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Liquisolid Technique for Enhancement of Dissolution Properties of Lornoxicam

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ABSTRACT: Objective: Liquisolid technique is a new approach for delivery of drugs through oral route. This technique is suitable for poorly or water insoluble drugs and also for immediate or sustained release formulations. Design of this technique was according to new mathematical model proposed by Spireas *et al*. The in vitro dissolution property of slightly water soluble Lornoxicam was improved by exploring the potential of Liquisolid system (LS) using two non solvents. **Material & Methods:** Different 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. Avicel PH 102, Aerosil 200 and Explotab, polyethylene glycol 400 and propylene glycol were employed as carrier, coating material, disintegrant and non volatile solvent respectively for preparing LS compacts. **Evaluation:** The in vitro release pattern of LS compacts and directly compressed tablets were studied using USP-II apparatus. The prepared LS compacts were evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio. The interaction between drug and excipients in prepared LS compacts were studied IR spectroscopy. The drug release rates of LS compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution. The LS-1 of LS powder system showed acceptable flowability, Carr's compressibility index and Hausner's ratio. The DSC and XRD studies conforms the no significant interaction between the drug and excipients used in LS compacts. **Conclusion:** From this study it concludes that the LS technique is a promising alternative for improvement of dissolution property of water-insoluble drugs.

KEYWORDS: Liquisolid Technique; Lornoxicam; Dissolution Enhancement; Oral Bioavailability .

INTRODUCTION

A large proportion of new drug candidates have poor aqueous solubility which poses difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal. Various formulation strategies were reported to overcome such a problem. The most promising method for promoting dissolution is the formation of liquisolid tablets. [1] A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, nonadherent, free--flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials. Various grades of

cellulose , starch lactose etc may be used as the carriers where as very fine particle size silica powder may be used as a coating material. [2], [3]

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability. [4]

The aim of the present study was to study the Effect of two different non volatile solvents polyethylene glycol 400 and propylene glycol on the dissolution rate of Lornoxicam using liquid solid technique. Lornoxicam (6-chloro-4-hydroxy-2-pyridyl-2H-thieno [2, 3-e]-1, 2-thiazine-3-carboxamide-1,1-dioxide) is a non-steroidal antiinflammatory drug (NSAID) with marked analgesic properties. Lornoxicam (LXM) a novel highly selective COX-2 inhibitor is used for a variety of acute and chronic inflammatory diseases [5].However, it's low aqueous solubility and poor dissolution in upper gastric fluid cause formulation problems and limits its therapeutic application by delaying rate of absorption and finally the onset of action [6].Lornoxicam is a BCS CLASS II drug which is used as a non steroidal anti-inflammatory drug for the treatment of arthirits. [5]

MATERIALS & METHODS

Material

Lornoxicam was received as a gift sample from (Glenmark Pharmaceuticals Ltd).Avicel PH 102, Explotab , Aerosil 200 and polyethylene glycol 400, propylene glycol was obtained from S.D. Fine Chem. Ltd. Mumbai. All reagents used were of analytical grade.

Mathematical Model For Designing The Liquisolid System

In the following study, PEG400 was used as liquid vehicle; Avicel PH 102 and Aerosil 200 were used as carrier and coating materials respectively. Several factors were varied in order to achieve solubility of Lornoxicam in liquisolid formulations, it includes concentration of the liquid vehicle PEG400 and Propylene Glycol (10, 20, 30 & 40 g percent), and ratio of carrier: coating material (different R values) (10, 20, 30 and 40). In order to calculate the appropriate amounts of powder excipients (carrier and coating materials) of liquisolid compact a mathematical model is used. This mathematical model is required to produce liquisolid system of acceptable flowability and compressibility. This mathematical model is based on two powder properties which are constant for each powder material with liquid vehicle - Flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-number). [7][8][9][10]. However, according to new theories the carrier and coating materials can retain only certain amount of liquid for maintain acceptable flow and compression properties. This is expressed by the term R which is the ratio between the weights of carrier (Q)and coating (q).Depending on the excipient ratio (*R*) of carrier material (Q) and coating material (q) an acceptably flowing and compressible liquisolid system can be achieve only if a maximum liquid load on the carrier material is not exceeded.

$$R = Q/q \quad \text{..... (1)}$$

This liquid/carrier ratio is termed "liquid load factor *Lf* "[w/w] and is defined as the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system

$$Lf = W / Q \quad \text{..... .....(2)}$$

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

$$\Phi Lf = \Phi + \varphi . (1/R) \quad \text{..... (3)}$$

where Φ and φ are the Φ-values of the carrier and coating material, respectively.
The liquid load factor for production of liquisolid systems with acceptable compactability (*ΨLf)* can be determined by:

$$\Psi Lf = \Psi + \psi . (1/R) \quad \text{..... (4)}$$

where Ψ and *ψ* are the Ψ-numbers of the carrier and coating material, respectively. Therefore, the optimum liquid load factor (*L o)* required to obtain acceptably flowing and compressible liquisolid systems is equal to either *ΦLf or ΨLf* whichever represents the lower value.

The outline of the constituents of each of the formulae prepared from the previously mentioned variable is depicted in Table no I and Table II.

Table I: Different Formulations of Liquisolid Compacts of Lornoxicam Using Polyethylene Glycol

% of non-volatile solvent	10				20				30				40			
R values	10	20	30	40	10	20	30	40	10	20	30	40	10	20	30	40
Formula name	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16

Table II: Different Formulations of Liquisolid Compacts of Lornoxicam Using Propylene Glycol

% of non-volatile solvent	10				20				30				40			
R values	10	20	30	40	10	20	30	40	10	20	30	40	10	20	30	40
Formula name	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	F28	F29	F30	F31	F32

Drug Excipient Compatibity Study

The drug excipient compatibility studies was carried out using FTIR studies.

Solubility Studies

Solubility studies of Lornoxicam were carried out in distilled water, PEG400 and Propylene glycol. The saturated solution of Lornoxicam and distilled water, the saturated solution of Lornoxicam and PEG 400 and Lornoxicam and Propylene Glycol were kept in Orbital shaker at 25˚C for 48 hrs. The solutions were filtered and concentration was determined by using UV spectrophotometer (Shimadzu 1800,Shimadzu Corporation .Japan) at 374 nm. The results were extrapolated to determine the percent w/w of Lornoxicam) in different solvent (distilled water, PEG400 and Propylene glycol).

Preparation of Lornoxicam Liquisolid Compact and Conventional Tablet

A conventional formulation of Lornoxicam (denoted as DCT) was directly compressed into tablets. Each tablet contained 8 mg of drug. In addition, the previously weighed desired quantities of the solid drug and the liquid vehicle (PEG400 and Propylene Glycol) were mixed and heated to 80-90˚C with continuous stirring, the solution was then sonicated until homogenous drug solution was obtained. Then the calculated weight of drug solution was incorporated into the mixture of carrier (Q) and coating material (q). After that each liquisolid formula further blended with 5% of the disintegrant sodium starch glycolate. The prepared liquisolid systems were compressed by using single punch tablet press machine.

Precompressional Studies of the Prepared Liquisolid Compacts

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. 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.[11]. The angle of repose was determined by the fixed funnel method. The bulk density and tapped density were determined for the calculation of Hausner's ratio and Carr's index.

Evaluation of Lornoxicam Liquisolid Tablets

On the basis of the flow properties, 5% Explotab (disintegrants) were added to the selected batches and tablets were compressed using a single punch machine (Cadmach Machinery Co Ltd., Ahmadabad). The prepared liquisolid tablets were further evaluated. Lornoxicam drug content was determined in selected formulations. Ten tablets of each formulation were weighed and average weight is calculated. Each tablet was then crushed and dissolved in 0.1N HCL, then the solution was filtered, properly diluted, and then measured spectrophotometrically using spectrophotometer UV at 374nm against pH-1.2 of 0.1 N HCL as blank.

The friability of the prepared formulations was measured using Roche friabilator. The hardness of the tablets was determined using Monsanto hardness tester. The disintegration time of the selected batches was determined using USP disintegrator tester.

The *in-vitro* release profiles of the prepared liquisolid compacts of Lornoxicam in PEG 400 and Propylene Glycol and the directly compressed tablets were obtained using a dissolution test apparatus USP Dissolution test apparatus -II (Veego). The dissolution study was carried out for 90 mins in 900 ml 0.1 N HCl dissolution medium at 37˚C ± 2˚C and 50 rpm. The sample is collected every 10 mins. The withdrawn samples were filtered and analyzed spectrophotometrically at 374 nm. The experiments were done in triplicates for each of the selected liquisolid batches and for conventional directly compressed tablets containing also an equivalent of 8 mg for comparison.

RESULTS & DISCUSSION

Drug Excipient Interaction studies

The results of IR spectra of active ingredient and excipients revealed that there was no considerable change observed in bands of Lornoxicam as evident from figure 1(a) and figure 1 (b) and figure 1(c).

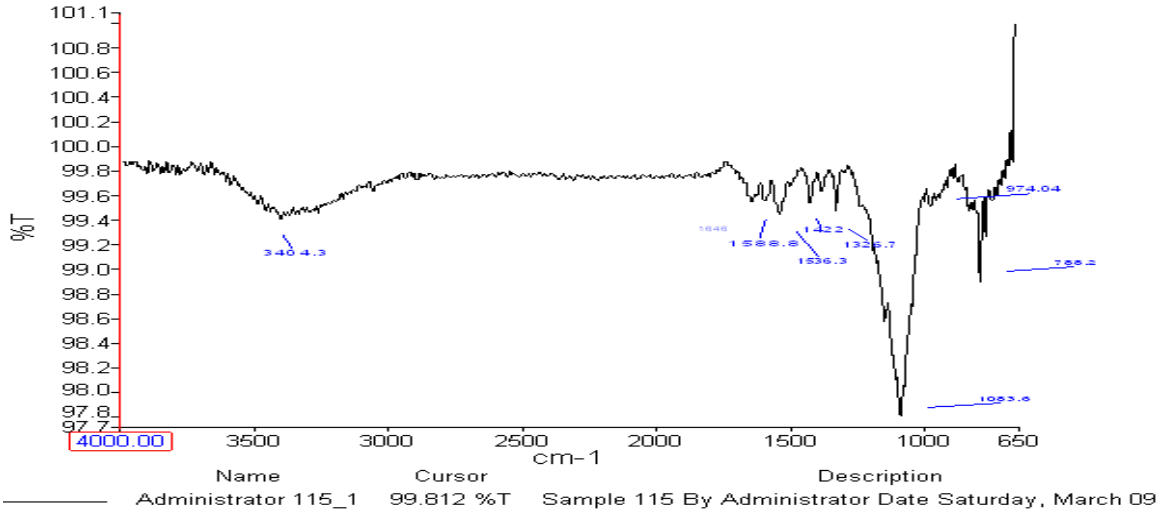

Fig.1(a) IR spectra of pure Lornoxicam

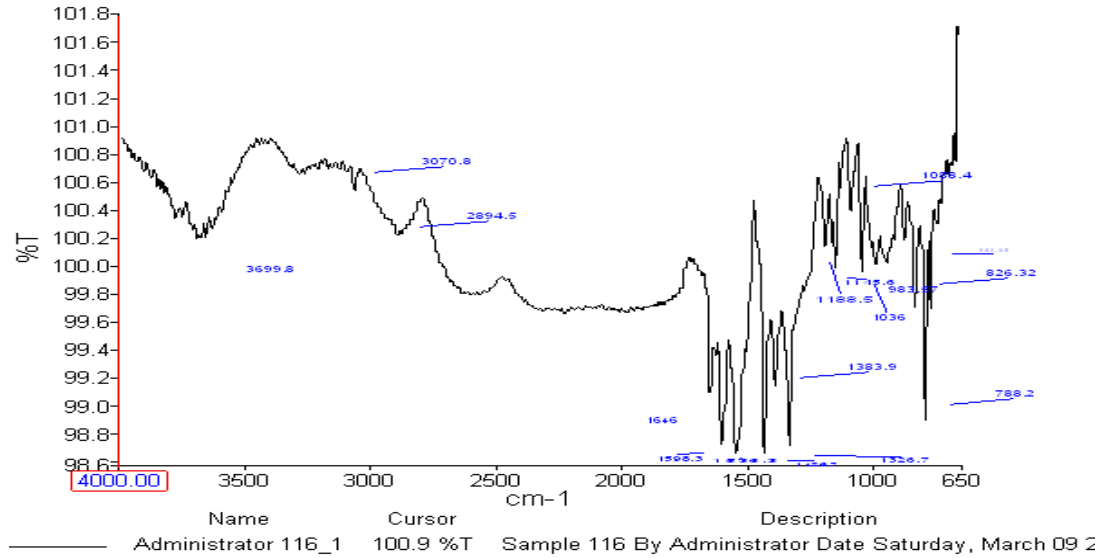

Fig 1(b) IR spectra of physical mixture of Lornoxicam and Aerosil 200

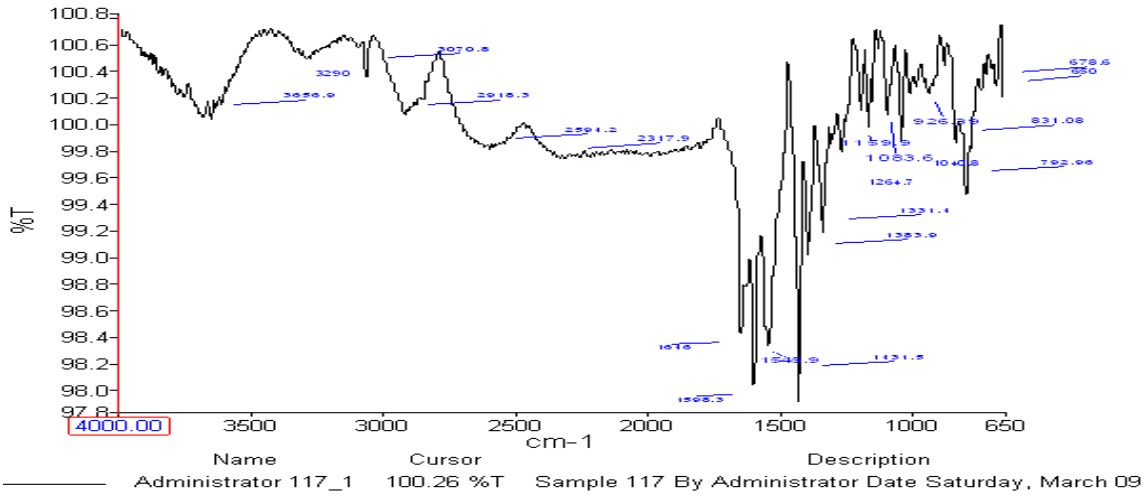

Fig 1(c) IR spectra of physical mixture of Lornoxicam and Avicel pH 102

Solubility And UV Analysis Of Lornoxicam

All the standard curves of Lornoxicam solutions obeyed Beer's law which was linear over the concentration range tested from 5–60 µg/ml. The solubility in distilled water, polyethylene glycol and propylene glycol was found to be 1.25mg/100ml 4.01g/100 ml and 3.28 g/100ml respectively.

Mathematical model for designing the liquisolid system

In order to calculate the required ingredient, flowable liquid retention factor *(ΦLf)* was used for calculations.The Φ value used for Aerosil 200 was equal to that of Cab-O-Sil as they both possessed the same specific surface area and density. [12].

The corresponding L*f* value was calculated for each R value used as depicted by Table no III.

The amounts of carrier (Q) and coating material (q) were calculated using equation 1 and 2.

Table IV represents the exact qualitative and quantitative composition for those batches which showed good flow properties and were further tableted.

TABLE III: Lf values for PEG 400 and PG

	PEG-400		PG	
R	**ΦL_f**	**ΨL_f**	**ΦL_f**	**ΨL_f**
10	0.331	0.3073	0.4910	0.2800
20	0.168	0.2747	0.3255	0.2520
30	0.1136	0.2638	0.2703	0.2427
40	0.0865	0.2583	0.2428	0.2380

TABLE IV: Composition of different Lornoxicam batches prepared according to the mathematical model

Formula no.	% of solvent (w/w)	R	Lf (g)	W (g)	Q=W/Lf (g)	q=Q/R (g)
F1	10	10	0.3073	0.4	1.3017	0.1302
F5	20	10	0.331	0.2	0.6042	0.0604
F6	20	20	0.168	0.2	1.1905	0.0595
F9	30	10	0.331	0.1333	0.4028	0.0403
F10	30	20	0.168	0.1333	0.7937	0.0397
F13	40	10	0.331	0.1	0.3021	0.0302
F17	10	10	0.28	0.4	1.4286	0.1429
F21	20	10	0.28	0.2	0.7143	0.0714
F22	20	20	0.252	0.2	0.7937	0.0397
F25	30	10	0.28	0.1333	0.4762	0.0476
F26	30	20	0.252	0.1333	0.5291	0.0265

Table V: Flow Properties of Lornoxicam Liquisolid Compact (MEAN± S.D, N=3)

Sl no	Batch name	Angle of repose(θ) ±SD	Carr's index ± SD	Hausner's ratio ± SD
1	F1	34.9˚± 0.0020	19.70 ± 0.330	1.170± 0.002
2	F5	35.03˚± 0.018	20.20± 0.110	1.200± 0.017
3	F6	24.69˚± 0.011	19.06± 0.320	1.073±0.05
4	F9	22.18˚± 1.250	19.90± 0.150	1.192± 0.011
5	F10	22.5S8˚± 1.350	19.70± 0.330	1.068± 0.01
6	F13	35.34˚± 0.055	18.50± 0.009	1.190± 0.04
7	F17	32.30˚± 0.006	18.30 ± 0.330	0.850± 0.002
8	F21	30.60˚± 0.038	19.34± 0.110	0.790± 0.017
9	F22	25.19˚± 0.071	20.74± 0.320	1.073±0.05
10	F25	35.48˚± 1.042	19.33± 0.150	1.192± 0.011
11	F26	30.68˚± 1.110	18.30± 0.330	1.068± 0.01
12	F29	30.74˚± 0.023	18.78± 0.009	0.89± 0.04

Drug Excipients Compatibility Studies

The results of IR spectra of active ingredient and excipients revealed that there was no considerable change observed in bands of Lornoxicam as evident from figure 1(a) and figure 1 (b) and figure 1(c).

Flow properties of the Lornoxicam liquisolid compacts

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. 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 .The angle was repose was determined by the fixed funnel method . The bulk density and tapped density were determined for the calculation of Hausner's ratio and Carr's index. Angle of repose is a characteristic of the internal friction or cohesion of the particles. The greater the angle of repose, the greater is the cohesiveness of powder. As depicted in Table no V , Batch F1, F5, , F6, F9 , F10, F13,F17, F21 ,F22,F25, F26, and F29 (θ) values of 34.9˚, 35.03˚, 24.69˚,22.18˚,25.18˚,35.34˚,32.30˚,30.60˚, 25.19˚, 35.48˚ 30.68˚ and 30.74˚ were accepted. The remaining batches showed higher angle of repose and hence were non acceptable. Powders having Carr's index up to 20.7˚ were considered of acceptable flow. Hausner found that the ratio of D_{Bmax} /D_{Bmin} was related to inter particle friction. The lower the inter particle friction between the particles, the better the flow property. Hence the powders which had Hausner's ratio approximately upto 1.25 were selected.

Hardness, Friability, Weight variation, and Disintegration test

The results of the various parameters hardness, friability, weight variation and disintegration have been tabulated. The collective data regarding Lornoxicam tablets

hardness, friability and disintegration test have been tabulated in Table VI. All the selected liquisolid tablet system possessed acceptable friability as in none of these formulated tablets, the percentage friability exceeded 1%. None of the tablets were cracked, split or broken in either formula. Since all the prepared batched passed the friability criteria, they are expected to show acceptable toughness and withstand abrasion duration handling, packaging and shipment.

The mean hardness of all the selected liquisolid tablet systems was found to be in the range of 3.4-4.4kg/cm^2. Therefore it can be said that that all the selected liquisolid tablet systems had acceptable hardness. This can be explained on the basis of the fact that the presence of hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel pH102 account for this. [13] The disintegration test for all the batches was found to be less than 1 minute.

DISSOLUTION STUDIES

The dissolution properties of Liquid solid tablets formulations prepared with PEG 400 and PG are shown in Fig 2(a) and Fig 2(b).The dissolution profiles of the selected Liquid solid tablets formulations prepared with PEG 400 and PG together with the dissolution profile of DCT are presented in Fig 2(c).

Table VI: Results of Drug Content, Hardness, Friability, And Disintegration Test of The Liquisolid Tablet System

Batch name	Average Famotidine Content(%)	Hardness (kg/cm²) ± SD	Friability (%) ± SD	Disintegration time(sec) ± SD
F1	84.00%	3.8 ± 0.03	0.33± 0.06	67± 1.09
F5	85.42%	3.4 ± 0.02	0.42± 0.03	73± 1.44
F6	87.56%	3.5 ± 0.05	0.24± 0.13	86± 0.6
F9	80.78%	3.8 ± 0.02	0.41± 0.11	42± 0.12
F10	79.78%	3.8 ± 0.03	0.33± 0.16	70± 0.18
F13	81.90%	4.4 ± 0.025	0.39± 0.18	47± 0.31
F17	81.00%	4.0 ± 0.12	0.37± 0.19	85± 1.22
F21	82.42%	4.4 ± 0.05	0.33± 0.01	80± 1.09
F22	82.56%	3.6 ± 0.25	0.44± 0.19	66± 0.36
F25	79.78%	3.8 ± 0.15	0.35± 0.08	52± 0.06
F26	85.78%	3.8 ± 0.02	0.33± 0.16	60± 0.10
F29	86.90%	4.2 ± 0.14	0.36± 0.08	67± 0.17

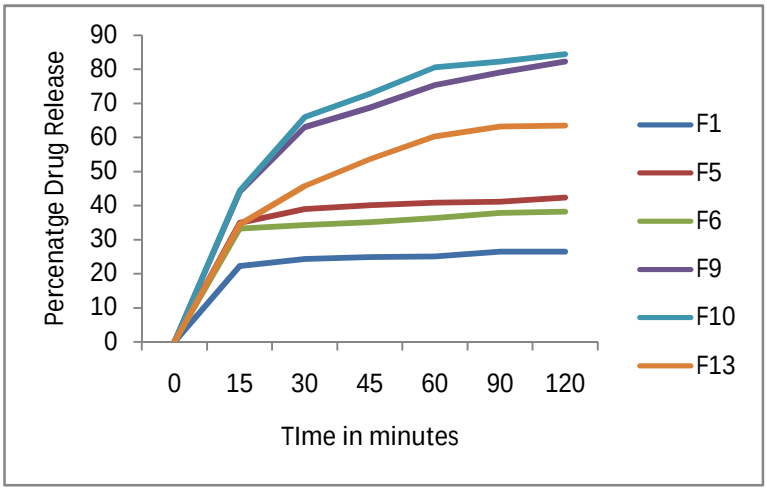

Fig 2(a): Dissolution Profile of Liquisolid Compacts prepared Using PEG 400

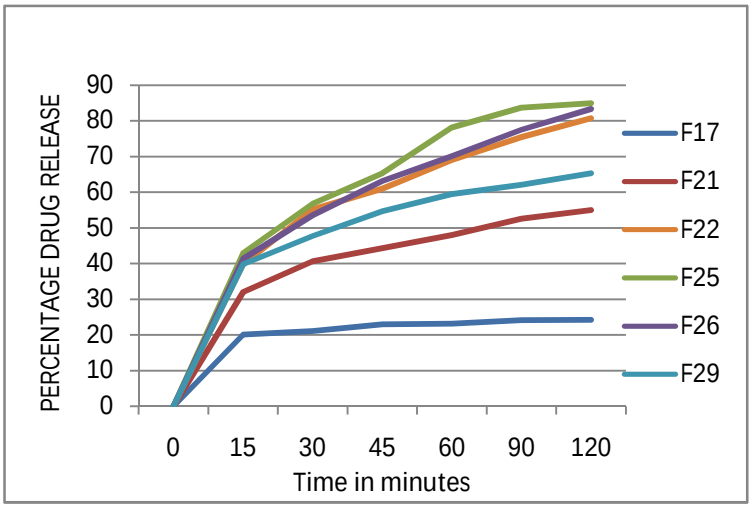

Fig 2(b): Dissolution Profile of Liquisolid Compacts prepared Using Propylene Glycol

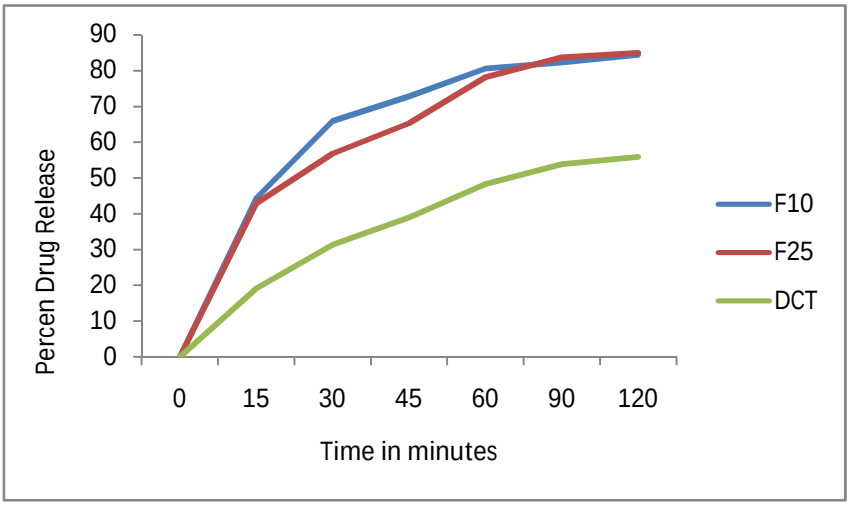

Fig 2(c) Comparitive Dissolution Profiles of Batches prepared using PEG 400, PG and DCT.

Independent t test was used to verify whether the differences in in-vitro dissolution profile obtained for both liquisolid compacts of PEG 400 and PG were significant. The p value obtained was 0.958 ($p>0.05$) which clearly shows that there was no significant difference between liquisolid compact prepared with PEG400 and PG.

Liquisolid compacts displayed more distinct in-vitro release characteristics than their directly compressed counterparts. From the fig 2(c), it can be observed that at the end of 120th min, the percentage of drug release from Batch F10, F25 and DCT was 84.41,84.94 and 55.84.The percent of drug dissolved from Batches F10, F25 and DCT after 15 mins (Q_{15}) and the drug release rate (D_R) was taken as a measure of the extent and rate of drug dissolved from the prepared tablets respectively as presented in Table no VII. It is clearly visible from the table that the value of Q_{15} was highest for liquisolid batch F10. It dissolved 44.32% of its content during first 15mins.

The most important observation can be made from Fig 2(b) and Fig 2(c) is that for all the selected batches larger amount of drug dissolved in the first 15 minutes (Q_{15}) than the conventional directly compressible tablets of Lornoxicam. This can be explained according to "Noyes-Whitney" equation and the "diffusion layer model" dissolution theories, the dissolution rate of a drug (D_R) is equal to

$$D_R = (D/h)S(Cs-C)$$

Where h is the thickness of the stagnant diffusion layer formed by the dissolving liquid around the drug

TABLE VII: COMPARISON OF $Q_{15\%}$ AND D_R.

Formulation no	$Q_{15\%}$	D_R (µg/min)
F10	44.32	236.48
F25	42.92	228.86
DCT	19.09	101.82

particles. D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution. C is the drug concentration in the bulk of the dissolving medium, and finally Cs is the saturation solubility of the drug in the dissolution medium and thus it is a constant rotational paddle (50rpm) and identical dissolution medium, it can be safely assumed that the thickness of the stagnant diffusion layer (h) and the diffusion coefficients of the drug molecules remain almost identical. From the previous equation, the drug dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs-C), but also to its surface area (S) available for dissolution. [14],[15].

Since the liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution is tremendously increased. In essence, after tablet disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, where as the directly compressible tablets are merely exposing micronized drug particles. In other words, in case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means is much greater than that of the Lornoxicam particles delivered by the plain, directly compressed tablets.

Therefore the hypothesis that significantly increased surface of the molecularly dispersed in the Lornoxicam liquisolid compact tablets may be chiefly responsible for their observed higher drug dissolution rate appears to be fundamentally valid.

CONCLUSION

Liquisolid technique thus proved to be an effective technique to improve the dissolution rate of poorly water soluble drug like Lornoxicam. Both Propylene glycol and Polyethylene glycol 400 can be used as non volatile solvent for Lornoxicam as there was statistically no significant difference in the dissolution profile of Lornoxicam in both the solvents.

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