Original Article

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Preparation of 200 mg fenofibrate hard capsule with high dissolution profile with microparticle entrapped micelles technology

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Abstract

Fenofibrate, a drug of fibrate class, is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. However, bioavailability of fenofibrate is often low and unpredictably due to its poor solubility. Microparticle entrapped micelles (MEM) technology is a novel method of incorporating surfactants in solid dosage form for improving in vitro and in vivo performance of poorly water soluble drugs. Increasing the fenofibrate solubility by MEM technology has not been reported in the literature. In this study, the formulation of fenofibrate modified by MEM technology (FB-MEM) was studied. The FB-MEM was then filled in the hard capsules with high dissolution profile. Fenofibrate was solubilized in various surfactants (tween 80, tween 60, Kolliphor P407, Acrysol K140, Gelucire 44/14) at different concentration of 0.5; 1; 3 and 5 % at cloud point temperature; the dispersion was dried to obtain solid product. The FE-MEM with highest solubility was then characterized by DSC and FTIR spectra. By using Acrysol K140 as surfactant, the FE-MEM solubility was enhanced up to 644 mg fenofibrate / 1 g surfactant. DSC diagram and FTIR spectra showed that there was no chemical interaction between fenofibrate and Acrysol K140. The high solubility of FE-MEM was thus possibly due to low melting point of this mixture and small size of FE-MEM. By using Primellose as disintegration excipient, hard capsule containing 200 mg of fenofibrate (FE-MEM) showed an equivalent dissolution profile with Lipanthyl (the similariry factor f2 = 53).

Keyword: fenofibrate, microparticle entrapped micelles (MEM), hard capsule, high dissolution profile.

1. INTRODUCTION

The bioavailability from conventional formulations of poorly soluble drug candidates may be unacceptable and represent focus for formulation development. According to biopharmaceutical classification system (BCS), drugs belonging to class II having good absorption property exhibit limited bioavailability due to their poor solubility. Earlier reports describe number of formulation strategies to improve the bioavailability of BCS class II drugs either by increasing the dissolution rate or by maintaining the drug in solution state in the gastrointestinal tract such as inclusion of complexation with hydroxypropyl-β-cyclodextrins, solid dispersion, use of surfactants, fluid energy mills etc[1]. Various formulation strategies have been reported to improve solubility and dissolution rate of poorly water soluble drugs. However, weak points of these methods are expensiveness (for complexation with hydroxypropyl-β-cyclodextrins) and instability in chemical and physical properties (for fluid energy mills)[2]. The application of micellar drug delivery system is owing to the minimization of drug degradation, prevention of harmful side effects and improvement of bioavailability. Micellar systems can solubilize poorly soluble drugs and thus increase bioavailability of those drugs. It is recognized that solubilization in aqueous surfactant solutions

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at surfactant concentrations exceeding the critical micelle concentration is the means to formulate a variety of slightly soluble to practically insoluble compounds in the solution state[3].

Surfactants as solubility enhancers are included in all kinds of dosage forms with some rationale. Surfactants in a tablet formulation improve wetting, disintegration and/or dissolution rate of drug. The current formulation practice is to include surfactant in solid dosage form by various methods such as dry blending of surfactant with granules, spraying surfactant solution on granules or inclusion of surfactant during wet granulation. These approaches at best can improve dissolution marginally by producing finer particles (by increasing surface area) on disintegration and enhancing the wettability of hydrophobic drug particles. In such approach even if surfactant concentration is adequate to form micelles, effective solubilization can not be achieved because of slow and lesser extent of release of drug molecules from drug particles which in turn normally would get entrapped/interact with micelle. For effective micellar solubilization, a continuous release of molecules of drug from particles is necessary to maintain sink-condition between drug molecules and micelle. Any methods, which can augment such a sink-condition will improve micellar solubilization capacity. Temperature is a driving force for the release of molecules from the particle and hence in the present study drug was added to the surfactant solution at the cloud point temperature (CPT). Micellar solubilization improves the solubility of drugs. A sensible product development program should aim at converting the aqueous micellar-solution containing drug into a solid since it is convenient over the solution because of ease of administration and patient compliance.

Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood[4]. Originally launched in 1975, it is currently on the market in more than 85 countries. The compound is practically insoluble in water and has high lipophilicity (log P = 5.24) .Thus the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract. A number of reports suggest different formulation strategies for improving the solubility and dissolution rate of fenofibrate. These include solid dispersion with hydrophilic carriers, micronization with hydrophilic polymer[5], self-microemulsifying drug delivery systems[6] etc. The present study deals with assessing the potential of MEM technology to improve the aqueous solubility of fenofibrate and dissolution rate of hard capsule containning fenofibrate. Briefly, the present work is an attempt to convert micellar-solubilized aqueous fenofibrate dispersion into a solid product by dry-drying simply and subsequently to formulate it into a solid dosage form, a hard capsule. In vitro dissolution studies were performed in 0.1M SLS and included comparison with commercial fenofibrate product, Lipanthyl.

2. MATERIALS AND METHODS

2.1. Materials

Fenofibrate (FFB) was purchased from CoFFBentlab, India. Poloxamer 407 (Kolliphor P407) was kindly gifted from BASF (Germany). Poly Oxyl 40 Hydrogenated Castor Oil (Acrysol K140) was obtained from Corel Pharma Chem (India), Gelucire 44/14 was sent from Gattefosse (France), Syloid XDP was kindly gifted from Grace (US). Other chemical compounds were purchased from Xilong (China).

2.2 Methods

2.2.1. Micellar solubilization

Micellar solubilization of FFB was performed by employing cloud point technique, wherein drug was solubilized in surfactant solution at CPT. Aqueous surfactant solutions of 0.5, 1, 3 and 5 % (w/v) of tween 80, tween 60, Kolliphor P407, Acrysol K140, Gelucire 44/14 were used as solubilizing media. The surfactant solutions (5 mL) were taken in centrifuge tubes, heated in a water bath up to CPT and excess amount of FFB was added under stirring, solutions were cooled to room temperature (RT) and the solubility of FFB was estimated. Briefly, those solutions were shaked and kept

stand for 24 hours to attain equilibrium. The aliquots of these samples were centrifuged, filtered through a 0.45 µm nylon membrane filter (Millipore Millex-HN), suitably diluted with methanol and were subjected to UV spectrophotometric (Shimadzu 1800) analysis of FFB at 291 nm. Solubility studies were performed in triplicate (n=3).

2.2.2. Solid state conversion of micellar solubilized FFB

Among the various surfactant solutions employed in the solubility study, Acrysol K140 (1%) which allowed maximum solubility of FFB (644 mg FB /1g Acrysol K140) was chosen as the product candidate for further studies. For the purpose of drying the required quantity of Primellose and Xyloid XDP was added in the surfactant solution containing dissolved FFB after water eliminated on water heat bath. This mixture was then dried in drying oven for more 8 hours (FFB-MEM). The resultant powders of dried FFB-MEM was stored in a dessicator at ambient temperature.

2.2.3. Characterization of FFB-MEM

The dried powders were evaluated based on yield, bulk density (BD) and tapped density (TD) of the samples. The flow properties have been evaluated by the measurement of angle of repose whereas, Carr's Index values and Hausner's ratio were calculated from BD and TD data, as a measure of the compressibility aspect of the powders. FFB content in FFB-MEM was analyzed by dispersing 50 mg of FFB-MEM in 5 mL of methanol in order to extract FFB. The suspension was kept in an ultrasonic bath for 15 minutes and then was centrifuged for 15 minutes at 2500 rpm and filtered through a 0.45 µm nylon membrane filter. After suitable dilution, the content of FFB was determined UV spectrophotometrically at 291 nm using a standard plot (5-30 mcg/mL) with a correlation coefficient (r^2) of 0.9997.

Dissolution studies

The dissolution rates of FFB and FFB-MEM corresponding to 200mg of FFB were determined according to European Pharmacopoeia by using no.2 dissolution test apparatus at 37°C, stirring at 75 rpm. The dissolution medium was 1000 ml solution of 0.05M sodium laurylsulphate. 5 ml of dissolution medium were withdrawn and replaced by 5 ml solution of 0.05M sodium laurylsulphate from the dissolution vessels at selected intervals and analyzed for FFB content due to the absorbance at 291 nm on an UV spectrophotometer (Shimadzu, Japan). The results are the mean and standard deviations of three determinations.

Differential thermal sacanning analysis (DSC)

Differential scanning calorimetry (DSC) thermograms of FFB, FFB-MEM and physical mixture of FFB-MEM components were recorded using a thermal analysis system (Mettler Toledo, DSC-1, Switzerland). Samples were heated at 10 °C/min in the range of 25 – 300 °C.

Fourier transform infrared spectroscopy (FTIR)

FFB, FFB-MEM and physical mixture of FFB-MEM components were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Fourier Transform IR spectrophotometer (Shimadzu, Japan). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 2 cm^{-1}.

2.2.3. Formulation of hard capsule containing CTH and CTH solid dispersions.

FFB, FFB-MEM were encapsulated into hard capsule to obtain the final dosage form. FFB, FFB-MEM were mixed with 2% magnesi stearate and 6% primellose until a homogenous mixture obtained. The dissolution profile of hard capsules were performed by using no.1 dissolution test apparatus at 37°C, stirring at 75 rpm in the 0.05M sodium lauryl sulphate medium.

3. RESULTS AND DISCUSSIONS

3.1. Cloud point studies

With increasing in surfactant concentration, the CPT of the surfactants decreased (Table 1). Gelucire 44/14 showed lower CPTs while compared to other three surfactants. Kolliphor P407 and Acrysol K140 exhibited higher CPT than Gelucire 44/14 with a higher alkyl chain length. The effect of concentration on CPT was insignificant for Kolliphor P407 and Acrysol K140, where as this effect was more pronounced in case of Tween 80.

Table 1. CPT of various surfactants at different concentrations

Surfactants							
Tween 80		Kolliphor P407		Acrysol K140		Gelucire 44/14	
Concentration (%)	CPT (°C)	Concentration (%)	CPT (°C)	Concentration (%)	CPT (°C)	Concentration (%)	CPT (°C)
0.5	90	0.5	95	0.5	95	0.5	76
1	89	1	94	1	93	1	72
3	82	3	92	3	90	3	70
5	78	5	88	5	88	5	69

3.2. FFB Solubility

Broadly, with increasing in surfactant concentration, aqueous solubility of FFB increased (Table 2) with all surfactants. The highest solubility (>1 mg/mL) was achieved by Tween 80 and Gelucrie 44/14 a surfactant concentration of 50 mg/mL whereas, at a concentration of 10 mg/mL, Acrysol K140 and Gelucire 44/14 has imparted a better solubility of FFB around 0.25 and 0.81 mg/mL than any other employed surfactants. However, the solubility and surfactant concentration did not exhibit a linear relation over the range of concentrations employed. Thus, the solubilization capacity (SC=number of mg of drug solubilized by number of mg of surfactant) for a given surfactant did not remain constant, but decreased beyond a certain surfactant concentration. With increase in surfactant concentration SC gradually increased in case of Gelucire 44/14 and decreased in case of other three surfactants. The maximum SC was observed at a specific concentration for each surfactant. In general, the amount of drug solubilized in a micellar system increases with increase in temperature. To test this, we have studied SC at RT and CPT. The SC at CPT showed that Acrysol K140 at 1% had the highest SC for FFB (644 mg FB/ 1g Acrysol K140). Acrysol K140 at concentration of 1% was thus chosen for further investigation.

3.3. Solid state conversion of FFB in micellar system.

Since, Acrysol system rendered highest solubility of FFB at 1% w/v concentration and thus Acrysol K140 was selected for preparation of micellar system followed by drying process. The optimized weight ratio of drug : surfactant : excipient was present in Table 3. The drug loading in FFB-MEM was 306.67 mg FB in 1 g of FB-MEM. The powder recovery from the drier was 75-85% and the FFB-MEM had only around 1% moisture. The details of flow and compression characteristics of FB-MEM were recorded in Table 4. The FFB and FFB-MEM showed acceptable flow and compressible properties.

3.3.1. DSC thermograms

DSC thermograms of FFB, FFB-MEM and physical mixture components of FFB-MEM were shown in Figure 1. The thermal curve of pure FFB was typical of crystalline substance

with endothermic peak corresponding to a melting point of 80.63 °C. FB-MEM has a broad melting point of 70.73 °C. But physical mixture has a melting point at 80.8 °C. Thus, in the FB-MEM, the interaction intra molecular was weaker than those in FB material.

Table 2. Enhancement of FFB solubility of various surfactants

Surfactants	Concentration (g/100ml)	Solubility of FFB (mg/ml)		Solubilization capacity (SC) of surfactant (mg FFB/ g surfactant)	
		RT	CPT	RT	CPT
Tween 80	0.5	0.21	0.35	42.0	70.0
	1	0.20	0.49	20.0	49.0
	3	0.62	0.88	20.7	29.3
	5	1.05	1.62	21.0	32.4
Kolliphor P407	0.5	0.04	0.26	8.0	52.0
	1	0.06	2.12	8.0	52.0
	3	0.32	2.49	10.7	83.0
	5	0.33	4.69	6.6	212.0
Acrysol K140	0.5	0.13	1.03	26	206
	1	0.25	6.44	25	644
	3	0.68	6.99	22.7	233
	5	0.75	10.05	15.0	201
Gelucire 44/14	0.5	0.11	0.53	22	106
	1	0.81	3.54	81	354
	3	1.12	5.49	37.3	183
	5	1.50	8.03	30	160.6

Table 3. Compositions of dry FFB-MEM

Composition	Quantity (g)	
Fenofibrate	6.44	Active pharmaceutical ingredient
Acrysol K140	10	Surfactant
Primellose	0.4	Disintegration excipient
Syloid XDP	0.4	Absorb excipients

Table 4. Flow characteristics of FB-MEM

	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
FFB	0.15 ± 0.007	0.19 ± 0.005	18.92 ± 0.32	1.24 ± 2.26	28 ± 2.5
FFB-MEM	0.33 ± 0.005	0.39 ± 0.003	15.42 ± 1.12	1.18 ± 0.12	39.72 ± 1.5

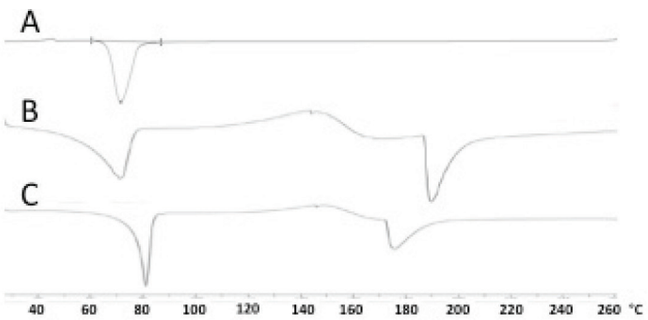

Figure 1. DSC thermogram of (A) FFB, (B) FFB-MEM and (C) physical mixture of FFB-MEM components.

3.3.2. FTIR spectra

Fourier transform infrared spectra of FB, Syloid XDP, Primellose, Acrysol K140 and FB-MEM is shown in Figure 2. FB spectra showed 2 absorption peaks at a wavelength of 1729 cm^{-1} and 1650 cm^{-1} respectively corresponding to the C = O group of ester and of cetone, the ester group was confirmed by the absorption characteristics at 1248 cm^{-1}. The characteristic peaks of FB was not altered in the FB-MEM spectrum.

The results of DSC and FTIR spectra spectrum thus showed that FB interacted with Acrysol K140 in a physical way and there was no chemical interaction. The increase of FB solubility was probably due to the phenomenon that FFB was wrapped in micelle of surfactant resulting in the reduction the melting temperature of FB-MEM.

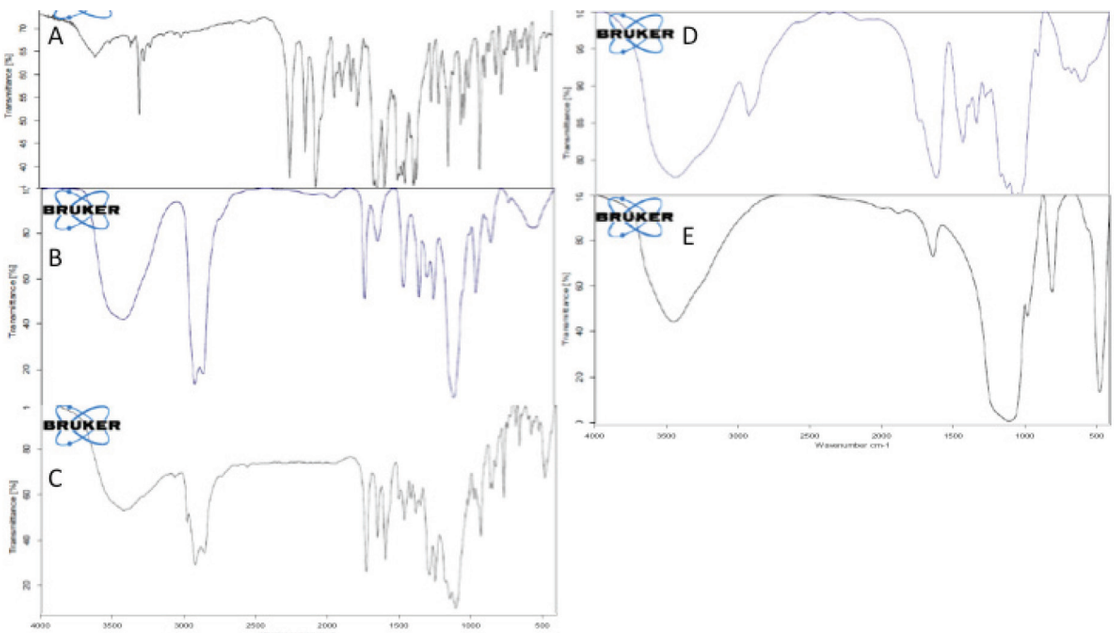

Figure 2. FTIR spectra of (A) FFB, (B) Acrysol K140, (C) FFB-MEM, (D) Primellose and (E) Syloid XRD.

3.4. Dissolution profiles of FFB, FFB-MEM, Hard capsule of FFB-MEM (FFB-MEM HC) and Lipanthyl

The dissolution profiles of FFB, FFB-MEM, hard capsule contains FFB-MEM (FB-MEM HC) and Lipanthyl were shown in Figure 3. FFB-MEM enhanced tremendously the dissolution profile of FFB. The dissolution profile of hard capsule of FB-MEN met the standards of USP 36, (FFB released more than 70% after 40 minutes). The similar factor f2 (53) proved that FFB-MEM HC and Lipanthyl has the equivalent dissolution profile. However at the initial time, the FFB was released slowly form the hard capsule, that could be due to the long time disintegration of capsule shell.

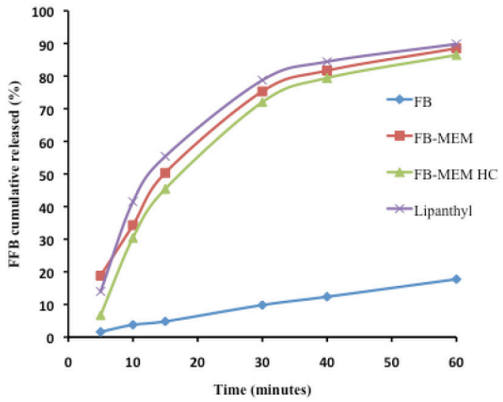

Figure 3. Dissolution profiles of CTH and CTH solid dispersions (n=6, the error bars were very small).

4. CONCLUSIONS

In this study, the formulation of fenofibrate modified by MEM technology (FFB-MEM) was studied. The FFB-MEM was then used to prepare the hard capsule with high dissolution profile. By using Acrysol K140 as surfactant, the FFB-MEM solubility was enhanced up to 644 mg fenofibrate / 1 g surfactant. DSC diagram and FTIR spectra showed that there was no chemical interaction between fenofibrate and Acrysol K140. The high solubility of FFB-MEM was thus possibly due to low melting point of this mixture. By using Primellose as disintegration excipient, hard capsule containing 200 mg of fenofibrate (FFB-MEM) showed an equivalent dissolution profile with Lipanthyl (the similar f2 is 53).

5. COMPETING INTERESTS AND AUTHORS' CONTRIBUTION

We declare that we have no competing of interest.

Vu, T.H.M. participated in experiments. Q.T. Tran and V.T. Tran -Supervising and directing the project, participating in experiments, manucscript preparation. V.T. Tran checked the grammatical mistakes and corrected the final manuscript. All authors read and approved the final version of the manuscript.

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