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DEVELOPMENT AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY OF A POORLY WATER SOLUBLE NSAID

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ABSTRACT

The present work was aimed at formulating a SMEDDS (self microemulsifying drug delivery system) of Mefenamic acid and evaluating its *in-vitro* and *in-vivo* potential. The solubility of Mefenamic acid was determined in various vehicles. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area, and the release rate of Mefenamic acid was investigated using an in vitro dissolution test. The SMEDDS formulations were evaluated for parameters like macroscopic evaluation, visual assessment, self emulsification, transmittance test, droplet size, zeta potential and particle size distribution. Formulation development and screening was done based on results obtained from solubility data and phase diagrams. The optimized formulation for in vitro dissolution, Analgesic activity and Anti- inflammatory studies was composed of Sefsol 218 (oil), Labrasol (surfactant) and Cremophor EL (co-surfactant). Droplet size ranged between 17 and 26 nm. Formulations were clear and almost near to 100% transmittance after dilution with water. The SMEDDS formulation showed more than 80 % of the active was released in 20 min. as compared with the plain drug, which showed a limited dissolution rate. Thus, the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Mefenamic acid to improve its bioavailability.

KEYWORDS: Mefenamic acid; Ternary phase diagram; Self-emulsifying drug delivery system; Droplet size; Zeta potential.

INTRODUCTION

In recent years, much attention has turned to lipid-based formulations with the aim of improving the oral bioavailability of poorly water soluble drugs. Lipid-based formulations encompass a diverse group of formulations, very different in physical appearance, ranging from a simple tri-glyceride vehicle to more sophisticated formulations. Lipid based drug delivery systems offer a wide variety of options. They can be made as solutions, emulsions, suspensions, microemulsions, solid lipid nano-particles, liposomes, self-emulsifying drug delivery systems (SMEDDS), or dry emulsions.[1-2] Moreover, it is possible to form blends that are composed of several excipients: they can be pure triglyceride (TG) oils or blends of different TG, diglyceride (DG) and monoglyceride (MG) oils, or blends of different TG, DG and MG. In addition different types of surfactants (lipophilic and hydrophilic) can be added, as well as hydrophilic co-solvents.[3] The type of lipid component of the delivery system has a great influence on its capability to enhance absorption. Non-digestible lipids, including mineral oils, sucrose polyesters and others, are not absorbed from the gut lumen. They remain in the gastrointestinal lumen, tend to retain the lipophilic drug within the oil, and thus, may limit the absorption of the drug. Digestive lipids, including triglycerides, diglycerides, phospholipids, fatty acids, cholesterol and other synthetic derivatives, are suitable oils for drug delivery systems of lipophilic compounds.[4]

SMEDDS have gained great importance as a promising technology to improve the bioavailability of poorly water-soluble drugs. A substantial amount of individual reports about the potential SMEDDS formulations has been published during the last decade and the number is continuously increasing per year. Furthermore, successful commercialization of the products Fortovase\ (Saquinavir) and Norvir® (Ritonavir) (all based on SMEDDS technology) is sufficient to establish the commercial viability of this delivery strategy.[5]

SMEDDS are defined as isotropic mixtures of lipid, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water (O/W) emulsion when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the gastrointestinal tract. The spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastro intestinal physiology and the fed/fasted state of the patient.[6]

Mefenamic acid, the newest member of the oxicam class, is a nonsteroidal anti-inflammatory drug (NSAID). It interferes in the synthesis of prostaglandins from arachidonic acid by the inhibition of the cyclooxygenase isozymes. The existence of an acidic group in NSAID is important for pharmacodynamic reasons. Because the acidity of oxicams is derived from enolic group, not from carboxylate moiety like other NSAIDs, it does not increase the frequency and severity of unwanted effects. Mefenamic acid is absorbed rapidly and almost completely from the gastrointestinal tract. The absolute bioavailability of Mefenamic acid is 90 to 100 % and almost 99.7 % strongly binds to serum albumin. Unlike other oxicams, it has relatively short half-life (3–5 h). Mefenamic acid undergoes extensive hepatic metabolism in humans, and as many other NSAIDs, the cytochrome P450 2C9 appears to play a major role in the metabolism of Mefenamic acid. Moreover, because Mefenamic acid has potent anti-inflammatory and analgesic activities, low dose therapy is possible and this results in less risk of the side effects of classical NSAIDs.[7]

The main objective of the investigation is to formulate, optimize and stabilize SMEDDS containing Mefenamic acid with suitable surfactants and co-surfactants. Mefenamic acid, which is poorly soluble in gastric fluid through conventional dosage forms (tablet), SMEDDS are prepared to increase their solubility in gastric fluid and improve bioavailability by increasing gastrointestinal absorption through passive diffusion.

MATERIALS AND METHODS

Mefenamic acid was a gift sample from M/s Amoli Organics Pvt., Captex 200, Capmul PG-8, Capmul MCM, Capmul MCM C8, Labrasol and cremophor EL were gift samples from Abitec Corporation, U.S.A. Acrysol K140, Acrysol K150, Acrysol K135 were gifted by Corel Chemical Ltd, Ahmedabad. Capryol 90, Labrafil 2125 CS, Labrafac, Labrafac PG were gift from Gattefosse. Polyethylene glycol 400, Tween 80 and Tween 20 grade were purchased from S.D. Fine Chemical Ltd, Mumbai. Sefsol 218 was gift sample from nikko chemical co. ltd china.

Solubility study of Mefenamic acid in various excipients

The solubility of Mefenamic acid in various components (oils, surfactants, and co surfactants) was determined as follows: 500 mg of each of the selected vehicles was added to each cap vial containing an excess of Mefenamic acid. After sealing, the mixture was heated at 40ºC in a water bath to facilitate the solubilisation. Mixing of the systems was performed using a vortex mixer. Formed suspensions were then shaken with a shaker at 25ºC for 48 hours. After

reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 minutes, and excess insoluble Mefenamic acid was discarded by filtration using a membrane filter (0.45 μm). The concentration of Mefenamic acid was then quantified by HPLC.[8]

Pseudoternary Phase Diagrams

Pseudo ternary phase diagrams of oil, surfactant/ co surfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a drop wise manner. For each phase diagram at a specific ratio of S/CoS (ie, 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5 and 1:3 wt/wt) a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 minutes. Then each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addition on the microemulsion boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component. Phase diagrams were then constructed using sigma plot software. Self microemulsifying region could be obtain upon dilution and gentle agitation containing Sefsol 218 (oil), Labrasol (surfactant) and Cremophor EL (co-surfactant).[9]

Fourier Transform-Infrared spectroscopy

FT-IR spectroscopy was performed using FT-IR model Shimadzu 8400S, Japan. Mefenamic acid drug and formulation was analyzed. A small amount of the sample was directly placed on the disk and sample was scanned for absorbance over the range from 4000 to 400 wave numbers (cm^{-1}) at a resolution of 1 cm^{-1}.[10]

Preparation of SMEDDS Formulations

A series of SMEDDS formulations were prepared using Labrasol and Cremophor EL as the S/CoS combination and Sefsol 218 as the oil. From the phase diagram study it was evident that 1:2 ratio of the Surfactant:Co-surfactant show highest microemulsion area. From this three different formulations (F1, F2 and F3) were prepared with 10%, 15% and 20% Oil and with 1:2 ratio of surfactant and co surfactant (Table 1). In all the formulations, the amount of Mefenamic acid was kept constant (120 mg). Accurately weighed Mefenamic acid was placed in a glass vial then oil, surfactant, and co-surfactant were added. The components

were mixed by gentle stirring until Mefenamic acid was perfectly dissolved. The mixture was stored at room temperature until further use.[11]

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.[11]

Self Emulsification time

Different compositions were categorized on speed of emulsification, and clarity of the resultant emulsion. This was done by visual assessment that was performed by drop wise addition of the preconcentrate (SMEDDS) into 100, 250 and 1000 ml of distilled water, 0.1N HCl and pH 6.8 phosphate buffer. This was done in a glass beaker at room temperature, and the contents were gently stirred with glass rod.[11]

Emulsion droplet size measurement

Size analysis of microemulsion was carried out by dynamic light scattering with Zetasizer HSA 3000 (Malvern Instruments Ltd., Malvern, UK). Samples were placed in square glass cuvettes and droplet size analysis was carried out of optimized microemulsion formulation. Optimized microemulsion was diluted with excess (100 times) water and then droplet size of the system was also determined.[12]

Refractive Index

Refractive index proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333).If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.[13]

Zeta potential measurement

Zeta potential for microemulsion was determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were

recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.[14]

Transmission electron microscopy

The morphology of SMEDDS was observed by transmission electron microscope (PHILIPS TECNAI 20, Holland). TEM was operated at 200 kV at 20,000 x magnification. Sample was diluted with distilled water 1:25 and mixed by slightly shaking. The drop of sample obtained after dilution was placed on copper grids. The excess was drawn off with filter paper. TEM was conducted with negative staining of phosphotungstic acid solution (1%, w/v) and dried in air at room temperature before loading in the microscope.

***In-vitro* drug release profile**

SMEDDS of Mefenamic acid (equivalent to 100 mg of Mefenamic acid) was filled in hard gelatin capsules. *In-vitro* release profiles of SMEDDS of Mefenamic acid, and pure Mefenamic acid powder were studied using United States Pharmacopeia (USP) XXIII apparatus I at 37±0.5°C with a rotating speed of 100 rpm in buffer pH 6.8 as the dissolution media. During the study, 5 ml of aliquots were removed at predetermined time intervals (5, 10, 20, 30, 40, 50 and 60 min) from the dissolution medium and replaced with fresh media. The amount of Mefenamic acid released was determined by HPLC method after filtration through 0.45µ membrane filter.[15-16]

***In- vivo* study**

Approval to carry out *in vivo* study was obtained from animal ethics committee of Shree S. K. Patel College Pharmaceutical Education and Research, Ganpat University Kherva (SKPCPER/IAEC/2013-02/09) and their guidelines were followed for the studies. The animals used for *in vivo* experiments were adult Wistar rats and Swiss albino mice. Animals were kept under standard laboratory conditions, temperature at 25±2°C and RH of 55±5% and utilized in different studies as given below

Anti-inflammatory activity

Carrageenan-induced rat paw edema model: Carrageenan-induced rat paw edema model was used to assess the anti-inflammatory effect of the optimized formulation. The overnight fasted rats were divided into three groups (n=5) and treated as following

Group I: Mefenamic acid (10 mg/kg) in 0.5% CMC; p.o.

Group II: Final formulation containing equivalent amount of Mefenamic acid (10 mg/kg) in 0.5% CMC; p.o.
Group III: 2.5 ml of 0.5% CMC; p.o.

After 30 min of drug administration, all the rats were challenged by a subplantar injection of 0.05 ml of 1% solution of carrageenan in saline into left hind paw. The paw volumes were measured with a digital plethysmometer, prior to administration of carrageenan and after 1–5 h of administration. Right paw served as reference. The percent inhibition of edema for all time intervals was calculated. The results of anti-inflammatory study are tabulated in table 2.[17]

Analgesic activity of optimised formulation using Acetic acid induced writhes

Writhing test was used to evaluate the non-narcotic analgesic activity of the drug when administered as optimised formulation (10 mg/kg of drug).[18] The overnight fasted mice were divided into three groups (n = 5) and treated orally as given in the above procedure. After 1 h of post-dose, they were injected with 1% acetic acid (0.1 ml/10 g) intraperitonially (I.P.). Then the number of writhes was recorded for 10 min. The analgesic activity was evaluated in terms of the percentage of writhe inhibitions. The results of analgesic activity are tabulated in table 3.

Stability Studies

Chemical and physical stability of Mefenamic Acid SMEDDS formulations was assessed at 40±2°C/ 75±5% RH as per ICH guidelines. SMEDDS formulation M3 was filled in amber colored vial, and stored for 6 months (180 days). Samples were charged in stability chambers (Thermolab, Mumbai, India) with humidity and temperature control. Samples were analyzed at 0, 90, and 180 days time interval for physical characteristics, drug content, mean globule size, polydispersiblity index, zeta potential, % transmittance, self emulsification and precipitation assessment test and *in- vitro* dissolution profile.[11] The results of stability study are tabulated in table 4.

RESULTS AND DISCUSSION

Solubility study of mefenamic acid in various excipients

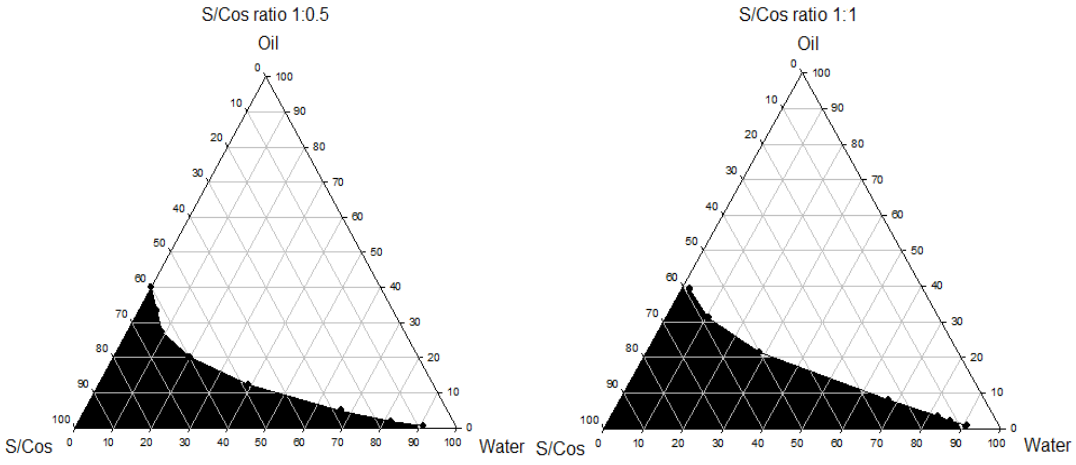
Solubility is major concern when formulating self emulsifying drug delivery system. Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of microemulsion so as the precipitation

of drug during shelf life of formulation and after dilution in GI lumen can be avoided. Therefore, the solubility of Mefenamic acid was determined in various oils, surfactants and cosurfactant mixtures. Among the various components studied Sefsol 218 is selected as oil, Labrasol as surfactant and Cremophor EL as co-surfactant for the further studies.

Pseudo ternary Phase Diagrams

Self microemulsifying systems form fine oil/water emulsions with only gentle agitation upon their introduction into aqueous media. Surfactant and co surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation. Therefore, the selection of oil and surfactants, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion.

A series of SMEDDS formulations were prepared (Fig 1) using Labrasol and Cremophor EL as the S/CoS combination and Sefsol 218 as the oil. From the phase diagram study it was evident that 1:2 ratio of the S: CoS show highest microemulsion area. From this study, three different formulations (F1, F2 and F3) were prepared with 10%, 15% and 20% oil and a 1:2 ratio of S:CoS in them. Amongst all the formulations, F3 shows maximum water uptake and highest microemulsion zone compared to the other formulations.



A **B**

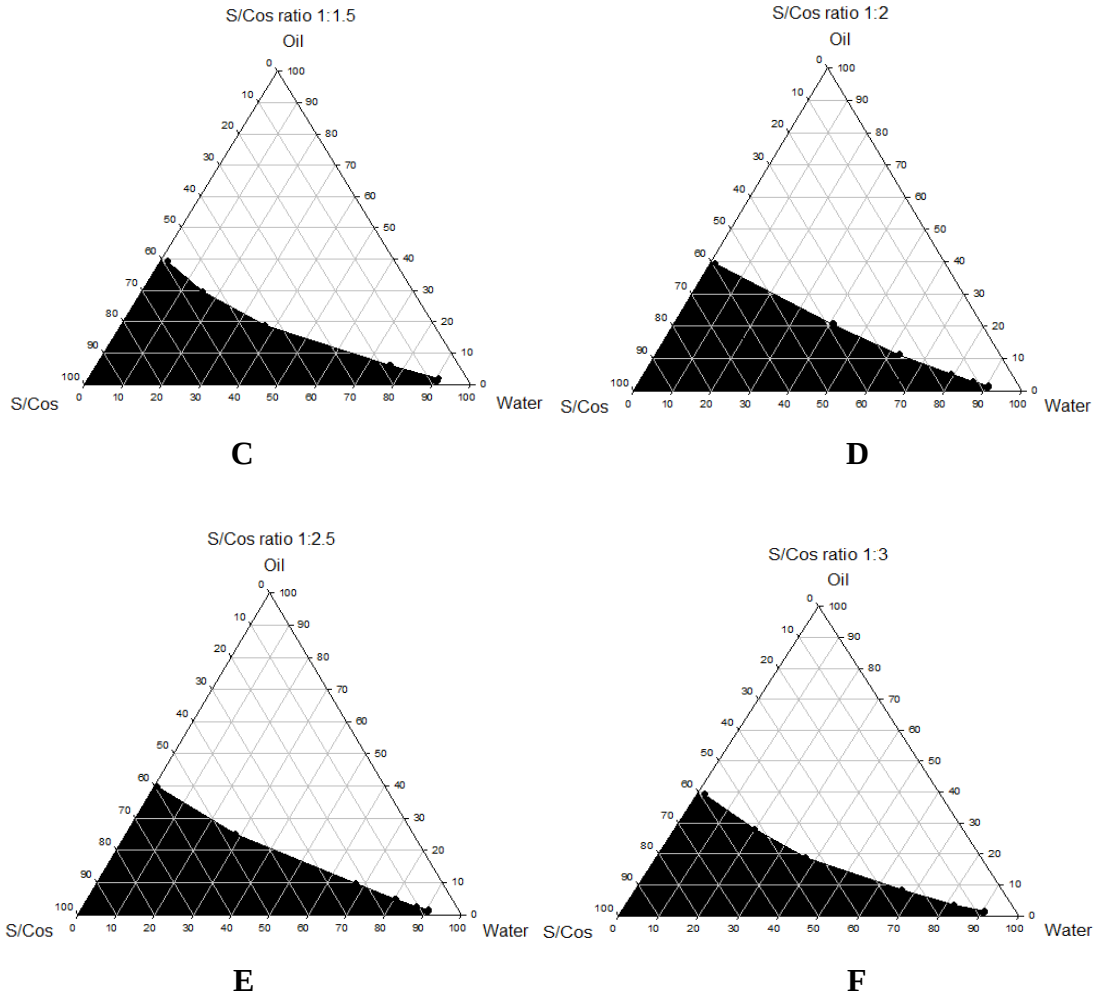
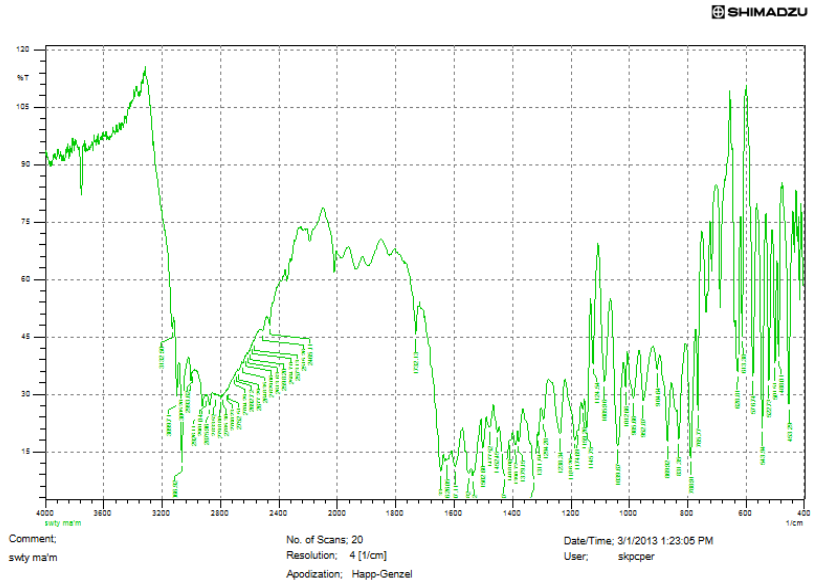


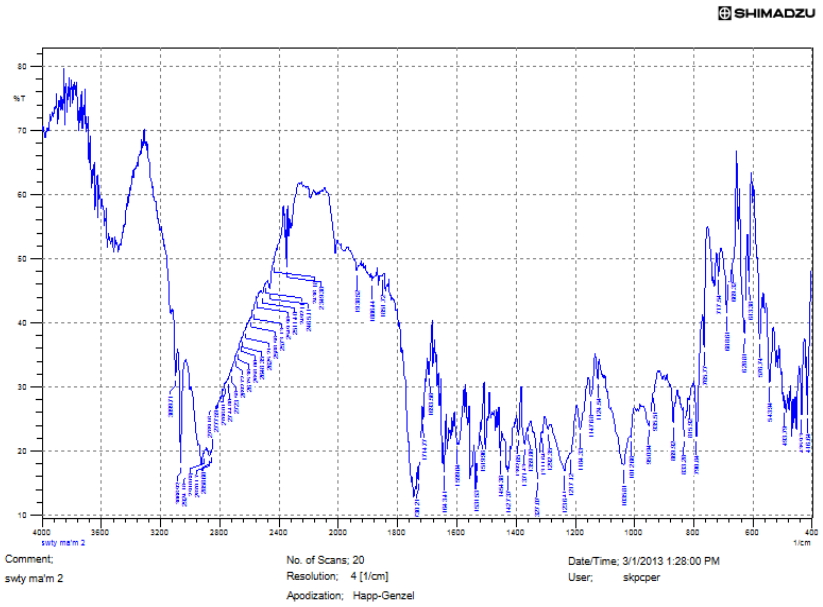
Fig. 1 Phase diagram of different ratio of surfactant and co-surfactant A) 1:0.5, B) 1:1 C) 1: 1.5 D) 1:2 E) 1: 2.5 and F) 1:3

Fourier Transform-Infrared Spectroscopy

Mefenamic acid contains characteristic peaks at 1255 cm-1(-OH group bending and vibrations of COOH), 1647 cm-1(N-H stretching vibration), 1572 cm-1(C=O stretching), 1504 cm-1(Aromatic C-H plane deformation), 1163 cm-1(Aromatic-O-CH3) and 757(Aromatic C-C vibration for ortho substitution). The carbonyl group is more favorable in hydrogen bonding over the tertiary amine because of the steric hindrance of the latter group. The spectrum of physical mixture shown in Figure 2 was simple summation of pure drug and excipients, revealing no perceptible interaction between the two components.



(A)



(B)

Fig. 2: FTIR spectra of A) pure Mefenamic acid, and B) prepared formulation.

Freeze Thawing

The thermal cycling study created a thermodynamically unstable microemulsion, which had larger droplet size distribution upon dilution. Visual observation indicated that there was no phase separation in all three formulations and the physical appearance of all formulations was also similar. The overall stability of the formulation under normal conditions was found to be acceptable.

Self Emulsification

Emulsification time was assessed visually. Result was shown in Table 1. Emulsification time is most important parameter for SMEDDS and microemulsion formulation. A microemulsion that is formed within in a 1 min. is said to be of Grade I.[12] In case of all the batches F1, F2 and F3 Grade I type self emulsion was obtained.

Emulsion droplet size measurement

The stable formulations were subjected to size analysis by Zetasizer. It was concluded by size analysis study that initially, as the amount of surfactant increases, globule size decreases due to an increase in adsorption of surfactants around the oil water interphase of a droplets and a decrease in interfacial tension as shown in Table 1. After reaching a particular amount of surfactant, further increase in surfactant amount results in increased globule size. It could have occurred because excess adsorption of surfactant on the interphase resulted in retardation of efficiency of emulsification and more energy was required to produce an emulsion. In all the formulations droplet size ranges between 17-26 nm and PDI was also near to zero. (Fig.3 A,B,C).

Zeta potential measurement

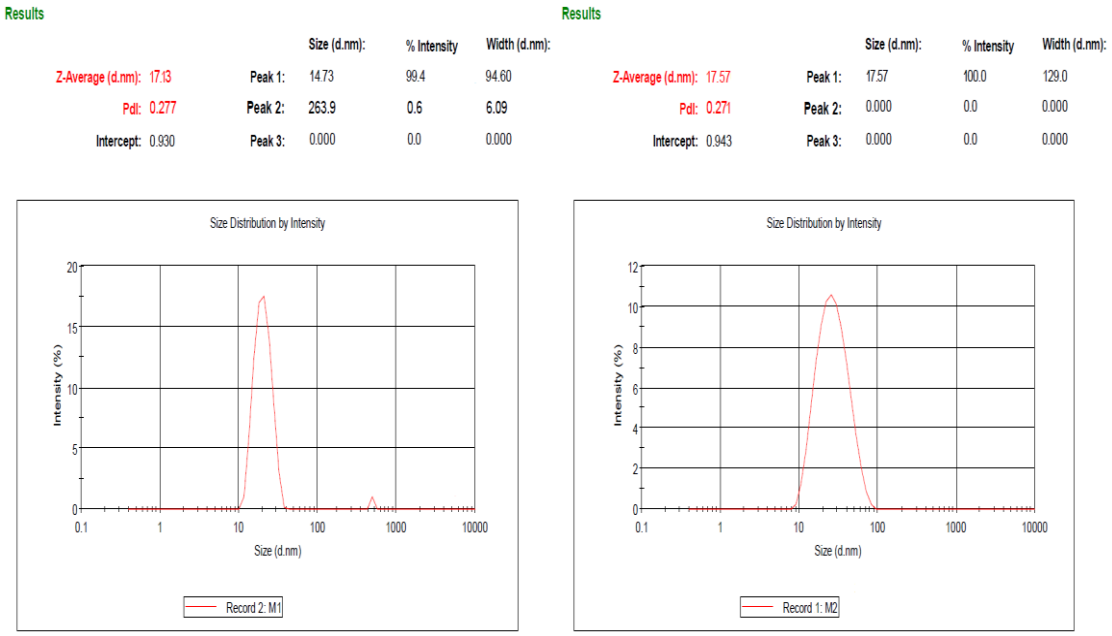
Zeta potential can be defined as the difference in potential between surface of the tightly bound layer (shear plane) and the electroneutral region of an emulsion. It has got practical application in the stability of emulsion since Zeta -potential governs the degree of repulsion between adjacent, similarly charged, dispersed droplets. If the Zeta -potential is reduced below a certain value (which depends on a particular system being used), the attractive forces exceed the repulsive forces, and the particles come together leading to flocculation. The zeta potential of the formulations was found between –11.45 to –19.11 mV as given in Table 1. In general, the zeta potential value of ±30 mV is desirable for the stability of a microemulsion. All formulations comply with the requirement of the zeta potential for stability.

Refractive index

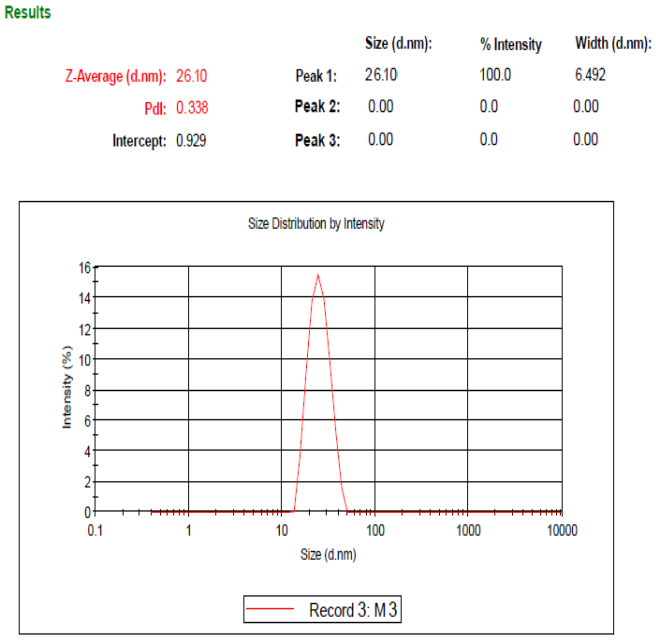
Refractive index of all the three formulations were found near to 1.33(Table 1) which showed transparency of formulations were good. So we can say that all the formulations have transparent in nature.

Tables: 1 Evaluation data of the SMEDDS formulations

Batches	Emulsification time (sec)	Droplet size (nm)	Polydispersity index	Zeta potential (mv)	Refractive index
F1 (10% oil)	39	17.13 ± 0.38	0.277 ± 0.22	-11.45 ±0.32	1.381 ± 0.0004
F2 (15% oil)	32	17.57 ± 0.27	0.271 ± 0.35	-15. 42±0.51	1.361 ± 0.0002
F3 (20% oil)	20	26.10 ± 0.34	0.338 ± 0.23	-19.11 ±0.25	1.33 ± 0.0004



A **B**



(C)

Fig. 3 (A,B,C): Globule size of formulation

Transmission electron microscopy

The morphology of SMEDDS was examined with a transmission electron microscope. The droplet on the microemulsion appears dark with the bright surroundings. TEM photographs (fig.4) further conformed that the globules are spherical in shape.

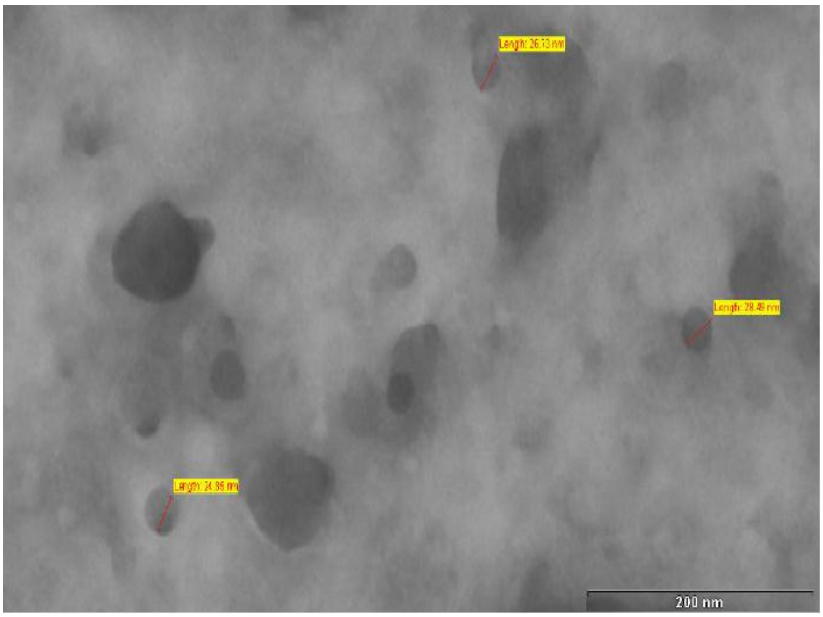


Fig. 4: TEM image of formulation F3

***In-vitro* drug release profile**

Drug release from the SMEDDS formulations (batches F1, F2 and F3) was found to be significantly higher as compared with that of plain Mefenamic acid. 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 Mefenamic acid. Thus, this greater availability of dissolved Mefenamic acid from the SMEDDS formulation could lead to higher absorption and higher oral bioavailability. The *in-vitro* drug release is shown in Fig. 5. Amongst the obtained data, formulation F3 shown around 83% drug released at the end of 20 minutes, which is much is significant in comparison to other two formulations and the pure drug. At the end of 1 hr more than 98% drug released from the F3 formulation which is because of emulsion formation. Thus based on the various studies carried out formulation F3 was selected for *in-vivo* study.

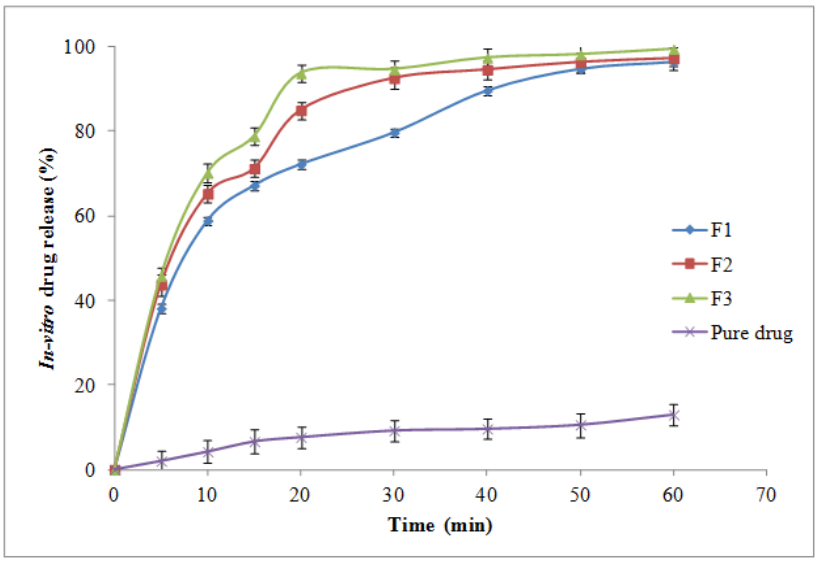


Fig. 5 *In-vitro* drug release of formulations

In vivo study

Anti-inflammatory activity: The anti-inflammatory activity of the optimized SMEDDS formulation F3 in comparison with Mefenamic Acid was evaluated on the basis of its ability to inhibit the edema produced in hind paw of rats after challenging with the carrageenan. The increase in paw volume in different groups was compared to assess possible improvement in activity of drug. The difference in paw edema volume values before and after drug administration was calculated and % inhibition of edema at each time point was calculated (Table 2). The optimized SMEDDS formulation F3 showed maximum inhibition of edema (81.27 ± 1.01 % at 240 min); whereas Mefenamic Acid provided maximum activity of 51.04 ± 1.22 % at 300 min. Although the values corresponding to maximum effect were significantly different from each other, the optimized SMEDDS formulation F3 showed rapid anti-inflammatory effect when compared with that of Mefenamic Acid.

Table 2: Effect of Mefenamic Acid SMEDDS formulation on the rat paw edema induced by carrageenan in Wistar rats

Time (min)	Paw volume (ml)			% Inhibition	
	Control	Mefenamic Acid	Formulation F3	Mefenamic Acid	Formulation F3
30	1.24 ± 0.37	1.22 ± 0.36	1.09 ± 0.28	1.61 ± 0.37	12.09 ± 2.48
60	1.40 ± 0.35	1.30 ± 0.34	0.90 ± 0.31	7.14 ± 0.85	35.71 ± 2.68
120	1.90 ± 0.42	1.65 ± 0.41	0.80 ± 0.29	13.15 ± 1.38	57.89 ± 1.52
180	2.04 ± 0.34	1.58 ± 0.33	0.61 ± 0.40	22.54 ± 2.94	70.09 ± 1.29
240	2.19 ± 0.52	1.31 ± 0.51	0.41 ± 0.45	40.18 ± 1.92	81.27 ± 1.01
300	2.39 ± 0.31	1.17 ± 0.30	0.58 ± 0.36	51.04 ± 1.22	75.73 ± 2.48

**All values are expressed as mean ± S.D., n=5.*

Analgesic activity

The effect of Mefenamic Acid and its SMEDDS (F3) on acetic acid-induced abdominal contractions in mice was compared to control group (no drug treatment). The control animals showed 36.60 ± 1.34 contractions. The analgesic activity from dispersed drug was rapid (8.20 ± 0.44 contractions) and percentage inhibition of contractions (77.59 ± 0.89 %) was high compared to those of pure drug (No. of contractions: 14.80 ± 0.44; Inhibition of contractions: 59.56 ± 1.23 %). These observations as seen in table 3 confirmed the advantage of enhanced analgesic activity which might be due to improved rate of absorption and bioavailability of Mefenamic Acid from solid SMEDDS.

Table 3: Comparative study of analgesic activity of Mefenamic Acid formulation

Treatment	Number of abdominal Writhing	% Inhibition (%)
Control	36.60 ± 1.34	
Mefenamic Acid	14.80 ± 0.44	59.56 ± 1.23
Formulation M3	8.20 ± 1.48	77.59 ± 0.89

** All values are expressed as mean ± S.D., n=5.*

Stability Studies

No change in the physical parameter was observed during the stability studies. Interestingly, no significant decline in the Mefenamic acid content was observed at the end of three and six months at accelerated condition (40°C/75% RH) indicating that Mefenamic acid remained chemically stable in SMEDDS formulation. It was also seen that no significant change in parameters such as emulsification time, Polydispersity index, zeta potential, drug content, droplet size, drug content, refractive index (Table 4) and *in-vitro* drug release(Fig. 6) was observed for the Mefenamic acid SMEDDS formulation.

Table: 4 Stability Studies data of Formulation batch F3

Sampling time	Visual inspection	Emulsification time (sec)	PDI	Zeta potential (mV)	Droplet size (nm)	Refractive index	% Drug Content (%)
0 days	Clear	20	0.338 ± 0.23	-19.11 ± 0.25	26.10 ± 0.34	1.337 ± 0.0004	98.31 ± 2.987
3 Months	Clear	21	0.336 ± 0.14	-19.09 ± 0.11	26.06 ± 1.26	1.335 ± 0.0004	98.11 ± 2.867
6 Months	Clear	21	0.335 ± 1.05	-19.08 ± 0.19	26.04 ± 0.53	1.337 ± 0.0004	97.56 ± 2.867

** Data are presented as the mean ± SD (n=6)*

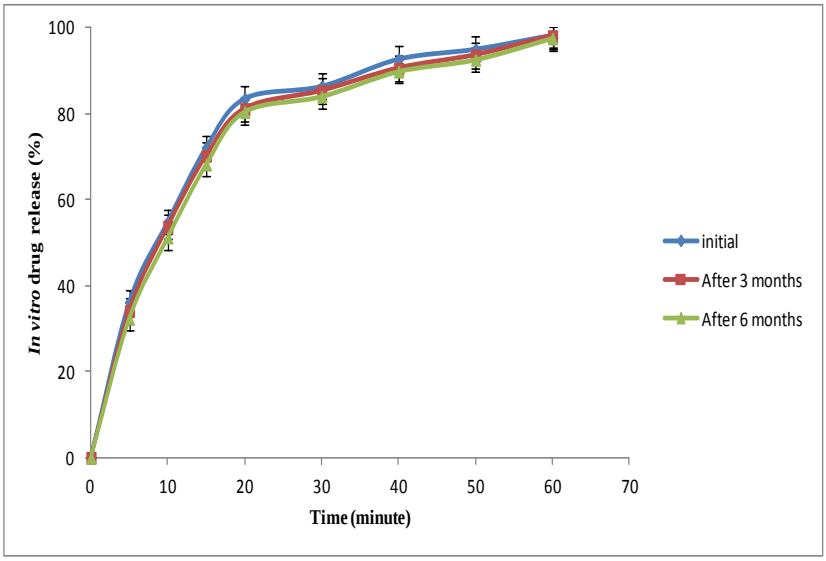


Fig. 6: Comparison of dissolution profile before and after stability studies of F3. (n=6)

CONCLUSION

The present study dealt with the formulation of SMEDDS of a poorly soluble candidate, Mefenamic acid using Sefsol 218 as oil, Labrasol as surfactant and Cremophor EL as co-surfactant. The studies revealed that the drug can be successfully formulated into an oil-surfactant mixture that improves the dissolution of Mefenamic acid in a simple and economic manner. Rapid improvement in the *in-vitro* dissolution rate proves the possible high advantage of such formulations in oral drug therapy, with faster onset of action and better therapeutic efficacy. The physicochemical characterization of the formulation indicated that the enhancing effect on dissolution was mainly attributed to the solublization of Mefenamic acid in oil and the utilization of the surfactants to reduce the tension between the oily and aqueous phases and the results of *in -vivo* study confirmed the advantage of enhanced analgesic activity and anti-inflammatory activity which might be due to improved rate of absorption and oral bioavailability of Mefenamic acid from self emulsifying formulation. Results from stability studies confirmed the stability of the developed formulation. Thus, our study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Mefenamic acid to improve its bioavailability.

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REFERENCES

1. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacothe, 2004; 58: 173-82.
2. Pouton CW. Lipid formulaions for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. Eur. J. Pharm Sci., 2000; 11(2): S93.
3. Wasan KM. Formulation and physiological and biopharmaceutical issues in the development of oral lipid based drug delivery systems. Drug Dev. Ind. Parm. 2001; 27(4): 267-6.
4. Dahan A, Hoffman A. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. J. contro. Rel, 2008; 129: 1-10.
5. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm. Res, 2004; 21:201–30.
6. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv. Drug Deliv. Rev, 2000; 45:89–121.
7. Lee JH, Chun IK. Effects of various vehicles and fatty acids on the skin permeation of Mefenamic acid. J. Pharma. Inves, 2012; 42: 235–1.
8. Shen H, Zhong M. Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin. Pharma. Pharmaco, 2006; 58: 1183-91.
9. Wei L, Li J, Guo L. Preparation and evaluation of SEDDS and SMEDDS containing Carvedilol. Drug Develop. Ind. Pharm, 2005; 31: 785-4.
10. Nazzal S, Smalyukh I, Lavrentovich OD et al. Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. Int. J. Pharm., 2002; 235: 247-65.
11. Patel AR., Vavia PR. Preparation and In Vivo Evaluation of SMEDDS (Self-Microemulsifying Drug Delivery System) Containing Fenofibrate. AAPS J., 2007; 9 (3): E344-E352.
12. Zhang P, Liu Y, Feng N. Preparation and evaluation of self-microemulsifying drug delivery system of oridonin. Int. J. Pharm, 2008; 355: 269-76.
13. Pal V, Bhopal AP. Formulation Design and Evalution Of Rutin Loaded Selfemulsifying Drug Delivary System (SEDDS) Using Edible Oil. Asian J Pharm Clin Res, 2012; 5(1): 76-8.

14. Patel MJ, Patel NM, Patel RB. Formulation and evaluation of self-microemulsifying drug delivery system of lovastatin. A J P S, 2010; 5(6): 266-5.
15. Yu XL, Wang TJ, Hussain SA. Evaluation of USP apparatus 3 for Dissolution testing of immediate release products, AAPS Pharm sci article, 2002; 4(1): E1.
16. Odeberg JM, Kaufmann P, Kroon KG. Lipid drug delivery and rational formulation design for Lipophilic drugs with low oral bioavailability, applied to Cyclosporine, Eur. J. Pharm. Sci, 2003; 20: 375-2.
17. Brambilla G, Martelli A. Genotoxicity and carcinogenicity studies of analgesics, anti \inflammatory drugs and antipyretics. Pharmacol Res, 2009; 60: 1-17.
18. Bianchi M, Panerai AE. Effects of lornoxicam, piroxicam, and meloxicam in a modelof thermal hindpawhyperalgesia induced by formalin Injection in rat tail. Pharmacol Res, 2002; 45(2): 101-5.