Research Article *ISSN: 2277-8713*
Bakshi Madhura, IJPRBS, 2013; Volume 2(1): 29-53 *IJPRBS*

FORMULATION DESIGN AND EVALUATION OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF CIPROFLOXACIN

BAKSHI MADHURA, MAHAJAN SC, BHANDARI GOVIND

IJPRBS-QR CODE

PAPER-QR CODE

Mahakal Institute of Pharmaceutical Studies, Ujjain, M.P., India.

Accepted Date:

27/12/2012

Publish Date:

27/02/2012

Keywords

Sustain release, Oral bioavailability,

Pseudo ternary phase diagram,

Ciprofloxacin,

Self micro emulsifying drug delivery system (SMEDDS).

Corresponding Author

Ms. Bakshi Madhura

Abstract

The objective of the present research work has to formulate self micro emulsifying drug delivery system (SMEDDS) of Ciprofloxacin drug, a poorly water soluble anti-microbial drug that exhibits low bioavailability. Solubility of ciprofloxacin in various oils, surfactants and co surfactants was determined. Phase diagram were constructed at different ratios of surfactants (tween 80, pluronic F_{127}), co surfactant (ethanol) and oil (oleic acid) to determine microemulsion existence region to find out the optimized formulation. Pluronic F_{127} used as a surfactant to shown solubilizing agent profile. There are different ratios of formulations were prepared, out of them three formulations (F3, F4 & F5) were selected as o/w microemulsion formulations and evaluated for in-vitro dissolution studies, percent drug content and stability studies to find out the optimized o/w microemulsion formulation. Drug content of F3 was more than F4 & F5 because of increased solubility of drug in excipients. F3 formulation is the optimized o/w microemulsion formulation than F4 & F5 formulations with respect the results obtained by percent drug content, *in-vitro* dissolution release and stability study profile. Shape morphology of F3 o/w microemulsion is approx 338.46nm to 554.70nm. Size distribution and zeta potential of F3 is 360nm and -7.64mv respectively. This indicates plateau of moderate stability & no agglomerates. All formulations (F3, F4 & F5) were shown good physical stability and slightly reduced chemical stability due to results found from % drug content studies. The developed SMEDDS highlight safety for use and potential applications of used components in the development of novel drug delivery system.

INTRODUCTION

Over recent years, much attention has been focused on lipid microemulsion formulations, with particular emphasis on liquid self-microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs (**Balakrishnan *et al.,* 2009; Cui *et al.,* 2009; Woo *et al.,* 2008**). Emulsion-based delivery systems are being used increasingly for encapsulating lipophilic bioactive components in the pharmaceutical industry (**Porter *et al.,* 2007)**. Oil-in-water (O/W) emulsions, or nanoemulsions, can be prepared by solubilizing the lipophilic bioactive components within the oil phase, and then homogenizing this phase with an aqueous phase containing a water-soluble emulsifier. The size of the droplets produced depends on the composition of the system and the homogenization method used (**Solans *et al.,* 2005**). The oral delivery of lipophilic drugs presents a major challenge because of the low aqueous solubility. Lipid-based formulations have been shown to enhance the bioavailability of drugs administered orally (**Hou *et al.,* 2003; Sarkar, 2002; Gao *et al.,* 2004; You *et al.,* 2005**). Self-microemulsifying drug delivery systems (SMEDDS) recently have gained great interest in drug delivery research for its potential in improving oral bioavailability of poorly water soluble drugs. SMEDDS are defined as isotropic mixtures of oil, surfactant, cosurfactant and drug that rapidly form o/w microemulsion when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in GI tract. SMEDDS presents the drug in nanosized droplets offering large interfacial area for drug diffusion (**Gursoy *et al.,* 2004; Lawrence *et al.,* 2000.**). The pre-mixture can be stored for a very long period in capsules because of the high thermodynamic stability. Such formulations can be encapsulated into various types of capsules. The finished product is then administered to the patient as a solid dosage form **(Yamahira *et al.,* 1979).**

Ciprofloxacin is a broad-spectrum anti-infective agent of the fluoroquinolone class. Ciprofloxacin has *in-vitro* activity against a wide range of gram positive and gram negative micro-organism. The bactericidal action of ciprofloxacin results from inhibition of the enzymes Topoisomerase II

(DNA gyrase) and Topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, strain supercoiling repair and recombination. Drug rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of ciprofloxacin is 69% with no substantial loss by first pass metabolism. Peak plasma concentration is 8.3 µg/mL, and half life is 4hr.

SMEDDS are regarded as an attractive approach because of high drug Solubilizing capacity and improvement in both rate and extent of absorption by the lymphatic uptake. Ideally, these novel formulations allow the drug to remain in dissolve state throughout the transit through the gastrointestinal tract thereby enhancing the bioavailability of poorly water soluble therapeutic agents with reproducible plasma profile **(Constantinides, 1995; constantinides and scalar, 1997**). Considering these advantages, SMEDDS could be a valuable strategy in overcoming problems associated with the delivery of Ciprofloxacin. The objective of study was to design and evaluation of Ciprofloxacin SMEDDS for improving its solubility, bioavailability, dissolution rate and therapeutic efficacy. The present study, for the first time, reports the successful development of SMEDDS of Ciprofloxacin that can improve its delivery.

Materials and methods

Materials

Ciprofloxacin base was give as gift sample by Ranbaxy PVT LTD, Dewas (M.P). Oleic acid, tween 80 and ethanol obtained from (SD fine chem. Ltd., Mumbai), pluronic F_{127} obtained from (Sigma Lab, Mumbai), Disodium hydrogen phosphate and Dihydrogen potassium phosphate obtained from (Merck Ltd., Mumbai).

Screening of components (Mandawgade *et al.,* 2008)

The saturation solubility of ciprofloxacin in various oils, surfactants, co surfactants was determined. Briefly, excess amount of drug was added to each test tube containing 1ml of oil, surfactant, and co-surfactant. After sealing, the test tubes were shaken in an isothermal shaker (37.0±2 °C) for 24 hour. Each tube was centrifuged at 3000-5000rpm for 15min and the amount of drug present in the supernatant was determined by UV spectroscopy. The components were

selected for further studies depending on the maximum drug solubility in oil phase, surfactant and co-surfactant.

Construction of pseudo-ternary phase diagram (Borhade *et al.,* 2008)

Pseudo-ternary phase diagrams of oil, surfactant, cosurfactant and water were developed using titration method at 25±2 °C. Phase behavior of systems was studied at various ratios of surfactant to cosurfactant (Km) viz. 1:0.5, 1:1 and 1:2. Mixtures of surfactant and cosurfactant (at a specific Km) with water were prepared at ratios (w/w) of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10. A small amount of oil in 0.5% w/w increment was added in vials; vortexed and allowed to equilibrate. Resulting mixtures were evaluated visually for transparency and flow properties; and by polarizing microscope for optical isotropy. Endpoint of titration was the point, Where mixture became turbid or phase separation was observed. At this point, amount of water, oil, surfactant and cosurfactant added was noted. Monophasic, clear, low viscous and non-birefringent systems were considered as microemulsion (ME) and shown as ME region.

Preparations of SMEDDS of ciprofloxacin (Porter *et al.,* 2007)

SMEDDS are composed of oil, hydrophilic surfactant, and a co-solvent. The primary step during formulation of a SMEDDS is the identification of specific combinations of excipients and constructs a phase diagram which shows various concentrations of excipients that possess self-emulsification. A hydrophilic surfactants (tween 80, pluronic F_{127}), and a cosurfactant (ethanol) was dissolved and homozinased at 40-60°C with 70-80 rpm by using homoziniser. After proper mixing added an oil (oleic acid) containing accurately weighed ciprofloxacin in a beaker with the mixture ratio, given in table no.1. Then water was added to preparation and homozinised for 1-2 hr., and 20mg of ciprofloxacin entrapped o/w microemulsion were prepared. Different ratios of formulations were show in table no.1.

2.5 Drug content estimation (Porter *et al.,* 2007)

Microemulsions containing 20mg of drug was dissolved in50ml of suitable media (phosphate buffer 6.8 pH) taken in volumetric flask. The drug was allowed to dissolve in the suitable solvent. The solution was filtered. 1ml was taken in100ml of volumetric flask and diluted up to mark with suitable media and analyzed spectrophotometrically at 271nm. The concentration of ciprofloxacin in mg/ml was obtained by using standard calibration curve of the drug in suitable media.

Determination of shape and surface morphology and zeta potential measurement (Porter *et al.,* 2007; Borhade *et al.,* 2008)

The shape and surface morphology of the o/w microemulsions was studied by using scanning electron microscope. Zeta potential measurement is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is negative due to presence of free fatty acids. Measuring the zeta potential of the particles by zeta meter.

***In-vitro* dissolution study (**Porter *et al.,* 2007; Borhade *et al.,* 2008)

The optimized SMEDDS formulations were filled volumetrically in transparent hard gelatin capsules (size zero, 2). *In vitro* drug release profile of the ciprofloxacin from the SMEDDS was evaluated using USP XXIII Dissolution Testing Apparatus I at 100 rpm, with dissolution medium 0.1 N HCl and phosphate buffer 6.8 pH (900ml), at temperature 37.0±1.0 °C. After appropriate time intervals (0, 1, 2, 3, 4, 5, 6 to 12 hr), 1ml sample was withdrawn from media and equal volume of fresh media was added to replace the withdrawn sample. The samples were analyzed by UV spectrometer at 271 nm. The release profile of developed SMEDDS of ciprofloxacin was evaluated.

Stability studies (Porter *et al.,* 2007)

Formulations F3, F4 and F5 of ciprofloxacin o/w microemulsion were tested for stability according ICH guidelines. Preparations were divided into 3 sets and were stored at 4°C (refrigerator), room temperature and 40°C (thermostatic oven). After 15, 30 days drug content of all formulations was determined by the method discussed previously in *in-vitro* drug release and percent drug content is determined.

RESULTS AND DISCUSSION

Screening of contents

The solubility of ciprofloxacin in various excipients and oils and surfactants are shown in figure no.1 (a) and (b). As it is important to achieve optimum drug loading, solubility study was aimed to identify suitable SMEDDS components that possess good solubilizing capacity for selected drug. Ciprofloxacin showed high solubility in oleic acid (oil). In the surfactants tween 80 and pluronic F_{127} shows maximum drug solubility and in co-surfactants ethanol show high drug solubilization property. It was observed that ciprofloxacin showed complete miscibility and no phase separation with oleic acid (oil), tween 80, pluronic F_{127} (surfactants) and ethanol (co surfactant). Selection of surfactants and co-surfactants was governed by their emulsification efficiency for selected oily phases rather than their ability to solubilize ciprofloxacin. Solubility study also indicated that ciprofloxacin has poor aqueous solubility and was independent of pH of the medium.

Construction of pseudo ternary phase diagram

Phase diagrams were constructed to obtain the proportion of components that can result in maximum microemulsion existence area. Only certain combinations of oil, surfactant and a co-surfactant in a certain composition range will produce a fine microemulsion upon aqueous dilution. To check emulsification efficiency of SME (self micro emulsifying) mixtures, test for emulsification was performed on all ten combinations and the resultant dispersions were visually assessed. Resulting dispersions either formed a clear microemulsion, a slightly turbid emulsion or a milky emulsion which immediately phase separated. In Fig. 2 (a), (b) & (c) the area bound by the points in the phase diagram displays the concentration range of SME mixture components that resulted in a clear microemulsion out of all the ten concentrations. All the three combinations (F3, F4 & F5) under test formed a microemulsion region. Results from fig. 2 (c) shows that SME mixtures containing F5 formulation took more time to emulsify than the F3 & F4 formulations. The F3 formulation possessed the largest SME region in the phase diagrams and took the least time to micro-emulsify. They were

completely emulsified within a minute and the dispersion was clear and transparent. The microemulsion existence area of three formulations of developed SMEDDS is shown in Fig. 2 (a), (b) & (c).

Preparation of SMEDDS

Based on the results of screening and solubility of drug in various excipients (oil, surfactant and co-surfactant), oleic acid, tween 80 & pluronic $F_{127,}$ ethanol were selected as oil phase, surfactant and co-surfactant respectively. By using different Smix & oil ratios, there are ten formulations were prepared. From all ten formulations some were shown cloudy, milky and transparent appearance. After visual inspection and constructing the phase diagram there are three formulations (F3, F4 & F5) were selected as o/w microemulsion with the different ratios of Smix and oil. These three formulations were going to be evaluated for percent drug content, percent drug release, and stability study. Based on the results of above evaluations optimized formulation of o/w microemulsion was determined. The Smix and oil ratios of all formulations are shown in table no.1 and composition of selected o/w microemulsion were shown in table no.2.

Drug contents

For a successful delivery of drugs via SMEDDS, the entire dose of the drug should be soluble in an acceptable volume of SME mixture. If the drug solubility is inadequate there are chances of drug precipitation upon aqueous dilution. Thus the solubility of the drug in the excipients is an important criterion for selection apart from the excipients self-microemulsifying tendency. The percent drug content was evaluated in all three formulations (F3, F4, and F5) of ciprofloxacin o/w microemulsions. Percent drug content of F3, F4 and F5 was found to be 80.5%, 68.25% and 54.6% respectively. It was observed that the drug content of F3 was more than F4, F5 microemulsions. This may be due to of increased solubility of drug in excipients. Based on the results of percent drug content of all three (F3, F4 & F5) formulations, F3 formulation was selected as an optimized o/w microemulsion for drug delivery. The percent drug content results of o/w microemulsion formulations were shown in table no.3 and fig.no.3.

***In-vitro* dissolution studies**

The *in-vitro* dissolution studies are performed in order to ensure the quick release of the drug in the dissolution medium. The in-vitro profile of formulations F3, F4, & F5 were performed in 0.1 N HCl (gastric fluid), and phosphate buffer 6.8 pH (intestinal fluid) using a USP XXIII dissolution apparatus Type I with a paddle, speed of 100 rpm, with appropriate time intervals (0, 1, 2, 3, 4, 5, 6 to 12 hr). Based on the results of all the selected SMEDDS formulations (F3, F4 & F5), F3 o/w microemulsion formulation gives better drug released profile and selected as optimized o/w microemulsion. It is observed that within 12hr, 86.30% drug was released from the optimized formulation (F3) in 0.1 N HCl and phosphate buffer 6.8 pH media. The rapid release of the drug from the oil droplets suggests that the polarity of the oil of ciprofloxacin was appropriate, thus enabling the drug to partition out from the oil droplet. This establishes that SMEDDS can effectively increase the drug dissolution rate of poorly water soluble drugs and can be formulated as an immediate release dosage form for poorly water soluble drugs The SMEDDS are expected to quickly present ciprofloxacin in solubilized form in intestinal fluids after ingestion and would provide large interfacial area for absorption into intestinal area. The results of dissolution profile of o/w microemulsion formulations were shown in table no.4 and fig no.4.

Determination of shape and surface morphology

Scanning electron microscopes are scientific instruments that use a beam of highly energetic electrons to examine objects on a very fine scale. This examination can yield information about the topography (surface features of an object), morphology (shape and size of the particles making up the object), composition (the elements and compounds that the object is composed of and the relative amounts of them) and crystallographic information (how the atoms are arranged in the object).Scanning electron micrograph of formulation (F3) is shown in fig.no.5. Surface morphology of F3 o/w microemulsion was found to be approx 338.46nm to 554.70nm. Shape of optimized formulation F3 was smooth and oval.

Droplet size distribution and zeta potential measurements

The droplet size of the nanoemulsion is important since it determines the rate and extent of drug release and absorption. The drug can diffuse faster from smaller droplets into the aqueous phase, thereby increasing the drug dissolution (Shah *et al.,* 1997). Smaller droplet size presents large surface area for drug absorption. Reduction in droplet size improved bioavailability of ciprofloxacin emulsion when compared to a coarse emulsion (Tarr and Yalkowsky, 1989). The reduction in droplet size can be attributed to the stabilization of oil droplets due to localization of surfactant monolayers at the oil-water interface (Gursoy and Benita, 2004). Size distribution of F3 optimized formulation was 360nm. Result of F3 is shown in fig no.6.

The surface charge (zeta potential) of the nanoemulsion formed from SMEDDS is believed to play a role in its bioavailability. Because of the presence of fatty acids in the structure of the excipients used, generally the surface charge of the droplet is negative. Surface charge of the oil droplets present in the nanoemulsion may affect its interaction with the luminal intestinal mucosal cells. These cells are negatively charged with respect to mucosal solution in lumen (Bambeke *et al.,* 2005). If the surface charge of the droplet is positive, then there may be an electrostatic interaction between the mucosal cell surface and the droplets. This leads to an increased absorption of the administered drug and hence its bioavailability. The stability of the microemulsion was evaluated by measuring the zeta potential of the particles by Malvern zeta meter. The zeta potential result of optimized formulation F3 is shown in fig.no.7. Resulted potential of formulation F3 o/w microemulsion was in the range of -7.46mili volts, which indicates moderate stability and no agglomerate.

Stability studies

In formulation development research, the chemical stability of the active ingredient in the developed formulation and the physical stability of the developed formulation are criteria that govern the acceptance or rejection of developed formulation. The physical instability could be due to interaction of the drug with the excipients used in the formulation. The degradation of the drug may occur due to its inherent instability or due to its interaction with excipients used in the formulation No

change in the physical parameters such as homogeneity and clarity was observed during the stability studies. The studies revealed that there is slight reduction in the drug content of o/w microemulsion formulations after storage for 30 days. The data of % drug content studies of the o/w microemulsion formulation (F3, F4 & F5) shows that stored at 4°C has shown & % drug content, the one which was stored at 40°C has shown & % and at room temperature has shown & % drug content after 30 days. The formulations under investigation were shown good Physical stability but slight reduction in Chemical stability during the 30 days stability studies. The data of stability studies was shown in table no.5 and fig.no.8 (a),(b),(c)

CONCLUSION

The goal of this research work is to develop and formulate a self micro emulsifying drug delivery system (SMEDDS) of ciprofloxacin to evaluate it for various parameters like visual observation, surface morphology, size distribution, zeta potential analysis, percent drug content, *in vitro* drug release, stability studies.

From the results of the present research work, it could be summarized as successful development of SMEDDS for lipophilic anti-microbial drug ciprofloxacin, using an oleic acid (oil), tween 80 and pluronic F_{127} (surfactant) and ethanol (co surfactant) as a novel components. In SMEDDS formulation oil, surfactant and co-surfactant were selected on the basis of solubility and emulsification ability. Oleic acid, tween-80 pluronic F_{127} and ethanol was selected on the basis of solubility and emulsification ability for the SMEDDS formulation. Here, pluronic F_{127} used as a surfactant to shown solubilizing agent. Thus use of all these excipients would be a safe and promising alternative in the field of novel drug delivery system. Significant improvement in drug solubility, absorption rate and overcome dissolution rate-limited absorption of ciprofloxacin was realized with *in-vitro* dissolution drug release studies. SMEDDS of ciprofloxacin, as oral sustain release capsule dosage form deemed to be the efficacious and patient compliant delivery system in the anti microbial therapeutics.

Ciprofloxacin was formulated as a SMEDDS in an attempt to increase its solubility. An

optimized formulation of SMEDDS containing ciprofloxacin was developed through the construction of pseudo-ternary phase diagram, *in-vitro* dissolution study, particle size analysis and zeta potential and other evaluation study. SMEDDS provided significant increase in the solubility compared to a marketed formulation. SMEDDS appeared to be an interesting approach to improve problems associated with oral delivery of ciprofloxacin. Ciprofloxacin SMEDDS formulation was superior to marketed formulation with respect to *in-vitro* dissolution profile activity. Thus, SMEDDS can be regarded as novel and commercially feasible alternative to current ciprofloxacin formulations.

Oral route has been the major route of drug delivery for the chronic treatment of many diseases. Nearly 40% of new drug candidates exhibit low water solubility and hence high intra- and inter-subject variability and lack of dose proportionality. The formulation of such poorly water-soluble drugs is one of the most challenging tasks to the formulation experts. An enhancement in the solubility and dissolution rate can improve the oral bioavailability of such drugs, which further improves the therapeutic efficacy and patient compliance.

Self emulsifying drug delivery system (SMEDDS) represents an interesting prospect for the development of formulation for use as vehicle to deliver the lipophilic drug to the body. Hydrophobic drug can often be dissolved in SMEDDS allowing them to be encapsulating as unit dosage forms for oral administration.

ACKNOWLEDGMENT

I sincerely Thankful to my Guide and Institute, Mahakal Institute of Pharmaceutical Studies, Ujjain, India, to providing me the facilities for carrying out my research work. I also Thankful to Ranbaxy laboratories Pvt. Ltd., Dewas, M.P., India, for providing gift samples of ciprofloxacin drug; RGPV, Bhopal, M.P., India; Diya labs, Mumbai, Maharashtra, India, for providing best results in my research work. A special Thanks to my Batch mates for their expandable support in research work.

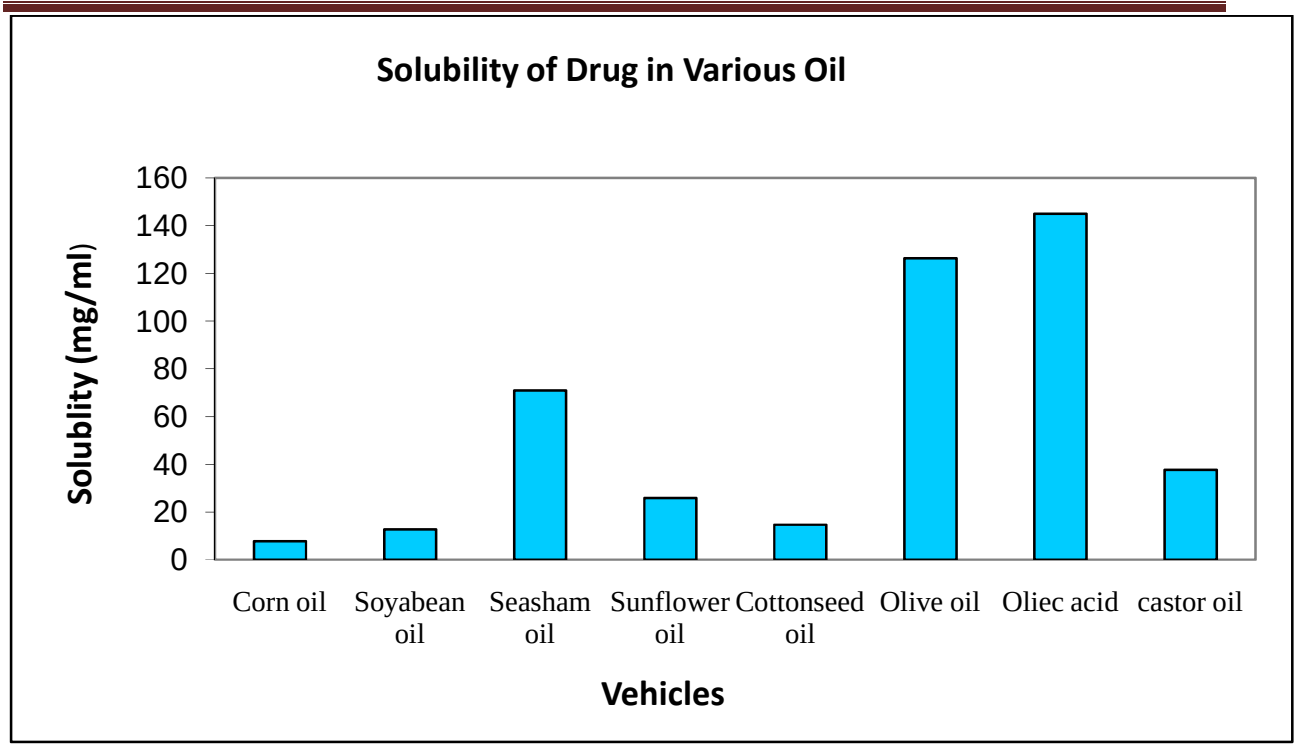


Fig.no. 1 (a) Screening of drug in various oil

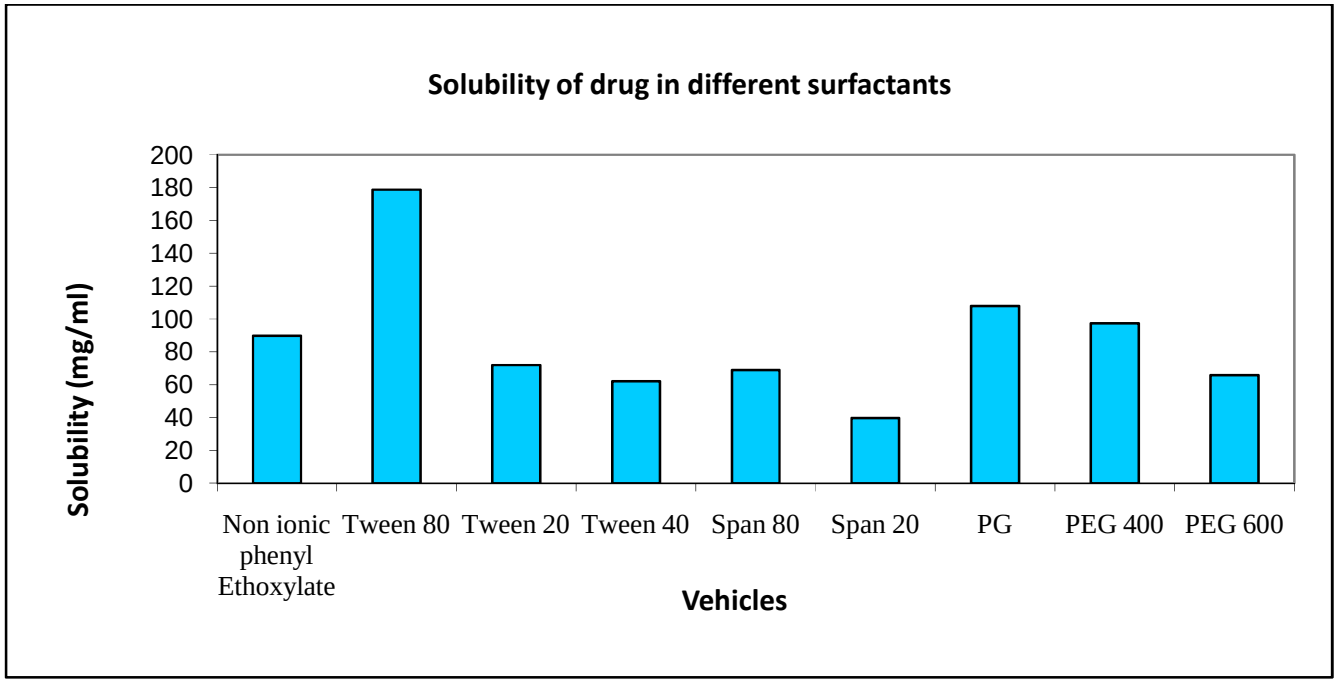


Fig.no. 1 (b) Screening of drug in different surfactant

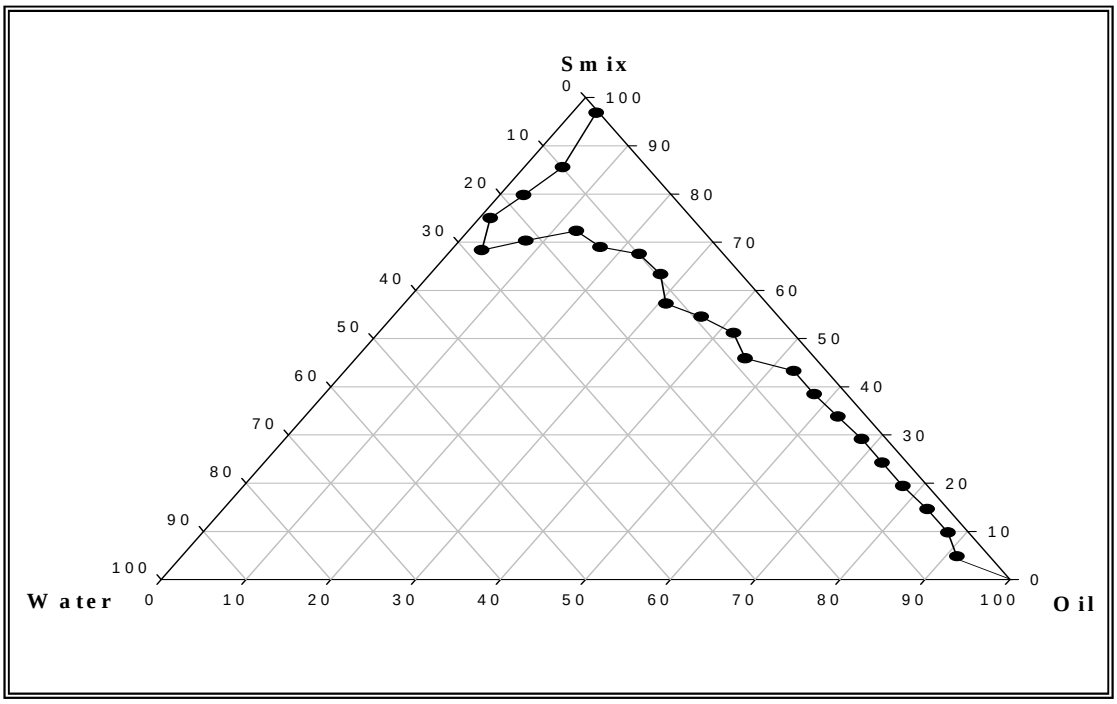


Fig.no.2 (a) Pseudo ternary phase diagram of formulation F3

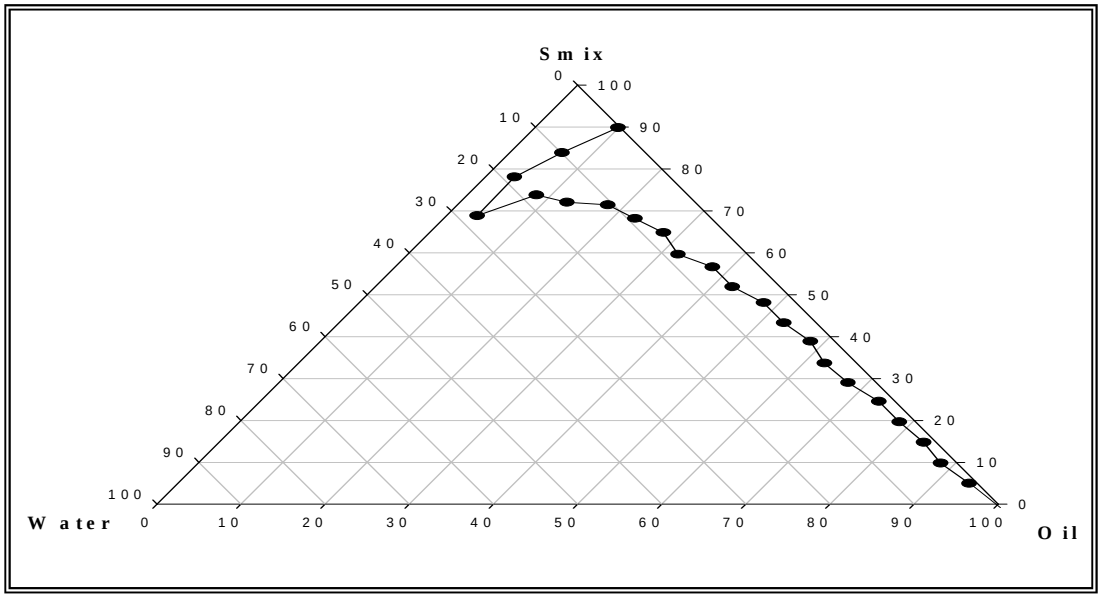


Fig.no. 2 (b) Pseudo ternary phase diagram of formulation F4

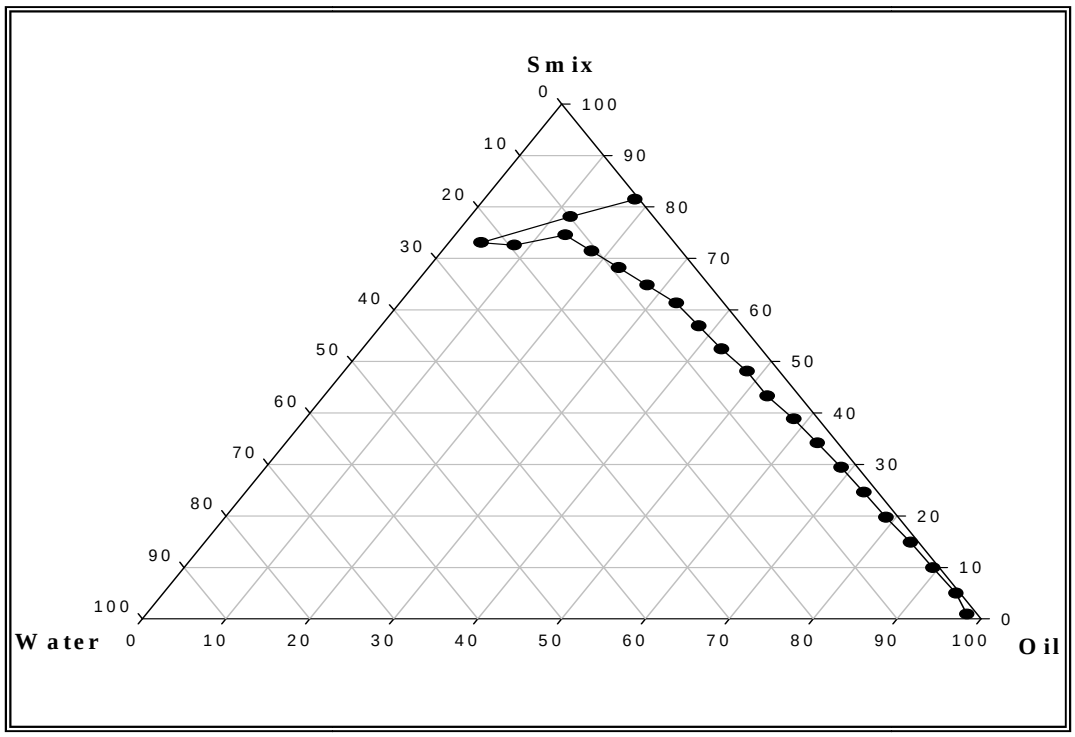


Fig.no.2 (c) Pseudo ternary phase diagram of formulation F5

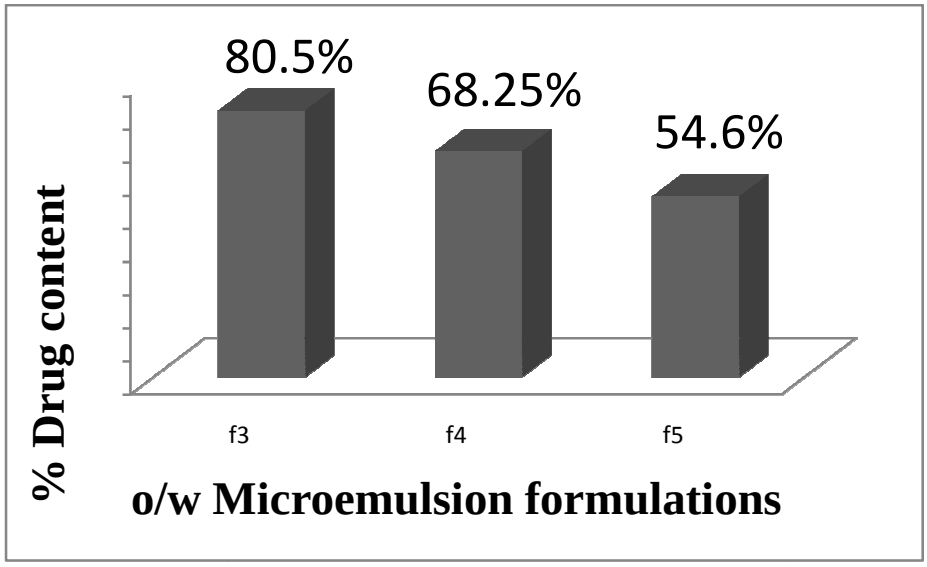


Fig. no.3 % Drug content of o/w microemulsion formulations

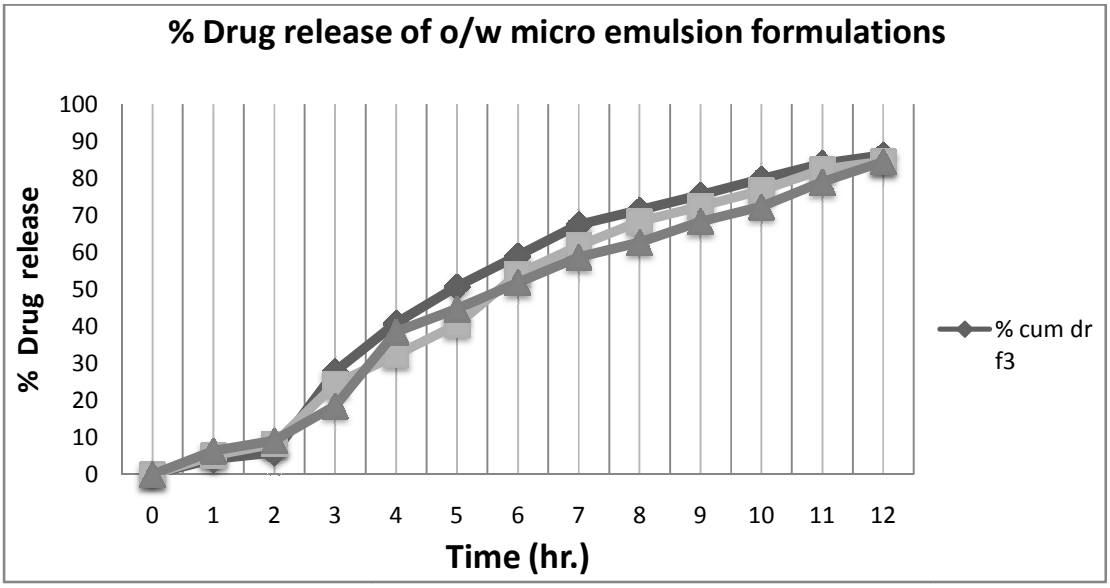


Fig.no.4 % Drug release results of formulations

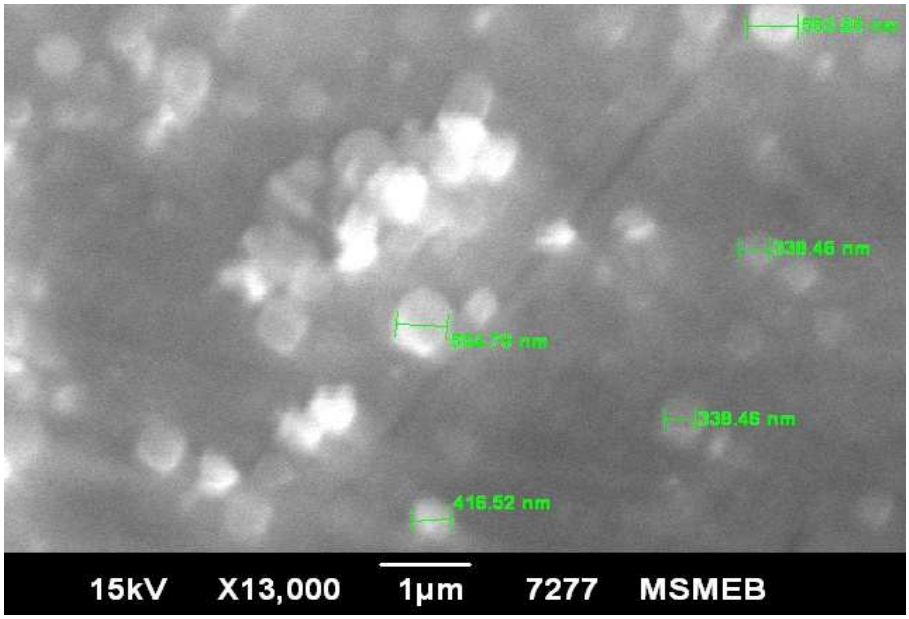


Fig.no.5 Surface morphology of f3 formulation (SEM)

Results

			Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm):	1250	Peak 1:	360.6	90.9	56.58
PdI:	0.985	Peak 2:	20.28	9.1	2.708
Intercept:	0.570	Peak 3:	0.000	0.0	0.000
Result quality	Refer to quality report				

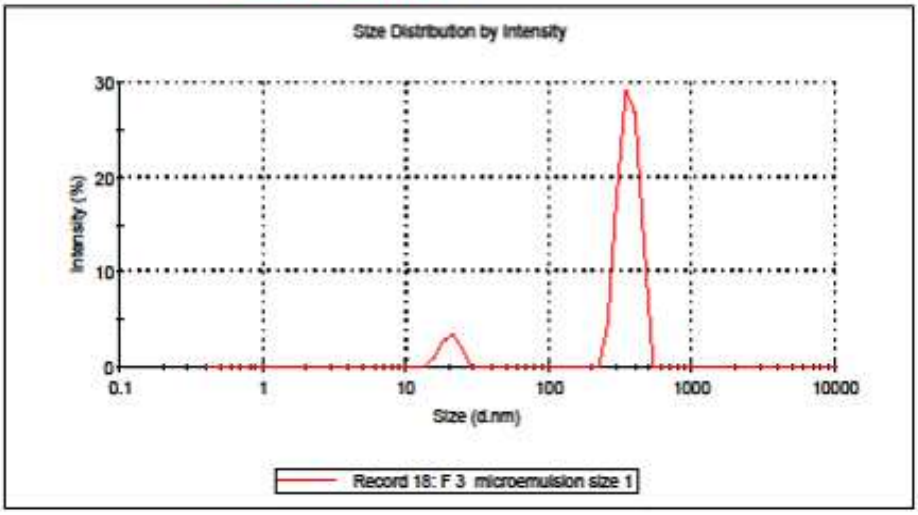


Fig.no.6 particle size distribution of f3

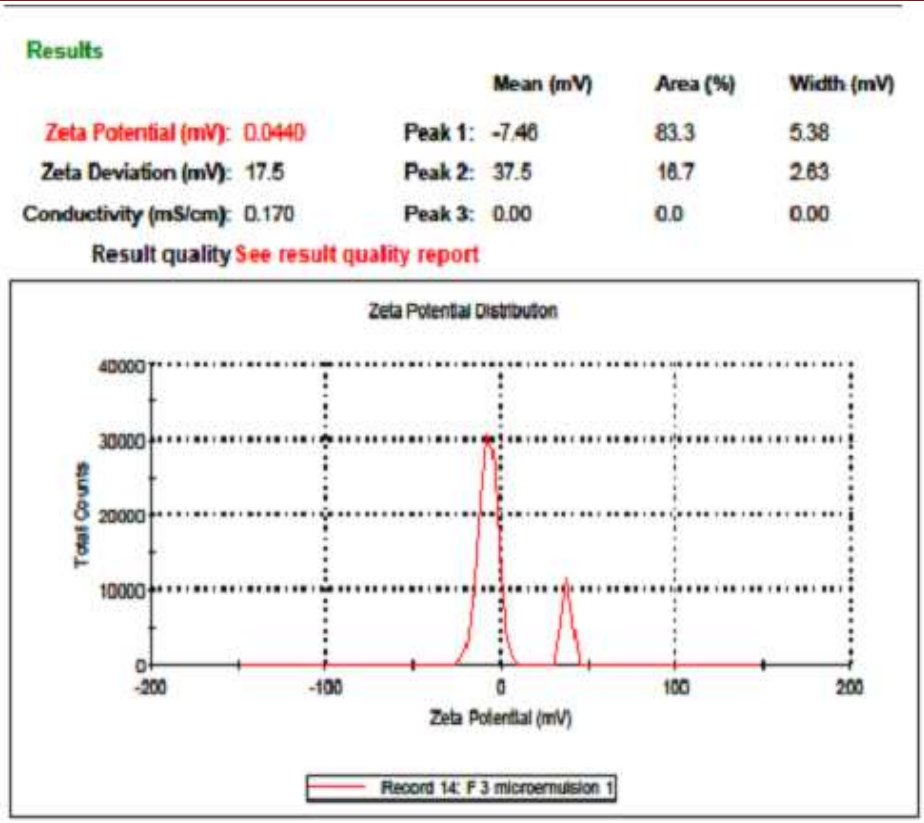
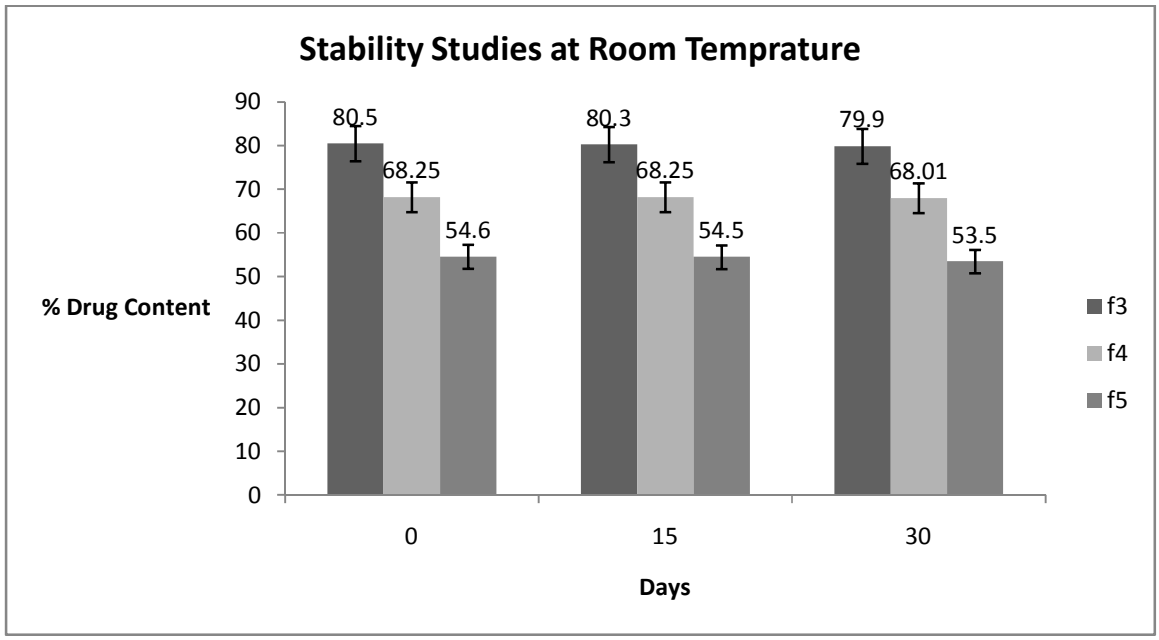
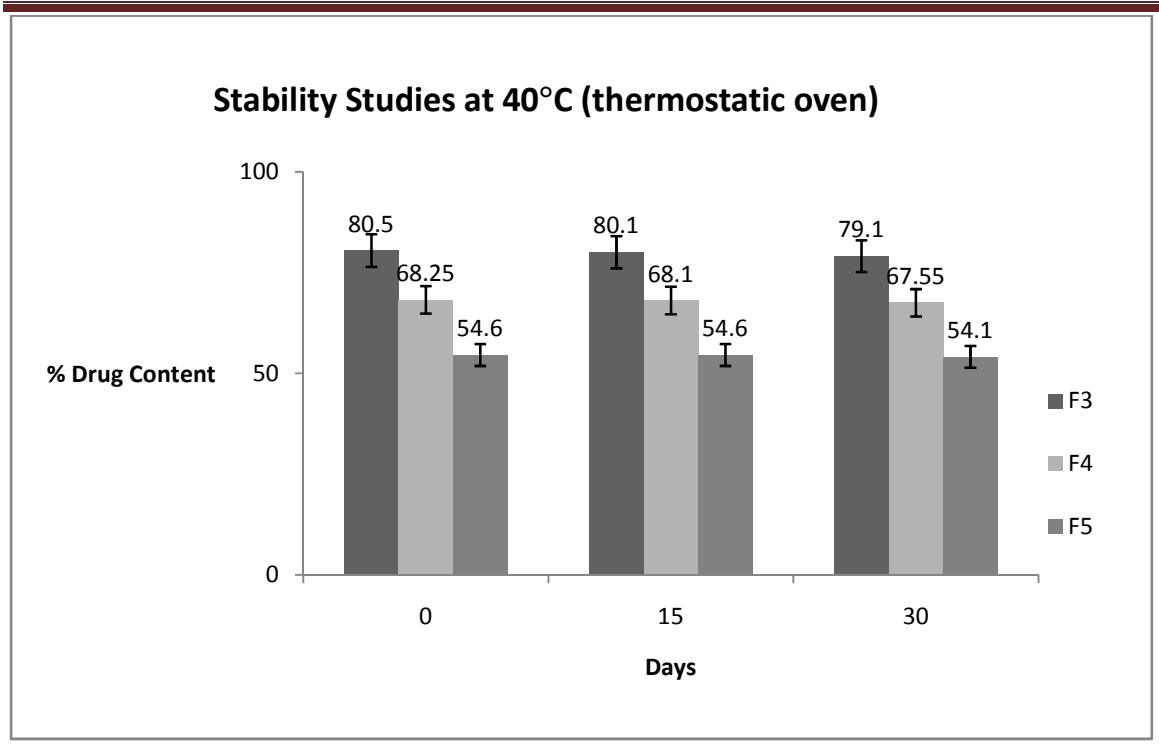


Fig.no.7 zeta potential of f3




Stability Studies at 40°C (thermostatic oven)
100
50
0
% Drug Content
80.5
68.25
54.6
80.1
68.1
54.6
79.1
67.55
54.1
0
15
30
Days
F3
F4
F5

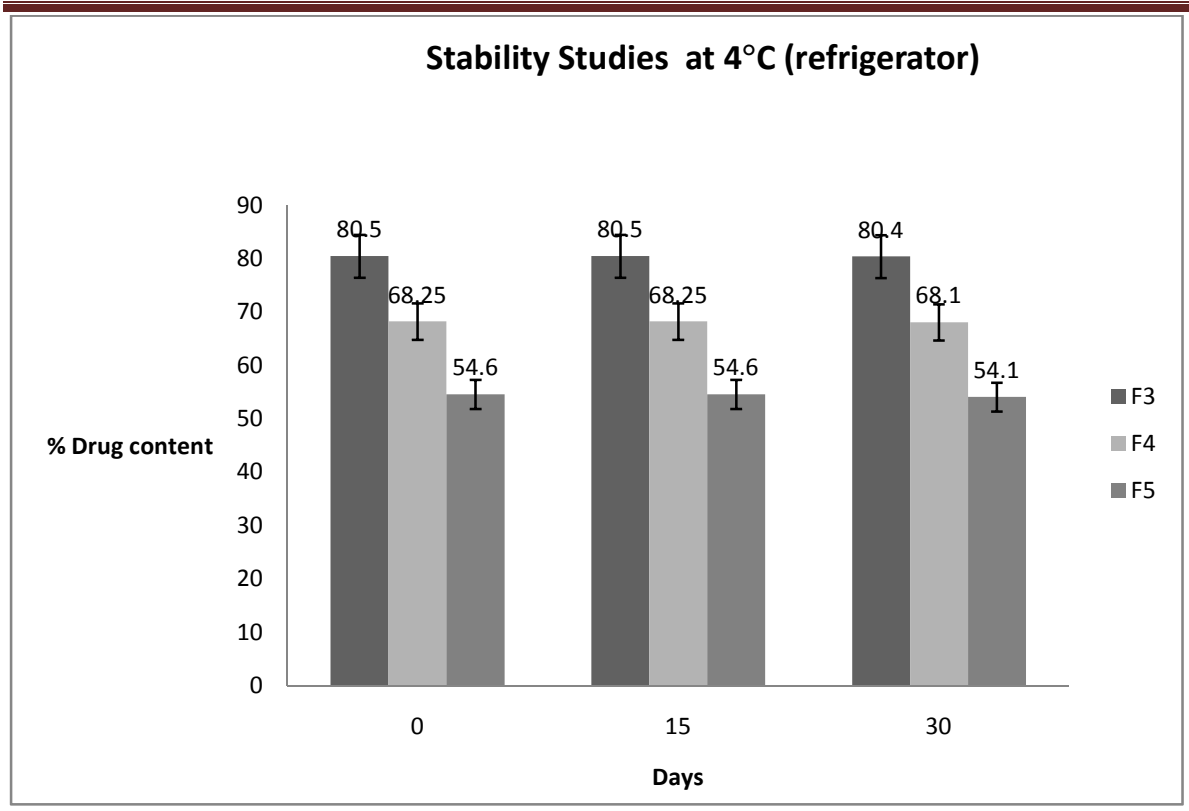

Stability Studies at 4°C (refrigerator)
% Drug content
90
80
70
60
50
40
30
20
10
0
80.5
68.25
54.6
80.5
68.25
54.6
80.4
68.1
54.1
0
15
30
Days
F3
F4
F5

Table 1

Different ratios of formulation

Sr. No	Formulation	Ratios of different excipients (S1:S2)	(S:CoS)	(Smix: O)	Appearance
1	**F1**	**3:1**	**1:1**	**1:1**	**Cloudy**
2	**F2**	**3:1**	**2:1**	**3:1**	**Cloudy**
3	**F3**	**3:1**	**2:1**	**4:1**	**Transparant**
4	**F4**	**4:1**	**2:1**	**4:1**	**Transparant**
5	**F5**	**-**	**2:1**	**4:1**	**Transparant**
6	**F6**	**3:1**	**3:1**	**1:1**	**Milky**
7	**F7**	**3:1**	**3:2**	**1:1**	**Milky**
8	**F8**	**3:1**	**4:1**	**1:1**	**Cloudy**
9	**F9**	**3:1**	**5:1**	**1:1**	**Cloudy**
10	**F10**	**3:1**	**5:3**	**1:1**	**Cloudy**

(S1:S2)=surfactant 1& 2 (S:CoS)= surfactant: co-surfactant (Smix: O)=ratio of surfactant and co surfactant: oil

Table 2

Composition of SMEDDS formulations

S.No.	Components	Composition		
		F3	**F4**	**F5**
1	**Ciprofloxacin**	**200 mg**	**200mg**	**200mg**
2	**Oleic acid**	**20 %**	**20 %**	**20 %**
3	**Tween 80**	**60 %**	**60 %**	**80 %**
4	**Pluronic F_{127}**	**20 %**	**30 %**	**30 %**
5	**Ethanol**	**40%**	**30 %**	**40 %**

Table 3

% Drug content of o/w microemulsion formulations

S.No.	Formulation	% Drug content
1	**F3**	**80.5**
2	**F4**	**68.25**
3	**F5**	**54.6**

Table 4

% Drug release results of formulations

S.No	Time (hour)	Dissolution medium	% Cumulative drug release		
			F3	F4	F5
1	**0**	**0.1N HCl**	**0**	**0**	**0**
2	**1**		**4.18±0.618**	**5.14±0.21**	**6.36±0.465**
3	**2**		**5.92±0.512**	**8.30±0.74**	**9.18±0.46**
4	**3**	**Phosphate buffer pH 6.8**	**27.82±2.648**	**24.37±1.03**	**18.613±0.92**
5	**4**		**40.87±4.616**	**32.35±1.41**	**38.516±1.09**
6	**5**		**50.73±1.762**	**40.44±0.34**	**44.77±0.83**
7	**6**		**59.02±3.396**	**54.21±1.15**	**51.79±0.99**
8	**7**		**67.49±4.11**	**61.79±2.85**	**58.74±1.025**
9	**8**		**71.37±2.97**	**68.32±1.73**	**62.65±0.88**

10	**9**	**75.45±3.676**	**72.44±0.132**	**68.30±1.10**
11	**10**	**79.82±4.187**	**76.75±3.882**	**72.29±0.98**
12	**11**	**83.94±1.617**	**82.37±0.941**	**78.95±1.20**
13	**12**	**86.30±1.243**	**84.56±0.870**	**84.43±1.006**

Table 5

Stability study of o/w microemulsion

s. no	Formulations	% Drug content results at different storage conditions								
		at Room temperature			**at 4°C (refrigerator)**			**at 40°C oven)**		**(thermostatic**
		0 days	**15 days**	**30 days**	**0 days**	**15 days**	**30 days**	**0 days**	**15 days**	**30 days**
1.	**F3**	**80.5±1.4**	**80.3±1.5**	**79.9±1.3**	**80.5±1.1**	**80.5±1.0**	**80.4±1.7**	**80.5±0.8**	**80.1±1.6**	**79.1±2.0**
2.	**F4**	**68.25±0.7**	**68.25±0.6**	**68.01±1.5**	**68.25±1.1**	**68.25±1.1**	**68.10±1.3**	**68.25±0.5**	**68.10±2.7**	**67.55±2.5**
3.	**F5**	**54.6±0.7**	**54.5±1.0**	**53.5±1.1**	**54.6±0.6**	**54.6±1.5**	**54.1±2.8**	**54.6±2.4**	**54.6±1.5**	**54.1±2.4**

REFERENCES

1. Yamahira Y, Noguchi T, Takenaka H, Maeda T: Absorption of diazepam from a lipid-containing oral dosage form. Chem Pharm Bull 1979; 27: 1190-98.

2. Constantinides PP: Lipid microemulsion for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm Res 1995; 12: 1561-72.

3. Constantinides PP, Scalar J: Formulation and physical characterization of water-in-oil microemulsion containing long-verses medium-chain glycerides. Int J Pharm 1997; 158: 57-68.

4. Borhade V, Nair H, Hedge D: Design and formulation of self-microemulsifying drug delivery system (SMEDDS) of Tacrolimus. AAPS PharmSciTech 2008; 9: 13-14.

5. Gursoy RN, Benita S: Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004; 58: 173–182.

6. Lawrence MJ, Rees GD: Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 2000; 45: 89–121.

7. Pouton CW: Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci 2000 ; 11 Supplement: S93–S98

8. Hou DZ, Xie CS, Huang K, Zhu CH: The production and characteristics of solid lipid nanoparticles (SLN). Biomaterials 2003; 24: 1781–85.

9. Sarkar NN: Mifepristone: bioavailability, pharmacokinetics and useful effectiveness. Eur J Obstet Gynaecol Reprod Biol 2002; 101: 113–120.

10. Gao P, Guyton ME, Huang T, Bauer JM, Stefanski KJ, Lu Q: Enhanced oral bioavailability of a poorly water soluble drug PNU-91325 by super saturable formulations. Drug Dev Ind Pharm 2004; 30: 221–9.

11. You J, Cui F, Li Q, Han X, Yu Y. Yang M: A novel formulation design about water-insoluble oily drug: preparation of zedoaryl turmeric oil microspheres with self emulsifying ability and evaluation in rabbits. Int J Pharm 2005; 288: 315–323.

12. Stegemanna S, Leveillerb F: When poor solubility becomes an issue: from early stage to proof of concept. Eur J Pharm Sci 2007; 31: 249-61.

13. Hoffken G, Borner K, Glatzel PD, Koeppe P, Lode H: Reduced enteric absorption of ciprofloxacin in the presence of antacids. Eur J Clin Microbiol 1985; 4: 345.

14. Lomaestro BM, Bailie GR: Absorption interactions with fluoroquinolones. Drug Safety 1995; 12: 314–333.

15. Drlica K, Franco RJ: Inhibitors of DNA topoisomerases. Biochemistry 1988; 27: 2253-59.

16. Gursoy RN and Benita S: Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004; 58: 173–182.

17. Shah N, et al: Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. International journal of pharmaceutics 1997; 106(1): 15-23.

18. Gursoy N, Benita R and S: Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedi & Pharmacoth 2004; 58(3): 173-182.

19. Tarr B and Yalkowsky S: Enhanced intestinal absorption of cyclosporine in rats through the reduction of emulsion droplet size. Pharm res 1989; 6(1): 40-43.

20. Robinson JR. Introduction: semi-solid formulations for oral drug delivery. Buletin Technique Gatefosse 1996; 89: 3–11.

21. Lipinski CA: Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods 2000; 44: 235–49.

22. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997; 23: 3–25.

23. Gursoy RN, Benita S: Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004; 58: 173–82.

24. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Hong MJ, Jee JP, Kim JA, Yoo BK, Woo JS, Yong CS, Choi HG: Enhanced oral bioavailability of dexibuprofen by a novel solid self-nanoemulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm 2009; 72: 539–545.

25. Cui SX, Nie SF, Li L, Wang CG, Sun JP: Preparation and evaluation of self-microemulsifying drug delivery system containing vinpocetine. Drug Dev Ind Pharm 2009; 35: 603–11.

26. Woo JS, Song YK, Hong JY, Lim SJ, Kim CK: Reduced food-effect and enhanced bioavailability of a self-microemulsifying formulation of itraconazole in healthy volunteers. Eur J Pharm Sci 2008; 33: 159–165.

27. Porter CJH, Trevaskis NL, Charman WN: Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs. Nature Reviews Drug Discovery 2007; 6(3): 31–248.

28. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ: Nanoemulsions. Current Opinion in Colloid & Interface Sci 2005; 10(3–4): 102–110.

29. Mandawgade SD, Sharma S, Pathak S, Patravale VB: Development of SMEDDS using natural lipophile: application to artemether delivery. Int J Pharma 2008; 362: 179–183.