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Research Article

DESIGN AND DEVELOPMENT OF SOLID SELF-MICRO-EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) OF FENOFIBRATE

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ABSTRACT

Formulating Fenofibrate in oral solid preparation has challenged oral hyperlipidemia therapy with Fenofibrate. The present work was formulating a solid self-microemulsiy formulation of fenofibrate and evaluating its *in vitro* preparation. The solubility of Fenofibrate was determined in various vehicles. Fenofibrate was dispersed with a surfactant used for the self-microemulsifying drug delivery system (SMDDS), Tween 20, Cremophor, capmul and mixture was solidified with four kinds of adsorbents, microporous calcium silicate (Florite ™ RE), magnesium alminometa silicate (Neusilin ™ US2), silicon dioxide (Sylysis ™ 320) and microcrystalline cellulose. SMDDS formulations were tested for microemulsifying properties and the resultant microemulsions were evaluated for clarity, precipitation, and particles size distribution. The SMDDS formulation showed release faster as compared with the plain drug and conventional marketed formulation, showed a limited dissolution rate. The optimized formulation was then subjected to stability studies as per International Conference on Harmonization (ICH) guidelines and was found to be stable over three months. It has been found that dissolution profile of Fenofibrate from SMEDDS was much improved than Fenofibrate.

Keywords: Fenofibrate, Self-Microemulsifying, Adsorbent; Microporous calcium silicate, Magnesium alminometa silicate, Silicon dioxide and Microcrystalline cellulose.

INTRODUCTION

Lipid-based formulation approaches, particularly the self-microemulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs,[1] which are associated with poor water solubility and low oral bioavailability.[2] SMEDDS formulations are isotropic mixtures of an oil, a surfactant, a cosurfactant (or solubilizer), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption.[3,4] Fenofibrate is a Biopharmaceutical Classification System (BCS) Class II drug with a high dose number. Thus, it can be assumed that the low oral bioavailability of fenofibrate is due to its solubility and dissolution limitations. Researchers have tried various methods (e.g., cyclodextrin complexation, comicronization, solid dispersion) to overcome these limitations.[5]

The main objective of the study were to develop and evaluation an optimal SMEDDS formulation containing Fenofibrate and compared with Fenofibrate marketed formulation.

MATERIALS

Fenofibrate was a gift sample from Zydus (Zydus Cadila Moraiya, Ahmedabad Ind.) Ltd. Cremaphor RH 40, Castor oil Captex oil 300, Capmul MCM NF Plurol oleique CC 497, (S.D.Fine Chemical, New Delhi India) Polyethylene Glycol 400, Polyethylene Glycol 200, Polypropylene Glycol 200, Tween 20, Span 20, 80 Castor oil, Corn oil, (Loba chem. Pvt, Ltd), All these excipients and reagents were used as received. All other chemicals and reagents used were of AR and HPLC grade.

METHODS

Solubility Studies

The solubility of Fenofibrate in various components (oils, surfactants, cosurfactants) was determined as follows: briefly an excess amount of Fenofibrate was added to each ependroff tube containing 1 ml of the selected vehicles. After sealing the mixture was vortexed using a cyclomixer for 10 min. in order to facilitate proper mixing of VPA with the vehicle. Mixtures were than shaken for 24 h in incubator shaker maintained at 37±1 ^{o}C. Mixtures were centrifuged at 5000 rpm for 5 min. followed by filtration through membrane filter (# 0.22 µm). The concentration of Fenofibrate was then determined by UV method. No interference was observed from the excipients used to solubilize Fenofibrate.[6]

Preparation of SMEDDS Formulations

A series of SMEDDS formulations were prepared using Tween 20 and Cremophor EL as the S/CoS combination and Capmul MCM as the oil In all the formulations, the level of fenofibrate was kept constant (i.e., 40 mg). Briefly, accurately weighed fenofibrate was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated at 40 ºC on a magnetic stirrer, until fenofibrate was perfectly dissolved. The mixture was stored at room temperature until further use.

Table 1: Composition of Microemulsion

S. No	mg	F1	F2	F3	F4	F5
1	40	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate
2	200	Oleic acid	Captex oil	Olive oil	Capryol	Capmul
3	530	Tween 20	Span 20	Lebrasol	Tween 80	Tween 20
4	560	Cremophor EL	PEG 400	Propylene Glycol	Cremophor EL	Cremophor EL

Formulation of Solid Microemulsion Preconcentrate of Fenofibrate

It was observed that solid adsorbents such as dicalcium phosphate, lactose, Microcrystalline Cellulose, magnesium carbonate and calcium carbonate did not have good adsorption capacity to yield a free flowing solid microemulsion preconcentrate whereas Silicon dioxide (170 mg), Magnesium alminometa silicate(70 mg), microporous calcium silicate (170 mg), Microcrystalline Cellulose

(200 mg) exhibited good adsorption capacity to yield free flowing solid microemulsion.

Briefly the microemulsion preconcentrate was added dropwise over the solid adsorbent contained in a broad bottom beaker. After each addition the mixture was homogenized using glass road to ensure uniform distribution of the droplet. The solid microemulsion preparation was then filled in a #000 enteric capsule.

Freeze Thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at – 4 °C for 24 hours followed by thawing at 40 °C for 24 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.[7]

Emulsion Droplet Size Analysis

One hundred microliters of each SMEDDS formulation was diluted to 250 mL in a beaker and gently mixed using a glass rod. The resultant emulsion was then subjected to particle size analysis (using Malvern Mastersizer (Worchestershire, UK) equipped with 2000 Hydro MU) with a particle size measurement range of 0.02 to 2000 µm. Particle size was calculated from the volume size distribution. All studies were repeated in triplicate, with good agreement being found between measurements.[8]

Self-Emulsification and Precipitation Assessment

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessment as previously reported. In brief; different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by dropwise addition of the preconcentrate (SMEDDS) into 250 mL of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm.

Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours).[9,10]

In Vitro Dissolution Studies

The quantitative in vitro release test was performed in 900 mL of buffer pH 1.2 using US Pharmacopoeia XXIV dissolution apparatus 2. The paddles were rotated at 100 rpm. The SMEDDS formulations were put into hard gelatin capsules (000 sizes) and used for drug release studies; results were compared with those of plain fenofibrate. During the release studies, a 5-mL sample of medium was taken out and subjected to drug analysis using HPLC. The removed volume was replaced each time with 5 mL of fresh medium. Dissolution studies were also performed in media buffer pH 4.5 7.2 and o.75% sodium laural sulphate to examine the effect of pH on drug release.[11]

UV Analysis of Fenofibrate

The concentration of fenofibrate in the samples was determined by UV Spectrophotometer (Shimadzu UV-16601). The drug content was calculated and to estimate the recovery of the loaded drug.[12]

Stability Studies

The SMEDDS formulations were put into empty hard gelatin capsules (size 000) and subjected to stability studies at 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH. Samples were charged in stability chambers (Thermolab, Mumbai, India) with humidity and temperature control. They were withdrawn at specified Accelerated conditions and 3months for long-term conditions. Drug content of the capsules was analyzed using a previously developed and validated stability-indicating UV method.[13, 14]

RESULTS AND DISCUSSION

Solubility Studies

One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in Figure 1. As seen from the figure and capmul MCM showed the highest solubilization capacity for fenofibrate. Thus, for our study we selected capmul MCM as oils and Tween 20 and Cremophor EL as surfactant and cosurfactant, respectively.

Droplet Size Analysis

The droplet size distribution of various formulations is given in Table 2. An increase in the ratio of the oil phase (Capmul MCM) resulted in a proportional increase in particle size,. It is well known that the addition of surfactants to the microemulsion systems causes the interfacial film to stabilize and condense, while the addition of cosurfactant causes the film to expand; thus, the relative proportion of surfactant to cosurfactant has varied effects on the droplet size.

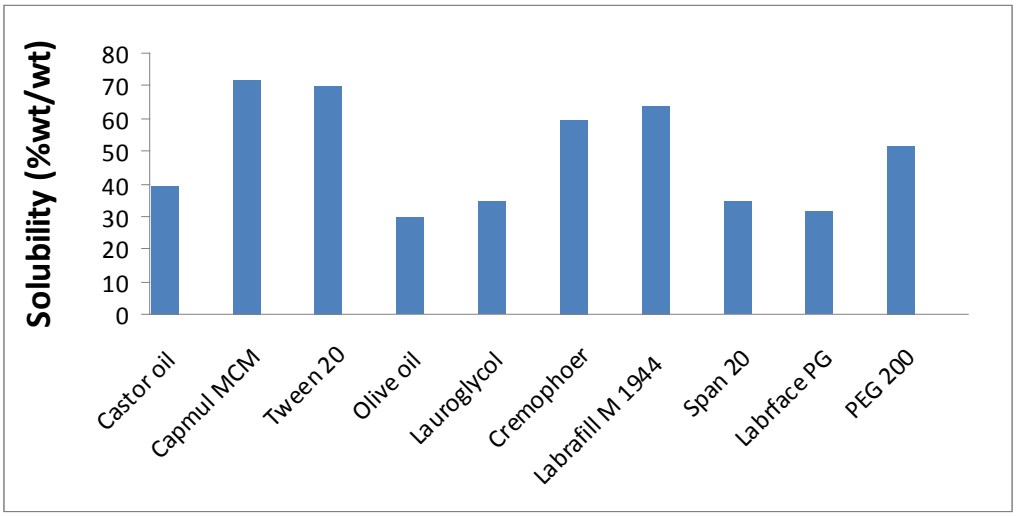

Fig. 1: Solubility of fenofibrate in various components. PEG indicating Polyethylene Glycol

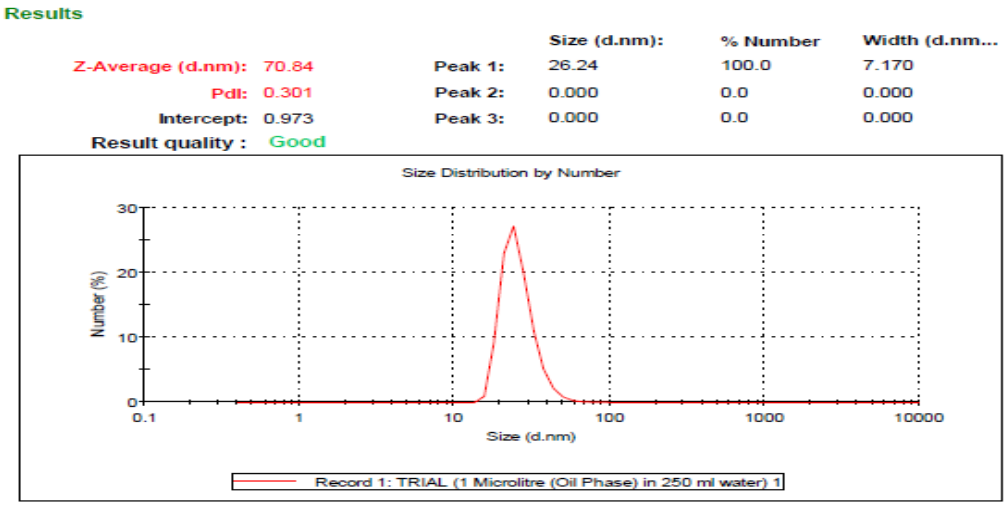

Fig. 2: **Evaluation Parameters of Various Formulations**

Self-Emulsification and Precipitation Studies

The results of self-emulsification and precipitation studies are given in Table 3. The decrease in self emulsification time can be assumed to be due the relative decrease in surfactant concentration, leading to decreased viscosity of the formulation. However, it was found that the resultant dispersion showed precipitation and thus was not stable, because of the presence of Cremophor EL. Cremophor EL can be assumed to act as a cosolvent for fenofibrate (as seen from solubility studies), and thus it increases the solubilization capacity of the vehicle (Capmul MCM).

Table 2: Evaluation of various formulations

Formulation	Dispersion time (sec)	Clarity	Precipitation
F1	78±5	Clear	Unstable
F2	65±4	Clear	Unstable
F3	64±4	Clear	Unstable
F4	51±5	Not Clear	_
F5	59±3	Clear	Stable

In Vitro Dissolution Studies

Drug release from the SMEDDS formulation (was found to be significantly higher as compared with that of plain fenofibrate (Figure 3). It could be suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain fenofibrate. Thus, this greater availability of dissolved fenofibrate from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. It was also seen that changes in the dissolution medium (buffer pH 1.2, 4.5 and 7.2) had no effect on the drug release from either plain fenofibrate or the SMEDDS formulation (Figure 3). This observation can be explained by the fact that fenofibrate has no ionizable group and thus its solubility and dissolution is pH-independent.

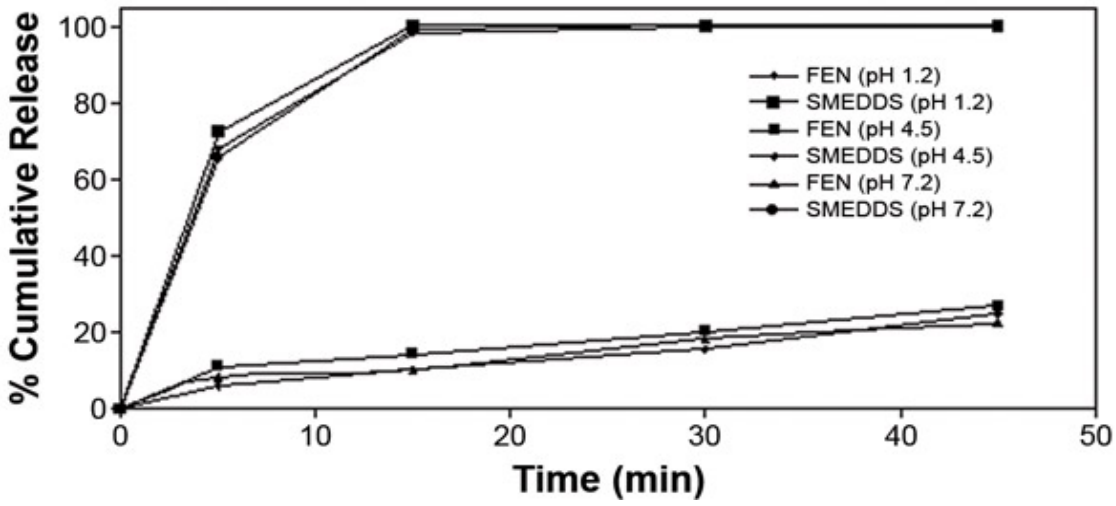

Fig. 3: Comparative results of drug release from plain Fenofibrate and SMDDS formulation in different composition media. FEN indicates Plain Fenofibrate, SMDDS indicates Self-Microemulsifying Drug Delivery System

Stability Studies

Generally, SMEDDS formulations are put into hard gelatin capsules as the final dosage form. However, hard gelatin capsules are susceptible to leakage, and the entire system has a very limited shelf life owing to its powder characteristics. Thus, the developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form.

The results of the evaluation test conducted on stability samples. There was no significant change in the drug content, drug release (t90%). It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. There were also no significant changes in the appearance, or microemulsifying property. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules.

CONCLUSION

SMEDDS appeared to be an interesting approach to improve problems associated with oral delivery of Fenofibrate optimization. Fenofibrate SMEDDS formulation was superior to commercial formulation with respect to in vitro dissolution profile. Thus SMEDDS can be considered as novel and commercially feasible alternative to current marketed Fenofibrate.

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