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Research Article

FORMULATION AND EVALUATION OF PIROXICAM LIQUISOLID COMPACTS

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ABSTRACT

Objective: The purpose of the present research was to investigate the in vitro dissolution properties of poorly water soluble piroxicam by utilizing liquisolid technique. Different liquisolid (LS) compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture.

Methods: Avicel PH 102, Aerosil 200 and croscarmellose sodium were employed as carrier, coating material and disintegrant respectively for preparing LS compacts. LS compacts were prepared and evaluated for their tabletting properties. Fourier transform infrared (FTIR) analysis, differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD) were performed.

Results: The tabletting properties of the liquisolid compacts were within the acceptable limits and drug release rates of all prepared LS compacts were distinctly higher as compared to directly compressed tablets, and marketed capsules. Both DSC and XRPD suggested loss of piroxicam crystallinity upon liquisolid preparation indicating that even though the drug existed in a solid dosage form, it is held within the powder substrate in a solubilized, almost molecularly dispersed state, which contributed to the enhanced drug dissolution properties. The FTIR spectra showed disappearance of the characteristic absorption band of piroxicam (3338.78 cm^{-1}) in liquisolid formulations which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle; this resulted in drug dissolution enhancement.

Conclusion: From this study it concludes that the LS technique is an effective approach to enhance the dissolution rate of piroxicam.

Keywords: Piroxicam; Liquisolid compacts; PEG 400; Dissolution rate

INTRODUCTION

Over the years, different methods have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medications. The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilization, micro encapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs, however, among them, the technique of "liquisolid compacts" is one of the most promising techniques [1-6].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medication may be converted into a dry-looking, non adherent, free-flowing, and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. However, even though in the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [4-8]

Piroxicam is an oxicam derivative with potent non-steroidal anti-inflammatory activity (NSAID). It is used in various acute and chronic musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis and in acute gout, dysmenorrhoea and sometimes for pain associated with inflammation 9. For poorly soluble, highly permeable (class II) drugs (like piroxicam), the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract [10].

Therefore, together with permeability, the solubility and dissolution behavior of a drug are key determinants of its oral bioavailability. This undesired property, may also increase the amount of GI damage, due to long contact of drug with the mucous of GI. Thus, it is an ideal candidate for testing the potential of rapid-release liquisolid compacts.

MATERIALS AND METHOD

Materials

The following materials were used: Piroxicam (Sigma, Germany), Avicel PH 102 and Aerosil 200 (Mingtai chemical, Taiwan), croscarmellose sodium (Rajesh Chemicals, Mumbai; India), Propylene glycols (Fluka AG, Buchs SG, Switzerland), polyethylene glycol (PEG 400) (Mfg. of lab chemfine chemicals-Mumbai, India), Methanol (ScharLab, Spain), Potassium dihydrogen ortho-phosphate (BDH Chemicals, Ltd, England). All reagents used were of analytical grade.

Method

Solubility studies

Solubility studies of piroxicam were carried out in SGF, SIF, propylene glycol and PEG 400. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker (J Lab Tech, Korea) for 48h at 25 ± 0.5°C under constant vibration. After this period the solutions were filtered, diluted and analysed by UV-spectrophotometer (Specord, Japan). Three determinations were carried out for each sample to calculate the solubility of piroxicam.

Application of the mathematical model for designing the liquisolid systems

In this study, PEG 400, Avicel PH 102 (Micro crystalline Cellulose-MCC), and Aerosil 200 were used as a liquid vehicle, carrier, coating respectively. The concentration of the drug in liquid vehicle was varied and the carrier: coating ratio was kept constant in all formulations (R=20:1).

In order to address the flowability and compressibility of liquisolid compacts, simultaneously, the "new formulation mathematical model of liquisolid systems" was employed as follows to calculate the appropriate quantities of excipients required for producing liquisolid systems of acceptable flowability and compressibility.

This mathematical model was based on new fundamental powders properties (constants for each powder material with the liquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential ψ-number) of the constituent powders (carrier and coating materials) [1,2,7,8].

According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where

R=Q/q ... (1)

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

Lf=W/Q ... (2)

Spireas et al. [4] used the Flowable liquid retention potentials (Φ - values) of powder excipients used to calculate the required ingredient quantities, hence, the powder excipients ratios R and liquid load factors Lf of the formulations are related as follows:

Lf = Φ + Φ (1/R) ... (3)

Where, Φ and Φ are flowable liquid retention potential of carrier and coating material respectively. So in order to calculate the required weights of the excipients used, first, from Eq. (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used.

So, by knowing both Lf and W, the appropriate quantities of carrier (Qo) and coating (qo) 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 directly compressible tablet (dct) and liquisolid compact

Directly compressible tablets (DCT) of piroxicam were prepared by direct compression using single tablet punch machine, each containing 10 mg drug with Avicel PH 102, Aerosil 200 and croscarmellose sodium. Various LS compacts (LS-1 to LS-5) containing 10 mg of piroxicam were prepared by dispersing in nonvolatile vehicle (PEG 400). Then a binary mixture of carrier (Avicel PH 102) and coating material (Aerosil 200) was prepared at a ratio of 20:1.

This binary mixture was added to the admixture of drug and vehicle. Finally 5% croscarmellose sodium as disintegrant was added in above powder blend and mixed. The final powder blend was subjected to compression.

Precompression studies of the prepared liquisolid powder systems

Differential scanning calorimetry (DSC)

DSC was performed using Shimadzu differential scanning calorimeter Mettler, in order to assess the thermotropic properties and thermal behaviour of the drug (piroxicam), and the liquisolid compacts prepared. About 5 mg of the sample were sealed in the aluminium pans and heated at the rate of 10 °C/min, covering a temperature range of 40°C to 300°C.

X-ray diffractometery (XRD)

It has been shown that polymorphic changes of the drug are important factors, which may affect the drug dissolution rate and bioavailability. It is therefore important to study the polymorphic changes of the drug [11]. For characterization of crystalline state, the X-ray diffraction (XRD) patterns for Piroxicam, the conventional formulation, the liquisolid compacts prepared, and Avicel PH 102 were studied.

Fourier transform infrared spectroscopy

FT-IR was performed for the pure drug (piroxicam), conventional formulation and liquisolid powders to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic stretching vibration of the compound.

Flow properties of liquisolid system

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies otherwise high dose variations will occur.

Flow properties of the liquisolid were estimated by tap density, bulk density, Angle of repose, Carr's compressibility index and Hausner's ratio [12].

Evaluation of piroxicam liquisolid tablets

Friability and hardness

The friability of the prepared formula was measured using Friabilator TAR 200 (Erweka, Germany), and the percentage loss in weights were calculated and taken as a measure of friability. The hardness of the liquisolid tablets prepared was evaluated using Hardness tester TBH 100 (Erweka, Germany), the mean hardness of each formula was determined [13].

Disintegration test

The disintegration time was determined in 0.1N HCl pH 1.2. Disintegration apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used (Disintegration tester ZT 3-4 Erweka, Germany). A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded [14].

Uniformity of dosage units

Five tablets were weighed individually and powdered. The powder equivalent to 20mg of piroxicam was weighed and dissolved in 10 ml of methanol and volume was adjusted to 100 ml with pH 6.8 buffer. The solution was then filtered and from this solution 1 ml was taken and make up with PH 6.8 buffer in 100 ml standard volumetric flask. The amount of drug present in each tablet was determined spectrophotometrically at 333nm using UV–visible spectrophotometer. The percentage content was determined using standard graph [15].

In vitro dissolution studies of liquisolid tablets

The dissolution test was used to compare between liquisolid tablets, DCT, and marketed piroxicam capsule. The USP paddle method (Caleva, England) was used for all the in vitro dissolution studies. In this method, simulated gastric fluid (pH 1.2), and intestinal fluid (pH 6.8) without enzyme were used as dissolution media. The rate of stirring was 50 ± 2 rpm. The amount of piroxicam was 10 mg in all formulations. The dosage forms were placed in 900 mL of gastric fluid (HCl solution) or intestinal fluid (phosphate buffer) and maintained at 37 ± 0.1°C. At appropriate intervals (5, 10, 20, 30, 40, 50, 60, and 70 min), 5 mL of the samples were taken and filtered through a 0.45-mm Millipore filter.

The dissolution medium was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed at 333nm by UV/visible spectrophotometer (Specord, Japan). The mean of three determinations was used to calculate the drug release from each of the formulations.

For assessment and comparison, drug dissolution rates (*D*R) of drug were used. For this mean, amount of drug (in µg) dissolved per min that presented by each tablet formulation during the first 10 min were calculated as follows:

$DR = (M \times D) / 1000$ .... (4)

Where *M* is the total amount of piroxicam in each tablet (in this study, it is 10,000 µg) and *D* denotes percentage of drug dissolved in first 10 min.

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

RESULTS AND DISCUSSION

Solubility Studies

The solubility of piroxicam in various solvents is given in Table 1. The table shows that the solubility of piroxcam was increased by the presence of non-volatile solvents (PG and PEG400). The higher solubility of the drug in PEG 400 compared with PG may be due to the longer non-polar chain of PEG 400. The longer non-polar part is thought to reflect hydrophobic interactions of the drug with the liquid vehicle molecule [16]. The table also shows that an increase in pH resulted in an increase in the solubility of piroxicam; this is because piroxicam is acidic [17].

Table 1: Solubility of piroxicam in various solvents.

Solvent	Solubility(%w/w) ± S.D.*
SGF (PH 1.2)	0.0076 ± 0.000551
SIF (PH 6.8)	0.0281 ± 0.001546
PG	0.847 ± 0.00265
PEG 400	2.663 ± 0.04726

*S.D. Standard deviation from mean .n=3

Application of the mathematical model for designing the liquisolid systems

Spireas et al. [18] clarified that the liquisolid hypothesis suggests that when the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics [1,2,18,19].

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized. In polyethylene glycol 400, Φ - Values of the carrier and coating materials were found to vary according to the liquid vehicle used.

In polyethylene glycol 400, the Φ - value of Avicel PH 102 was found to be 0.005, while for Aerosil 200 the Φ -value used was equal to that of Cab-O-Sil M5 as they both possessed the same specific surface area and density thus, Aerosil 200 and Cab-O-Sil M5 are expected to have similar adsorptive power [1,2,18,19]. Therefore, the Φ -value used for Aerosil 200 in PEG 400 was 3.26. This relatively high Φ -value is advantageous as it results in smaller sizes of the formulated tablets [18]. Using ''the new formulation mathematical model", the straight line equation for Avicel PH 102 and Aerosil 200 in PEG 400 will be:

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

For R-value used, the corresponding Lf value can be calculated. As soon as the optimum liquid load factor Lf of a given excipients ratio is established for each formula and W is calculated according to Piroxicam concentration in PEG 400, the appropriate quantities of Avicel PH 102 (Qo) and Aerosil 200 (qo) required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, were calculated using equation (1) and (2). Table 2 represents the exact qualitative and quantitative composition for each formula.

Table 2: Composition of different Piroxicam liquisolid formula prepared using PEG 400 as a liquid vehicle according to the mathematical model.

Liquisolid System	Drug concentration in liquid medication (%w/w)	Carrier: Coating Ratio (R)	Liquid Load factor (Lf)	Liquid Vehicle (mg) PEG400	Active ingredient (mg) Piroxicam	Carrier Q (mg) Avicel PH102	Coating Q (mg) Aerosil 200	Disintegrant Croscarmello-se (mg)	Unit dose (mg)
LS-1	10	20	0.168	90	10	595.24	29.76	38.16	763.16
LS-2	15	20	0.168	56.67	10	396.85	19.84	25.44	508.8
LS-3	20	20	0.168	40	10	297.62	14.88	19.08	381.58
LS-4	25	20	0.168	30	10	238.1	11.9	15.26	305.26
LS-5	30	20	0.168	23.33	10	198.39	9.92	12.72	254.36

Precompression studies of the prepared liquisolid powder systems

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation.

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (Piroxicam) and the liquisolid compacts prepared. The DSC thermogram of the drug (figure 1) indicating a sharp characteristic peak around its melting point. This shows that Piroxicam used was in pure crystalline state.

On the other hand, the liquisolid system thermogram in figure 2 displayed complete disappearance of characteristic peak of Piroxicam; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e. the drug was molecularly dispersed within the liquisolid matrix. Such disappearance of the drug peaks upon formulation of the liquisolid system was in agreement with McCauley and Brittain who declared that the complete suppression of all drug thermal features, undoubtedly indicate the formation of an amorphous solid solution [20].

The X-ray diffraction patterns in figure 3 revealed that pure piroxicam was clearly in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 8.65, 11.69, 14.53, 17.70, 21.76 and 27.39. Piroxicam characteristic peaks were observed in the conventional formulation (figure 4), demonstrating that its crystalline structure remained unchanged during the physical mixing, and that the loss of crystallinity was due to liquisolid system formation. On the other hand, the liquisolid powder X-ray diffraction pattern (figure 5) showed only one sharp diffraction peak at 2 θ angle of 22.5 belonging to Avicel PH 102 (figure 6), indicating that only Avicel PH 102 maintained its crystalline state.

Such absence of Piroxicam constructive reflections (specific peaks) in the liquisolid X-ray diffractogram indicates that drug has almost entirely converted from crystalline to amorphous or solubilized form, such lack of crystallinity in the liquisolid system indicates that Piroxicam solubilization in the liquid vehicle.

This amorphization or solubilization of piroxicam in the liquisolid system may contribute to the consequent improvement in the dissolution rate, apparent solubility and therefore the bioavailability of piroxicam. Such results were also in good agreement with Mura et al. [21] and Ghebremeskel et al [22].

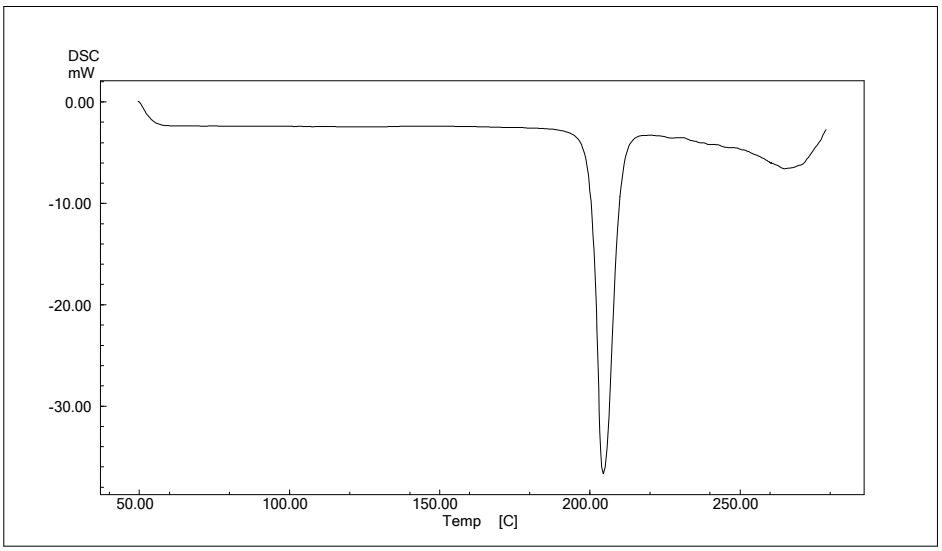

Fig. 1: DSC thermogram of Piroxicam

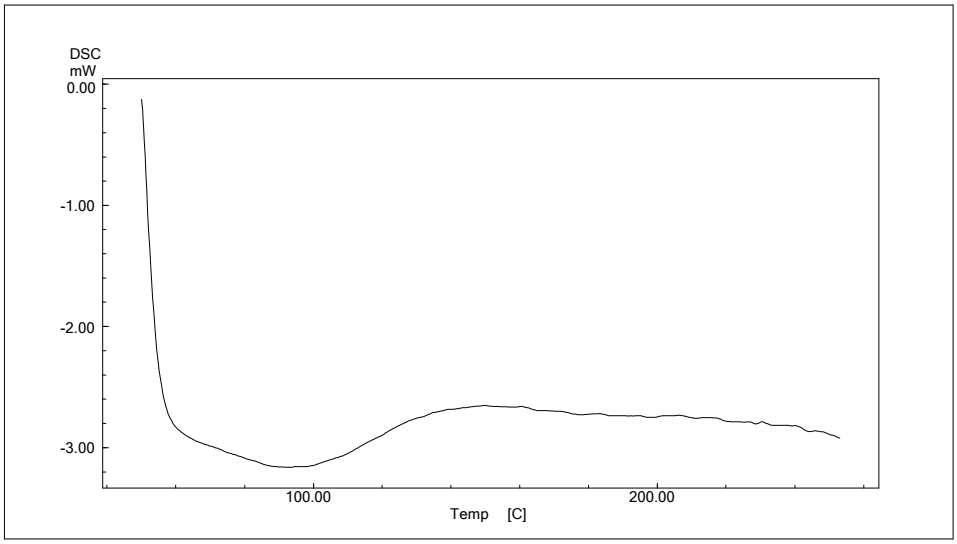

Fig. 2: DSC thermogram of Liquisolid powder system

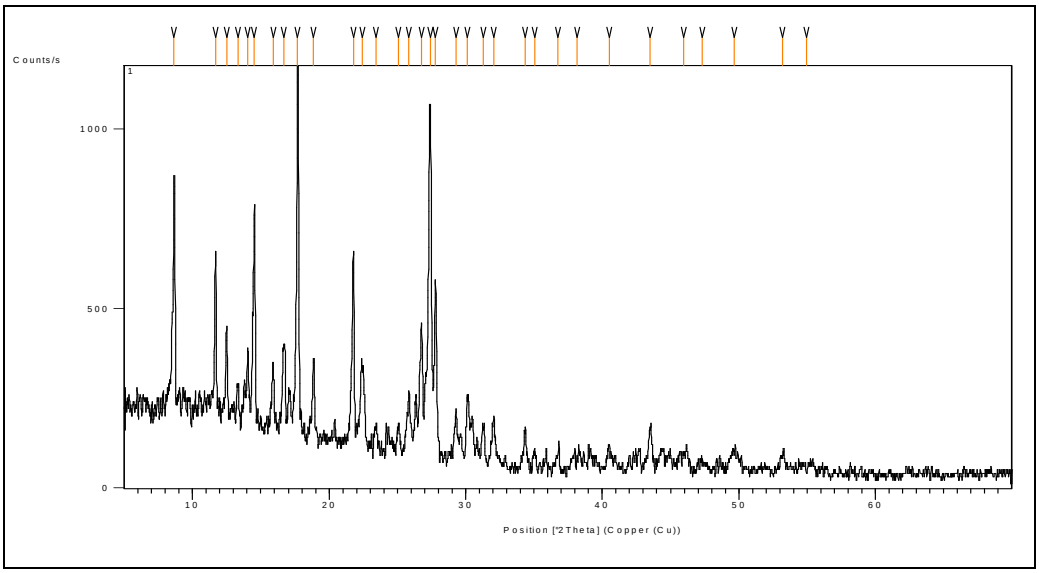

Fig. 3: X-ray diffraction of pure piroxicam

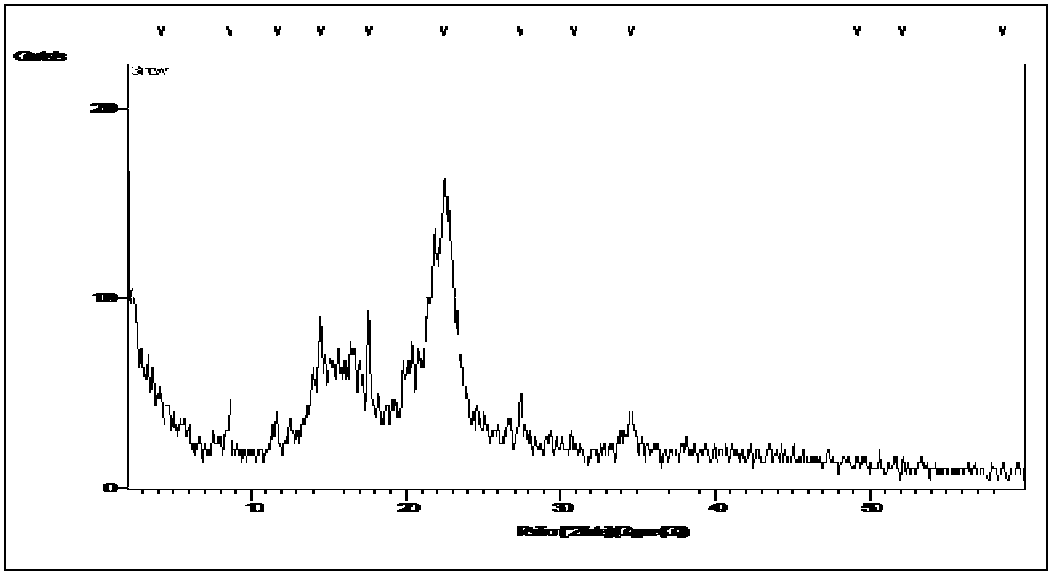

Fig. 4: X-ray diffraction of conventional formulation

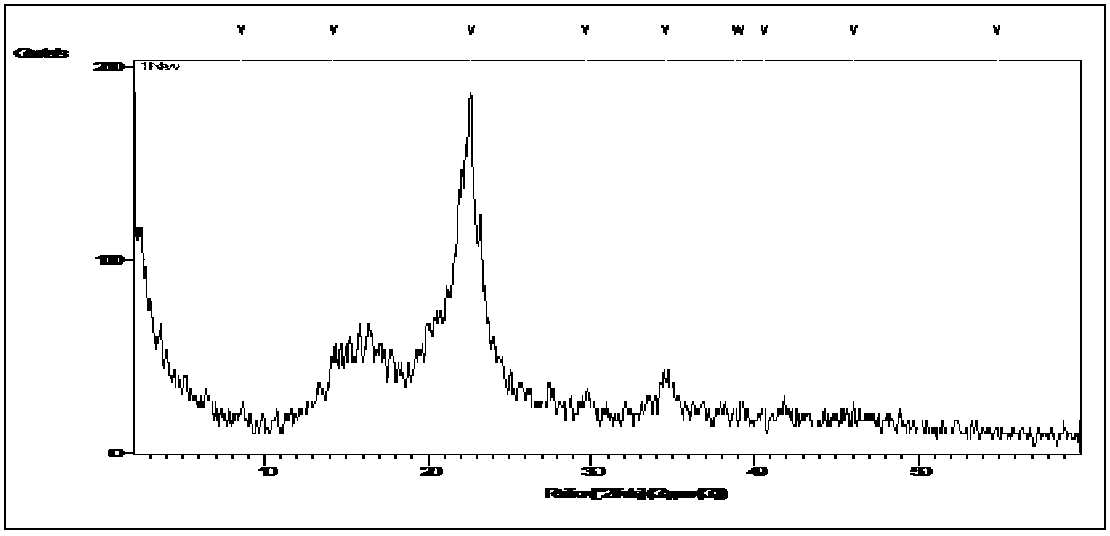

Fig. 5: X-ray diffraction of liquisolid powder

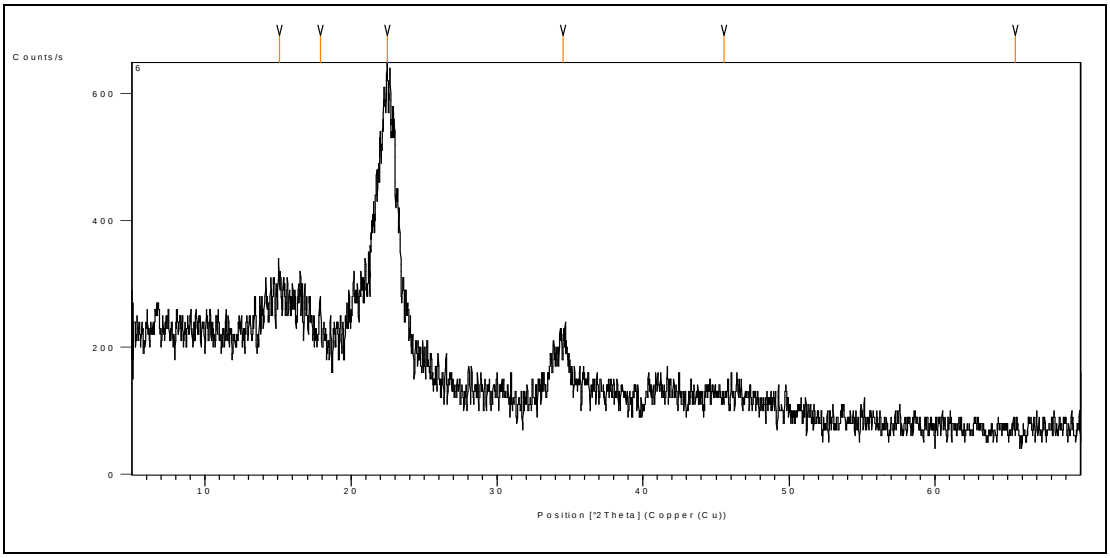

Fig. 6: X-ray diffraction of Avicel PH 102

The *FT-IR* 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 piroxicam.

FTIR spectra of piroxicam show a band at 3338.78 cm^{-1} (Figure 7) which indicates that the drug is in the cubic polymorphic form. Other characteristic bands are attributed to the stretching of different group vibrations: 1629.85 cm^{-1} stretching of amide carbonyl, 1529 cm^{-1} stretching of the second amide band, 1435 cm^{-1} stretching of asymmetric methyl group, 1352 cm^{-1} stretching of symmetric methyl group, 1149 cm^{-1} stretching of –SO2-N- group and 775 cm^{-1} as stretching of *ortho*-disubstitued phenyl [23]. Pattern of conventional formulation (figure 8) show band at 3336.88 cm^{-1}which indicates that the piroxicam was remained in the cubic polymorphic form and no interaction with excipients occurred.

Disappearance of the characteristic absorption band of piroxicam (3338.78 cm^{-1}) (figure 9) was observed in liquisolid formulation, which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle; this resulted in drug dissolution enhancement as shown by dissolution data.

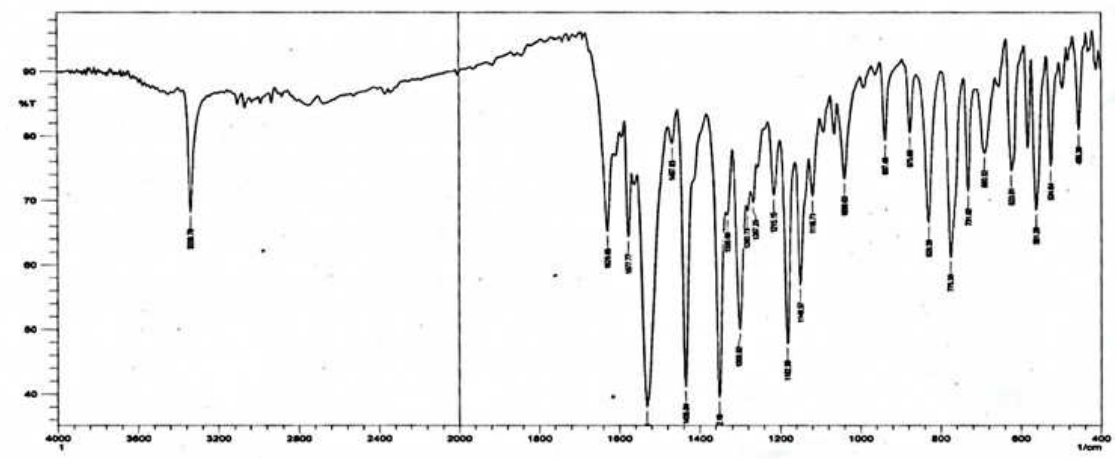

Fig. 7: FT-IR spectrum of pure piroxicam

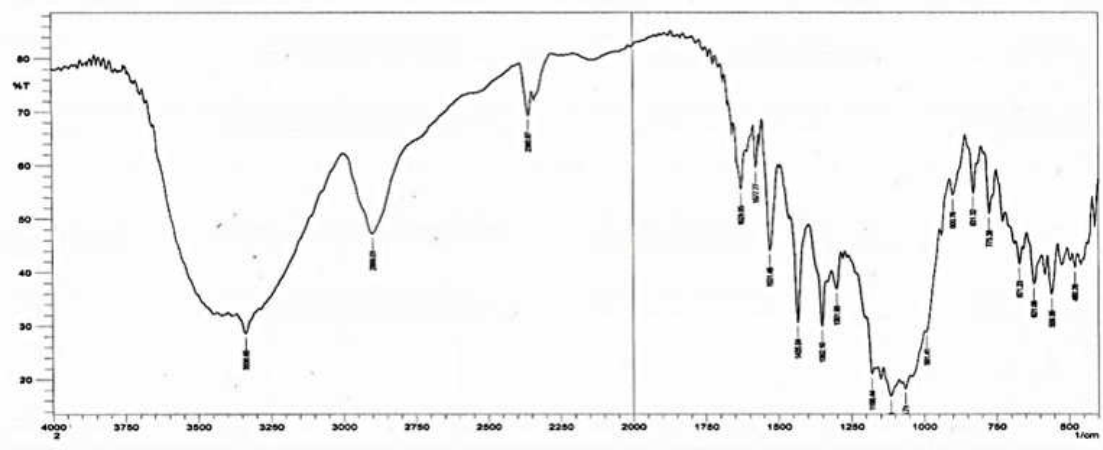

Fig. 8: FT-IR spectrum of conventional formulation

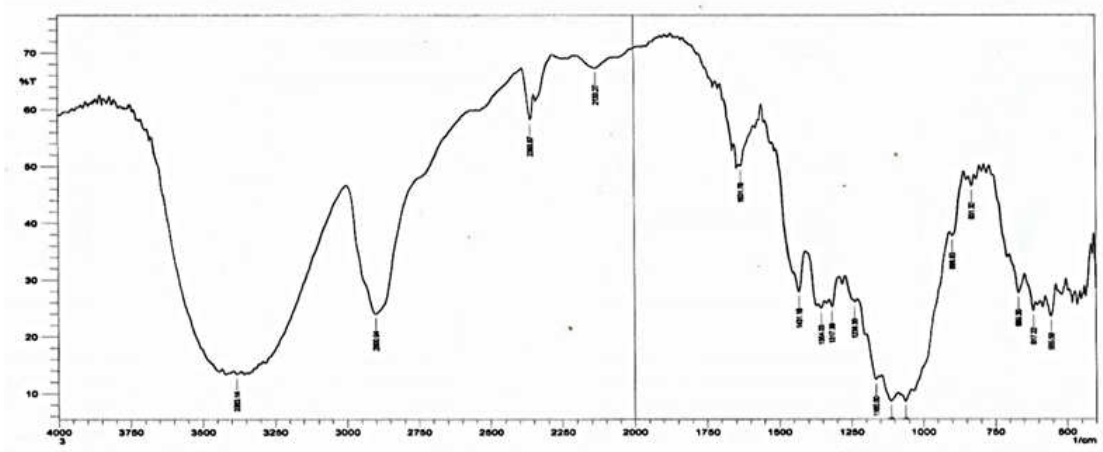

Fig. 9: FT-IR spectrum of liquisolid powder

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors' list is long and includes physical, mechanical as well as environmental factors [24].

Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio and their results are presented in Table 3.

As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. As presented in Table 3, LS-1, LS-2 showed (θ) values of 33.42, 34.033 respectively, were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable. Powders showing Carr's index (Ci) up to 21 are considered of acceptable flow properties [25,26].

In addition to Carr's index, Hausner found that the ratio was related to the inter particle friction, so that powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow [25,26]. Therefore, formula LS-1, LS-2, and LS-3 were selected as acceptably flowing as they had average Ci of 14.53, 15.083, and 18.437, respectively, and average Hausner's ratios of 1.14, 1.16, and 1.22, in the same order.

Table 3: Flowability parameters of piroxicam liquisolid powder systems.

Liquisolid System	Angle of repose (θ) ±S.D.*	Carr's compressibility index (%) ± S.D.*	Hausner' s ratio ± S.D*
LS-1	33.42±0.285	14.53±0.412	1.14±0.011
LS-2	34.033±0.666	15.083±0.243	1.16±0.012
LS-3	36.51±0.449	18.437±0.435	1.22±0.01
LS-4	39.6±0.695	21.067±0.153	1.26±0.01
LS-5	40.31±0.839	23.220±0.3	1.28±0.01

*S.D. Standard deviation from mean .n=3

Evaluation of Piroxicam Liquisolid Tablets

All the piroxicam liquisolid tablets had acceptable friability as none of the tested formula had percentage loss in tablets weights that exceed 1%; also, no tablet was cracked, split or broken in either formula. Since all the prepared formula met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment. In general, formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution.

In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing [27,28].

The mean hardness of each liquisolid formula was determined and is presented in Table 4 proving that all the liquisolid tablet formula had acceptable hardness. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel PH 102 may account almost exclusively for the strength and cohesiveness of compacts according to Shangraw [28]; the high compressibility and compactness of Avicel PH 102 can be explained by the nature of the microcrystalline cellulose particles themselves which are held together by hydrogen bonds, when compressed, such particles are deformed plastically and a strong compact is formed due to the extremely large number of surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed [28].

Disintegration time was found to be in the range of 53.33±7.64 to 185±5.Faster disintegration time indicate rapid release rates. These are in accordance with dissolution rates.

Table 4: Hardness, friability and disintegration of liquisolid formulation.

Liquisolid System	Hardness (kg/cm2) ± S.D.*	%Friability	Disintegration time (sec) ±S.D.*
LS-1	6.4±0.30	0.33	53.33±5.64
LS-2	6.15±0.34	0.35	85±5
LS-3	6.22±0.31	0.26	105±5
LS-4	6.09±0.47	0.40	119.67±4.5
LS-5	6.8±0.23	0.30	185±5

*S.D. Standard deviation from mean. n=3

Drug content

The drug content of the prepared liquisolid tablets were found to be in the range of 96.56–102.23% which is due to acceptable uniformity of content of the prepared liquisolid tablets.

In vitro dissolution studies

The dissolution profiles of piroxicam liquisolid tablets directly compressed tablets (DCT) and marketed capsule in SGF and SIF are shown in figures 10 and 11, respectively. Dissolution rates of liquisolid formulations were compared with DCT and marketed capsule. Liquisolid formulations initially show greater release than DCT and marketed formulation. This is indicated by percentage release at 10 min.

The statistical analysis showed that there is significant difference in dissolution rates compared to marketed formulation ($P < 0.05$). The percentages of drug released from LS-1, DCT and marketed capsule after 10 min were 94.33%, 47.95% and 40.25% respectively at pH 1.2 (SGF medium). In SIF (PH 6.8), LS-1, DCT, and marketed capsule were 100.12%, 59.03%, 50.58% respectively.

This shows that the tablets containing PEG 400 (liquisolid compacts) produced faster dissolution rate in comparison with other formulations.

The Noyes–Whitney equation can be used to explain the dissolution results as follow:

$$DR = (D/h)\, S\, (Cs\text{-}C) \quad \ldots..(5)$$

Where DR is the dissolution rate of the drug particles, D is the diffusion coefficient of the dissolved drug particles, which affected by the viscosity of the dissolution medium; S is the surface area exposed to dissolution; h is the thickness of the diffusion layer, and it is affected by agitation; Cs is the saturation solubility of the drug in solution in the diffusion layer, and C is the concentration of the drug in the dissolution medium. All the dissolution tests were stirred under the same paddle speed (50 rpm) and dissolution media with same viscosity; therefore, h and D were assumed to be constant [6-8],[29-30]. Therefore, this leaves S and (Cs _ C) as the factors affecting dissolution rates of liquisolid formulations.

The drug particles in liquisolid formulations were dispersed in selected hydrophilic liquid vehicle (piroxicam in PEG 400), which means the wetting properties of the drug particles were increased; hence, the surface area of drug particles available for dissolution increased tremendously After liquisolid tablet was disintegrated, the primary particles of liquisolid suspended in

the dissolution medium contained drug particles in a state of molecular dispersion.

For conventional tablet, the surface exposed for dissolution is very limited, due to the hydrophobicity of the drug particles. Accordingly, the higher dissolution rates observed in liquisolid formulations may be attributed to significantly larger surface area of the molecularly dispersed drug particles [6-8],[29-30].

Since the drug particles in liquisolid formulations are in a state of molecular dispersion, its saturation solubility (Cs) might be increased. The small amount of liquid vehicle (PEG 400) in a liquisolid tablet might not be adequate to increase the overall saturation solubility of drug particles in the dissolution medium.

Nevertheless, in the diffusion layer (the solid/liquid interface between primary liquisolid particles and dissolution medium), in such a micro-environment, it is highly possible that infinite amounts of PEG 400 diffuse with the drug particles away from the primary liquisolid particles. In this case, small amount of liquid vehicle might be sufficient to improve the solubility of drug particles by acting as a cosolvent with the dissolution medium of the diffusion layer. As a consequence of increase in Cs, the concentration gradient (Cs _ C) of the drug will be increased, and hence, the drug dissolution rate will be increased [6-8][29-30].

The effect of drug concentration (*C*d) in the liquid medication (PEG 400) on the 10- min dissolution rate (*D*R) of piroxicam from the liquisolid compacts in SGF and SIF media is shown in Figure 12. The figure 12 shows that the drug concentration in the liquid medication is one of the main factors on the performance of a liquisolid compact and has considerable effect on the piroxicam 10-min dissolution rate. It can be seen that *D*R decreased with an increase in the concentration of drug or reduction in the concentration of PEG 400. Such differences in the *D*R values of piroxicam from liquisolid compacts observed in Figure 12 may be justified using the differences in the amount of soluble form of the drug or molecular dispersion states of the drug in the formulations.

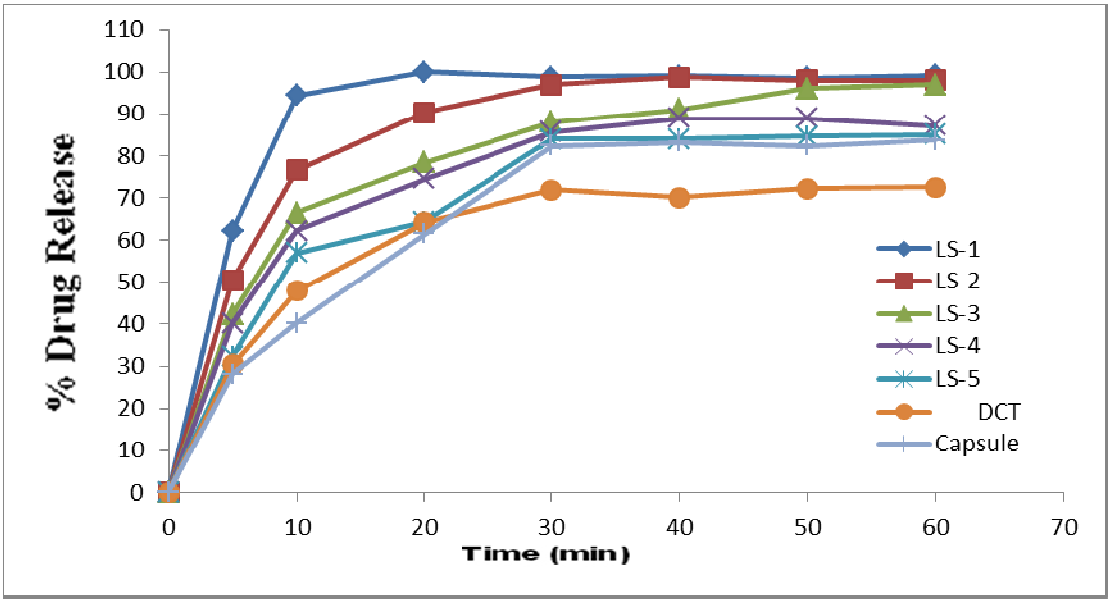

Fig.10: Dissolution profiles of liquisolid compacts, directly compressed tablets (DCT) and commercial capsule at SGF

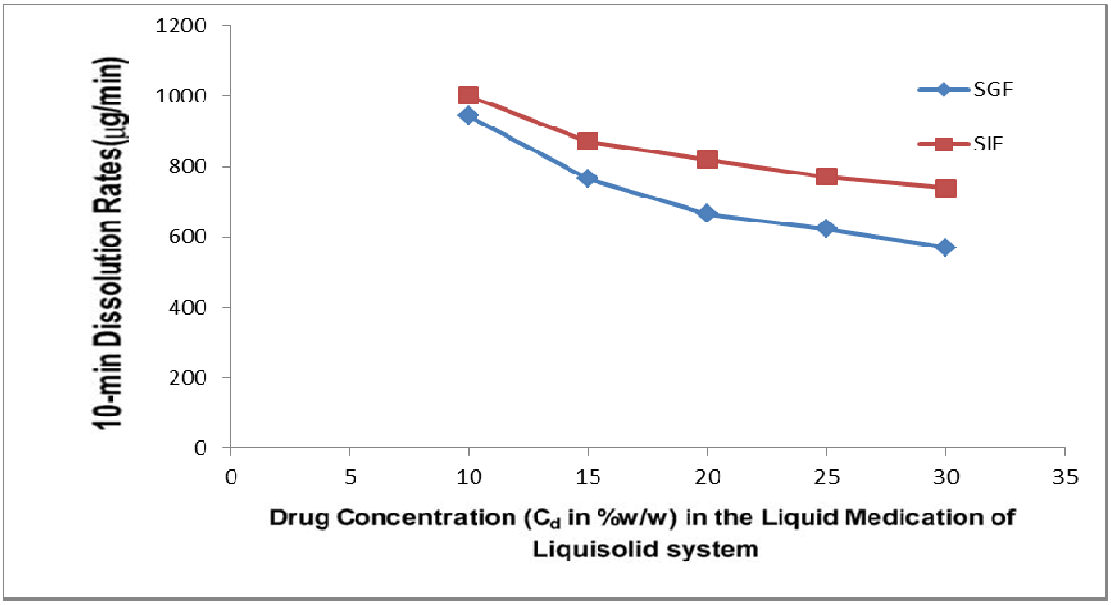

Fig. 11: Dissolution profiles of liquisolid compacts, directly compressed tablets (DCT) and commercial capsule at SIF

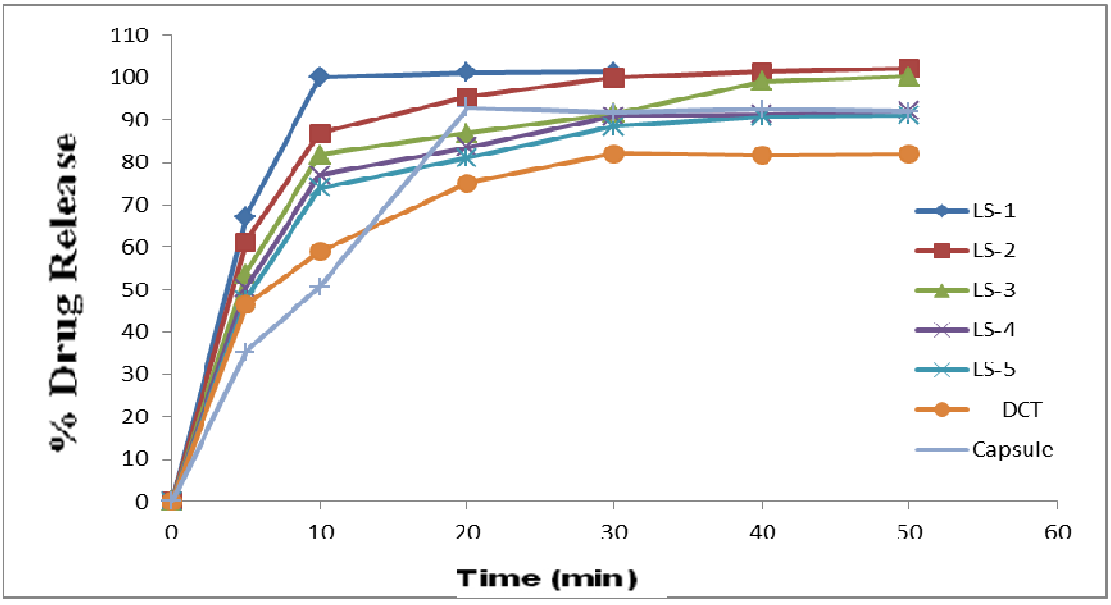

Fig. 12: Effect of drug concentration (Cd) in the liquid medication on the 10min dissolution rate (DR) exhibited by different liquisolid formulations at various dissolution media

CONCLUSIONS

The liquisolid compacts technique can be a promising alternative for the formulation of water insoluble drugs, such as piroxicam into rapid release tablets. The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and solubility of drug in the liquid vehicles. It has been shown that the solubility of the drug in the liquid medication of the liquisolid compacts is directly proportional to their piroxicam dissolution rates.

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