# FORMULATION AND DEVELOPMENT OF SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) OF FLURBIPROFEN

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## ABSTRACT

A self micro-emulsifying drug delivery system (SMEDDS) has been developed to enhance diffusion rate and oral bioavailability of Flurbiprofen. The solubility of Flurbiprofen was checked in different oils, surfactants, and co-surfactants and ternary phase diagrams were constructed to evaluate the micro-emulsion domain. The Flurbiprofen SMEDDS was prepared using Capmul MCM (oil), Tween 80 (surfactant), and polyethylene glycol 400 (co-surfactant). The particle size distribution, zeta potential, and Polydispersity index were determined and found to be 12.3 nm, −0.746, and 0.138, respectively. Diffusion rate of Flurbiprofen was measured by in vitro dialysis bag method using phosphate buffer pH 6.8 as diffusion media. Developed high-performance liquid chromatography method was used to determine drug content in diffusion media. Oral bioavailability of Flurbiprofen SMEDDS was checked by using mice model. Results of diffusion rate and oral bioavailability of Flurbiprofen SMEDDS were compared with those of pure drug solution and of marketed formulation. Diffusion of Flurbiprofen SMEDDS showed maximum drug release when compared to pure drug solution and marketed formulation. The area under curve and time showed significant improvement as the values obtained were 607 ng h/mL and 1 h for

SMEDDS in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase (p<0.01) in oral bioavailability of Flurbiprofen SMEDDS.

**KEY WORDS**: Flurbiprofen, Surfactant, Zeta Potential, Polydispersity Index and Bioavailability.

**INTRODUCTION**

In modern drug discovery techniques, there has been a consistent increase in the number of poor water soluble drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Various techniques are used to improve the bioavailability of those drugs like salt formation, pH change, β-cyclodextrines complex, micro-emulsion etc. Self micro-emulsifying drug delivery (SMEDDS) is one of the methods for the improvement of oral bioavailability. SMEDDS are class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant (sometimes with added co-surfactant) that form emulsion on mixing with water with little or no energy input (Verma and B. Razdan, 2009).

Lipid-based formulation approaches, particularly the self micro-emulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability. SMEDDS formulations are isotropic mixtures of an oil, a surfactant, a co-surfactant (or solubilizer), and a drug (K.R. Shirsagar and B. Kuchekar, 2011).

The basic principle of this system is its ability to form fine oil-in-water (O/W) micro-emulsions under gentle agitation following dilution by aqueous phases (i.e., the digestive motility of the stomach and intestine provide the agitation required for self-emulsification in vivo in the lumen of the gut). This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption (Pouton, C.W., 2000).

Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. Selection of a suitable self-emulsifying formulation depends upon the assessment of the solubility of the drug in various components, the area of the self-emulsifying region as obtained in the phase diagram, and the droplet size distribution of the resultant emulsion following self-emulsification (Gurley B, 2001).

According to Nazzal, S. and M.A. Khan (2006), SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro-emulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.

The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates has poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy (Liu Yang, 2008).

Flurbiprofen, a nonsteroidal anti-inflammatory drug, is frequently prescribed to treat gout, musculoskeletal disorders, rheumatic diseases, post-operative pain, dysmenorrhoea and migraine (Nazzal, S. and M.A. Khan, 2006).

The main objective of the study was to develop and evaluate an optimal SMEDDS formulation containing Flurbiprofen and to assess its pharmacodynamic effect in terms of lipid lowering potential. In this research paper, a bioequivalence study was performed where a comparative study between two types of drug (marketed Flurbiprofen and SMEDDS Flurbiprofen was designed and the key pharmacokinetic (PK) parameters for both drugs were assessed. Besides, we examined the stability of the dosage form and then evaluated the influence of the formulation aging on the drug release and subsequently drug bioavailability.
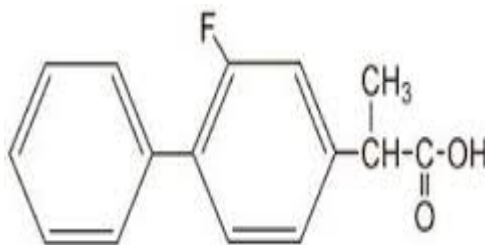


**Fig. 1 Chemical Structure of Flurbiprofen**

**MATERIALS AND METHODS**

Flurbiprofen was purchased from Sigma Aldrich, Malaysia. The rest materials such as; Cremophore RH 40 (Polyoxyl 40 hydrogenated castor oil), Cremophore EL, Captex 200, Captex 355, Capmul C10, Capmul MCM, Labrafil 2125, Labrafac PG, Plurol Olique, Tween 80 (Polysorbate 80), polyethylene glycol 400 (PEG 400), High-performance liquid chromatography (HPLC) grade methanol and acetonitrile were purchased from Scientex Laboratories, Malaysia. All other chemicals were of analytical grade.

**Solubility Studies**

One gram of each solvent (Oil, surfactant, and co-surfactant) was filled in 10 mL screw capped test tube. Twenty-five milligrams of Flurbiprofen was added in each tube. The tightly closed tubes were shaken for 48 h at 50 strokes per minute in water bath maintained at 30°C temperature.

After visual assessment of solubility of drug, additional drug in fraction of 25 mg was subsequently added in each tube to determine maximum solubility of drug in particular solvent. After 48 h, each tube was centrifuged at 3,000 rpm for 5 min to separate excess insoluble drug. The concentration of dissolved Flurbiprofen was determined by HPLC. All the experiments were repeated thrice (Thia *et al*., 2009).

**Construction of Ternary Phase Diagram**

The ratios of surfactant/co-surfactant were prepared in specific manner, i.e., 2:1, 1:1, and 1:2 (w/w). Each of these ratios was mixed with increasing percentage of oil, i.e., 10%, 20%, 30%, 40% up to 90% of oil to get phase diagram. Then, each mixture was titrated with water, and agitation was provided by magnetic stirrer (Thia *et al*., 2009).

**Preparation of SMEDDS**

A series of micro-emulsions of SMEDDS were prepared (Table 1) with varying ratios of oil, surfactant, and co-surfactant. Formulations A, B, and C were prepared using Capmul MCM as oil, Tween 80 as surfactant, and PEG 400 as co-surfactant. Similarly, formulations D, E, and F were prepared with Captex 200 P as oil, Cremophore EL as surfactant, and PEG 400 as co-surfactant. In all the formulations, the level of Flurbiprofen was kept constant to 5% of SMEDDS.

**In-Vitro Drug Release Test**

-A volume of 0.5 mL of Flurbiprofen micro-emulsion was put in a dialysis bag (3.8 cm in length). Dialysis tubing consisted of regenerated cellulose, a material chemically and physically treated to increase its resistance (MWCO 12,000–14,000 Da, 25-Å pore diameter, SERVA Electrophoresis GmbH, Heidelberg, Germany). Both ends were tied. The dialysis bag was suspended in 1000 mL Phosphate Buffer at pH 7.4 and maintained at $37 \pm 0.5$ °C. The dispersion was rotated at 200 rpm in a shaker (GFL 3032 Shaker, LABOTEC, Germany). At predetermined time intervals of 0, 2, 4, 6, 8, 10, 12, 14, 18 and 24 h, 5 mL samples were withdrawn at predetermined intervals, and the same volume of fresh dissolution medium was replenished, which was maintained at $37 \pm 0.5$ °C. Drug concentrations were quantified using HPLC and all experiments were conducted in triplicate (Thia *et al*., 2009).

The release of Flurbiprofen from SMEDDS was compared with that of from marketed capsule formulation. The suspension of marketed capsule formulation was prepared by milling powder from capsule with 2.5% hydroxyethylcellulose solution and was put in a dialysis bag (3.8 cm in length), the step was similar in the above explanations. Samples (20 µL) were injected into HPLC to determine the released Flurbiprofen. The study was repeated three times (Thia *et al*., 2009).

### HPLC Analysis of Flurbiprofen in Rat Plasma

The concentration of the drug in rat plasma was determined by validated HPLC method using C18 column, with water and acetonitrile as mobile phase (50:50) at 1ml/min flow rate, detected at 225 nm of UV detection. 200 µl of plasma containing drug was mixed with 200 µl of acetonitrile, Vortexed for 5 min, centrifuged at 5000 rpm for 15 min. the supernatant of 20µl was injected into HPLC (Edwards GA, 1998).

### Data analysis

The pharmacokinetic parameters were calculated by using one compartment model and peak time ($t_{max}$), peak level $C_{max}$ were estimated by PK solver. Area under the whole blood concentration time curve ($AUC_{tot}$) was also calculated by the trapezoidal rule for the mean whole blood levels. All results were expressed as mean $\pm$ SD. Differences between two related parameters were assessed by student t test or one way ANOVA (Edwards GA, 1998).

### Estimation of Flurbiprofen by RP-HPLC

A High Performance Liquid Chromatography (HPLC) equipped with Shimadzu LC solution was employed for the present investigation. The system consisted of Shimadzu UFLC 20-

AD as binary solvent delivery system, Shimadzu 7D Rheodyne injector as loop injector and Photo Diode Array (PDA) detector as a source of detection (Edwards GA, 1998).

**RESULTS & DISSCUSSION**

**Solubility Studies**

Solubility of Flurbiprofen was checked in a number of solvents and presented in graphical manner in Figure 2. Based on the solubility data, Capmul MCM was selected as oil phase, Tween 80 as surfactant, and PEG 400 as co-surfactant since these solvents showed better solubility.

**Pseudo-ternary Phase Diagram Study**

In order to form self micro-emulsifying O/W and W/O micro-emulsions, oil, a blend of two surfactants, and an aqueous phase were used. These four component systems can be best described by pseudo-ternary phase diagram where a constant ratio of two of the components was used and other two were varied (A.A. Kale, 2003).

The particle size of micro-emulsion is less than 100 nm and as the energy required to form micro-emulsion is very low, it is a thermodynamically spontaneous process (A.A. Kale, 2003). This process is facilitated by presence of surfactant. The surfactant forms a layer around oil globule in such a way that polar head lies toward aqueous and non-polar tail pull out oil and thereby reduces surface tension between oil phase and aqueous phase (C.M. Rodricks *et al*., 2008).

Six different formulations were prepared using different oils, surfactants, and co-surfactants in varying ratio (Table 3). SMEDDS A, B, and C were formulated using same excipients with three different S/CoS ratios of 2:1, 1:1, and 1:2 and diluted to get micro-emulsion region (Table 2). Micro-emulsion regions were observed visually. Initially, the concentration of oil taken was maximum i.e., 90%, and amount of S/CoS was kept to minimum, i.e., 10%. Gradually, oil concentration was decreased and that of S/CoS was increased. It was observed during these experiments that high concentration of oil forms poor emulsion with entrapment of very less amount of water upon dilution. Another observation was that as concentration of S/CoS increases, the time estimated to form micro-emulsion decreases.

A series of micro-emulsions were prepared at different concentrations of oil and S/CoS, but concentration of oil was found to be a rate-limiting factor and in all cases, high oil concentration resulted in poor emulsion region. Hence, it was decided to keep the oil concentration less than 10%.

Other important factors affecting micro-emulsions were concentration and ratio of S/CoS. In the present study, three S/CoS ratios, 2:1, 1:1, and 1:2, were tried (Figure 3). The black region in Figure 3 shows self micro-emulsifying (SMEDDS) region having particle size less than 100 nm, whereas gray region indicates formation of self micro-emulsifying (SMEDDS) domain with particle size 100 to 300 nm (Sawant, 2009). Since phase diagrams were constructed after infinite dilution of SMEDDS, Table 2 gives clear picture for composition of formed micro-emulsion region.

It is clear from Table 2 and Figure 3a that after dilution, SMEDDS A contains 5% of oil, 13.33% of surfactant, 6.66% co-surfactant, and 75% of water. Alternatively, it can also be concluded that 20% of S/CoS mixture with ratio of 2:1 could solubilized 5% of oil in 75% of water. When equal amount of co-surfactant added (S/CoS mix 1:1), micro-emulsion region increased and oil solubilized up to 10% with surfactant, co-surfactant, and water concentration of 17.5%, 17.5%, and 55%, respectively (Figure 3b).

When co-surfactant concentration was further increased up to S/CoS mix 1:2, Figure 3c revealed that oil concentration was decreased to 4% with 3% of surfactant, 6% of co-surfactant, and remaining 87% of water. On comparing all three cases, it can be concluded that equal amount of surfactant and co-surfactant is required to get optimum concentration of oil. Moreover, since the drug is lipid soluble, oil concentration is important factor to entrap required amount of drug dose. It is also clear from Figure 3b that formulation B covers maximum micro-emulsion region (black region) as compared to formulations A and C.

If concentration of surfactant is kept high as in formulation A (Figure 3a), it gives limited micro-emulsion region but the micro-emulsion formed is of small particles size (17.8) with zeta potential value of −12.1. In many self micro-emulsion studies, it is reported (G. Lambert, 2011) that zeta potential plays an important role. Increase of repulsive forces between micro-emulsion droplets prevents coalescence of micro-emulsion droplets. If S/CoS ratio decreased, it results in milky, white emulsion. This problem can be evaluated by increasing ratio up to 1:1.

The phase diagram clearly shows that SMEDDS prepared with S/CoS ratio of 1:1 (Figure 3b), cover maximum self micro-emulsifying region as compared to other two ratios, and the time required to form micro-emulsion is less than 2 min.

In the case with S/CoS ratio (1:2) when concentration of co-surfactant (PEG 400) was increased, the micro-emulsion region was found to be decreased, and time required to form micro-emulsion was increased by more than 2 min (Figure 3c). After comparing the three conditions, S/CoS ratio 1:1 was considered as optimal ratio to form rapid and clear micro-emulsion. SMEDDS D, E, and F were prepared with S/CoS ratio of 2:1, 1:1, and 1:2, respectively (Figure 4). Phase diagram study shows that SMEDDS D, E, and F forms only self micro-emulsification region (gray region).

**In-Vitro Characterization of SMEDDS**

**Robustness to Dilution**

Diluted SMEDDS did not show any precipitation or phase separation on storage in various dilution media. This reveals that all media were robust to dilution.

**Particle Size Analysis and PDI Determination**

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases increasing the surfactant concentration could lead to droplets with smaller mean droplet size such as in the case of a mixture of saturated C8–C10 polyglycolized glycerides. This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases, the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase (G. Lambert, 2011).

The particle size determination following self micro-emulsification is a critical factor to evaluate a self micro-emulsion system as droplet size is reported to have an effect on drug absorption. The smaller the droplet size is, the larger the interfacial surface area provided for drug absorption (Osol, A., 1975).

The optimization of SMEDDS was based on micro-emulsion domain obtained and particle size of SMEDDS. The mean particle size and PDI for all the SMEDDS have been summarized in Table 3. The results show that particle sizes of SMEDDS D, E, and F were more than 100 nm and with higher PDI. Polydispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation.

The higher the value of Polydispersity, the lower is the uniformity of the droplet size in the formulation. The Polydispersity values of SMEDDS A, B, and C are 0.127, 0.138, and 0.202, respectively, which indicates uniformity of droplet size within the formulation.

In contrast to that, these values are increased for SMEDDS D, E, and F to 0.342, 0.442, and 0.386, respectively, which indicates non-uniformity of particles in micro-emulsion. A less solubility of drug in solvents may be the reason behind this. This leads to precipitation of drug and thereby increases particle size of SMEDDS.

SMEDDS with increased particle size causes agglomeration of globules and suffers with instability of system. Moreover, pseudo-ternary phase diagram also revealed that these three formulations do not fall under self micro-emulsion region; hence, they were dropped for further study. SMEDDS A, B, and C were found having particle size less than 100 nm which fulfil the criteria of micro-emulsion and low PDI shows uniformity of particles. Therefore, SMEDDS A, B, and C were considered for further in vitro and in vivo studies.

**Zeta Potential Measurement**

The surfactant (Tween 80) and co-surfactant (PEG 400) used in this study are non-ionic which do not contribute any charge to the micro-emulsion particle. Lu et al. and Cui et al. reported stable SMEDDS using same excipients (R. Junin, 2009). This indicates that negative charge particle do not affect the stability of micro-emulsion. SMEDDS B reports negative zeta potential value −0.746.

So considering the above *in-vitro* characteristic, it can be concluded that SMEDDS B with S/CoS ratio 1:1 generates maximum micro-emulsion region and forms rapid micro-emulsion with lesser particle size 12.3, low PDI 0.138, and zeta potential −0.746. Therefore, SMEDDS B was considered as optimal self micro-emulsifying system for *in-vitro* and bioavailability studies.

**In-Vitro Release Study**

*In-vitro* release of Flurbiprofen was checked for SMEDDS B, conventional capsule (Froben®), and standard drug solution by using dialysis bag method. The release of Flurbiprofen from these dosage forms was evaluated in buffers of pH 1.2, 4.5, and 6.8. The data showed that release of Flurbiprofen was faster in phosphate buffer of pH 6.8 than other two media (Figure 5). The pH-dependent solubility of drug can be responsible for higher release. The release pattern shows that drug release form SMEDDS B is faster than other two, conventional capsule and standard drug solution. Moreover, SMEDDS B release more than 90% drug within an hour while release rate is very slow in case of conventional capsule suspension, i.e., only 58% and same for standard drug suspension is only 19% within first hour.

The factors affecting drug release may be (a) SMEDDS with reduced particle size provides more surface area to release drug from solvents and thereby increases drug release rate and (b) oil phase of SMEDDS may act as carrier molecules which itself does not diffuse through the barrier but allow drug molecules to get diffused form membrane of dialysis bag. Although exact mechanism is not known, it is confirmed that any of these factors affect the bioavailability of drug.

**In-Vivo Release Study**

Proper analysis is an important component in formulation and development of any drug molecule. A suitable and validated method has to be available for the analysis of drug(s) in bulk, drug delivery systems, *in vitro* and *in vivo*. If such suitable method for specific need is not available then it becomes important to develop a simple, sensitive, accurate, precise, reproducible method for the estimation of drug samples. The present investigation was aimed to develop and validate bio-analytical HPLC method for estimation of Flurbiprofen in rat plasma.

**Selection of Chromatographic Conditions**

The chromatographic conditions were selected on the basis of back pressure, peak resolutions, peak shapes and day-to-day reproducibility of the retention time. For selecting a mobile phase initial trial was taken using methanol and potassium dihydrogen phosphate buffer (pH 3.5) in various phase ratios but the peaks were not of a good shape. Utilization of acetonitrile in place of phosphate buffer improved the peak shapes and hence, 70:30 of methanol-acetonitrile was selected as mobile phase for further trials.

**Validation**

**Linearity and Range**

The mean regression equation of three standard curves was y = 525.83x + 27330, where y presented peak area of drug and x was the plasma concentration of drug. The precisions (% CV) of the slope and intercept were less than 2% for both drugs which indicated minimum variations. The calibration curve was linear over the studied concentration range (10–1000 ng/ml) with a mean correlation coefficient more than 0.99.

**Selectivity**

It is the ability of an analytical method to differentiate and quantify analyte in the presence of other components of the samples. Each blank sample was evaluated for interference with respective drug. The results revealed that the analyte (Flurbiprofen) was well separated from co-extracted material under the adopted chromatographic conditions. The retention time ($R_t$) was 6.75 min.

**TABLES AND FIGURES**

**Table 1 Composition of Formulations**

| Vehicle (%, w/w) | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| Flurbiprofen | 5 | 5 | 5 | 5 | 5 | 5 |
| Captex 200 P | – | – | – | 10 | 10 | 10 |
| Capmul MCM | 10 | 10 | 10 | – | – | – |
| Tween 80 | 60 | 45 | 30 | – | – | – |
| Cremophore EL | – | – | – | 60 | 45 | 30 |
| PEG 400 | 30 | 45 | 60 | 30 | 45 | 60 |

**Table 2 Compositions of Micro-emulsion after Dilution**

| | | Weight/weight percentage component in micro-emulsion formulation | | | |
|---|---|---|---|---|---|
| Formulation | S/CoS Ratio | Oil | S | CoS | Aqueous |
| SMEDDS A | 2:1 | 5 | 13.66 | 6.33 | 75 |
| SMEDDS B | 1:1 | 10 | 17.5 | 17.5 | 55 |
| SMEDDS C | 1:2 | 4 | 3 | 6 | 87 |

**Table 3 Mean Particle Size and Polydispersity Index and Zeta Potential**

| Formulation | Mean Particle Size (nm) | Polydispersity Index | Zeta Potential |
|---|---|---|---|
| SMEDDS A | 17.8 ± 1.9 | 0.127 | −12.1 |
| SMEDDS B | 12.3 ± 2.1 | 0.138 | −0.746 |
| SMEDDS C | 97.1 ± 2.2 | 0.202 | −4.65 |
| SMEDDS D | 111.9 ± 1.9 | 0.341 | −0.249 |
| SMEDDS E | 135.4 ± 2.7 | 0.442 | −0.381 |
| SMEDDS F | 157.5 ± 1.8 | 0.386 | −0.563 |

**Table 4 Pharmacokinetic Parameters for SMEDDS B and Capsule Suspension**

| Parameters | SMEDDS B | Capsule Suspension |
|---|---|---|
| $t_{max}$ (h) | $1 \pm 0.44$ | $1.36 \pm 0.39$ |
| $C_{max}$ (ng/mL) | $112.61 \pm 9.13$ | $69.24 \pm 3.99$ |
| $AUC_{0\rightarrow t}$ (ng h/mL) | $607.93 \pm 45.06$ | $445.36 \pm 70.50$ |
| $AUC_{0\rightarrow\infty}$ (ng h/mL) | $1{,}124.57 \pm 79.66$ | $893.72 \pm 116.56$ |
| $AUMC_{0\rightarrow t}$ (ng h/mL) | $4{,}752.96 \pm 102.70$ | $3{,}848.13 \pm 265.20$ |
| $AUMC_{0\rightarrow\infty}$ (ng h/mL) | $37{,}933.75 \pm 1{,}609.08$ | $33{,}804.48 \pm 1{,}761.19$ |
| $MRT_{0\rightarrow\infty}$ (h) | $33.73 \pm 1.11$ | $37.82 \pm 1.40$ |
| Relative Bioavailability (%) | 178.70 | – |

SMEDDS: Self Micro-emulsifying Drug Delivery System

$t_{max}$ : Time of Peak Concentration

$C_{max}$ : Peak of Maximum Concentration

$AUC_{0\rightarrow t}$ : Area Under The Concentration Time Profile Curve Until Last  Observation

$AUC_{0\rightarrow\infty}$ :  Area Under The Concentration Time Profile Curve Extrapolated to  Infinity

$AUMC_{0\rightarrow t}$ : Area Under Moment Curve Computed To The Last Observation $AUMC_{0\rightarrow\infty}$ : Area

Under Moment Curve Extrapolated To Infinity

$MRT_{0\rightarrow\infty}$ : Mean Residence Time
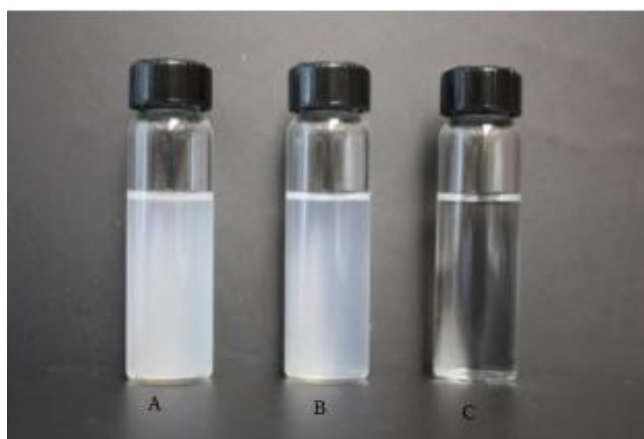


**Figure 2 Results from Test of Emulsification**
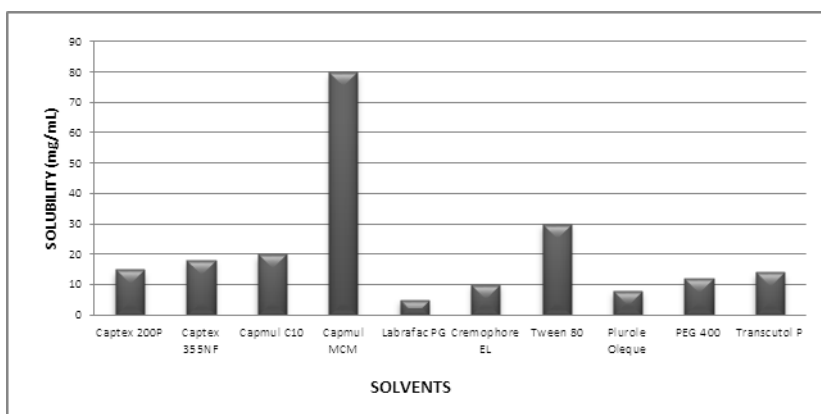
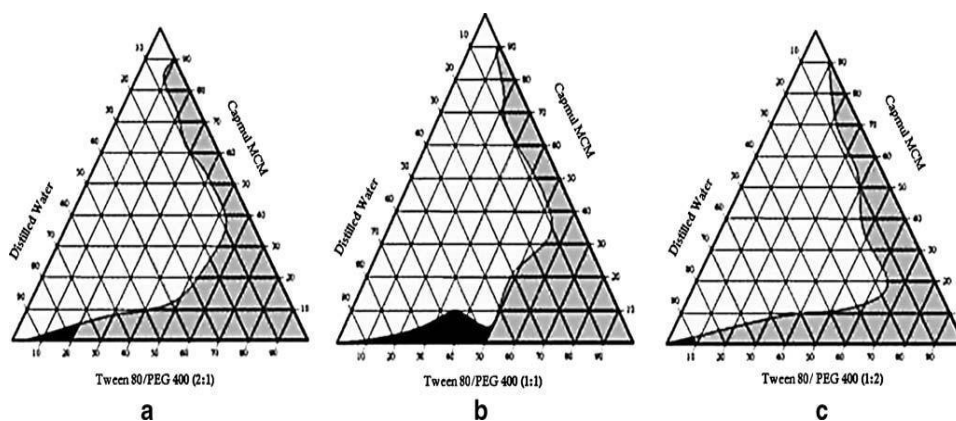**Figure 2 Graph showing solubility of Flurbiprofen in different solvents**



**Figure 4  Phase diagram prepared with the following components: oil Capmul MCM, surfactant Tween 80, and co-surfactant PEG 400. S/CoS ratio of a is 2:1, b is 1:1, and c is 1:2**
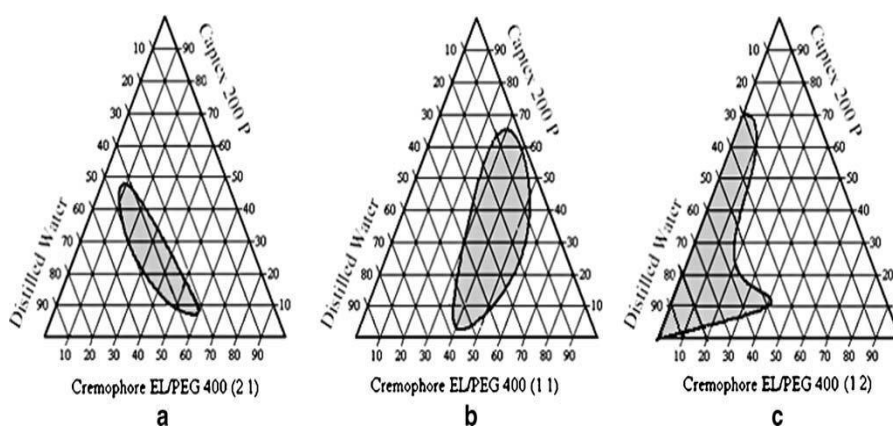


**Figure 5 Phase diagram prepared with the following components: oil Captex 200 P, surfactant Cremophore EL, and co-surfactant PEG 400. S/CoS ratio of a is 2:1, b is 1:1, and c is 1:2**
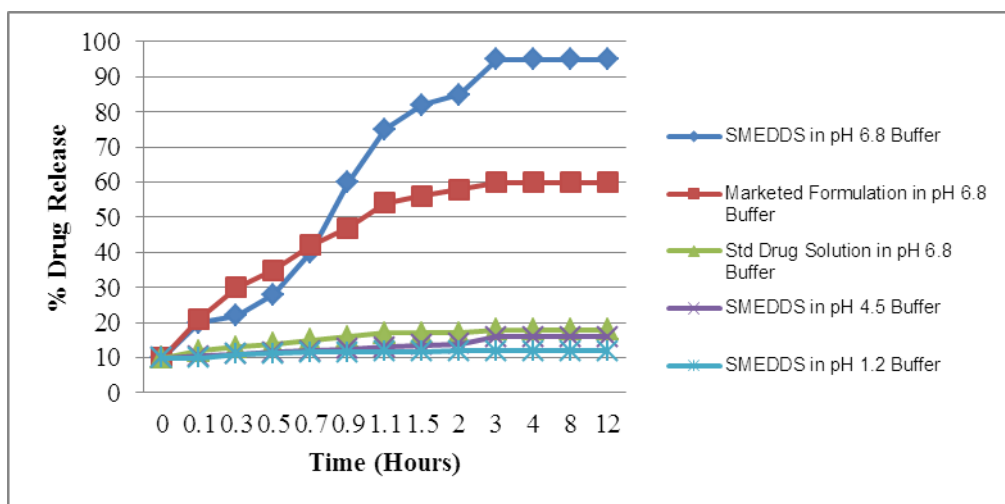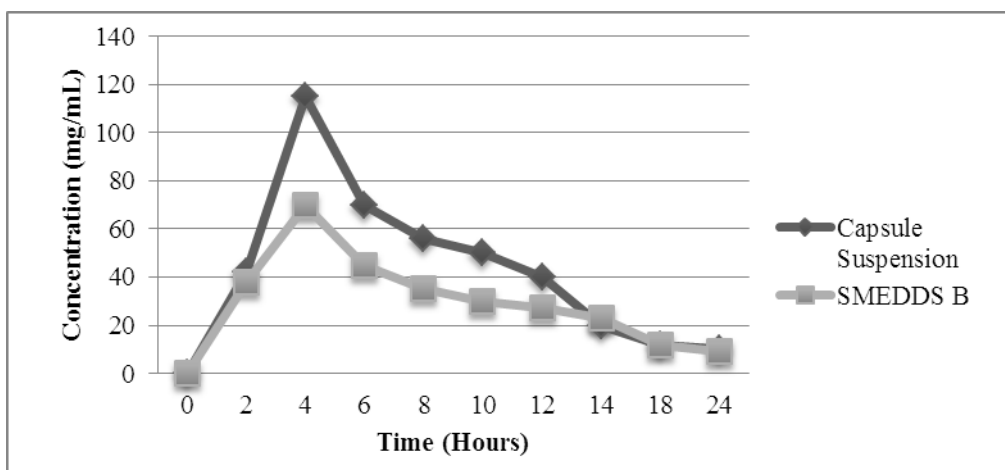
**Figure 6 *In-Vitro* Release of Flurbiprofen in Different Media**



**Figure 7 Plasma Concentration Time Profiles of Flurbiprofen SMEDDS and Capsule Suspension**
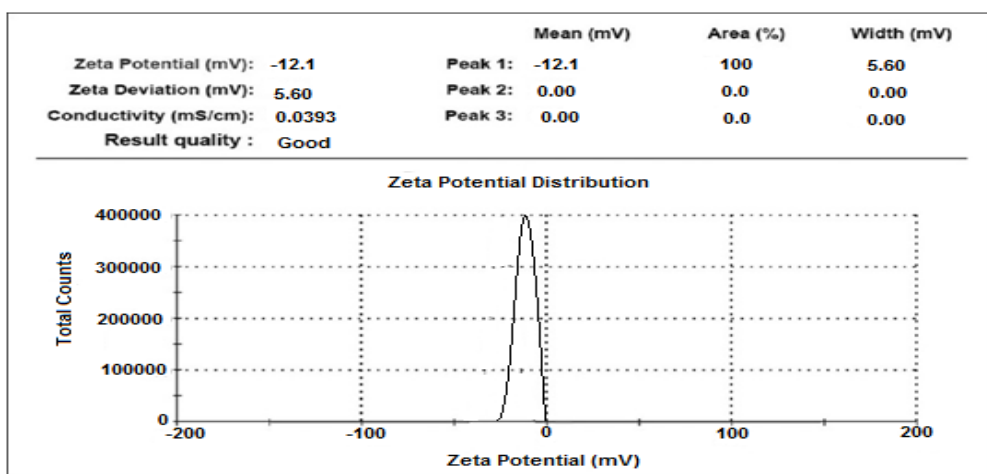


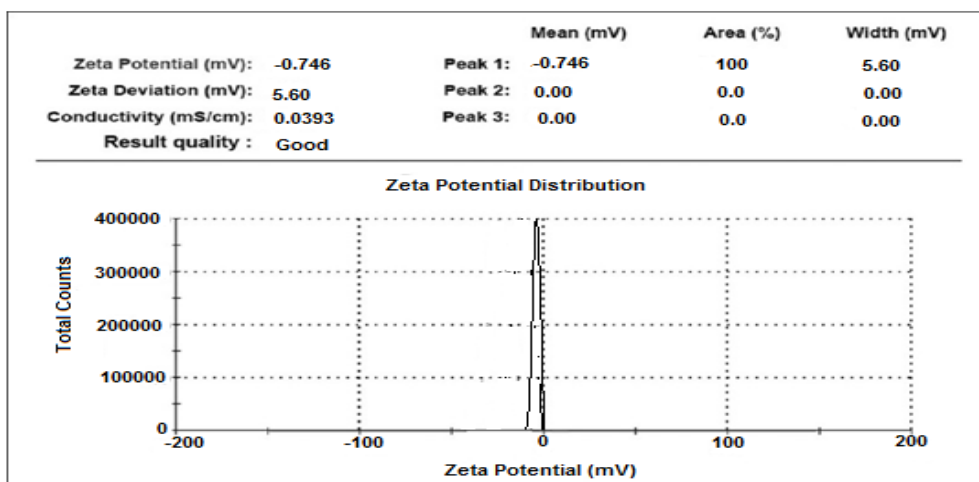**Figure 8 Zeta Potential Reports for SMEDDS A**
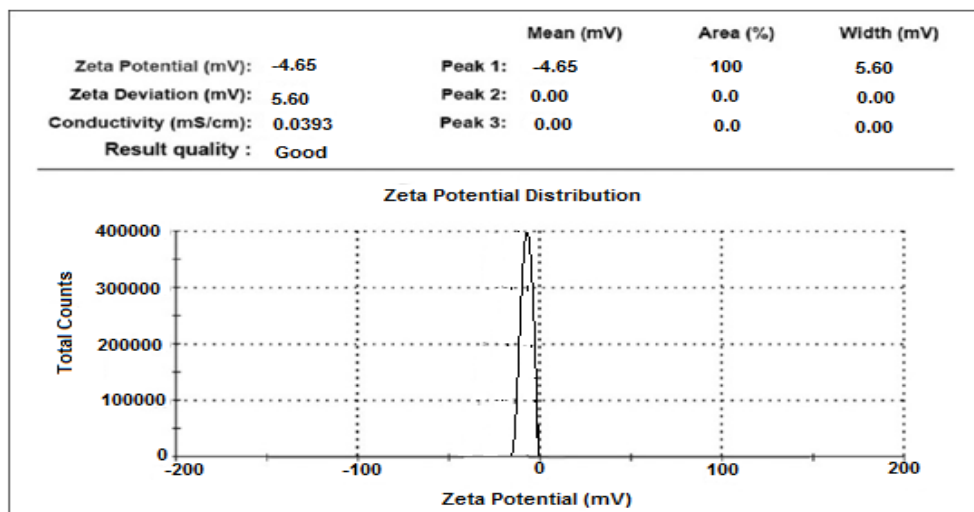
**Figure 9 Zeta Potential Reports for SMEDDS B**



**Figure 10 Zeta Potential Reports for SMEDDS C**

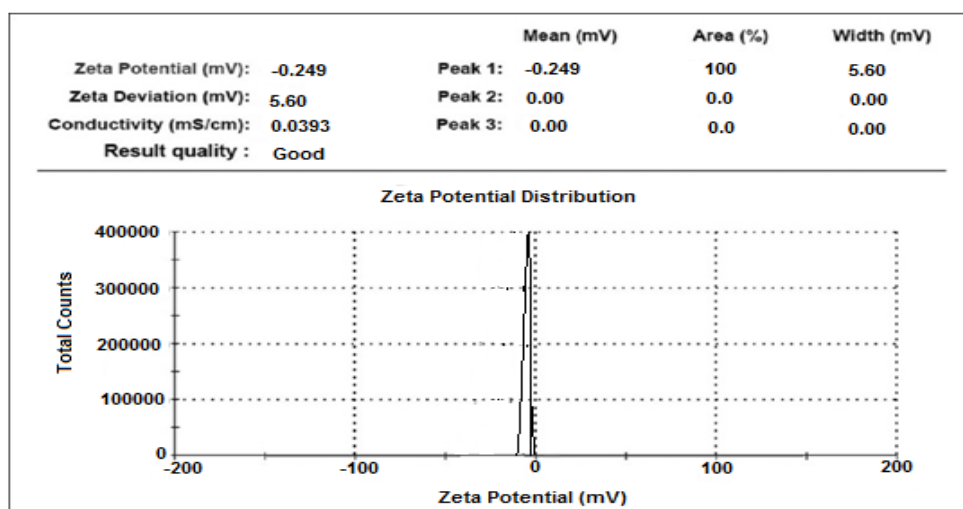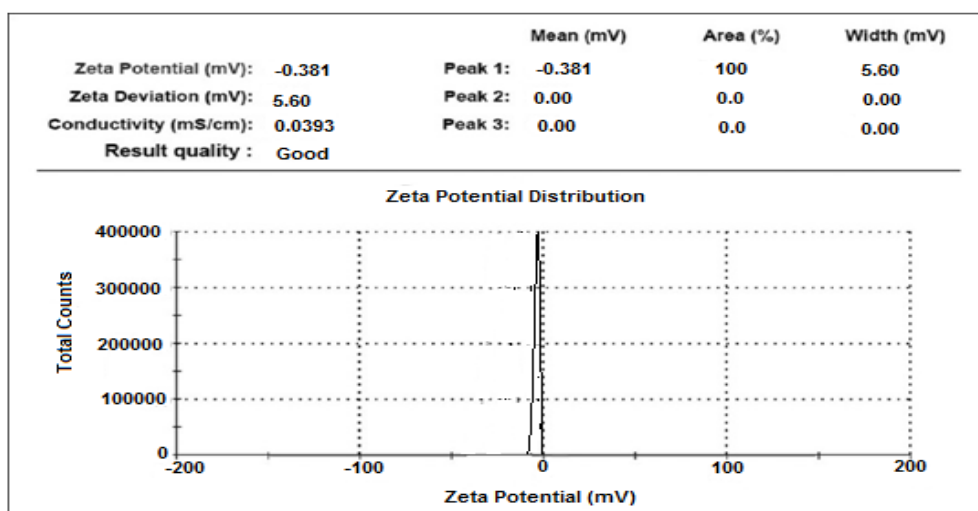

**Figure 11 Zeta Potential Reports for SMEDDS D**

| | | | Mean (mV) | Area (%) | Width (mV) |
|---|---|---|---|---|---|
| Zeta Potential (mV): | -0.381 | Peak 1: | -0.381 | 100 | 5.60 |
| Zeta Deviation (mV): | 5.60 | Peak 2: | 0.00 | 0.0 | 0.00 |
| Conductivity (mS/cm): | 0.0393 | Peak 3: | 0.00 | 0.0 | 0.00 |
| Result quality : | Good | | | | |

**Zeta Potential Distribution**

**Figure 12: Zeta Potential Report for SMEDDS E**

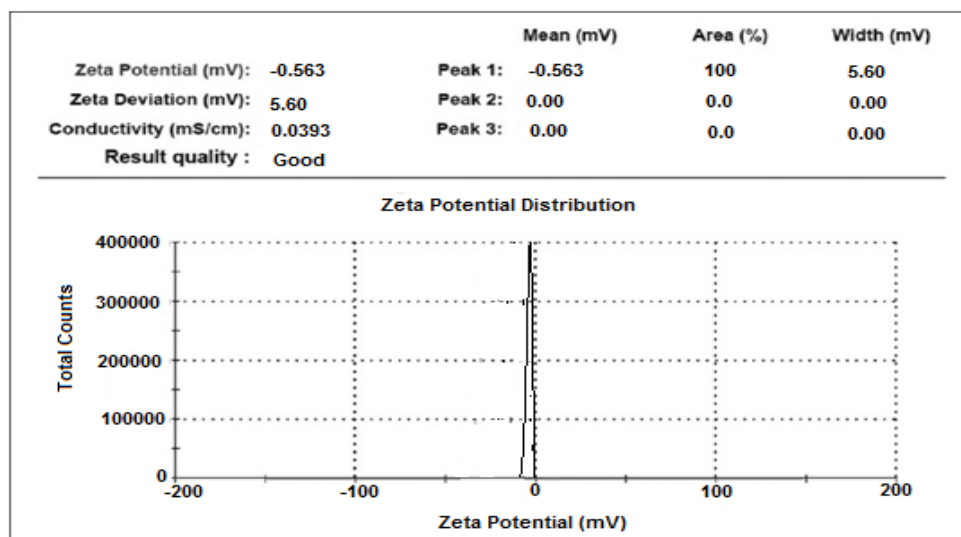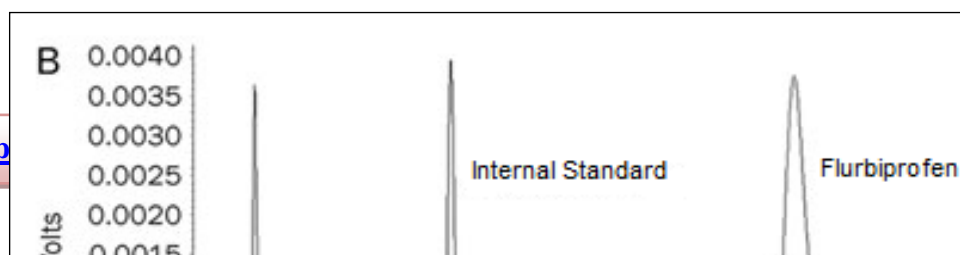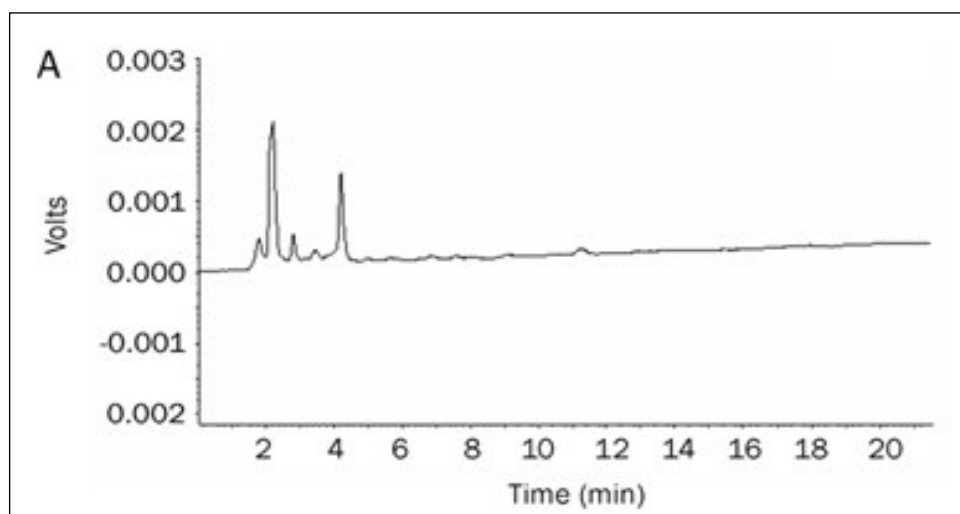| | | | Mean (mV) | Area (%) | Width (mV) |
|---|---|---|---|---|---|
| Zeta Potential (mV): | -0.563 | Peak 1: | -0.563 | 100 | 5.60 |
| Zeta Deviation (mV): | 5.60 | Peak 2: | 0.00 | 0.0 | 0.00 |
| Conductivity (mS/cm): | 0.0393 | Peak 3: | 0.00 | 0.0 | 0.00 |
| Result quality : | Good | | | | |

**Zeta Potential Distribution**

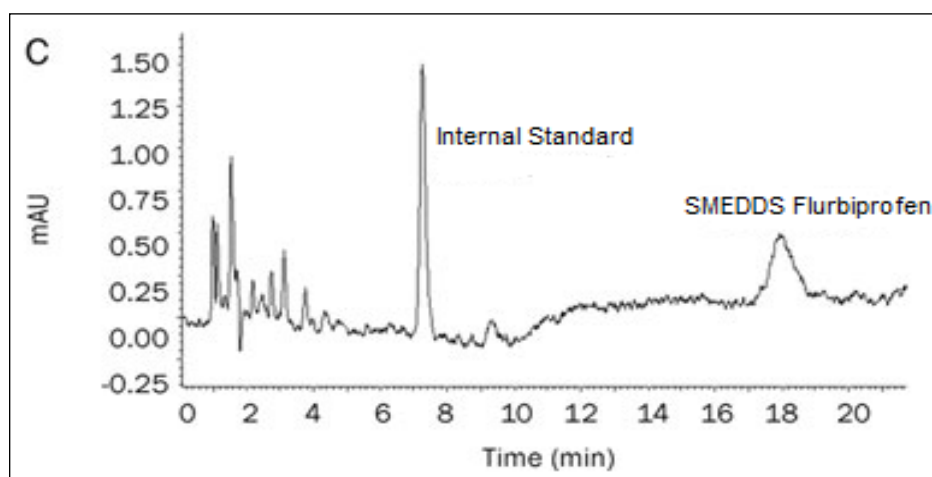**Figure 13 Zeta Potential Reports for SMEDDS F**

**Figure 14 (A) Blank mice plasma (B) Blank Mice Plasma spiked with Flurbiprofen (C) A sample after oral administration of SMEDDS Flurbiprofen**

**CONCLUSION**

SMEDDS of Flurbiprofen was prepared and optimized by using in vitro parameters like particle size, Polydispersity index, zeta potential, *in-vitro* release, and bioavailability studies. Optimal SMEDDS contains Capmul MCM as oil phase, Tween 80 as a surfactant, and PEG 400 as co-surfactant. The combination of all three components, i.e., oil/ surfactant/co-surfactant in the ratio of 10:45:45, formulates SMEDDS with lower particle size 12.3, PDI 0.138, and zeta potential −0.746. This optimized SMEDDS showed good *in-vitro* release which is increased more than 90% when compared with marketed formulation and drug suspension. *In-vivo* study revealed significant improvement in extent of absorption of Flurbiprofen in mice to 1.78-fold compared to with conventional capsule formulation. This

study illustrated the potential use of self micro-emulsified drug delivery system to dispense lipid-soluble drug by oral route.

**ACKNOWLEDGMENTS**

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