



Dissolution Rate Enhancement of Fenofibrate using Lquisolid Tablet Technique

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SUMMARY. Fenofibrate is more effective drug as compared to other fibrates. But low bioavailability of it is due to its poor aqueous solubility. The purpose of present study was to improve fenofibrate dissolution through its formulation into lquisolid tablets and then to investigate in vitro performance of prepared lquisolid systems. By use of this technique, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powders with acceptable flow properties and compression behavior by using suitable powder excipients. X-ray powder diffraction and Differential Scanning Calorimetry were used for evaluation of physicochemical properties of Fenofibrate in lquisolid tablets. Stereomicroscopy was used to assess morphological characteristics of lquisolid formulation. Enhanced drug release profiles due to increased wetting properties and surface of drug available for dissolution was obtained in case of lquisolid tablets.

INTRODUCTION

Fenofibrate, Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate, is a fibric acid derivative that reduces elevated plasma concentrations of triglycerides. It also decreases elevated plasma concentrations of LDL and total cholesterol ¹⁻³. Low bioavailability of it is due to its insolubility in water. Thus dissolution testing is critical step for insoluble or poorly water soluble drugs, where absorption is dissolution rate limited.

Various techniques have been used to enhance dissolution rates and in turn absorption and bioavailability of Fenofibrate. These include solid dispersion ⁴, micronization, co-grinding, and spray drying ⁵. Out of them, "lquisolid compacts" is one of the most prominent techniques ⁶⁻¹³. The lquisolid systems show acceptable flow properties and compressibility. Liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid

medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with use of carrier and coating materials. As the drug is in the form of liquid medication, it is in either solubilized or molecularly dispersed state. Due to increased wetting and surface area for dissolution, lquisolid tablets of water insoluble drugs show improved dissolution properties and in turn increase in bioavailability ¹⁴. Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique.

In the present study, Fenofibrate was used as it is poorly water soluble and thus can be effectively used for formulation of lquisolid systems. New formulation mathematical model as described by Spireas *et al.* ⁶ was used to calculate appropriate amounts of carrier and coating materials based on new fundamental properties of powder called flowable liquid retention poten-

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tial (Φ value) and compressible liquid retention potential (Ψ number) of powder ingredients, previously determined by Spireas *et al.*⁶⁻⁷.

MATERIALS AND METHODS

Materials

Fenofibrate was kindly gifted by Lupin Laboratories (India). Avicel PH 102 (microcrystalline cellulose) and Aerosil 200 were kindly gifted by Okasa Pharmaceuticals (India) and Sodium starch glycolate was gifted by Shital Chemicals (India). Propylene glycol and Sodium lauryl sulfate were purchased from Loba Chemie (India). All other reagents and chemicals were of analytical grade.

Application of mathematical model for design of liquisolid tablets

The formulation design of liquisolid systems was done in accordance with new mathematical model described by Spireas *et al.*⁶. In this study, propylene glycol was used as liquid vehicle; Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. To attain optimal Fenofibrate solubility in the liquisolid formulations, concentration of the liquid vehicle propylene glycol was taken as 10, 20, and 30 g% and the carrier: coat ratios were varied from 30, 40 and 50. According to new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility.

The excipients ratio R of powder is defined as

$$R = Q / q \quad [1]$$

where R is the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation.

Liquid load factor (L_f) is 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.*

$$L_f = W / Q \quad [2]$$

Flowable liquid retention potential (Φ value) of powder excipients was used to calculate the required ingredient quantities. Therefore, powder excipients ratios R and liquid load factors L_f of the formulations are related as follows:

$$L_f = \Phi + \Phi (1 / R) \quad [3]$$

where Φ and Φ are the Φ values of carrier and

coating materials, respectively. Hence to calculate the required weights of the excipients used, first from Eq. [3], Φ and Φ are constants, therefore, according to ratio of carrier / coating materials (R), L_f was calculated.

By use of above mathematical model, liquisolid tablets were formulated as indicated in Table 1.

Determination of Solubility of Fenofibrate in propylene glycol

Saturated solutions were prepared by adding excess of Fenofibrate to the propylene glycol and shaking on the shaker for 48 h at 25 °C under constant vibrations. The solutions were filtered through a 0.40 micron filter, diluted with 0.05 M sodium lauryl sulfate in water and analyzed by Shimadzu 1700 UV-Vis spectrophotometer at 289.2 nm against blank sample (blank sample was solution containing same concentration of used without drug). Three determinations were carried out for each sample to calculate the solubility of fenofibrate.

Preparation of liquisolid tablets

Calculated quantities of fenofibrate and propylene glycol was accurately weighed in 20 ml glass beaker and then heated to 80 °C. Resulting hot medication was incorporated into calculated quantities of carrier and coating materials. Mixing process is carried out in three steps as described by Spireas *et al.*⁶. During first stage, system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In second stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles. In third stage, powder was scraped off the mortar surfaces by means of aluminum spatula and then blended with 8% sodium starch glycolate, for another 30 seconds in a similar to first stage. This gives final formulation of liquisolid tablets. Prepared liquisolid formulation was compressed by single punch tablet press machine.

Precompression studies

Flow properties

Flow properties of liquisolid formulation were studied by angle of repose, Carr's index and Hausner's ratios¹⁵. Each analysis was carried out in triplicate. Bulk density measurements

Formulation Batch Code	Drug concentration in Propylene glycol (% w/w)	R	Lf	Avicel PH 102 (mg) (Q = W/Lf)	Aerosil 200 (mg) (q= Q/R)
LS 1	10%	30	0.270	197.5	6.58
LS 2		40	0.243	219.46	5.48
LS 3		50	0.226	235.97	4.71
LS 4	20%	30	0.270	395.03	13.10
LS 5		40	0.243	438.93	10.97
LS 6		50	0.226	471.94	9.43
LS 7	30%	30	0.270	592.59	19.75
LS 8		40	0.243	658.43	16.46
LS 9		50	0.226	707.96	14.15

Table 1. Formulation design of liquisolid tablets.

were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. Cylinder is then tapped at a constant velocity till a constant volume was obtained. Then tapped density was calculated. Angle of repose was calculated by fixed height cone method.

Differential Scanning Calorimetry (DSC)

DSC SDT2960 (TA Instruments Inc., USA) was performed using assess thermotropic properties and thermal behaviors of Aerosil 200, Fenofibrate, Avicel PH102, Fenofibrate: Aerosil 200 (1:1) mixture, Fenofibrate: Avicel PH102 (1:1) mixture, Fenofibrate: Avicel PH102: Aerosil 200 (1:1:1) mixture and of liquisolid system prepared. Samples (3-5mg) were placed in aluminum pans and lids at constant heating range of 15 °C/min, covering temperature range to 250 °C. Nitrogen was used as purge gas through DSC cell.

X-ray powder diffraction (XRD)

XRD patterns were studied using Philips PW 3710 X-ray diffractometer. Samples were irradiated with Cu radiation of wavelength 1.540 Å and analyzed between 5 to 40° (2θ). XRD pattern were determined for Fenofibrate, Avicel PH 102, physical mixtures (1:1) of Fenofibrate: Avicel PH 102 and Fenofibrate: Aerosil 200, and for liquisolid system. It is not necessary to perform XRD study of Aerosil 200, as it was previously proven to be a non-gritty amorphous powder¹⁵.

Stereomicroscopy of liquisolid system

Stereomicroscopy was used to determine morphological characters of prepared liquisolid system using Nikon SMZ800 Stereomicroscope.

Evaluation of Liquisolid tablets

The *hardness* of liquisolid tablets was determined by using Pfizer Hardness Tester (Pfizer). Mean hardness of each formula was determined. The *friability* of prepared liquisolid tablets was determined using Digital tablet friability tester (Roche). The *disintegration time* was measured using USP disintegration tester (Electrolab). All the studies were done in triplicate.

In vitro Dissolution studies of liquisolid tablets

The dissolution studies were performed using USP Apparatus II dissolution tester (LabIndia, India). Liquisolid tablets were placed in dissolution vessel containing 1000 ml 0.05M Sodium lauryl sulfate in water¹⁶ maintained at 37 ± 0.5 °C and stirred with paddle at 50 rpm. Samples were collected periodically and replaced with dissolution medium. After filtration through Whatman filter paper 41, concentration of Fenofibrate was determined spectrophotometrically at 289.2 nm (Shimadzu 1700 UV-Vis Spectrophotometer). Dissolution profiles of liquisolid tablets were compared with dissolution profiles of three different marketed formulations. All studies were done in triplicate.

RESULTS AND DISCUSSION

Application of new mathematical model for design of liquisolid systems

Fenofibrate was selected as model drug for this study as it is poorly soluble in water and thus ideal candidate for evaluating rapid release potential of liquisolid tablets. Liquisolid hypothesis of Spireas *et al.*¹⁷ states that drug candidate dissolved in liquid nonvolatile vehicle and incorporated into carrier material having porous

structure and closely matted fibers in its interior, phenomenon of both adsorption and absorption occurs. This concludes that drug in the form of liquid medication is absorbed initially in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal and external surfaces of carrier. Coating materials such as Aerosil 200 which have high adsorptivity and grater surface area lead the liquisolid systems desirable flow properties¹⁷.

Mathematical model equation for Avicel PH 102 and Aerosil 200 in propylene glycol can be given according to values of Phi (Φ) as given by Spireas et al.⁶⁻⁷

$$L_f = 0.16 + 3.31 (1 / R) \quad [4]$$

Based on this equation, L_f is calculated by using different R values.

Determination of Solubility of Fenofibrate in propylene glycol

Determination of solubility is most important aspect in formulation of liquisolid systems. It is needed ascertain formation of molecular dispersion of the drug in non-volatile solvent such as propylene glycol. The solubility of Fenofibrate in propylene glycol was found to be 34.254 ± 0.34 mg/ml.

Precompression studies for liquisolid systems

Flow properties

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Results of measurements such as angle of repose, Carr's index, and Hausner's ratio are represented in the Table 2. Angle of repose is characteristic to the flow rate of powder. In general, values of angle of repose $\geq 40^\circ$ indicate powders with poor flowability¹⁸. The results are according to this statement. Also

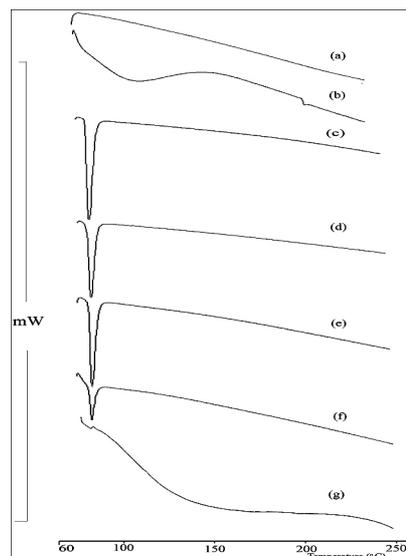


Figure 1. Differential Scanning Calorimetry (DSC) thermograms of (a) Aerosil 200 (b) Avicel PH 102 (c) Fenofibrate (d) Fenofibrate: Aerosil 200 (1:1) physical mixture (e) Fenofibrate: Avicel PH 102 (1:1) physical mixture (f) Fenofibrate: Aerosil 200: Avicel PH 102 (1:1:1) physical mixture (g) Liquisolid formulation.

results of Carr's index and Hausner's ratio show good flow behavior.

Differential Scanning Calorimetry behavior

DSC studies were carried out to determine interaction between drug and excipients in prepared liquisolid formulation. This will also indicate success of stability studies¹⁹. DSC thermograms of Aerosil 200, Avicel PH 102, Fenofibrate and physical mixtures of Fenofibrate: Avicel PH 102 (1:1), Fenofibrate: Aerosil 200 (1:1), Fenofibrate: Avicel PH 102: Aerosil 200 (1:1:1) and final liquisolid formulation system were represented in Figure 1. Fenofibrate peak was clearly seen in its DSC thermogram (Fig. 1c) indicating a sharp characteristic peak at temperature range

Formulation Batch Code	Average Angle of Repose (θ) \pm SD	Average Carr's Index (%) \pm SD	Average Hausner's Ratio \pm SD
LS 1	41.07 \pm 0.05	18.47 \pm 0.05	1.23 \pm 0.01
LS 2	39.32 \pm 0.32	19.51 \pm 0.23	1.25 \pm 0.01
LS 3	38.64 \pm 0.03	21.19 \pm 0.12	1.28 \pm 0.02
LS 4	39.95 \pm 0.15	20.07 \pm 0.06	1.23 \pm 0.01
LS 5	39.35 \pm 0.37	21.92 \pm 0.10	1.27 \pm 0.01
LS 6	38.02 \pm 0.12	25.19 \pm 0.08	1.31 \pm 0.01
LS 7	39.49 \pm 0.20	21.2 \pm 0.17	1.27 \pm 0.01
LS 8	38.34 \pm 0.11	23.83 \pm 0.15	1.30 \pm 0.01
LS 9	37.33 \pm 0.39	25.2 \pm 0.22	1.33 \pm 0.02

Table 2. Results of flowability parameters of liquisolid powder systems for different formulation batches.

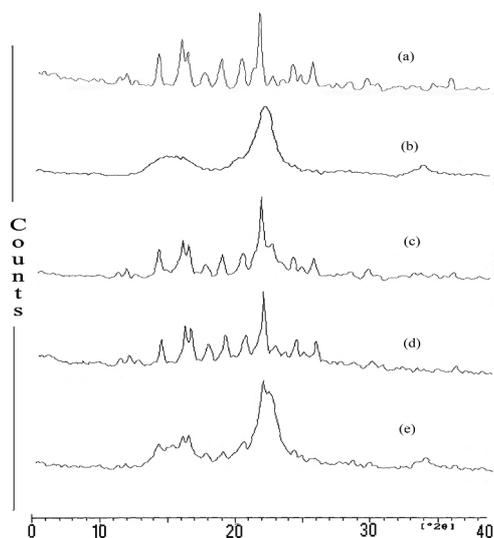


Figure 2. X-ray diffraction (XRD) patterns of (a) Fenofibrate (b) Avicel PH 102 (c) Fenofibrate: Avicel PH 102 (1:1) physical mixture (d) Fenofibrate: Aerosil 200 (1:1) physical mixture (e) Liquisolid system.

79-82 °C corresponding to its melting temperature (T_m). This shows that Fenofibrate used was in pure form. Fig 1b shows thermogram of Avicel PH 102 indicating endothermic peak at range of 200-220 °C. However, thermogram of Aerosil 200 (Fig. 1a) does not show sharp endothermic peak. Physical mixtures of pure components showed characteristic endothermic peaks of Fenofibrate. This behavior is also observed in case of mixture of all three components. These two results indicate that there is no incompatibility between drug and excipients. The DSC thermogram of liquisolid system (Fig. 1g) indicates only mere presence of characteristic peak of Fenofibrate. This ensures formation of drug solution in liquisolid formulation and hence confirms that drug was molecularly dispersed in liquisolid system.

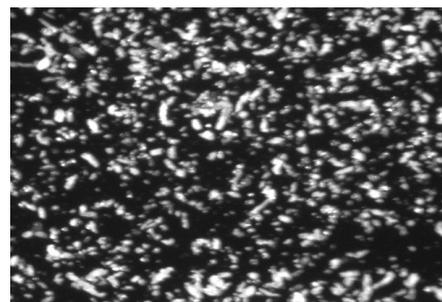


Figure 3. Stereomicroscopic image of liquisolid system.

X-ray Diffraction Studies

Sharp distinct characteristic peaks at 2θ diffraction angles for Fenofibrate at 14.285°, 16.105° and 22.190° indicated its crystalline state (Figure 2a). Liquisolid powder X-ray diffraction pattern (Fig. 2e) showed absence of these distinct peaks. Hence absence of specific peaks (constructive reflections) in liquisolid system revealed that Fenofibrate has been completely converted to molecular form or solubilized form. This lack of crystallinity in the formulation might be due to solubilization of drug in liquid vehicle which was absorbed into carrier material and adsorbed onto carrier and coating materials. Whereas, presence of certain Fenofibrate peaks is due to the fact that after saturation of absorption process, adsorption occurs on the surface of carrier. These results that are in accordance with DSC results suggest that Fenofibrate formed solid solution within the Avicel PH 102 (carrier material). However, physical mixtures of Fenofibrate with Avicel PH 102 and Aerosil 200 in 1:1 ratio indicate that characteristic peaks of Fenofibrate were retained and thus crystalline structure is remained in physical mixture. Therefore, loss of crystallinity in liquisolid system was due to liquisolid formulation method. Thus, solubilization of Fenofibrate in liquisolid system will lead to improved dissolution rate, and therefore bioavailability of Fenofibrate ²⁰.

Formulation Batch Code	Average Hardness (N) ± SD	Percentage fines obtained during friability test (%)	Average Disintegration time (min) ± SD
LS 1	28.45 ± 2.45	0.165	5.43 ± 0.25
LS 2	30.24 ± 1.82	0.214	4.63 ± 0.15
LS 3	30.12 ± 2.45	0.292	4.20 ± 0.20
LS 4	31.54 ± 1.67	0.194	9.54 ± 0.38
LS 5	37.48 ± 1.54	0.234	8.60 ± 0.36
LS 6	33.47 ± 1.92	0.278	7.73 ± 0.20
LS 7	33.10 ± 0.94	0.045	12.16 ± 0.37
LS 8	36.23 ± 2.31	0.092	10.36 ± 0.15
LS 9	35.34 ± 2.14	0.133	9.59 ± 0.34

Table 3. Results of Hardness, Friability and Disintegration tests of liquisolid tablet formulation batches.

Formulation Batch Code	Percentage Drug Release at 10 min	Percentage Drug Release at 45 min
LS 1	79.047 ± 1.65	94.107 ± 1.77
LS 2	81.054 ± 1.03	95.833 ± 1.68
LS 3	82.894 ± 1.28	96.282 ± 1.78
LS 4	77.313 ± 1.31	91.751 ± 1.80
LS 5	81.795 ± 1.06	92.428 ± 1.84
LS 6	83.488 ± 0.74	93.098 ± 1.56
LS 7	70.839 ± 1.22	89.182 ± 1.36
LS 8	71.380 ± 1.13	90.496 ± 1.78
LS 9	76.412 ± 1.07	91.255 ± 1.28
MKT 1	68.331 ± 1.16	88.440 ± 1.98
MKT 2	69.227 ± 1.03	88.727 ± 1.47
MKT 3	68.740 ± 1.50	88.460 ± 1.45

Table 4. Percentage drug release of liquisolid tablets compared with marketed formulations at 45 min (LS- Liquisolid tablet, MKT – Marketed Formulation).

Stereomicroscopic analysis

Complete disappearance of crystalline structure as indicated by DSC and XRD results were found to comply with stereomicroscopic image of liquisolid system (Figure 3). This reveals that drug is dispersed in molecular form inside the carrier matrix. Slight crystalline nature is due to Avicel PH102 which retains its structure.

Evaluation of liquisolid tablets

Results of hardness, friability, disintegration time are represented in Table 3. There should

be certain amount of strength or hardness and resistance to friability for the tablet, so that tablet should not break during handling. However, it has also effect on tablet disintegration and drug dissolution. Average *hardness* of liquisolid tablet ranges from 28.45 ± 2.45 to 36.23 ± 2.31 Newton. Compactness of tablet may be due to hydrogen bonding between Avicel PH 102 molecules²¹. As propylene glycol is an alcoholic compound, it might show hydrogen bonding due to presence of hydroxyl groups and may contribute to compactness of tablets. *Friability* studies of liquisolid tablets are in the range of 0.045% to 0.292%. This indicates that acceptable resistance is shown by liquisolid tablets to withstand handling. *Disintegration time* was found to be in the range of 4.2 ± 0.2 to 12.1 ± 0.37 min. Faster disintegration time indicate rapid release rates. These are in accordance with dissolution rates.

In vitro dissolution studies

Dissolution rates of liquisolid formulations were compared with three different marketed formulations (Table 4). Liquisolid formulations initially show greater release than marketed formulations. This is indicated by percentage release at 10 min. The statistical analysis (One Way ANOVA) showed that there is significant difference in dissolution rates compared to marketed formulations ($P < 0.05$, $R^2 = 0.9701$, $F = 70.88$). All liquisolid tablets show greater than

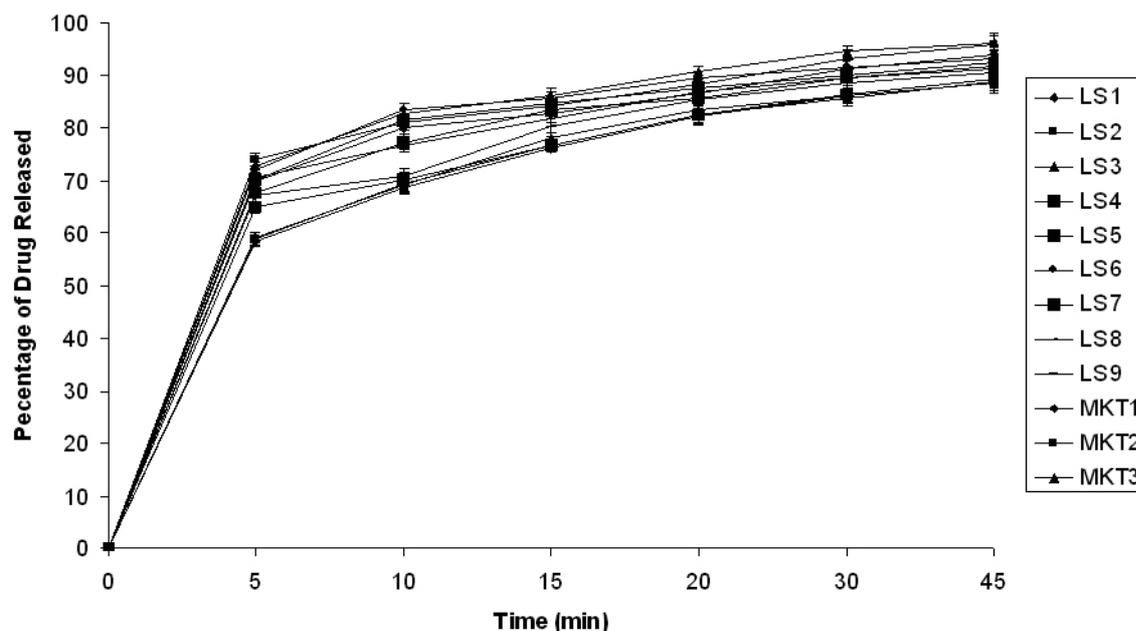


Figure 4. Dissolution Profile of liquisolid tablets (LS 1-9) compared to marketed formulations (MKT 1-3).

89.182 ± 1.36% drug release after 45 min. However, marketed formulations show less drug release at this time. According to "Diffusion layer model" for dissolution, dissolution rate is in proportion to concentration gradient in stagnant diffusion layer²². Not only the concentration gradient, drug dissolution is directly proportional to surface area available for dissolution¹¹. As liquisolid tablets contain a drug dissolved in propylene glycol, the drug surface available for dissolution is highly increased. In short, drug is present in the form of molecular dispersion, after its disintegration in the dissolution media. As all the dissolution tests for Fenofibrate liquisolid tablets were conducted at constant speed (50 rpm) and in same dissolution medium, the thickness of stagnant diffusion layer and diffusion coefficient for drug dissolution will be almost identical. Hence, molecularly dispersed drug in liquisolid tablets may be responsible for greater dissolution rates compared to marketed formulations. This will also reflect enhanced oral bioavailability. Also it was previously proved that low drug concentration in liquid medication; more rapid drug release will be ob-

served. It was due to the fact that, drugs in high concentration tend to precipitate within the silica pores (Aerosil 200). The dissolution profile of liquisolid tablets supports the above mentioned hypothesis.

CONCLUSION

The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Fenofibrate. Propylene glycol was used as a liquid vehicle. Enhanced dissolution rates obtained in the present study in turn indicates increase in oral bioavailability due to increased wetting and surface area available for dissolution. Enhanced dissolution rates obtained in the present study due to increased wetting and surface area available for dissolution. This novel approach to the formulation may be helpful to improve oral bioavailability.

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