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Dissolution Rate Enhancement of Fenofibrate Using Liquisolid Tablet Technique. Part II: Evaluation of *In Vitro* Dissolution Profile Comparison Methods.

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SUMMARY. **The present work deals with the comparison of *in vitro* dissolution profiles of fenofibrate liquisolid tablet formulations with those of marketed fenofibrate tablets, and the application of statistical methods to evaluate each method for its usefulness. The methods used to study dissolution profile comparison include Model independent method (Similarity factor, f_2); Model dependent methods (Zero order, First order, Hixson-Crowell, Matrix, Peppas, Higuchi models) and statistical methods based on ANOVA. Model independent method was found to be easier and simple to interpret. The f_2 value relates closeness of dissolution profiles. Dissolution profile followed Peppas model as "best fit" model. The application and evaluation of model dependent methods are more complicated. These methods give acceptable model approach which is indication of true relationship between percent drug release and time variables, including statistical assumptions. Statistical approach is very simple and is more discriminative of dissolution profiles. The liquisolid formulation of fenofibrate serves to be an effective way to enhance dissolution rate of fenofibrate.**

INTRODUCTION

Fenofibrate, BCS Class II drug is used for the treatment of hyperlipidemia [1,2]. Low bioavailability of it is due its poor solubility in water. Therefore, for such type of drugs dissolution is rate limiting step for absorption [3]. *In vitro* dissolution testing is critical parameter of pharmaceutical dosage forms. Under certain conditions it is used as surrogate for assessment of bioequivalence and sometimes as a means to correlate *in vitro* with *in vivo* drug release characteristics [4]. Based on this consideration, dissolution testing for solid dosage forms is used to assess batch to batch quality of product, to assess product stability and performance of product. In formulation development aspects, dissolution testing aids in judicious selection of excipients and comparison of test product with reference product [5]. *In vitro* dissolution profile comparison can be done by three ways: model dependent methods [6], model independent methods [7] and statistical methods [8].

Rapid release rates are obtained in liquisolid formulations [9]. Hence, these can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs [10]. 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, liquisolid tablets of water insoluble drugs show improved dissolution properties and in turn increase in bioavailability [11].

In the present study, an attempt is made to enhance dissolution rates of fenofibrate using liquisolid tablet technique and dissolution profiles of the liquisolid tablets were compared with marketed product. The discrimination of release profiles was compared with marketed tablets of fenofibrate using model independent

KEY WORDS: ANOVA, Dissolution, Fenofibrate, Liquisolid Tablets.

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method (similarity factor f_2) and statistical approach Two Way ANOVA. Model fitting was also done for different models such as zero order, first order, Hixon-Crowell, Peppas and Matrix models. New formulation mathematical model as described by Spireas *et al.* [12,13] was used to calculate appropriate amounts of carrier and coating materials based on new fundamental properties of powder called flowable liquid retention potential (Φ value) and compressible liquid retention potential (Ψ number) of powder ingredients (Previously determined by Spireas *et al.)* [12,13]. Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique [14].

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.

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.* [12-13]. fenofibrate was dispersed in propylene glycol (Propylene glycol was used as liquid vehicle to prepare liquid medication). Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. The excipients ratio R of powder is defined as [Eq. **1**]

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

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 [Eq. **2**]:

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

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 [Eq. **3**]

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

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 follows (Table 1).

Preparation of liquisolid tablets

Liquisolid tablets were prepared as follows. fenofibrate was dispersed in propylene glycol and melted at temperature 80 °C in water bath. Then a binary mixture of carrier–coating materials was added to the liquid medication under continuous mixing in a mortar. Mixing process is carried out in three steps as described by Spireas *et al.* [12,13]. 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

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

Table 1. Formulation design of fenofibrate liquisolid tablets.

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 surface by means of aluminum spatula. Final mixture was blended with 8% sodium starch glycolate. This gives final formulation of liquisolid tablets. Prepared liquisolid formulation was compressed by single punch tablet press machine.

Dissolution testing

The dissolution studies were performed using USP Apparatus II dissolution tester (LabIndia, India). Liquisolid tablets were placed in dissolution vessel containing 1000 ml 0.05 M Sodium lauryl sulfate in water [15] 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 spectophotometrically at 289.2 nm (Shimadzu 1700 UV-Vis Spectrophotometer). Dissolution profiles of liquisolid tablets were compared with dissolution profile of marketed formulations. All studies were done in triplicate.

Methods to compare dissolution profiles

Model independent approach

According to US FDA guidance for dissolution data equivalence, model independent approach is recommended. Use of pair wise procedure such as similarity factor (f_2) which provides simple means to compare the data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percentage dissolution between the two curves [Eq. **4**],

$$f_2 = 50 \times \log \{[1 + (1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\} \quad [4]$$

where *n* is the number of time points, R is the dissolution value of the reference at time t, and T is the dissolution value of the test at time t.

Model dependent methods

Fenofibrate release kinetics was analyzed by various mathematical models, which were applied considering amount of drug released in 0 to 45 min. Based on these estimations; mathematical models were described for dissolution profiles. The model fitting was represented in the form of following plots: cumulative percent drug release versus time (zero order kinetic model); log cumulative percent drug remaining *versus* time (first order kinetic model); cumulative percent drug release versus square root of time (Higuchi model); cube root of percent drug remaining versus time (Hixon-Crowell cube root law).

Statistical Methods

Two Way ANOVA was used to determine how dissolution is affected by two factors. The percentage dissolved was dependent variable and time was a repeated factor. Further analysis was done by Turkey test and paired sample t test.

RESULTS AND DISCUSSION

Application of new mathematical model for design of liquisolid systems

Due to poor water solubility of fenofibrate, it is selected as a model drug for this study and thus ideal candidate for evaluating rapid release potential of liquisolid tablets. Earlier studies with fenofibrate have demonstrated the solubility of fenofibrate in propylene glycol [16]. This is necessary aiming to guarantee the drug is readily soluble in such solvent before loading in carrier and coating materials. 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 greater surface area lead the liquisolid systems desirable flow properties [17].

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.* [12-13] [Eq. **5**]:

$$L_f = 0.16 + 3.31\ (1 / R) \quad [5]$$

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

Dissolution testing

Dissolution rates of liquisolid formulations were compared with marketed formulations. (Table 2). Liquisolid formulations initially show greater release than marketed formulations. This is indicated by percentage release at 10 min (Q_{10}%). All liquisolid tablets show greater than

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 layer [18]. Drug dissolution is directly proportional to surface area available for dissolution [19]. 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 may be almost identical. Hence surface area can be considered as a major factor responsible for enhancing dissolution rate. As liquisolid tablets contain a drug dissolved in propylene glycol (in the form of molecular dispersion), the drug surface available for dissolution is highly increased. Hence, molecularly dispersed drug in liquisolid tablets may be responsible for greater dissolution rates compared to marketed formulations. Also it was previously proved that low drug concentration in liquid medication; more rapid drug release will be observed. 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 (Fig. 1). As stated by Spireas & Sadu [19], the solid / liquid interface between an individual liquisolid primary particle and the dissolving fluid involves minute quantities of aqueous medium clinging onto the particle surface. At such a micro-environment, it is quite possible that the infinite amounts of propylene glycol diffusing with the drug molecules out of a single liquisolid particle, might be adequate to enhance solubility of drug acting as cosolvent with aqueous dissolution medium. Moreover, the use of superdisintegrant, sodium starch glycolate causes burst release of tablet which is shown to enhance dissolution rate of fenofibrate as indicated in Q_{10} % values (Table 2).

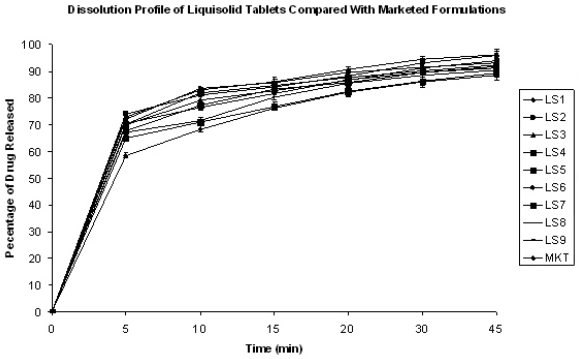

Figure 1. *In vitro* dissolution profiles of fenofibrate liquisolid tablets compared with marketed formulations.

Model independent methods

Pair wise procedure such as similarity factor (f_2) provides simple way to compare dissolution data. US FDA guidance proposes that f_2 values of 50–100 indicate equivalence in dissolution profiles. Table 3 shows f_2 values of all the batches. Batches showing f_2 values >50; which indicates similarity in dissolution profile (Table 3).

Model dependent methods

Although model independent methods are simple and easy to apply, they lack scientific justification [20-22]. Different models of dissolution profile comparison were used (Tables 4 and 5). The results of these models indicate all liquisolid compacts follow Peppas model as "best fit model". This is due to previously proved fact depending on R^2 value obtained from model fit-

Formulation Batch Code	Q_{10} %	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	68.331 ± 1.16	88.440 ± 1.98

Table 2. Percentage drug release at time 10 min and 45 min. Liquisolid tablets (LS1-LS9) and Marketed formulation (MKT).

Comparison	f_2	Dissolution profile
LS1 and MKT	56.45	Similar
LS 2 and MKT	51.39	Similar
LS 3 and MKT	49.63	Dissimilar
LS 4 and MKT	60.83	Similar
LS 5 and MKT	55.05	Similar
LS 6 and MKT	51.45	Similar
LS 7 and MKT	78.38	Similar
LS 8 and MKT	68.63	Similar
LS 9 and MKT	59.78	Similar

Table 3. Similarity factor (f_2) values of liquisolid compacts compared with marketed tablet.

Model	Parameter	LS1	LS 2	LS 3	LS 4	LS 5
Zero order	R^2	-	-	-	-	-
	K	3.0177	3.0799	3.1210	2.9643	3.0072
First order	R^2	0.7316	0.7787	0.7797	0.6337	0.5524
	K	-0.078	-0.086	-0.091	-0.725	-0.075
Matrix	R^2	0.7939	0.7786	0.7826	0.7950	0.7681
	K	17.9766	18.370	18.6256	17.6681	17.9829
Peppas	R^2	0.9894	0.9973	0.9817	0.9787	0.9633
	K	57.4170	61.2208	60.5321	55.6315	59.6246
Hixon-Crowell	R^2	0.4266	0.4597	0.4668	0.3079	-
	K	-0.0180	-0.091	-0.0199	-0.0172	-0.0177

Table 4. Model fitting of batches (LS1- LS 5).

Model	Parameter	LS 6	LS 7	LS 8	LS 9	MKT
Zero order	R^2	-	-	-	-	-
	K	3.0498	2.8374	2.9804	2.9585	2.8089
First order	R^2	0.5200	0.6817	0.6712	0.5889	0.7310
	K	-0.0798	-0.0636	-0.0685	-0.0719	-0.0620
Matrix	R^2	0.7533	0.8262	0.8163	0.7814	0.8611
	K	18.2689	16.8290	17.2793	17.6548	16.5943
Peppas	R^2	0.9559	0.9866	0.9692	0.9842	0.9796
	K	62.3160	50.2445	52.3446	57.8424	43.790
Hixon-Crowell	R^2	-	0.4332	0.4087	0.2036	0.5318
	K	-0.0183	-0.0156	-0.0165	-0.0171	-0.0153

Table 5. Model fitting of batches (LS 6- LS 9) and marketed formulation (MKT).

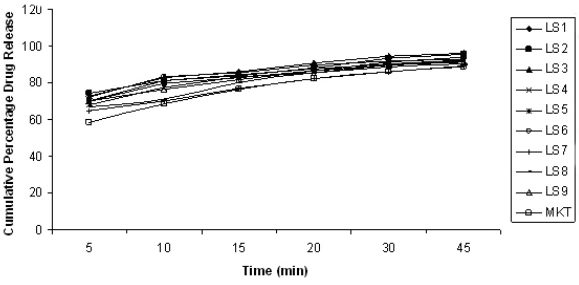

Figure 2. Zero order plot for liquisolid tablets compared with marketed formulations.

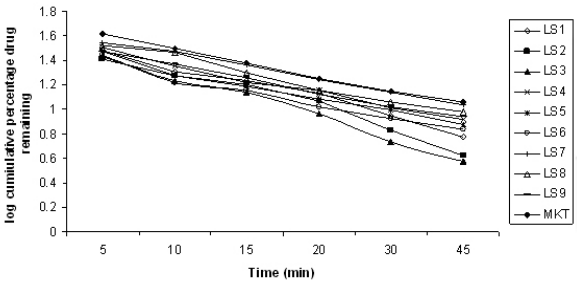

Figure 3. First order plots for liquisolid tablets compared with marketed formulations.

ting [23]. Considering the determination coefficients (R^2), the calculated zero order models failed to fit all batches.

Different models were characterized based on the plots which are shown in Fig 2-5.

Statistical methods

Statistical methods based on ANOVA are most simple ways to determine discrimination in dissolution profiles. From the results (Table 6) it was found that differences in mean values are greater than expected by chance, and that there is statistically significant difference (P value < 0.0001). For estimation of differences among the batches, post test such as Turkey test was performed on the results of ANOVA. Statistically significant difference was also found. Further analysis was done by paired sample t test com-

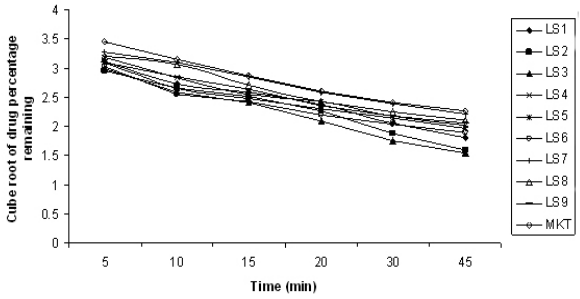

Figure 4. Hixon-Crowell plot for liquisolid tablets compared with marketed formulations.

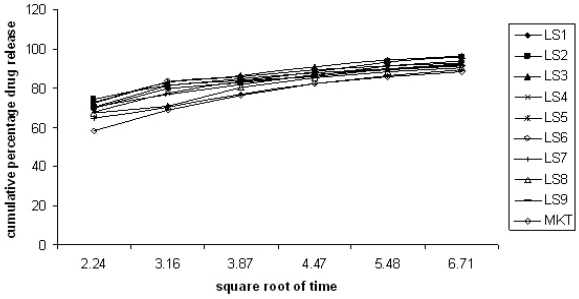

Figure 5. Higuchi plots for liquisolid tablets compared with marketed formulations.

Source of Variation	Degrees of freedom	Sum of squares	Mean squares	F value
Column factor	9	557.3	61.92	15.94
Row factor	6	62680	10450	2688.66
Residual (error)	54	209.8	3.885	
Total	69	63450		

Table 6. Results of Two Way ANOVA.

paring each formulation with marketed formulation indicating statistically significant differences. This fact confirms results of Turkey test. From the results it was concluded that statistical methods are more discriminative as compared to model independent method for comparing dissolution profiles of liquisolid tablets.

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