard deviation (SD). T-test was used to test for significance, at a 5% significance level. Statistical difference dealing (P<0.05) was considered significant [30].

RESULTS AND DISCUSSION

Saturation solubility studies

The solubility of furosemide in different media is presented in Table 2. Drug solubility in a non-volatile vehicle is the most important aspect in liquisolid systems. The solubility of the drug contributes to molecular dispersion in a non-volatile solvent which will improve the dissolution rate.

The solubility of furosemide in macrogol 400 (98.69 mg/ml) was approximately 10000 times higher than in water (0.006 mg/ml).
Angle of repose

Components or with individual components [33].

According to mathematical model proposed by Spireas et al., respectively.

The disintegration time for the prepared furosemide liquisolid tablets was shown in table 4. It was found that the mean of the disintegration times for all investigated tablets was less than 1 min, as shown in table 4. Generally, the ideal tablet hardness should be produced without applying excessive compression force where rapid tablet disintegration and drug dissolution are maintained at the same time [31].

Friability test

All furosemide tablets had acceptable friability as none of the tested formulas exceeded 1% loss in tablet weight as shown in table 4; also, no tablet was cracked, split or broken in either formulation. Since all the prepared formulas met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion. Formulations containing a higher level of nonvolatile solvent were able to reflect greater interparticulate bonding between particles, resulting in low friability percent [32].

The results of the angle of repose and carr's index were given in the table 3. The results showed that angle of repose was ranged from 30.8° to 34.8°. It was found that formula of highest drug concentration in PEG 400 has better flowability than another formula due to fewer amounts of vehicle presents on the surface of the carriers in liquisolid formulations.

Pre-compression evaluation

Angle of repose

Angle of repose provides a qualitative and quantitative assessment of internal cohesive and frictional force under low level of external load applied during mixing and tabletting. Values less than 35 indicate good flow whereas greater than 35 indicates poor flow.

Table 3: Flow properties of furosemide liquisolid powder and DCT

Table 4: Hardness, friability, disintegration time, drug content and weight variation of furosemide liquisolid tablets and DCT
Drug content

The drug content for tablets of all the formulations ranges from 96.6-99.6% (table 4). The results indicate that the contents for tablets of all the formulations were uniform and contains a therapeutic dose of the active ingredients.

In vitro dissolution test

The results of in vitro drug released are plotted against time in phosphate buffer solution pH 5.8 to obtain the dissolution profiles as shown in fig. 2 and 3. MDT, Q10 min, and % DE of each liquisolid formula and DCT were calculated and reported in table 5.

Table 5: Model-independent parameters of liquisolid compacts and DCT

<table>
<thead>
<tr>
<th>Formula</th>
<th>Q10 min</th>
<th>MDT (min)</th>
<th>%DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>74%</td>
<td>7.85</td>
<td>87</td>
</tr>
<tr>
<td>F2</td>
<td>90%</td>
<td>5.9</td>
<td>90</td>
</tr>
<tr>
<td>F3</td>
<td>67%</td>
<td>9.9</td>
<td>84</td>
</tr>
<tr>
<td>F4</td>
<td>78%</td>
<td>9.4</td>
<td>94</td>
</tr>
<tr>
<td>DCT</td>
<td>65%</td>
<td>13.8</td>
<td>77</td>
</tr>
</tbody>
</table>

Q10 min: percentages of drug dissolved at 10 min, MDT: mean dissolution time, DE: dissolution efficiency, DCT: direct conventional tablet. Values was represented as mean±SD

The percentage of furosemide released from liquisolid compacts containing PEG 400 (from F1 to F4) was found to vary from 67±0.32% to 90±0.78% in first 10 min, while 65%±0.3 of drug release from DCT. This indicates fast release of the drug is observed from above liquisolid tablets.

From the calculations of %DE and MDT, F2 (at drug concentration 50% w/w in liquid medication) formulation showed better improvement in dissolution and it is considered as optimized formulation. The reduction in mean dissolution time (MDT) values indicates the faster release of drug from formulation F2 compared to other formulations.

The release of furosemide from F2 was also compared with DCT (fig. 3) prepared in a similar manner without nonvolatile liquid to study the effect of nonvolatile solvents on drug dissolution.

The release from DCT was 78 % in 30 min compared to complete drug release from the liquisolid formulation. The difference in dissolution was found to be significant (p<0.05) using student’s t-test analysis. This clearly indicates the improvement in the dissolution of furosemide was due to the presence of the drug in nonvolatile solvent in the liquisolid formulation.

The increased dissolution from liquisolid formulation could be due to the presence of the drug insoluble state in the formulation, which contributes to the increased wetting properties, thereby enhancing the dissolution rate. Similarly, as the formulation disintegrates in dissolution media, the drug will be presented in a state of molecular dispersion. This will increase the effective surface area of the particles available for dissolution [15].

Concerning the drug concentration in the liquid vehicle, as the drug concentration decreased, the portion solubilized and molecularly dispersed in the liquid vehicle increased thus leading to better dissolution [37-39].

In addition, the more vehicles available, the more even the distribution of the vehicle over the remaining undissolved drug particles that would help in better wetting of the drug through the dissolution stage [40].

A pairwise procedure such as dissimilarity ($f_1$) and similarity ($f_2$) factors provides a simple way to compare dissolution data. Food and drug administration (FDA) guidance proposes that $f_1$ value between 0 and 15 and $f_2$ value between 50-100 indicate equivalence in dissolution profiles [25,26]. In comparison between the dissolution of F2 and the DCT, the results of $f_1$ and $f_2$ were 16.22 and 36.18 respectively gave an indication that the two dissolution profiles are equivalent.

Differential scanning calorimetry (DSC)

The differential scanning calorimetry (DSC) thermograms of furosemide, a physical mixture of F2 liquisolid and F2 liquisolid tablet are illustrated in fig. 4, 5 and 6 respectively. Furosemide exhibits two characteristics, sharp endothermic peak at 218.16°C and exothermic peak at 222.32°C, which are associated with the decomposition and melting points of the drug and indicate the crystalline nature of the drug [41, 42]. The physical mixture of liquisolid and liquid solid tablet showed the partial disappearance of the characteristic peak of furosemide, supporting the probable phenomena of getting molecularly dispersed into the liquisolid matrix system, which suggests conversion of the drug into an amorphous form. This supports the in vitro release studies data of improved drug release and indicating no interaction between furosemide and excipients [43].
Fig. 4: DSC thermogram of furosemide

Fig. 5: DSC thermogram of physical mixture of F2 liquisolid

Fig. 6: DSC thermogram of F2 liquisolid tablet
Fourier-transform infrared spectroscopy (FTIR)

FTIR was performed to detect any sign of interaction which would
be reflected by a change in the position or disappearance of any
characteristic stretching vibration of furosemide. Fig. 7 showed the
characteristic peaks of furosemide of N-H stretching at 3399 cm⁻¹, N-
H stretching in sulfonamide at 3349 and 3284 cm⁻¹. The C=O
stretching, the vibration was at 1671 cm⁻¹, S=O stretching, vibration
at 1141 cm⁻¹ and 1322 cm⁻¹, most important stretching vibration was
OH stretching at 3122 cm⁻¹, NH bending at 1563-1590 cm⁻¹\cite{44}.

As shown in fig. 8 and 9 respectively, The FTIR spectra of physical
mixture and tablet of liquisolid formulations F2 showed
characteristic distinct peaks mainly for Avicel PH 102, and furom-
semide. Thus, there is no undesired interaction between the drug
and excipients. It can be noticed a reduction in intensity of the
characteristic absorption bands of the drug in liquisolid
formulations which might be attributed to the hydrogen bonding
interaction of the amino and carboxyl group of furosemide with the
hydroxyl group of the liquid vehicles PEG-400 \cite{45}.

FTIR spectra of crospovidone and sodium starch glycolate were
shown in fig. 10 and 11 respectively, FTIR of co-processed
superdisintegrants showed retention of all the major peaks of
individual polymer (sodium starch glycolate and crospovidone)
which indicates the absence of chemical interaction between
polymers during processing as in fig. 12.

Fig. 7: FTIR spectrum of furosemide

Fig. 8: FTIR spectrum of physical mixture of F2 liquisolid

Fig. 9: FTIR spectrum of F2 liquisolid tablet

Fig. 10: FTIR spectrum of crospovidone

Fig. 11: FTIR spectrum of sodium starch glycolate
X-ray powder diffraction (XRPD)

Fig. 13, 14 and 15 show XRPD of pure furosemide, a physical mixture of F2 liquisolid compact and F2 liquisolid tablet. X-ray diffraction pattern in fig. 13 demonstrated that pure furosemide was clearly in crystalline state as it showed sharp distinct peaks at 2θ diffraction angles of 6°, 22° and 24° with high intensity. XRPD pattern of a physical mixture of F2 liquisolid compact and liquisolid tablet in fig. 14 and 15 respectively showed the absence of sharp peaks and appeared as a diffused pattern peaks at 2θ angles in the 15°, 16°, 20° and 22° with low intensity.

The disappearance of sharp peaks is evident that crystalline pure drug is converted into amorphous state due to its molecular solubilization of the drug in the non-volatile solvent that was absorbed into and adsorbed onto the carrier and coating material, which proves the enhancement of solubility by this technique. Results confirmed the formation of drug solution into a liquisolid system which again supports and confirms the DSC results [46].
CONCLUSION
The liquisolid technique succeeded to improve the dissolution rate of the practically insoluble drug such as furosemide. Among the liquisolid tablets tested, F2 prepared using PEG 400 as a non-volatile liquid vehicle, at the R-value of 25 and containing 50% drug concentration, possessed reasonable flow, rapid dissolution time and the highest dissolution rate compared to other formulations. The results of investigations demonstrate that 40 mg furosemide tablets with acceptable size, mass, fast and entire drug dissolution could be prepared by selection of suitable drug concentration in a liquid vehicle.

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CONFLICT OF INTERESTS
Declared none

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