Original Article

Effect of Ceolus KG-802 on the dissolution rate of fenofibrate liquisolid tablets: Preformulation and formulation development studies

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ABSTRACT: The purpose of the present research was to study the effects of Ceolus KG-802 on the dissolution behavior of fenofibrate liquisolid tablets. The fenofibrate liquisolid tablets were formulated using the mathematical model described by Spireas *et al.* In the present research, Ceolus KG-802, a different form of microcrystalline cellulose (PH 102 grade), was used as a carrier material. The developed formulations were subjected to preformulation studies such as differential scanning calorimetry, X-ray powder diffraction, and determination of flow properties. The liquisolid tablets prepared were studied for their *in vitro* dissolution and compared to liquisolid tablets prepared using Avicel PH 102. The *in vitro* dissolution profiles of liquisolid tablets prepared using Ceolus KG-802 indicated slower dissolution than those of liquisolid tablets prepared using Avicel PH 102, which was a subject of earlier studies. This might be due to the particle size, shape, and characteristic properties of Ceolus KG-802.

Keywords: Liquisolid tablets, fenofibrate, Avicel PH 102, Ceolus KG-802

1. Introduction

Dissolution remains a critical factor for absorption of drugs and especially so with water-insoluble drugs (*1*). Drugs whose absorption is dissolution rate-limited are classified as Biopharmaceutics Classification System (BCS) Class II. Innovative formulation approaches suited to these drugs should be designed to solve the bioavailability problem after oral administration. For water-insoluble drugs with poor solubility in both aqueous and organic media, formulation development remains a challenging task (*2,3*). Fenofibrate is a BCS Class II drug used to decrease elevated plasma concentrations of low density lipoprotein and total cholesterol (*4-6*). Although low bioavailability of the drug is due to its poor solubility in water, the problem can overcome by enhancing its dissolution rate. Liquisolid tablet formulations have proven effective at improving the dissolution rate of fenofibrate (*7-9*).

Liquisolid tablets or compacts can be defined as immediate or sustained-release tablets or capsules that are prepared using the technique of "liquisolid systems". Included are adjuvants required for tabletting or encapsulation, such as lubricants, and adjuvants required for rapid or sustained-release action, such as disintegrants or binders, respectively (*10,11*).

According to Spireas *et al.* (*10,11*), a carrier material is porous material with sufficient absorption properties. Microcrystalline cellulose is one such material. Earlier studies of fenofibrate with liquisolid tablets focused on use of Avicel PH 102 as a carrier material. Avicels (Trade mark of FMC Biopolymer) are purified, partially depolymerized α-celluloses. Their characteristic properties of compactibility, drug-carrying capacity, and rapid disintegration mean that they are a valuable tool for formulation development. Avicel PH 102 is a standard grade of Avicel with a large particle size and is used for direct compression, the dry phase of wet granulation, and dry granulation (*12*). Due to its properties, it has also been used to formulate liquisolid tablets of fenofibrate (*7*). Ceolus (a trademark of Asahi Kasei) is a type of microcrystalline cellulose prepared using Asahi Kasei's advanced processing technology. Ceolus grade KG-802 was initially introduced grade and is a super compactible grade of microcrystalline cellulose (*13*). Although both Avicel PH 102 and Ceolus KG-802 are types of microcrystalline cellulose, they have different physical properties that might result in different formulations.

The aim of the present study was to investigate the performance of liquisolid tablets prepared using Ceolus KG-802 as a carrier material for use in the formulation of liquisolid tablets.

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2. Materials and Methods

2.1. *Materials*

Fenofibrate was kindly donated by Lupin Laboratories (Mumbai, India). Ceolus KG-802 was supplied by Signet (Mumbai, India). Aerosil 200 and sodium starch glycolate were kindly donated by Okasa Pharmaceuticals (Maharashtra, India) and Shital Chemicals (Gujarat, India), respectively. Propylene glycol and sodium lauryl sulfate were purchased from Loba Chemie (Mumbai, India). All other reagents and chemicals were of analytical grade.

2.2. *Use of a mathematical model to design liquisolid tablets*

Formulations of liquisolid systems were designed in accordance with new mathematical model described by Spireas *et al.* (*10,11*) (Table 1). In this study, propylene glycol was used as liquid vehicle; Ceolus KG-802 was used as the carrier and Aerosil 200 was used as the coating material. The formulation design of the liquisolid tablets remained the same as that in previous studies of Avicel PH 102 by Karmarkar *et al.* (*7*). Concentrations of 10, 20, and 30% (w/v) of the liquid vehicle propylene glycol were used along with carrier:coat ratios of 30, 40, and 50 to attain optimal fenofibrate solubility in the liquisolid formulations.

2.3. *Preparation of liquisolid tablets*

Liquisolid tablets were prepared as described before (*1*). Briefly, calculated quantities of fenofibrate and propylene glycol were accurately weighed in a 20-mL glass beaker and then heated to 80°C. The resulting hot medication was incorporated into calculated quantities of carrier (Ceolus KG-802) and coating materials (Aerosil 200 P). The mixing process was carried out in three steps as described by Spireas *et al.* (*10,11*). During the first stage, the system was blended at an approximate mixing rate of one rotation per second for approximately 1 min in order to evenly distribute liquid medication in the powder. In the second stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5 min to allow the drug solution to be absorbed in the interior of powder particles. In the third stage, powder was scraped off the mortar surface by means of an aluminum spatula and then blended with 8% sodium starch glycolate for another 30 sec similar to the first stage. This yielded a final formulation of liquisolid tablets. The liquisolid formulations thus prepared were compressed with a tablet compression machine.

2.4. *Precompression studies*

2.4.1. *Flow properties*

Flow properties of liquisolid formulations were studied in terms of the angle of repose, Carr's index, and Hausner's ratio (*14*). Each analysis was carried out in triplicate. Bulk density measurements were carried out by placing a fixed weight of powder in a graduated cylinder and the volume occupied was measured and the initial bulk density was calculated. The cylinder was then tapped at a constant velocity until a constant volume was obtained. Then tapped density was calculated. The angle of repose was calculated using the fixed height cone method.

2.4.2. *Differential scanning calorimetry (DSC)*

A SDT2960 Differential Scanning Calorimeter (TA Instruments Inc., New Castle, DE, USA) was used to assess the thermotropic properties and thermal behavior of fenofibrate, Ceolus KG-802, and a liquisolid system. Samples (3-5 mg) were placed in aluminum pans and lids at constant heating of 15°C/min spanning a temperature range up to 250°C. Nitrogen was used as a purge gas through the DSC cell.

2.4.3. *X-ray powder diffraction (XRD)*

XRD patterns were studied using the Philips PW 3710 X-Ray Diffractometer. Samples were irradiated with Cu radiation at a wavelength of 1.540 Å and then analyzed between 10 and 40° (2θ). XRD patterns were determined for fenofibrate, Ceolus KG-802, and the liquisolid

Table 1. Formulation design of liquisolid tablets examined in this study

Formulation batch code	Drug concentration in propylene glycol (%, w/w)	Carrier:coating material ratio (R)	Ceolus KG-802 (mg)	Aerosil 200 (mg)
CLS 1	10	30	197.5	6.58
CLS 2	10	40	219.46	5.48
CLS 3	10	50	235.97	4.71
CLS 4	20	30	395.03	13.10
CLS 5	20	40	438.93	10.97
CLS 6	20	50	471.94	9.43
CLS 7	30	30	592.59	19.75
CLS 8	30	40	658.43	16.46
CLS 9	30	50	707.96	14.15

system. An XRD study of Aerosil 200 was unnecessary as it was previously found to be a non-gritty amorphous powder (*14*).

2.4.4. *Stereomicroscopic analysis*

Stereomicroscopy was used to determine the morphological characteristics of the prepared liquisolid systems using a Nikon SMZ 800 microscope (Nikon, Inc., Melville, NY, USA). The sample was placed on a glass slide and observed; photographs were then taken.

2.5. *Evaluation of liquisolid tablets*

The hardness of liquisolid tablets was determined using a Pfizer Hardness Tester (Pfizer, New York, NY, USA). The mean hardness of each formulation was determined. The friability of prepared liquisolid tablets was determined using a Digital Tablet Friability Tester (Roche, Basel, Switzerland). Disintegration time was measured using a USP Disintegration Tester (Electrolab, Mumbai, India). All studies were done in triplicate.

2.6. *In vitro dissolution studies of liquisolid tablets*

Dissolution studies were performed using a USP Apparatus II Dissolution Tester (LabIndia, Thane, India). Liquisolid tablets were placed in a dissolution vessel containing 1,000 mL of 0.05 M sodium lauryl sulfate in water (*16*) maintained at 37 ± 0.5°C and stirred with a paddle at 50 rpm. Samples were collected periodically and replaced with dissolution medium. After filtration through Whatman filter paper 41, the concentration of fenofibrate was determined spectrophotometrically at 289.2 nm using a Shimadzu 1700 UV-Vis Spectrophotometer (Shimadzu, Kyoto, Japan). Dissolution profiles of liquisolid tablets were compared to those of three different marketed formulations. All studies were done in triplicate ($n = 3$).

3. Results and Discussion

Previous work by Karmarkar *et al.* (*7*) focused on evaluation of the usefulness of the liquisolid tablet technique as a tool for dissolution rate enhancement; the carrier used in that work was Avicel PH 102. In the present work, fenofibrate was selected as a model drug as it is poorly soluble in water and thus an ideal candidate for evaluating the rapid release potential of liquisolid tablets. In the current work, Ceolus KG-802 was used as a carrier in order to prepare liquisolid tablets. Earlier studies with fenofibrate have noted its solubility in propylene glycol (*7*). This is necessary in order to guarantee that the drug is readily soluble in such a solvent before being loaded into carrier and coating materials. According to the liquisolid hypothesis (*15*), the phenomena of absorption and adsorption occur when a drug candidate (dissolved in a non-volatile solvent) is incorporated into a carrier and coating system. This is due to fact that the drug, in the form of a liquid medication, is initially absorbed into the carrier (here Ceolus KG-802); after saturation, the process of adsorption occurs. As Aerosil 200 has a high adsorptivity and large surface area, it yields liquisolid systems with desirable flow properties (*15*).

3.1. *Precompression studies for liquisolid systems*

3.1.1. *Flow properties*

The flowing nature of a blend/powder is an important part of the industrial production of a tablet dosage form. Flowability was therefore examined for various liquisolid formulations (CLS 1 to 9) prepared in the present study. Parameters such as the angle of repose, Carr's index, and Hausner's ratio are shown in Table 2. The angle of repose is characteristic of the flow rate of the powder. In general, an angle of repose ≥ 40° indicates a powder with poor flowability (*16*). All formulations except CLS 1 and 7 had an angle of repose within the aforementioned range.

3.1.2. *DSC behavior*

DSC studies were carried out to determine interaction between the drug and excipients in prepared liquisolid formulations. These results will also indicate the success of stability studies (*17*). DSC thermograms of Ceolus KG-802, fenofibrate, and liquisolid formulations with Ceolus KG-802 are shown in Figure 1. Figure 1A shows

Table 2. Flowability parameters for various formulated batches of liquisolid powder systems

Formulation batch code	Angle of repose (θ)*	Carr's index (%)*	Hausner's ratio*
CLS 1	43.0 ± 0.2	19.3 ± 0.1	1.22 ± 0.02
CLS 2	39.5 ± 0.3	20.2 ± 0.1	1.24 ± 0.02
CLS 3	38.6 ± 0.2	22.3 ± 0.2	1.26 ± 0.02
CLS 4	39.8 ± 0.2	20.1 ± 0.0	1.25 ± 0.01
CLS 5	39.4 ± 0.2	22.0 ± 0.2	1.29 ± 0.01
CLS 6	38.4 ± 0.3	23.3 ± 0.1	1.32 ± 0.01
CLS 7	41.1 ± 0.3	24.1 ± 0.6	1.25 ± 0.01
CLS 8	40.5 ± 0.3	23.8 ± 0.2	1.32 ± 0.01
CLS 9	39.4 ± 0.2	25.3± 0.2	1.35 ± 0.01

* Data are shown as means ± S.D.

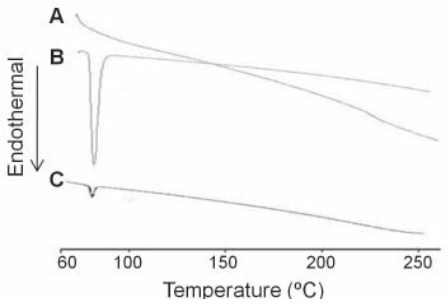

Figure 1. DSC thermograms of Ceolus KG-802 (A), fenofibrate (B), and a liquisolid system with Ceolus KG-802 (C).

a typical thermogram of Ceolus KG-802, indicating absence of an endothermic peak. In contrast, fenofibrate, as shown in Figure 1B, had a sharp characteristic peak in a temperature range of 79-82°C (with onset at 79.02 °C and endset at 81.93°C) corresponding to its melting temperature (T_m). This suggests that the fenofibrate used was in pure form. A DSC thermogram of the liquisolid system with Ceolus KG-802 merely suggested the presence of the characteristic peak of fenofibrate (Figure 1C). This ensures formation of a drug solution in the liquisolid formulation and hence confirms that the drug was molecularly dispersed in the liquisolid system.

3.1.3. *X-ray diffraction studies*

Figure 2 shows typical XRD patterns of fenofibrate, Ceolus KG-802, and the liquisolid system with Ceolus KG-802. Clearly distinct characteristic peaks for fenofibrate at a diffraction angle of 2θ, *i.e.,* at 14.3°, 16.1°, and 22.2°, indicated that fenofibrate was in a crystalline state (Figure 2A). In contrast, the X-ray diffraction pattern for liquisolid powder lacked these distinct peaks (Figure 2C). The disappearance of certain fenofibrate peaks might be due to drug adsorption on the surface of the carrier after saturation of the absorption process. The lack of specific peaks (constructive reflections) for the liquisolid system revealed that fenofibrate was completely converted to a molecular form or solubilized form. This lack of crystallinity in the formulation might be due to solubilization of the drug, which was absorbed into the carrier material and adsorbed onto the carrier and coating materials, in the liquid vehicle. These results agree with DSC results, suggesting formation of a solid solution of fenofibrate within Ceolus KG-802 (the carrier material). This phenomenon might be responsible for enhanced dissolution rates of fenofibrate liquisolid systems.

3.1.4. *Stereomicroscopic analysis*

Complete disappearance of the crystalline structure, as was indicated by DSC and XRD results, was also noted in stereomicroscopic images of the liquisolid system (Figure 3). This indicates that the drug is dispersed in molecular form inside the carrier matrix. However, the characteristic rod-shaped structure of Ceolus KG-802, which is responsible for the specific packing arrangement in the formulation, was retained in the formulation.

3.2. *Evaluation of liquisolid tablets*

Data on hardness, friability, and disintegration time for various formulated batches of liquisolid tablets are summarized in Table 3. A tablet should have a certain amount of strength or hardness and resistance to friability so that tablet will not break during handling. However, such aspects also affect tablet disintegration and drug dissolution. The average hardness of liquisolid tablets ranged from 30.4 ± 2.2 to 43.2 ± 1.0 N (Table 3). Tablet compactness may have been due to the highly compactable nature of Ceolus KG-802. As propylene glycol is an alcoholic compound, it might exhibit hydrogen bonding due to the presence of hydroxyl groups and may contribute to the compactness of tablets. Friability studies of liquisolid tablets resulted in values in the range of 0.002% to 0.205% (Table 3). This indicates that liquisolid tablets have sufficient durability to withstand handling. The low friability of the liquisolid tablets may also be due to Ceolus KG-802, as explained previously. The disintegration time was in the range of 6.46 ± 0.25 to 14.00 ± 0.26 min. This is a longer disintegration time than that obtained from liquisolid tablets with Avicel PH 102 (*6*). Hence, the longer disintegration time of formulations might be due to slower release rates. These findings are in accordance with dissolution rates.

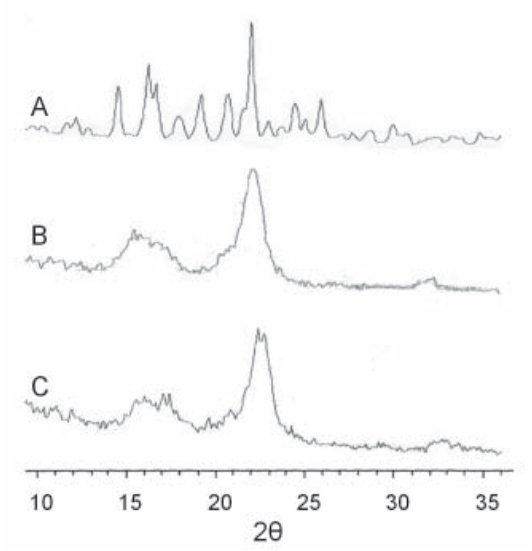

Figure 2. XRD patterns of fenofibrate (A), Ceolus KG-802 (B), and a liquisolid system with Ceolus KG-802 (C).

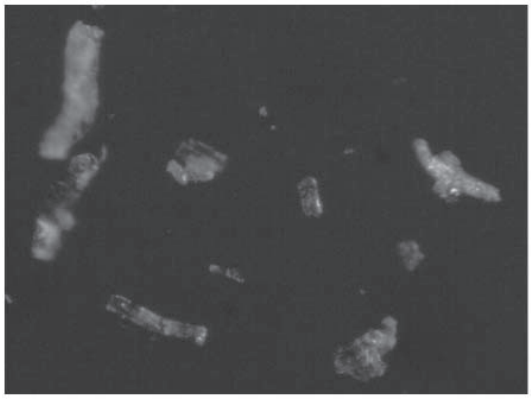

Figure 3. A typical stereomicroscopic image of a liquisolid system prepared with Ceolus KG-802 as a carrier.

Table 3. Hardness, friability, and disintegration data for various batches of liquisolid tablet formulations

Formulation batch code	Hardness (N)*	Percentage of grains obtained in a friability test (%)	Disintegration time (min)*
CLS 1	33.3 ± 2.3	0.102	6.46 ± 0.25
CLS 2	30.4 ± 2.2	0.005	7.06 ± 0.23
CLS 3	35.1 ± 2.1	0.002	8.13 ± 0.30
CLS 4	37.2 ± 1.4	0.167	10.40 ± 0.20
CLS 5	36.4 ± 1.7	0.188	9.16 ± 0.15
CLS 6	38.6 ± 1.5	0.123	8.36 ± 0.23
CLS 7	43.2 ± 1.0	0.205	14.00 ± 0.26
CLS 8	42.0 ± 2.1	0.112	12.20 ± 0.30
CLS 9	40.4 ± 2.1	0.115	11.36 ± 0.15

* Data are shown as means ± S.D.

Table 4. Drug release by various liquisolid tablets and marketed formulations

Formulation batch code*	Drug Release at 10 min (%)**	Drug Release at 45 min (%)**
CLS 1	79.0 ± 1.7	94.1 ± 1.8
CLS 2	81.1 ± 1.0	95.8 ± 1.7
CLS 3	82.9 ± 1.3	96.3 ± 1.8
CLS 4	77.3 ± 1.3	91.8 ± 1.8
CLS 5	81.8 ± 1.1	92.4 ± 1.8
CLS 6	83.5 ± 0.7	93.1 ± 1.6
CLS 7	70.8 ± 1.2	89.2 ± 1.4
CLS 8	71.4 ± 1.1	90.5 ± 1.8
CLS 9	76.4 ± 1.1	91.3 ± 1.3
MKT	68.3 ± 1.2	88.4 ± 2.0

* CLS, liquisolid tablets prepared using Ceolus KG-802; MKT, marketed formulation; ** Data are shown as means ± S.D.

3.3. *In vitro dissolution studies*

Dissolution rates of liquisolid formulations were compared to liquisolid tablets prepared using Avicel PH 102 in previous studies. As shown in Table 4, greater initial release or burst release (Q_{10}%, *i.e.*, amount of drug released in 10 min) of liquisolid tablets (CLS 1 to 9) indicated that CLS 1 to 9 were effective. All liquisolid tablets had drug release greater than 88.4 ± 2.0% after 45 min (Table 4). According to the "diffusion layer model" of dissolution, the dissolution rate is in proportion to the concentration gradient in the stagnant diffusion layer (*18*). Drug dissolution is directly proportional to the surface area available for dissolution (*19*). In the current work, all dissolution tests were conducted at a constant speed (50 rpm) and in the same dissolution medium. Therefore, the thickness of the stagnant diffusion layer and diffusion coefficient for drug dissolution should be almost identical. Hence, surface area can be considered as a major factor responsible for enhancing the dissolution rate. As the liquid medication contains a drug in a molecularly dispersed form (dissolved in propylene glycol), an increase in the drug surface available for dissolution may be responsible for greater dissolution rates. A lower drug concentration in the liquid medication has also been found to result in more rapid drug release. This is due to the fact that drugs at a high concentration tend to precipitate within silica pores (Aerosil 200). The dissolution profile of liquisolid tablets supports the aforementioned hypothesis. As noted by Spireas and 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. In such a micro-environment, the unlimited amounts of propylene glycol diffusing with the drug molecules out of a single liquisolid particle might be adequate to enhance the solubility of the drug by acting as a cosolvent with the aqueous dissolution medium. Moreover, the use of a superdisintegrant, sodium starch glycolate (used in each formulation at a concentration of 8% of the total weight), caused burst release by tablets. Such release has been found to enhance the dissolution rate of fenofibrate, as indicated by Q_{10}% values (Table 4).

Comparing the dissolution profiles of the liquisolid formulations (CLS 1 to 9) to those studied by Karmarkar *et al.* (*7*) indicated slower release from CLS 1 to 9. This might be due to use of Ceolus KG-802 instead of Avicel PH 102 in the present study. Ceolus KG-802 has a low bulk density and mainly exists as longer rod-shaped particles. It also has a larger length/diameter. Hence, during compression Ceolus KG-802 particles tend to arrange perpendicular to the applied force. This causes an increase in contact area and easy entanglement of particles (*13*). This nature might be due to the high hardness and low friability of CLS formulations 1 to 9. As a result, the drug might be released more slowly from the CLS formulations. The slower release by CLS formulations might be due to Ceolus KG-802's high polyethylene glycol retention capacity, which is also an indicator of liquid retention capacity (*13*). Thus, inhibition of liquid exudation may have led CLS formulations 1 to 9 to have slower release than formulations prepared using Avicel PH 102. However, release data indicating greater release than that from marketed formulations suggests that liquisolid formulations effectively enhanced dissolution rates.

4. Conclusion

The liquisolid tablet technique can effectively enhance dissolution rates of poorly water-soluble drugs such as fenofibrate. Propylene glycol was used as a liquid vehicle. Use of a highly compactable carrier such as Ceolus KG-802 resulted in slower dissolution rates compared to formulations prepared using Avicel PH 102. This might be due to the carrier's physical properties such as shape, size, bulk density, and liquid retention capacity.

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