Research Article

Development of Self Emulsifying Drug Delivery System: Application to Fenofibrate Delivery

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ABSTRACT

The objective of the research was to formulate Self Emulsifying Drug Delivery System (SEDDS) of Fenofibrate and was accomplished using Gelucire 44/14 as oily phase, Cremophor RH 40 as Surfactant and Lauroglycol 90 as Co-Surfactant. Fenofibrate SEDDS were characterized in aspects of Visual Assessment, Phase Separation, Emulsion Droplet Size Analysis, Pseudo Ternary Phase Diagram, HLB determination, Self-Emulsification Efficiency Assessment and In vitro dissolution study in comparison with Lipicard capsules, 200 mg of US-Vitamins Private Limited. Fenofibrate loaded SEDDS showed good self-emulsification efficiency and released more than 90% of the drug in 60 minutes whereas marketed product showed about 40% drug release. The mean globule size of optimized Fenofibrate SEDDS was 13.04 microns.

Keywords: Fenofibrate, Lipid-based drug delivery system, Self Emulsifying Drug Delivery System (SEDDS).

INTRODUCTION

Poorly soluble drug and their dosage forms often show incomplete absorption; to overcome such problem, in recent years much attention has been focused on lipid based formulation with particular emphasis on self emulsifying drug delivery system (SEDDS); which from a practical and aesthetic stand point were ideally prepared as a unit dose which could be filled into either a sealed hard (or) soft gelatin capsules.[1] The efficiency of oral absorption of the drug compound from SEDDS depends on many formulation related parameters, like 1) Surfactant concentration 2) oil/surfactant ratio 3) polarity of the emulsion 4) droplet size. Which in essential determine the self emulsification ability.[2]

Fenofibrate, a fibric acid derivative having chemical name 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methyl ethyl ester is a white solid powder, insoluble in water, soluble in methanol, molecular weight of 360.83, molecular formula of $C_{20}H_{21}O_4Cl$ and melting point of 79-82°C, is a lipid regulating drug with action on plasma lipid. It is used in the treatment of type IIa, type IIb, type III, type IV and type V hyperlipoproteinemias (Increased lipid level and increased triglyceride level).

The aim of the formulation development work was to develop Self Emulsifying Drug Delivery System (SEDDS) of Fenofibrate. By increasing the solubility; the drug will be more bioavailable, daily dose of the drug can be reduced thereby patient compliance can be improved through once daily dosing.

MATERIALS AND METHODS

Materials

Fenofibrate obtained from Unichem Laboratories; Gelucire 44/14 (PEG-32 Glyceryl Laurate and Polyglycolyzed Glycerides) obtained from Gattefosse; Cremophor RH 40 (PEG 40 Hydrogenated Castoroil (Or) Poloxyethylene Castoroil Derivatives) obtained from BASF; Lauroglycol 90 (Propylene Glycol Monolaurate) obtained from Gattefosse; Lutrol F68 (Poloxamer 188) obtained from BASF; Labrasol (Polyoxyglycerides) obtained from Gattefosse; Transcutol P (Diethylene Glycol Monoethyl Ether) obtained from Gattefosse; Capmul PG-8 (Propylene glycol Monocaprylate) obtained from Abitec Corporation; Lipicard Capsules, 200 mg (Fenofibrate) by US-Vitamins Pvt, Ltd, Mumbai; Size "00" Hard Gelatin Capsule Shells obtained from ACG Associated Capsules Private Limited.

Instruments

Magnetic Stirrer: Make - Remi, Mumbai; Thermostat: Make – Remi, Mumbai; Ultrabath Sonicator: Make – Crest, Germany; Minishaker (Cyclomixer): Make – KMS2 Minisaker, IKA; Micopipette (100-1000 microlitre): Make – Microlit, India; Weighing Balance: Make – Sartorius, Germany; UV-Visible Spectrophotometer: Model Cary UV 50, Make – Varian; Dissolution Test Apparatus (XXII): Make – Electolab, India; KBR Press (Pellet maker): Make – TSI Techno Search Instruments; pH Meter: Model 330, Make – Thermo Orion per PHec T log k Meter.

Methods

Preparation of Fenofibrate SEDDS Formulation

SEDDS formulation was prepared by mixing Fenofibrate with oil in a screw-capped glass vial and heated in a water bath at 50°C-60°C until the drug was completely dissolved. The mixture was cooled to ambient temperature and various proportions of surfactant, co-surfactant and co-solvent were added to the oily mixture as shown in Table 1. The vial was then recapped and placed in a water bath at 50°-60°C to facilitate solubilization, the components were mixed by shaking gently and vortex mixed for 5 min to obtain a clear,

uniform solution and again cooled to room temperature followed by equilibrating the mixture on a cyclomixer at room temperature for 10 min, then the formulation was kept under observation for at least 48 hrs and examined for signs of turbidity (or) phase separation prior to self-emulsification and particle size studies.

Filling and Banding of Capsules

Prepared SEDDS formulations were poured into size 00 (zero) hard gelatin capsules then hard gelatin capsules were banded with 2% W/W aqueous solution of gelatin, which is applied as thin layer on the top inner side of the cap using finer brush and joined with the body tightly by manual pressing. Sealed capsules are then air dried. Each capsule represents 50 mg of Fenofibrate in addition to the specified amount of oil, surfactant, co-surfactant and co-solvent. Filled capsules were stored at room temperature for 24 hrs and observed for any leakage of capsule contents before used for subsequent studies.[2]

Table 1: Formulation Trials

Name of the Ingredient		Quantity (µl/capsule) for 1 capsule											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Fenofibrate	Drug (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Gelucire 44/14	Oil	100	100	100	100	100	100	50	50	50	100	100	100
Cremophor RH 40	Surfactant	300	200	---	---	200	300	300	350	200	200	200	200
Lutrol F 68	Co-Surfactant	50	150	---	---	---	---	---	---	---	---	---	---
Labrasol	Surfactant	---	---	200	300	---	---	---	---	---	---	---	---
Lauroglycol 90	Co-Surfactant	---	---	150	50	150	50	100	50	200	100	150	200
Transcutol-P	Co-Solvent	50	50	50	50	50	50	50	50	50	100	---	---
Capmul PG-8	Co-Solvent	---	---	---	---	---	---	---	---	---	---	50	---

Intrinsic Dissolution

100 mg of Fenofibrate was placed in the 1.4 diameter die cavity of KBr pellet press and compressed to form a non-disintegrating translucent compacted pellet of 1.5386 cm^2 surface area, the pellet is pasted at the bottom of basket stainless steel rod (USP apparatus type - I) by using water insoluble cyanoacrylate glue stick. The assembly is immersed into the bottom of a dissolution vessel containing 1000 ml of dissolution medium (0.025%, 0.05%, 0.75% SLS) and the temperature was maintained at 37 ± 0.5°C, the dissolution test apparatus is rotated at 75 rpm for 60 min. Periodically 5 ml of sample was withdrawn at specified intervals and 5 ml of fresh medium was replaced at each sampling time to maintain sink condition.

Solubility Studies

The solubility of Fenofibrate in various oils, surfactant, co-surfactant and co-solvent was determined. To 1000 µl of oil, surfactant, co-surfactant and solvent taken individually; Fenofibrate was added in increments of 10 mg from 10 mg to 200 mg in the screw - capped glass vials and the mixture was heated to 50°C-60°C, (If required) to facilitate the solubilization and finally the sample was made into homogenous solution using Vortex mixer (or) ultra bath sonicator, these sample were assessed for Turbidity, Precipitation (or) Cloudiness upon standing for 7 days at room temperature.

Visual Assessment Test (Dilution Effect)

Formulation of about 0.50 ml was diluted to 1, 25, 50, 100, 150 & 200 fold respectively with 0.05% SLS, the contents were mixed gently with magnetic stir bar at 37°C, the tendency to emulsify spontaneously and also the progress of emulsion droplets were observed, the tendency to form an emulsion was Judged as "good", when droplets spread easily in the medium and formed a fine milky emulsion and it was judged 'bad' when there was poor (or) no emulsion formation with immediate coalescence of oil droplets, especially when stirring was stopped.[2]

Phase Separation Study

SEDDS formulation of about 0.5 ml was added to a screw capped glass vials containing 15 fold of 0.025%, 0.05% and 0.75% SLS at room temperature, after 1 min vortex-mixing, each mixture was stored for a period of 2 hrs. Visually the mixtures in which phase separation was not considerable during the 2 hrs period were used in the subsequent study.[1]

Emulsion Droplet Size Analysis

Liquid SEDDS was added to a flask containing 25 ml of distilled water. The flask was inverted and shaken gently to form a fine emulsion and was kept for 12 hours at room temperature. The particle size of emulsion was determined by laser diffraction study (particle size analyzer, Microtrac blue wave).[4]

Lamda (λ) Max Determination – UV Scanning

From the standard stock solution. 1 ml was prepared in 0.025%, 0.05% and 0.75% SLS and was scanned in the range of 200 - 400 nm; the wavelength of 286 nm was selected as the λ max and used for further analysis.

Pseudo Ternary Phase Diagram

Water was added drop by drop into the vials containing 0.50 ml of Fenofibrate SEDDS formulation. Following each water addition, the mixtures in vials were vortexed 2-3 min at room temperature and the mixture was titrated with water until it turned turbid (or) cloudy. The volume of water used was then recorded, water titration was continued until the mixture turned clear, transparent, translucent and again the water volume was recorded. The resulting mixture was evaluated by visual observation. For the phase diagram, Micro-emulsions were the region of clear transparent and Isotropic solution that might also contain micelle solution. Coarse emulsion was the region of visibly cloudy dispersions even by visual observation.[7]

Hydrophilic Lipophilic Balance (HLB) Value Determination

The HLB value of SEDDS formulation can be determined by following formula.

HLB blend of mixtures = (A×PA/100) + (B×PB/100) + (C×PC/100)

A, B, C → HLB value of oil, surfactant and Co-Surfactant respectively.

PA, PB, PC → Percentage of oil, surfactant and Co-Surfactant respectively in each formulation.

Assessment Self-Emulsification Efficiency

The efficiency of self-emulsification was assessed using a standard USP XXIII dissolution apparatus type 2. About 0.50 ml of each formulation was added to 200 ml of 0.025%, 0.05% and 0.75% SLS at 37°C, gentle agitation was provided by a standard stainless steel dissolution paddle apparatus rotating at 75 rpm, the lipid based formulation were assessed visually according to the rate of emulsification and the final appearance of the emulsion.

A. Denoting a rapidly forming Micro-emulsion with clear appearance.
B. Denoting a rapidly forming slightly less clear emulsion.
C. Denoting a bright white emulsion (similar in appearance to milk)
D. Denoting a dull white emulsion with a slightly oily appearance that was slow to emulsify.
E. Denoting a formulation which exhibited either poor (or) minimal emulsification with larger oil droplets present on the surface.[6]

In-Vitro Dissolution Study

In-Vitro release studies were performed using USP XXIII basket method (type 2 apparatus) rotating at 75 rpm, 1000 ml of 0.025%, 0.05%, 0.75% SLS were used as a dissolution media and the temperature was maintained at 37°C ± 0.5°C. Samples were taken at regular intervals for 60 minutes. 5 ml of sample was taken at each interval and 5 ml of fresh media was replaced at each sampling time. The sample was filtered through 0.45µm Mdi-Syringe filters (type – sy 25 NN) and 1 ml of the filtrate was diluted to 10 ml by using 0.025%, 0.05% and 0.75% SLS. Finally the diluted samples were measured spectrophotometrically at 286 nm.

RESULTS AND DISCUSSION

Intrinsic Dissolution

The intrinsic dissolution shows the rate of dissolution of a pure pharmaceutical active ingredient (Table 2). The intrinsic dissolution studies were performed with USP - type-I dissolution apparatus using 0.025%, 0.05%, and 0.75% SLS as a dissolution media. The Percentage release of Fenofibrate from the intrinsic dissolution was found to be 26.0±0.26, 16.1±0.31, and 15.2±0.31 in 0.05%, 0.025%, and 0.75% SLS medium respectively.

Table 2: Intrinsic Dissolution Profile

Time (min)	Percentage drug release ± S.D		
	0.025% SLS	0.05% SLS	0.75% SLS
10	4.2 ± 0.25	6.0 ± 0.13	----
15	----	----	5.2 ± 0.25
20	5.3 ± 0.35	17.4 ± 0.50	----
30	10.2 ± 0.76	22.3 ± 0.30	7.3 ± 0.50
40	13.2 ± 0.50	----	-----
45	----	26.0 ± 0.26	11.4 ± 0.41
60	16.1 ± 0.31	----	15.2 ± 0.31

Solubility Study

The results of the solubility study of Fenofibrate in various surfactant, co-surfactant, solvent and oils are shown in (Table 3). The data indicated that the solubility is related to the hydrophilicity of oil (or) oil-surfactant mixture with more hydrophilic systems resulting in greater solubility values.

Visual Assessment Test

A series of SEDDS were prepared and their self-emulsifying properties were observed visually Visual observations indicated that at higher levels of surfactant, the spontaneity of the self-emulsification process was increased. When a co-surfactant is added to the system, it lowers the interfacial tension.

Phase Separation Study

The results of the phase separation studies of SEDDS formulation indicated that the phase separation did not occur in the formulation (F-1, 2, 3, 6, 7, 9, 10, 11 & 12) but occurs in the formulation (F-4, 5 & 8).

Pseudo Ternary Phase Diagram

Pseudo ternary phase diagram was constructed to identify the self emulsifying regions and to establish, the optimum concentrations of oil, surfactant and co-surfactant. The phase diagrams of the systems containing oil, surfactant and co-surfactant are shown in Table 4 and

Figure 1. The results indicate that efficiency of emulsification was good when the surfactant concentration was more than 50%.

Assessment of Self-Emulsification Efficiency

The assessment was done visually. The SEDDS formulation F-11 and F12 formed micro-emulsions (Graded A). Formulation F-3 and F-7 formed emulsion (Graded C). Formulation F-8 and F-9 formed emulsion (Graded D). Formulation F-2, F-4, F-5 and F-10 showed un emulsified oil (Graded E).

***In-vitro* Dissolution Study**

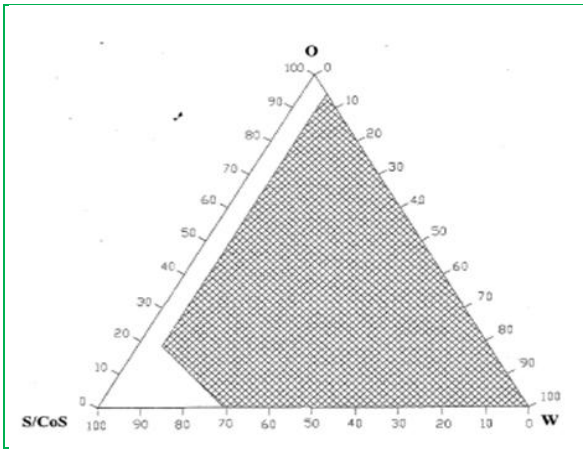
In-Vitro drug release studies were performed with USP 2 dissolution apparatus using 0.05%, SLS as a dissolution medium. Formulation F-12 showed 90% drug release where as the marketed product showed about 50% drug release at the end of 45 minutes. (Table 5 & Figure 2).

Table 3: Solubility Profile of Fenofibrate

Solubilizing Excipients	Maximum Solubility(Initial at 25°C) mg/ml	Maximum Solubility (7 days at 25°C) mg/ml	Observation (7 days at 25°C)
Transcutol-P	130	130	Clear
Labrasol	130	130	Clear
Lauroglycol 90	100	100	Clear
Gelucire 50/13	100	100	Clear
Lafrafil M 1944 CS	100	100	Clear
Gelucire 44/14	100	100	Clear
Cremophor RH 40	100	100	Clear
Capmul PG-8	125	125	Clear
Poloxamer 188	125	125	Color changed
PEG 400	80	80	Color changed
Captex 300	100	100	Clear
Sunflower Oil	80	80	Color changed
Capmul MCM NF	80	80	Color changed

Table 4: Pseudo Ternary Phase Diagram for Optimized Formulation (F-12)

Ingredients		Qty(µl)/ capsule	Percentage (%)
Gelucire 44/14	Oil phase	100	50.8
Cremophor RH 40	Surfactant	200	23.5
Lauroglycol 90	Co-Surfactant	200	
Water	---	1200	70.5
Pseudo Ternary Phase Diagram		Turbid-0.2 ml, clear and translucent-1.2 ml. It maintained up to 250 ml	



(O-Oil, S/Cos-Surfactant/Co-Surfactant, W- Water)

Figure 1: Pseudo Ternary Phase Diagram for the Optimized Formulation (F12)

Table 5: *In-vitro* Drug Release Studies of Marketed Product & Formulation 12

Time (min)	0.05% SLS Dissolution Media		
	Marketed Product	Formulation-12	Intrinsic Dissolution (ID)
10	24.0	61.4	6.0
20	35.2	82.2	17.4
30	49.2	93.2	22.3
45	50.7	99.1	26.0

Emulsion Droplet Size Analysis (F12)

The particle size of emulsion was determined by laser diffraction studies (particle size analyzer, Microtrac blue wave). The range of particle size was 5.08 µm, 13.04 µm, 131.6 µm, at d10, d50 & d90 respectively. (Figure 3)

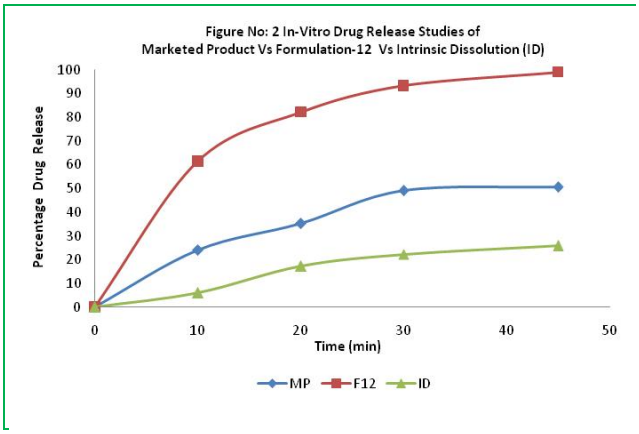


Figure 2: *In-vitro* drug release studies of marketed product Vs formulation-12 Vs intrinsic dissolution (ID)

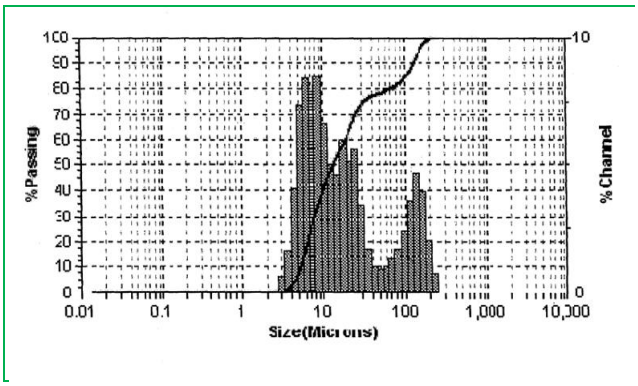


Figure 3: Emulsion Droplet Size Analysis

CONCLUSION

Self Emulsifying Drug Delivery System of Fenofibrate was prepared using Gelucire 44/14 as oily phase, Cremophor RH 40 as Surfactant and Lauroglycol 90 as Co-Surfactant. Prepared Fenofibrate SEDDS was characterized with respect to Visual Assessment, Phase Separation, Emulsion Droplet Size Analysis, Pseudo Ternary Phase Diagram, HLB determination, Self-Emulsification Efficiency Assessment and In vitro dissolution study in comparison with Lipicard capsules, 200 mg of US-Vitamins Private Limited. Fenofibrate loaded SEDDS showed good self-emulsification efficiency and released more than 90% of the drug release in 45 minutes whereas marketed product showed about 50% drug release. The mean globule size of optimized Fenofibrate SEDDS was 13.04 microns. So, it can be concluded that SEDDS of Fenofibrate will be more bioavailable, which may result in reduction in dose and will improve patient compliance.

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