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FORMULATION AND EVALUATION OF CAPTOPRIL SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this study was to formulate and evaluate a self-microemulsifying drug delivery system (SMEDDS) for Captopril, an antihypertensive drug with low bioavailability due to poor water solubility. The primary aim was to enhance the solubility and oral bioavailability of Captopril by developing an optimized SMEDDS formulation. The formulation process involved selecting appropriate oils, surfactants, and co-surfactants based on their emulsification efficiency and compatibility with Captopril. The selected formulations were evaluated for various physicochemical parameters, including droplet size, polydispersity index (PDI), zeta potential, and self-emulsification time. The self-emulsification time was found to be less than 60 seconds, confirming the rapid formation of a microemulsion. In vitro drug release studies demonstrated a significantly enhanced dissolution rate of Captopril from the SMEDDS compared to the pure drug and conventional formulations. The study concluded that the SMEDDS formulation successfully improved the solubility and dissolution rate of Captopril, suggesting its potential to enhance the drug's oral bioavailability. Further in vivo studies are recommended to evaluate the pharmacokinetic parameters and therapeutic efficacy of the developed SMEDDS.

Keywords: Captopril, self-microemulsifying drug delivery system (SMEDDS), solubility enhancement, bioavailability, in vitro drug release.

INTRODUCTION

It is estimated that approximately 40% of new drug candidates are insoluble in water, and their oral delivery is frequently associated with inferior bioavailability, a high degree of intra- and inter-subject variability, and a lack of dose proportionality. Various formulation strategies have been employed to overcome these challenges, including surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and solid dispersions [1]. Recent research on self-emulsifying drug delivery systems (SEDDS) has focused on improving the oral bioavailability of lipophilic drugs using lipid-based formulations [2, 3]. It is a mixture of oil, solid or liquid surfactants, or, alternatively, one or more hydrophilic solvents as well as co-solvents or surfactants that is defined as Self-Emulsifying Oil Formulations (SEOFs) [4]. The formulation of poorly water soluble drugs has evolved from micronization to solid dispersion to complexation with cyclodextrins [5]. Recent research has shown that poorly water soluble drugs may have increased oral bioavailability when administered with meals rich in fat, resulting in a growing interest in the formulation of poorly water soluble drugs in lipids. Self-microemulsifying drug delivery systems (SMIDDS) have been studied extensively to increase oral bioavailability through lipid suspensions, solutions, and emulsions [6].

Self-Micro Emulsifying Drug Delivery Systems

A SMEDDS is defined as a mixture of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and cosolvents/surfactants that can be agitated mildly and diluted in aqueous media, such as GI fluids, to form fine oil-in-water (o/w) microemulsions [7]. In the gastrointestinal tract, SMEDDS spread rapidly, and the digestive motility in the stomach and intestines provides the necessary agitation to cause self-emulsion. The basic difference between self emulsifying drug delivery systems (SEDDS), also known as self emulsifying oil formulation (SEOF) and SMEDDS is that SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm, while SMEDDS form transparent microemulsions with a droplet size of less than 100 nm. Additionally, SMEDDS contain less oil than SEDDS, where the oil concentration is between 40 and 80%.

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Advantages of SMEDDS:
Improvement in oral bioavailability
Manufacturing ease and scaling up [8].

Reduction of variability between and within subjects, as well as effects of food:

There are several drugs that show large inter-subject and intra-subject variations in absorption, resulting in decreased drug performance and non-compliance on the part of the patient. Drug therapeutic performance in the body is greatly affected by the food we consume. Such drugs benefit from SMEDDS. Numerous research papers have been published which demonstrate that SMEDDS can provide reproducible plasma profiles independent of food [9].

Deliverability of peptides that is susceptible to enzymatic hydrolysis in the gastrointestinal tract:

The unique properties of SMEDDS make them superior to other drug delivery systems in that they can deliver macromolecules such as peptides, hormones, enzyme substrates and inhibitors as well as provide protection from enzymatic hydrolysis. If polysorbate 20 is used as an emulsifier in a microemulsion formulation, intestinal hydrolysis of the prodrug by cholinesterase will be prevented [10]. A thermo-labile drug, such as a peptide, can be synthesized spontaneously without the aid of energy or heat. [11].

Excipients Used In SMEDDS:

The pharmaceutical acceptance of excipients as well as the toxicity issues associated with the components used make the choice of excipients very critical. There are a number of restrictions regarding the choice of excipients.

OILS:

SMEDDS contains oil as a major excipient, not only because it solubilizes the required dose of lipophilic drug or facilitates self-emulsification, but also because it increases lipophilic drug transport via the intestinal lymphatic system, increasing the absorption from the gastrointestinal tract depending on the molecular structure of the triglycerides.

SURFACTANTS:

The design of self-emulsifying systems can make use of a variety of compounds exhibiting surfactant properties, but the selection is limited since very few surfactants are orally acceptable. There are several non-ionic surfactants that are generally recommended, including those with a relatively high hydrophilic-lipophilic balance (HLB).

CO-SOLVENTS:

For the production of an optimal SEDDS, relatively high concentrations of surfactants are required (generally more than 30% w/w). Cosurfactant can be used to reduce the concentration of surfactant. Co-surfactants work together with surfactants to decrease interfacial tension to a very small, even transient, negative value. This value would cause the interface to expand into fine dispersed droplets, which would then adsorb more surfactant and surfactant / co-surfactant until their bulk condition had depleted enough to restore positive interfacial tension. In self-emulsifying systems, co-surfactants are not always required, particularly for non-ionic surfactants [12].

Factors Affecting SMEDDS:

Nature and dose of the drug:
Polarity of the lipophilic phase:
Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS)
Effect of Dispersion on Bioavailability [14, 15].

Solidification Techniques for Transforming Liquid/Semisolid SMEDDS to S-SMEDDS:

Capsule filling with liquid and semisolid self-emulsifying formulations

Filling capsules with liquid or semisolid SE formulations for oral administration is the simplest and most common method of encapsulation.

In the case of semisolid formulations, there are four steps: (i) heating of the semisolid substances (while stirring); (ii) filling the capsules with the molten mixture; and (iv) cooling to room temperature. There are two steps involved in the preparation of liquid formulations: filling the capsules with the formulation and sealing the body and cap of the capsule, either by banding or microspray sealing.

Spray drying:

A formulation can be prepared using this technique by mixing lipids, surfactants, drugs, and solid carriers, followed by solubilizing the mixture before spray drying. A spray of droplets is formed by atomizing the solubilized liquid formulation. A drying chamber is used to absorb the volatile phase (for example, the water in an emulsion) and form dry particles under controlled conditions of temperature and airflow [16].

Adsorption to solid carriers:

Liquid SE formulations can be converted into free-flowing powders by adsorption on solid carriers [17].

Melt granulation:

The melt granulation process involves adding a binder to powders in order to achieve powder agglomeration. Melt granulation offers several advantages over conventional wet granulation due to the absence of liquid addition and subsequent drying. Additionally, it is a viable alternative to the use of solvents.

Melt extrusion/extrusion spheronization:

- ✓ Melt extrusion is a solvent-free process that produces products with high drug loadings (60%) and uniform compositions. The process of extrusion involves forcing raw materials with plastic properties through a die under controlled temperature, product flow, and pressure conditions in order to produce a product of uniform shape and density [18].

METHODOLOGY

Analytical method:

Preparation of 0.1 N HCl solution:

0.1 N HCl was prepared by diluting 8.5 ml of concentrated hydrochloric acid to 1000 ml distilled water.

Calibration curve of captopril:

Preparation of calibration curve of captopril in methanol:

Captopril 10mg was dissolved in a 100ml methanol to obtain 100µg/ml stock solution in 100ml volumetric flask. 0.1 ml of stock solution was diluted to 10 ml with methanol to get 10µg/ml solution in 10ml volumetric flask. 5-30µg/ml concentration solutions were prepared from the stock solution. The samples were analyzed by UV spectrophotometer at 210 nm

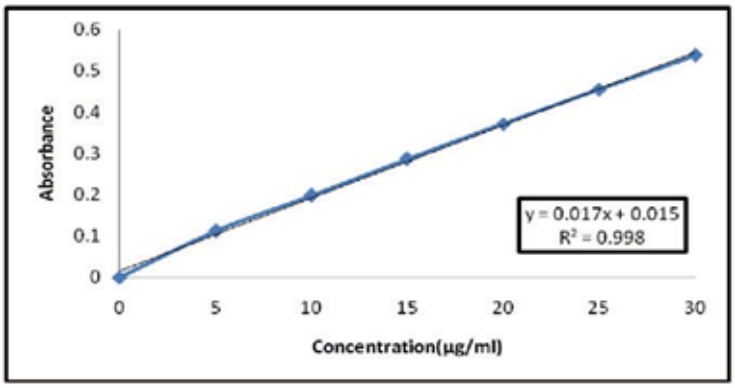

Figure 1: Calibration curve of captopril in methanol

Preparation of calibration curve of captopril in 0.1N HCL:

Captopril 10mg was dissolved in a 100ml 0.1N HCL to obtain 100µg/ml stock solution in 100ml volumetric flask. 1 ml of stock solution was diluted to 10 ml with methanol to get 10µg/ml solution in 10ml volumetric flask. 10-50µg/ml concentration solutions were prepared from the stock solution. The samples were analyzed by UV spectrophotometer at 210 nm.

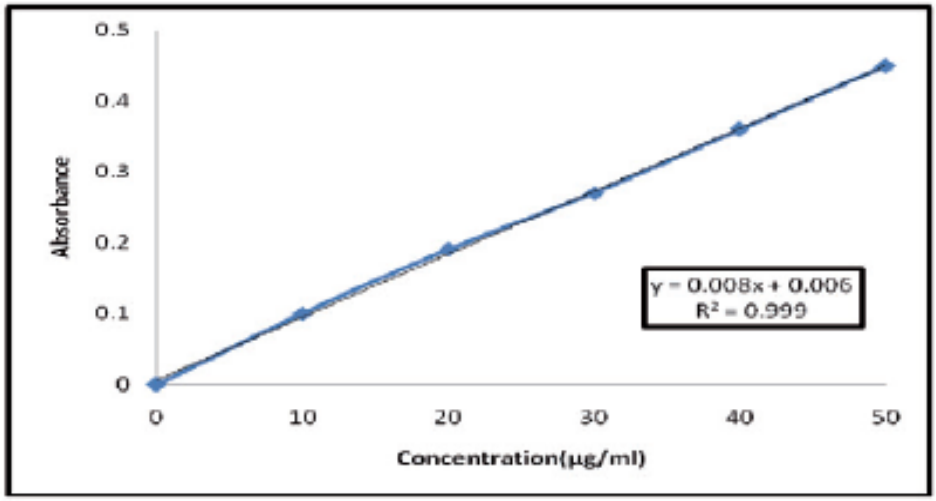

Figure 2: Calibration curve of captopril in 0.1N HCL

List of Materials:

Captopril, Polysorbate 80, Capryol 90, Tween 80, Polyethylene glycol 400, Labrasol, Peceol, Transcutol P, Captex 200, Captex 200P, Isopropyl myristate. Plurol Olieque, Labrofil, Capmul MCM.

List of Reagents:
0.1 M Hydrochloric Acid (HCl), Methanol, Distill water.

List of Equipment's:
Digital weighing balance, Digital pH meter, Magnetic Stirrer, Malvern zetasizer, Dissolution apparatus, UV spectrophotometer.

Preparation of Captopril SMEDDS:

As shown in Table 3, a series of SMEDDS formulations were prepared using various oils, surfactants, and co-surfactants. There was no change in the dose of captopril in any of the formulations (i.e., 10 mg). It is recommended that the amount of SMEDDS be calculated so that it completely solubilizes the drug (single dose). Into the mixture was added 10 mg of captopril. A vortex mixing method was then used to mix the components, and they were heated at 37 degrees Celsius after they had been combined. In order to preserve the quality of the mixture, it was stored at room temperature. Accordingly, prepared SMEDDS consisted of oils, surfactants, cosurfactants, and drugs.

Characterization of Smedds of Captopril
Viscosity and pH:

Rheological properties of formulations were determined by measuring their viscosities. To accomplish this, a Brookfield LVDV 111+ CP viscometer at 30°C was used with a CPE 42 spindle at 5 revolutions per minute. A pH meter was used to measure the pH of the formulations.

Dispersibility test:

A standard USP XXII dissolution apparatus 2 was used to assess the efficacy of self-emulsification of oral SMEDDS. 500 ml of water was mixed with a milliliter of each formulation at 37 degrees Celsius. The dissolution paddle rotated at a speed of 50 revolutions per minute in order to provide gentle agitation. Based on the grading system, the in vitro performance of the formulations was assessed visually.

Drug content:

A UV spectroscopic method was used to determine the drug content of captopril SMEDDS formulation. The 10 µg/ml of aliquot was prepared using SMEDDS formulation using methanol as a solvent. The samples were measured as 210 nm using UV spectroscopic method.

Particle size distribution

A gram of SMEDDS was dispersed in 100 ml of distilled water and 0.1 mol/l HCl at 37 ± 0.5˚C. A magnetic stirrer was used to gently agitate the emulsions for a period of 10 minutes. Moreover, it was used to determine the PSD and 3-potential of the final micro emulsion.

% Transmittance Measurement:

An UV spectrophotometer was used to measure the percent transmittance of various formulations at 210 nm while methanol was used as a blank.

Polydispersibility Index:

Particle size distribution follows the same procedure as A gram of SMEDDS was dispersed in 100 ml of distilled water and 0.1 mol/l HCl at 37 ± 0.5˚C. A magnetic stirrer was used to gently agitate the emulsions for a period of 10 minutes.

In-vitro diffusion study:

A study was conducted in vitro using a dialysis bag method for studying drug diffusion. After soaking the dialysis bag overnight in 0.1 N HCl, it was used for the experimental procedure the following day. At 37±0.5˚C, 500 ml of 0.1 N HCL as dissolution medium was instilled with 1 ml of Captopril SMEDDS, which was then placed in 1 ml of Captopril SMEDDS. During the revolution of the paddle, the speed was maintained at 50 revolutions per minute. At regular intervals (5 minutes), samples (5mL) were taken and replaced with aliquots of 0.1 N HCL. The SMEDDS formulation was compared with the conventional capsule formulation as well as the suspension of pure drug. An HPLC method at 210nm was used to determine the drug content of the samples.

Stability of Captopril SMEDDS:

Captopril SMEDDS samples were sealed in ampoules and then stored in Stability chambers at 25 and 40±0.5˚C for three months. In order to evaluate the stability of the samples, duplicate samples were taken at 0, 1, 2 and 3 months. Physical stability was assessed by visual inspection for physical changes, and particle size was determined by a particle size analyzer following dilution with water and 0.1 mol/l hydrochloric acid. A measurement of chemical stability was made by measuring the content of captopril by UV spectroscopy at 210nm.

RESULTS AND DISCUSSION
Viscosity and pH:

Rheological techniques can be used to monitor the viscosity of microemulsion systems. A variety of oils and surfactants may be used. All formulations were found to have a viscosity of less than 0.8877 centipoise. As a result of the formulation,

exhibits a viscosity of 0.8872 cP, which is highly similar to water's viscosity, which is 1.0. This indicates that SMEDDS forms an o/w microemulsion in which water remains the external phase and SMEDDS exhibits a viscosity that is close to that of water. This indicates that formulation c1 is a very clear, transparent, and low viscous liquid.

As another important parameter, pH was measured. The pH of the final preparation is determined by the excipients used in the formulation. It is possible that a change in pH may affect the zeta potential of the formulation, which can have an adverse effect on its stability. pH values for all formulations were similar, ranging from 5.3 to 6.0. As a result, pH does not affect the stability of the formulation. Therefore, it can be assumed that the drug does not diffuse in the external phase and remains in the oil phase. Since water constitutes the external phase of the system, the entire system displays the pH of water. As captopril is acid pH, the formulations here have an acidic to neutral pH, which is conducive to its stability.

Table 1: Viscosity and pH of SMEDDS formulation

Formulation code	Viscosity (cP)	pH
C1	0.9674	2.8
C2	0.9745	2.6
C3	0.9771	2.4
C4	0.9847	2.5

Dispersibility test:

Micro emulsion formulations can phase separate under infinite dilution, resulting in the precipitation of poorly soluble drugs as micro emulsions are formed at a particular concentration of oil, surfactant, and water. Due to dilution by gastrointestinal fluids, microemulsions administered orally gradually desorb surfactant located at the globule interface. Surfactants must maintain a concentration in aqueous phase equal to their CMC to be thermodynamically driven. We used distilled water as a dispersion medium because it has been reported that microemulsions prepared with nonionic surfactants in either water or simulated gastric or intestinal fluid do not differ significantly. After passing the Dispersibility test, Grade A and B formulations were selected for further research since they will remain microemulsions after dispersion in the gastrointestinal tract. Those formulations that scored in Grades C, D, and E of the Dispersibility test were discarded for further investigation. The use of a formulation that falls within Grade C for self-emulsifying drug delivery may be appropriate. Formulas were selected based upon criteria of increasing oil concentrations and using as little surfactant as possible for its solubilization, regardless of the Smix ratio used for each percentage of oil (5%, 10%, 15%). The optimal formulations were used for the analysis of in vitro release, globule size and viscosity.

Particle size distribution (PSD):

During self-emulsification, the droplet size of the emulsion plays an important role in determining the rate and extent of release and absorption of the drug. There is also evidence that smaller droplets of emulsion may promote faster absorption and enhance bioavailability. Captopril SMEDDS diluted with water and with 0.1mol/l HCl, respectively. As shown in Table 5, Captopril SMEDDS have a mean particle size of 0.30 microns. In water, R4IIB had a mean particle size of 10.17 nm and was the optimal batch. Due to SMEDDS, the resultant emulsion had a small mean size and a narrow particle size distribution regardless of the dispersion medium used. The charge of SEDDS is another important property that should be taken into consideration

Table 2: Particle size of the various SMEDDS formulations

Formulation code	**Avg. Particle size**	
	Water	**HCL**
C1	**26.5**	**25.4**
C2	**10.06**	**78.1**
C3	**214**	**197**
C4	**145**	**124**

% Transmittance:

Microemulsion clarity was assessed by measuring transmittance (%T) in terms of transparency. Due to the presence of water as an external phase, SMEDDS forms an o/w microemulsion. There is a 99% transmittance value

for Formulation C4. This indicates that the microemulsion is highly transparent. A %T value of 96% was observed in other systems, indicating a lack of clarity in microemulsions. The formulation may have a larger particle size, which may explain this phenomenon. Because oil globules have a larger particle size, they may reduce the transparency of microemulsions and thereby reduce the values of %T.

Table 3: % Transmittance

Period Days	% T	
	25°C	40°C
0	99.6±0.3	99.5±0.4
15	99.4±0.4	99.4±0.5
30	99.5±0.2	98.3±0.5
45	99.4±0.4	97.2±0.4
60	99.2±0.4	94.1±0.3
90	99.3±0.4	92.6±0.2
120	99.1±0.5	89.4±0.3

Polydisbersibility Index (PDI):

Measurement of polydisbersibility, which determines the size range of particles in a system, consists of the following formula:

(No.of particles having size greater than 100nm)
= ----------
(No.of particles having size less than 100nm)

There is an index that is referred to as Polydisbersibility Index (PDI) that measures polydisbersibility. SMEDDS are ideal if they have a wide distribution of nanoparticles with a maximum of 24% of particles less than 100nm. As shown in table 4, the data are as follows.

Table 4: Polydispersibility index of Captopril SMEDDS formulations

Formulation code	PDI
C1	0.134
C2	0.094
C3	0.247
C4	0.219

In- vitro diffusion study:

As a valuable tool for predicting the behavior of a formulation with regard to drug transport across membranes, in-vitro diffusion of formulations is an effective tool. It is possible to derive physicochemical parameters pertaining to formulations, such as flux, partition coefficient, and diffusion coefficient, through in-vitro evaluation techniques. Among all the liquid SMEDDS formulations, formulation C4 demonstrated the highest release rate, 99%. This formulation was therefore considered to be the optimal liquid SMEDDS formulation.

The UV method could not be developed for formulation due to interference of oil at the same wavelength as the drug, however, this interference did not occur after the drug was released across the dialysis bag. This indicates that oil globules do not diffuse through membranes, and only drugs are allowed to penetrate. The in-vitro study concluded that SMEDDS greatly enhanced the release of Captopril.

Based on the results, formulation C4 has the highest release rate at 60 minutes, i.e. 99 out of all the formulations at all times. Thus, it is the optimized batch for liquid SMEDDS formulations of Captopril.

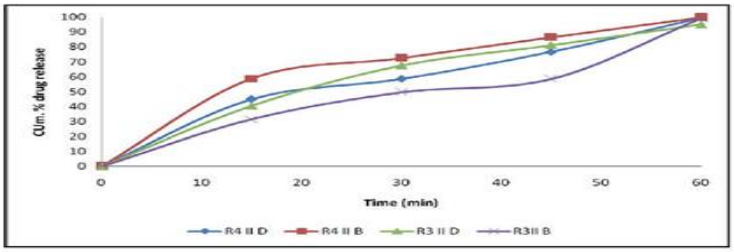

Figure 3: *In vitro* diffusion study of various SMEDDS formulation

Stability Studies

A vanderwaals attraction results in two particles coming closer to one another, causing flocculation, which results in an increase in the size of the droplet or microemulsion. The viscosity of the system increased proportionally to the size of the droplets. Additionally, the presence of oil droplets reduced UV light transmittance and, therefore, the transmittance percentage. The ICH guidelines specify that stability conditions can be determined based on a specific zone. In this study, two conditions were used, namely 25 C and 40 C, for a period of three months. Based on the data, formulation C4 appears to be more stable. A comparison was made between the two formulations based on their percentage T and drug content. The assay of C4 was found to show a reduction of 3% in amount of drug during the 3 months a reduction of 4% at 25˚C.

Table 5: Stability data of C4 and Marketed formulation for % Drug content

Period (days)	25˚C		40˚C	
	C4	M	C4	M
15	99.14	98.47	98.86	98.47
30	98.59	98.13	96.37	89.34
45	97.78	97.05	92.74	81.74
60	97.27	96.74	88.07	76.84
90	96.88	95.84	82.56	71.38
120	96.16	95.18	76.87	67.64

CONCLUSION

It was found that captopril is most soluble in Capryol 90 when compared to other oils, whereas it is least soluble in water- 0.09±0.01mg/mL. It was therefore decided that Capryol 90 would be the oil phase in which the formulation would be developed. It is observed that C1, C2, C3, C4 of the prepared SMEDDS formulations are clear when diluted. Microemulsions were poor when cosurfactant concentration was higher than surfactant concentration. As a result of the higher concentration of oil in SMEDDS, the possibility of a high concentration of captopril being dissolved and incorporated may be greater. All formulations were observed to have a viscosity lower than 0.8877 cp, which was an indication that all SMEDDS forms o/w microemulsions due to their low viscosity. In the formulation, it was found that the average particle size of the particles is at least 10.17 nm. There is evidence that formulation C4 has a higher stability profile than marketed conventional capsules of captopril based on the results of the stability studies. It is possible that the optimal formulation of captopril SMEDDS may enhance the bioavailability of captopril.

REFERENCES

1. Kommuru TR, Gurley B, Khan MA, Reddy IK, *et al*. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. *Int J Pharm* 212, 2001, 233-46.
2. Humberstone AJ, Charman WN, *et al*. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. *Adv Drug Del Rev* 25, 1997, 103-28.
3. Pouton CW. Formulation of self-emulsifying drug delivery systems. *Adv Drug Del Rev* 1997; 25: 47-58.
4. *Gursoy RN*, Benita S, *et al*. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomed Pharmacother* .58, 2004, 173-82.
5. Stegemanna S, Leveillerb F, *et al*. When poor solubility becomes an issue: from early stage to proof of concept. *Eur J Pharm Sci* 31, 2007, 249-61.
6. Murdandea SB, Gumkowskia MJ, *et al*. Development of a self-emulsifying formulation that reduces the food effect for torcetrapib. *Int J of Pharm.* 351, 2008, 15-22.
7. Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res*. 21, 2004, 201–230.
8. Tang J. Self-Emulsifying Drug Delivery Systems: strategy for improving oral delivery of poorly soluble drugs. *Cur Drug Th* 2007; 2: 85-93.
9. Kawakami K, Yoshikawa T, Moroto Y, Kanakao E, Takahuani K, Nishihara Y, Masuda K, *et al*. Microemulsion formulation for enhanced absorption of poorly soluble Drugs. I. Prescription design. *J of Contr Rel* 81, 2002, 75-82.
10. Lawrence MJ, Rees GD, *et al.* Microemulsion-based media as novel drug delivery system. *Adv Drug Deliv Rev* 45, 2000, 89-121.
11. Gursoy RN, Benita S, *et al*. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biom & Pharma*. 58, 2004,173–182.

12. Anand U. Kyatanwar, *et al.* Self-micro-emulsifying drug delivery system (SMEDDS): Review. *J of Phar Res* 3, 2010, 75-83.
13. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharm Res* 12, 1995, 1561–72.
14. Attama AA, Mpamaugo VE, *et al.* Pharmacodynamics of piroxicam from self-emulsifying lipospheres formulated with homolipids extracted from Capra hircus. *Drug Deliv* 13, 2006 , 133–137.
15. Porter CJH, Charman WN, *et al,* In vitro assessment of oral lipid based formulations. *Adv Drug Delivery Rev* 2001; 50: S127-S147.
16. Jannin V, *et al.* Approaches for the development of solid and semi-solid lipid-based formulations. *Adv Drug Deliv Rev* 60, 2008, 734–746.
17. Ito Y, *et al.* Oral solid gentamicin preparation using emulsifier and adsorbent. *J Control Release* 105, 2005, 23–31.
18. Verreck G, Brewster ME, *et al.* Melt extrusion-based dosage forms: excipients and processing conditions for pharmaceutical formulations. *Bull Tech Gattefosse*. 97, 2004, 85–95.