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Self-Emulsifying Drug Delivery System of Fenofibrate

Dhaval Patel, Nishith K. Patel, Hardeep Banwait

Department of Pharmaceutics and Pharmaceutical technology, A-One college of Pharmacy, Anasan, Ahmedabad, Gujarat, India

ABSTRACT:

In current study formulation of self emulsifying drug delivery system of Fenofibrate was carried out using Lipd phase, emulsifier and co emulsifier flax seed oil, tween 20 and polyethylene glycol 600 respectively. various oil, emulsifier and co emulsifiers were selected based on their solubility. Using water titration method ternary phase diagram ware prepared for SEDDS and emulsification region were analysed visually. All prepared formulations were evaluated for dilution studies, self emulsification time, drug content, in-vitro dissolution, droplet size determination, zeta potential measurement, viscosity determination and thermodynamic stability study. Based on stability study results, viscosity and usage of less emulsifier the final formulation were prepared. The comparison of invitro dissolution study of final formulation shows 5.4 fold and 1.8 fold increases in dissolution at 60 min with pure drug and marketed formulation respectively.

KEYWORDS: Atorvastatin calcium, SEDDS, microemulsion based tablet, Liquid retention potential, Career: coat ratio.

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For Correspondence:

Dhaval Patel

Student of Pharmaceutics,

A-One college of Pharmacy, Anasan, Ahmedabad, Gujarat, India.

(www.jpsbr.org)

INTRODUCTION:

Fenofibrate is an anti-lipidemic agent which reduces both cholesterol and triglycerides in the blood. mainly used for primary hypercholesterolemia or mixed dyslipidemia. Fenofibrate appears to decrease the risk of cardiovascular disease and possibly diabetic retinopathy in those with diabetes mellitus. It also appears to be helpful in decreasing amputations of the lower legs in this same group of people [1 2].

It is used in addition to diet to reduce elevated low-density lipoprotein cholesterol (LDL), total cholesterol, triglycerides (TG), and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL) in adults with primary hypercholesterolemia or mixed dyslipidemia.

It is used in addition to diet for treatment of adults with severe hypertriglyceridemia.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixture of oils, surfactant and co-solvents/ surfactant, which forms fine stable o/w emulsions, when introduced in the aqueous phase under condition of gentle agitation. The natural digestive motility of the stomach and intestine provides the agitation required for self-emulsification in vivo.15 16 The spontaneous formation of an emulsion upon release in the GI tract advantageously presents the drug in a dissolved form and the small droplets size provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve

bioavailability of the drug by permeating through the biological membrane[3].

For, lipophilic drug compound that exhibit dissolution rate limited absorption, these system offers an improvement in the rate and extent of absorption and result in more reproducible blood-time profile. These formulation can increased stability, improve drug transport, they are Less dependence on lipolysis, non-dependence on biles and meal food content, superior solubilisation and faster dissolution and release of drug can be achieved, consistent performance, and they are less prone to gastric emptying delays.

COMPONENTS OF THE SEDDS

(1) Natural product oils, (2) Semi-synthetic lipid excipients, (3) Co-solvents, (4) Surfactants.

The selection of oil (lipid) in current formulation of an anti-lipidemic agent was tough. The selection was made based on highest Mono-unsaturated Fatty acids and (ω-3) linolenic acid containing oil. That may further help to hypercholesterolemia patients[4 5] .

MATERIALS AND METHODS

Fenofibrate was obtained Intas Pharmaceutical, Ahmedabad. flaxseed oil from astron chemicals, ahmedabad, tween 20, sunflower oil from -loba chemicals, mumbai, india. capric acidwas obtained from colorcon asia ltd, mumbai, india

Spectrophotometric scanning of Fenofibrate was carried out by UV spectrophotometer. Priliminary study was carried out to select oil for development of SEDDS. Solubility study was carried out to find out highest solubility of active.

Preparation of Phase diagram

The following experiment was carried out to investigate the effects of fenofibrate on the self-emulsifying performance of SEDDS. Surfactant (Tween 20) and cosurfactant (PEG 600) were mixed (Smix) in different weight ratios (2:1, 1:1, 1:2). Required quantity of fenofibrate (as per the dose and solubility in oil) was added to the glass vials containing oil. The drug was solubilized using a vortex mixer. Nine different combinations of oil and Smix to weight ratios (1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1) were prepared. Slow titration with the water was performed for each combination of oil and Smix separately. Pseudoternary phase diagrams were developed using the water titration method.

In the phase diagrams, only emulsion points are shaded area, so that there is no overcrowding of the phases in the diagram, as for formulation development only the emulsion area is of interest.

Preparation of SEDDS formulations

Based on the area of emulsification from the phase diagrams, Smix ratio of 2:1 was selected for the formulation development studies. SEDDS formulations need to prepare using Tween 20 and PEG 600 as surfactant and co-surfactant with Smix ratio of 2:1 Level of fenofibrate in all the formulation was kept constant. In formulation weigh accurately fenofibrate and place in a glass vial with the respective required quantity of Flaxseed oil. Mix the components by vortex mixing. Add respective quantity of surfactant and co-surfactant to the vial and heat at 40°C for homogeneous mixing followed by vortex mixing. Store the mixture at room temperature.

In vitro evaluation of Fenofibrate SEDDS

1 Dilution Studies/ Robustness to dilution[6]

Dilution study was done to access the effect of dilution on pre-concentrates. In this study formulation was subjected to various dilutions (i.e. 1: 50, 1:100 and 1:250) with various diluents (i.e. distilled water, 0.1 N HCl).63 Dilution study was carried out in triplicate.

2 Self emulsification time [7]

The efficiency of self-emulsification of formulation was carried out using a standard USP type II dissolution apparatus. 500mg formulation was added to 500 mL of water at 37 ± 0.5°C The in vitro performance of the SEDDS was visually assessed and time required for emulsion formation was noted.

3 Drug content

The SEDDS was dissolved in 50 mL 0.1 n hydrochloric acid and stored for 2 h and absorbance was measured in UV-Vis spectrophotometer at 290nm keeping 0.1 n HCl as blank.

4 In-vitro dissolution[6]

The in vitro drug release test was performed in 900 mL of 0.1 N HCl maintained at 37 ± 0.5°C using USP XXV type II dissolution apparatus. The paddle rotation was set at 50 rpm. The SEDDS containing 30 mg fenofibrate was filled in size '00' hard gelatine capsule. Five mL aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through 0.45 µm whatman filter paper, were analyzed by UV-Vis spectrophotometer at 290nm. Dissolution of marketed formulation of Antara® (Lupin) capsules, 30 mg was performed by similar method. 1 % Tween 20 was added to maintain sink condition. Dissolution was performed in triplicate.

RESULTS

Solubility of fenofibrate in various vehicles are shown in Fig. 1 Flaxseed oil exhibited higher solubility for fenofibrate among the various oils testes. Tween 20 and PEG 600 showed the highest solubilizing potential for fenofibrate among the various surfactants, cosurfactants screened. Based on the solubility data, Flaxseed oil was selected as oil phase, Tween 20 as surfactant, PEG 600 as co-surfactant for formulating SEDDS of fenofibrate.

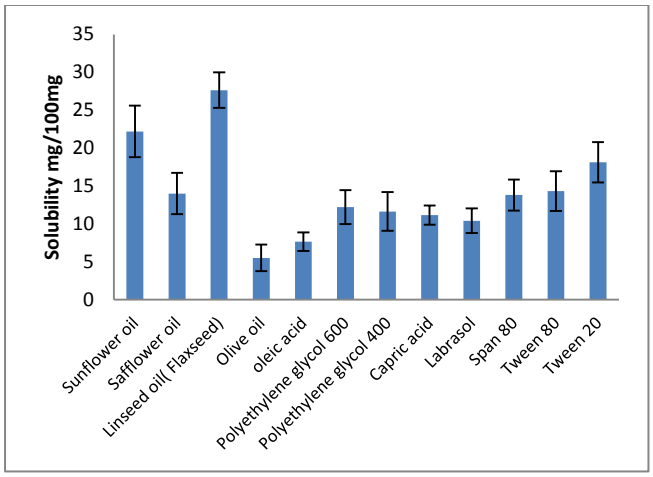

Figure 1 Solubility Study Results for Vehicles

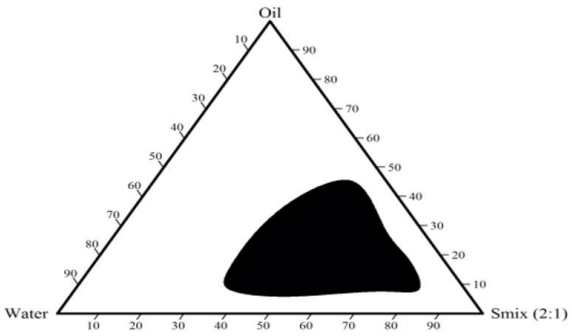

Figure 2 Phase diagrams of fenofibrate Tween 20-PEG 600 systems indicating nanoemulsion existence region with Tween 20/PEG 600 ratio of 2:1

There was not much significance difference observed between emulsification region of blank and drug loaded SEDDS. Larger the size of emulsion region in ternary phase diagram, greater is the self-emulsification efficiency. It was observed that Smix ratios has larger emulsification region in sequence of 2:1>1:2 >1:1. So, depending on the above results, Smix ratio of 2:1 and 1:2 were selected for further studies.

***In vitro* evaluation of Fenofibrate SEDDS**

Prepared formulation F1 to F5 were diluted with distilled water and 0.1 n HCl. All formulations pass the dilution test showing no sign of precipitation Table 1, All formulation showed low emulsification time in the range of 18-39 sec anticipating to rapid release of the drug with 96.14 to 99.06 % drug release.

Table 1 Result of dilution study

Formulation	Dilution with distilled water			Dilution with 0.1N HCl		
	1:50	1:100	1:250	1:100	1:1000	**1:2500**
F1	√	√	√	√	√	**√**
F2	√	√	√	√	√	**√**
F3	√	√	√	√	√	**√**
F4	√	√	√	√	√	**√**
F5	**√**	**√**	**√**	**√**	**√**	**√**

√ No precipitation observed; formulation passes the dilution test, **×** Precipitation observed; formulation fails the dilution test

Table 2 : Grading system used to evaluate SEDDS on dilution

Symbol	Inference
√	No precipitation observed; formulation passes the dilution test
×	Precipitation observed; formulation fails the dilution test

Table 3 Emulsification time

Formulation	Emulsification time (sec)	Drug Content n=3,mean±SD
F1	39	**98.25 ±0.45**
F2	26	**97.17 ±1.32**
F3	22	**96.14 ±0.95**
F4	17	**99.06 ±0.81**
F5	**18**	**97.35 ±0.76**

The *in-vitro* dissolution indicates that there was immediate release of fenofibrate in. More than 85 % release of fenofibrate is obtained by 60 min in all formulations except batch F1, Figure 3.

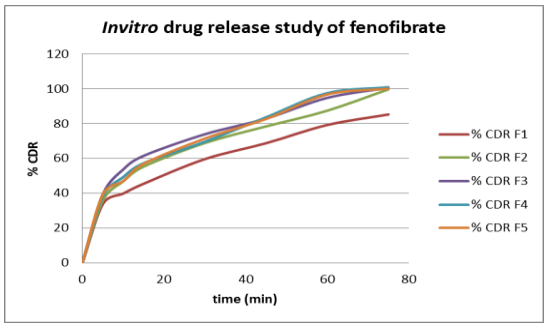

Figure 3 *Invitro* drug release study of fenofibrate SEDDS and marketed formulation

Results of thermodynamic stability study

Table 4 stability indicating dilution study with 0.1N HCl

Formulation	15th Day			30th Day		
	1:50	1:100	1:250	1:100	1:100	**1:250**
F1	√	√	×	√	√	×
F2	√	√	×	√	√	×
F3	√	√	×	√	√	×
F4	√	√	√	√	√	**√**
F5	**√**	**√**	**√**	**√**	**√**	**√**

√ No precipitation observed; formulation passes the dilution test, × Precipitation observed; formulation fails the dilution test

On 1:250 dilution, formulations F1,F2 and F3 showed precipitation on 15 day which whereas other formulations did not showed any precipitation on 15th as well as on 30th day.(Table 4) Precipitation can be attributed to the low concentration of lipid vehicle in these formulations, which on thermodynamic stability loses its potential solubilising capacity of Fenofibrate, as a consequence more amount of drug remains dissolved in emulsifier and co-emulsifier, which on dilution due to its high HLB dissolves in water or dissolution media leading to precipitation of Fenofibrate. Remaining two batches F4 and F5 were evaluated for globule size measurement.

CONCLUSION

Self-emulsifying drug delivery is promising drug delivery system for lipophilic drug phenopfibrate. The formulation showed promising improved dissolution cheracteristics and stability of formulation. Further the addition of oil provide advantages to the formulation as well as to the patients.

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