

Formulation and Evaluation of a Self-Microemulsifying Drug Delivery System (SMEDDS) of a Poorly Soluble Drug Aceclofenac

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Cite this article as:

Sahu S, Shende R, Prasad S, Ghatuwaray SK. Formulation and Evaluation of a Self Microemulsifying Drug Delivery System (SMEDDS) of a Poorly Soluble Drug Aceclofenac. Global Journal of Innovation and Research. 2025;1(1):46-63.

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Article Info:

Received 25 June 2025

Reviewed 29 July 2025

Accepted 30 July 2025

Published 25 August 2025

ABSTRACT

In this study, aceclofenac, a poorly soluble drug, was chosen as a model. The aim was to prepare a SMEDDS of aceclofenac and compare its performance with a normal drug suspension and a marketed product. Different oils, surfactants, and co-surfactants were tested for drug solubility. Capryol® 90, Cremophor® RH40, PEG, and Transcutol® P showed the highest solubility. Pseudo-ternary phase diagrams were used to find suitable microemulsion regions, and the best ratio of surfactant to co-surfactant (S_{mix}) was 3:1. The optimized formulation, containing Tween 80 and Oleic acid, was prepared by simple mixing. It showed fast self-emulsification on dilution, producing clear microemulsions with small droplet size (257 nm), uniform distribution (PDI 0.233), and good stability (zeta potential +42.7 mV). In vitro studies showed that the SMEDDS released more than 85% of the drug in 30 minutes in biorelevant media, which was higher than the marketed product (78.14%). Ex-vivo studies confirmed that drug permeability was about 2.3 times better than conventional formulations. The formulation was also stable for 3 months under accelerated conditions (40 °C/75% RH) with no major changes in quality. Overall, the developed SMEDDS of aceclofenac significantly improved drug solubility, dissolution, and absorption compared to conventional dosage forms. This study proves that lipid-based SMEDDS are a promising technique for enhancing the oral bioavailability of poorly soluble drugs.

KEYWORDS: SMEDDS, lipid-based formulations, aceclofenac, solubility enhancement, pseudo-ternary phase diagram, bioavailability

1. INTRODUCTION

A major cause of suboptimal oral bioavailability for BCS Class IV drugs is poor aqueous solubility and dissolution rate at physiological pH. Lipid-based drug delivery systems (LBDDS), particularly self-microemulsifying drug delivery systems (SMEDDS), offer a robust approach to circumvent dissolution limitations

by enhancing solubilization in the GI tract and promoting lymphatic uptake in some cases. SMEDDS are isotropic blends of oil, surfactant, and cosurfactant/co-solvent that spontaneously form fine oil-in-water microemulsions with droplet sizes typically <100 nm upon dilution and mild agitation. This increases interfacial surface area, maintains the drug in a solubilized

state, and can reduce the risk of precipitation during digestion¹⁻³.

Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) primarily used for its anti-inflammatory and analgesic properties. It is a phenylacetic acid derivative and is structurally similar to diclofenac. It works by inhibiting the cyclooxygenase (COX) enzyme, particularly COX-2, which leads to a reduction in the production of prostaglandins, inflammatory mediators. Aceclofenac is widely used in the treatment of various musculoskeletal disorders, including osteoarthritis, rheumatoid arthritis, and low back pain. It is also known for its relatively better gastrointestinal tolerability compared to some other NSAIDs⁴⁻⁸.

Therefore, the objective of the present research work is to develop and evaluate SEMDDS of aceclofenac for solubility improvement.

Materials and Methods

Materials

Aceclofenac (API, assay $\geq 99\%$) was obtained as gift sample from Themis Medicare Pvt Ltd SIDCUL Haridwar. Capryol® 90 (propylene glycol monocaprylate, oil), Labrafil® M2125 CS (oleoyl macroglycerides, oil), Cremophor® RH40 and EL (polyoxyl castor oils, surfactants), Tween® 80 (polysorbate 80, surfactant), Transcutol® P (diethylene glycol monoethyl ether, cosurfactant), PEG-400, and propylene glycol were obtained from SD Fine Chem LLP, Thane. All other chemicals were analytical grade.

2.2 Methods

2.2.1 Preformulation study

a. Determination of melting point

Precision melting point equipment was used to determine the melting points of aceclofenac. The fusion technique was used to seal one end of a capillary. By gently tapping the capillary to the sealed end after jabbing the capillary's open end against the drug's powder bed, the drug was inserted into the capillary up to a few millimeters in height. The device held the filled capillaries. As the temperature approached the melting point, the rate of increase was slowed to 1 °C per minute from the initial 5 °C per minute. Sintering and full drug melting temperatures were recorded^{9,10}.

Analytical method validation of aceclofenac

A stock solution of 1000 µg/mL of aceclofenac was prepared by dissolving 50 mg of aceclofenac in methanol. Standard dilutions of various concentrations were prepared by transferring stock solutions to 10 mL volumetric flasks. The λ_{max} of aceclofenac was determined by measuring 10 mg of aceclofenac and adding it to a 100 mL volumetric flask with 50 mL of methanol. A calibration curve was constructed by creating methanolic solutions of various concentrations. The method was validated for linearity, range, limit of detection, and limit of quantitation¹¹⁻¹⁵.

c. Solubility analysis

The extract was tested for its solubility in various solvents. It was determined by shaking 2 mg of extract sample in 5 ml of solvent (i.e. Dimethylsulfoxide, Water, Methanol, and Hexane, Methylene chloride Phosphate buffer pH 6.8, Phosphate buffer pH 7.4 and 0.1N HCL etc). Small test tube and observed to disappear the sample completely^{16,17}.

d. Drug-excipients compatibility studies

A procedure for isothermal stress testing was used. As indicated in the table, precisely 10 mg of the polymer (carbopol 940) and pure phytochemicals (curcumin and aloe-emodin) were weighed both alone and in combination with equal proportion. Glass jars with the proper labels were filled with individual phytochemical, excipient, and physical phytochemical-excipient samples. Following the addition of 10 μ L of ultra-pure water to each vial, a glass capillary was mixed and left inside the vials. Every vial was correctly sealed, wrapped in aluminum foil, and kept for four weeks at 50°C in a stability testing cabinet (T26/HAO-L, Technico). Organoleptic characteristics including color and texture were assessed at the beginning and at the conclusion of the first, second, third, and fourth weeks in order to detect the physical instability. Samples (samples 1–10) were used to trace the temperature using a Differential Scanning Calorimeter (DSC) from 30 - 300 °C at the rate of 30 °C/min, with a one-minute hold time at 30

°C in order to detect the chemical instability (Perkin Elmer, Japan)^{18,19}.

2.2.2 Screening of lipid excipients for SMEDDS

A SMEDDS is an isotropic mixture of oil, surfactants, and co-surfactant. The property of self-microemulsification is only exhibited by certain combination of these components²⁰.

2.2.3 Construction of ternary phase diagrams

The self-micro-emulsifying performance of SME mixtures was evaluated using ternary phase diagrams and time taken to produce a fine nanoemulsion. The results showed that certain combinations of oil, surfactants, and co-surfactants in a certain composition range produced a fine nanoemulsion upon aqueous dilution. The emulsification efficiency of SME mixtures was tested on all six combinations, with Tween 80-PEG 400, Cremphor RH 40-PEG 400-, and Cremophor RH 40-Transcutol being the largest SME regions. The time taken for complete emulsification was also considered, with Cremophor RH 40 taking more time to emulsify than Tween 80. The Tween 80-PEG 400 mixture had the largest SME region and the least time to micro-emulsify. Drug incorporation into SMEDDS did not affect the SME performance, suggesting that the presence of drugs does not affect the self-microemulsifying property of the SME mixtures.²¹⁻²³.

2.2.4 Preparation of liquid SMEDDS

After careful evaluation of phase diagrams,

Tween 80-Labrafac Lipophile WL 1349-PEG 400 were selected as a SME mixture for drug delivery. Liquid SMEDDS formulation was prepared by dissolving 200 mg of aceclofenac drug in the optimized SME mixture consisting of Tween 80(50%w/w), and PEG 400(25%). Drug containing SME mixture was vortexed until a clear solution was obtained. These mixtures were observed for any signs of turbidity or phase separation for a period of 48 hours^{24,25}.

2.2.5 Preparation of solid SMEDDS

The Liquid SMEDDS described in section 3.2.4 was adsorbed onto Tween 80 US2 by physical mixing in a small mortar and pestle. The resulting Solid SMEDDS was a free-flowing powder that was subsequently subjected to solid state characterization and dissolution studies. The formula of the optimized Solid SMEDDS is shown in table.

All six combinations were prepared with the ratios of Oil:(Surfactant or Cosurfactant) as 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and 1:7. The Surfactant/Cosurfactant ratio's (km) of 1:1, 2:1 and 3:1 were evaluated. Surfactant/cosurfactant mixtures are possessing various km ratios were prepared by weighing appropriate amount of surfactants and co-surfactant and were vortexed for 30 min to produce a homogenous mixture. Mixtures with 12-50% of the oil, 25-66% of the surfactant and 12-44% of cosurfactant were evaluated for their self- emulsifying properties. Thus such as, each combination had a total of 21 samples with different proportions of oil, surfactants and cosurfactants. These mixtures

were then mixed with the oil phases to form an isotropic self microemulsifying (SME) mixture²⁶⁻²⁸.

2.2.6 Characterization of prepared solid SMEDDS

a. Droplet size and zeta potential of Nano emulsions

The droplet size and zeta potential of the resultant nanoemulsion was measured using Dynamic Light Scattering. The nanoemulsion samples were taken in disposable Durex borosilicate glass culture tubes (VWR Scientific products) and volume weighted diameter was determined by placing the sample in the path of a Helium Neon laser of wavelength 658 nm at a scattering angle of 90°C and a temperature of 23°C²⁹.

b. Morphological analysis of solid SMEDDS

The surface morphology of Solid SMEDDS, US2 was analyzed in an FEI Quanta 3D FEG Dual Beam Electron Microscope. An accelerating voltage of 5 kV was used to visualize the samples. The samples were fixed on an aluminum stub using a double-sided carbon adhesive tape and were made electrically conductive by coating with palladium under vacuum³⁰.

c. Stability study

The physical stability of the formulations was evaluated by visual inspection for physical changes such as phase separation and drug precipitation (Pang *et al.*, 2007). The physical stability study was performed at 4°C, 25°C and 45°C for 15 days³¹⁻³³.

d. Drug release study in-vitro

USP type II dissolution equipment was used for the in-vitro dissolution investigations, and the previously defined procedures were followed. Briefly, two hours before use, the regenerated cellulose dialysis membranes with molecular weight cut-off 3500 Da (Spectrum Laboratories, Inc., Rancho Dominguez CA, USA) were soaked in buffer medium pH 6.8. Dialysis membrane tubes were sealed with 2 mL of ACF-SEDDS formulations (containing 40 mg of ACF) and 2 mL of ACF suspension in buffer pH 6.8 (containing 40 mg of ACF) in PEG 400 as a control for the release studies. The dialysis tubes were then suspended in 500 mL of PBS, pH 6.8 as a release medium that was kept at $37 \pm 0.5^\circ\text{C}$ and 100 rpm. At regular intervals, aliquots (3

mL) were taken out and replaced with an equivalent volume of brand-new medium. After passing through $0.45 \mu\text{m}$ PTFE membrane filters, aliquots were examined using UV spectroscopy set to 271 nm^{34-36} .

3. RESULTS

3.1 Preformulation study

a. Melting point determination

Melting point of the drug aceclofenac was recorded and complied with the literature. The melting point of aceclofenac was recorded as 157°C .

b. Analytical method validation

The absorption maximum (λ_{max}) of 271 nm (Figure 1) was observed for the drug aceclofenac. The optical features are tabulated in table 1. The linearity was observed between 0.1 to 0.7 mg/mL.

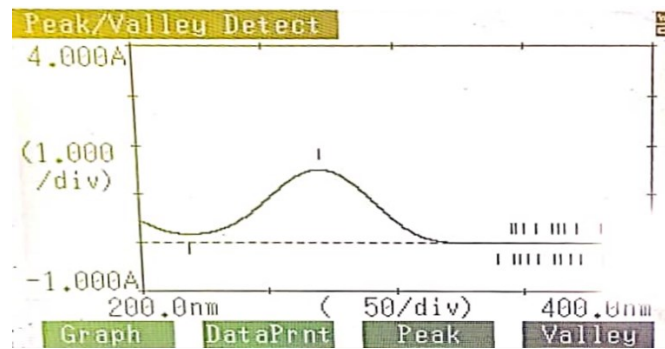


Figure 1: Scanning spectra of the drug aceclofenac in methanol for λ_{max} determination

Peak Detection			
λ (nm)	Abs	λ (nm)	Abs
336.70	0.005	271.00	0.511
379.90	0.006		
371.10	0.006		
365.70	0.006		
363.50	0.006		
351.00	0.006		
355.30	0.006		
350.00	0.006		
346.70	0.006		
345.10	0.006		

Figure 2: Characteristic absorbance of the drug aceclofenac in methanol at different wavelength and at λ_{max} 271 nm

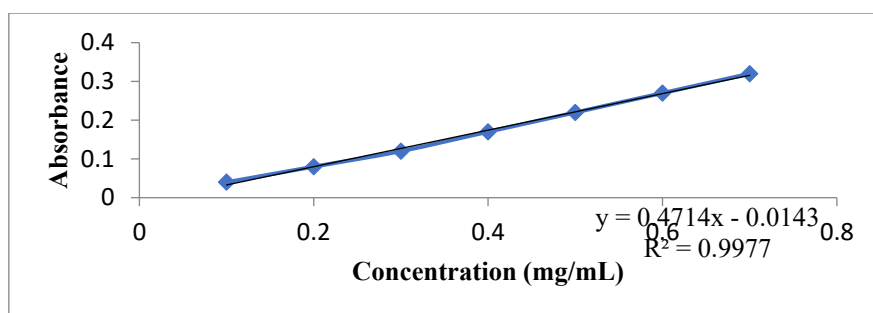


Figure 3: Calibration curve of the drug aceclofenac in methanol at 271 nm

Table 1: Data showing results of regression and optical features of the analytical method of aceclofenac

Parameters	Values
Linear dynamic range ($\mu\text{g/mL}$)	0.1-0.7
Regression equation	$y = 0.4714x - 0.0143$
Correlation coefficient (r)	$R^2 = 0.9977$
SE intercept	0.00451754
SD intercept	0.01195
LOD ($\mu\text{g/mL}$)	0.2431
LOQ ($\mu\text{g/mL}$)	1.0523
Variance of the calibration line	0.05153

c. Solubility analysis of pure aceclofenac API

Solubility of the pure aceclofenac drug was recorded as 0.0265 ± 0.015 mg/mL which was found comparable with reported 0.056 mg/mL³⁷.

d. Drug Solubility studies

Capryol® 90 (oil), PEG, Cremophor® RH40 (surfactant), and Transcutol® P (cosurfactant) showed the highest aceclofenac solubility (208.11 ± 8.95 , 207.20 ± 19.69 , 145.35 ± 3.29 , 319.02 ± 23.21 and 182.56 ± 23.39 mg/g, respectively).

Table 2 Solubility of the pure aceclofenac API

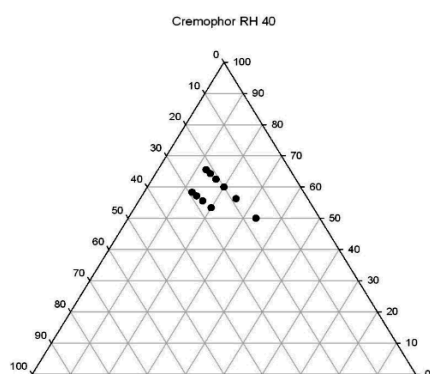
S. No.	Drug	Solvent	Solubility (mg/mL \pm SD)	Reported Value (mg/mL)
1	Aceclofenac	Distilled water	0.0265 ± 0.015	0.056

Table 3: Solubility of aceclofenac in various solvents

S. No.	Solvent	Solubility
1.	Capyrol 90	208.11 ± 8.95
2.	PEG 400	207.20 ± 19.69
3.	Cremophor RH 40	145.35 ± 3.29
4.	Transcutol P	319.02 ± 23.21
5.	Tween 80	182.56 ± 23.39

Table 5: Different volumes of surfactants and co-surfactant taken to make a stock mix

Formulation	Ratio of Smix
F1	1:1
F2	2:1
F3	1:2
F4	1:3
F5	1:4
F6	3:1

**Figure 4: Ternary phase diagrams of SME mixture with Tween 80, PEG 400 and LL WL 1349**

3.2 Screening of lipid excipients

Six different mixes of surfactant and cosurfactant was produced and analyzed using water titration method.

3.3 Optimization of ratio of surfactant and cosurfactant

The formula of the optimized Solid SMEDDS is shown in table 6.

Table 6: Composition of an optimized Solid SMEDDS

Formula components	Proportions
Tween 80	750 mg
Oleic acid	375 mg

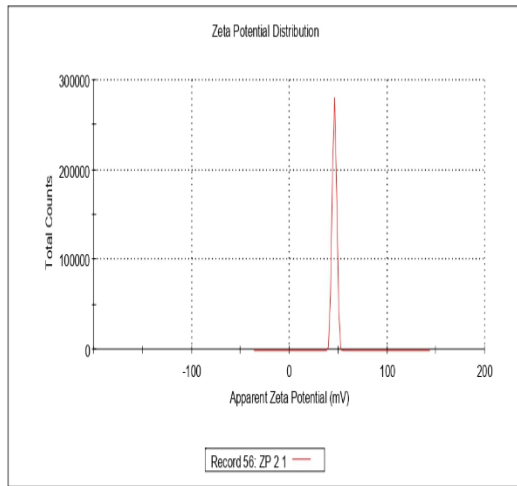
3.4 Pharmaceutical characterization

a. Droplet size analysis

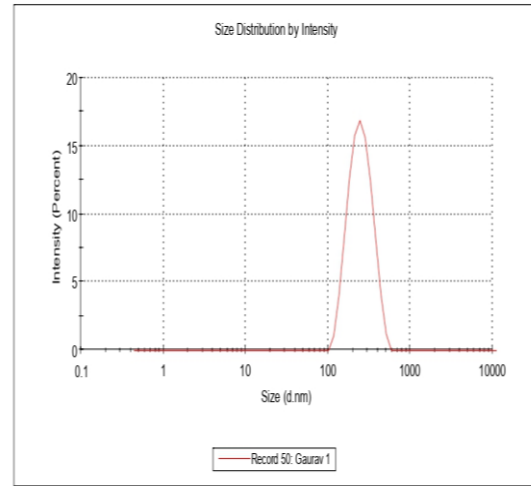
The droplet size of the nanoemulsion was measured using dynamic light scattering and found as 247 nm.(Figure 6).

Zeta potential, particle size and PDI of the selected nanoparticle formulation were recorded 42.7, 257 and 0.233 respectively when observed using Malvern Zetasizer (Figure 5a-b).

b. Zeta potential



a



b

Figure 5: Data obtained from Malvern zetasizer for a) Zeta potential and b) particle size

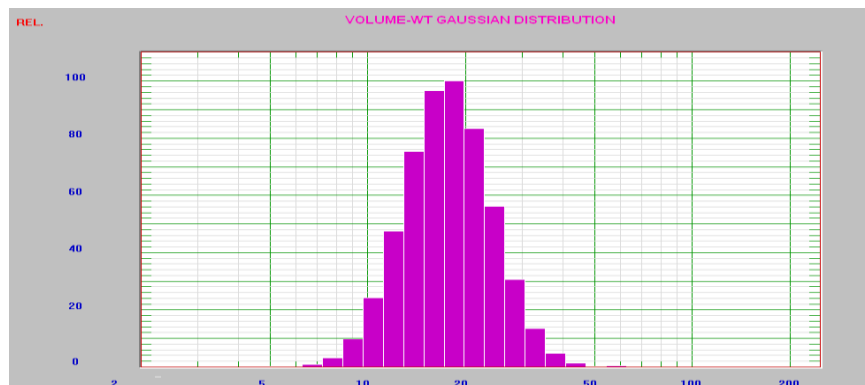


Figure: 6: Droplet size distribution chart for SMEDDS

c. Morphology of SMEDDS:

For converting a Liquid SMEDDS into the solid state, a highly porous powder with good oil adsorbing capacity is required. Such powders can adsorb oil components of the Liquid SMEDDS and convert them into a free-flowing powder. US2 has a highly porous structure which is capable of adsorbing up to three times its weight of oil. Scanning electron microscopy reveals the morphology of solid SMEDDS. From the aceclofenac drug appeared to be made of smooth rectangular crystalline structures. Similar observations about ibuprofen micrographs were made by other

researchers. Tween 80 appears to be spherical porous particles of size of 75 approximately 100 μm . Micrographs of Solid SMEDDS shows Liquid SMEDDS adsorbed onto the surface of Tween 80 particles. Since the formulation process involved facilitating adsorption through physical mixing, partially covered Tween 80 are also visible in the field of vision. Crystalline structures characteristic of solid ibuprofen is not seen in Solid SMEDDS micrographs suggesting that the drug is present in a completely dissolved state in the Solid SMEDDS^{52,53}.

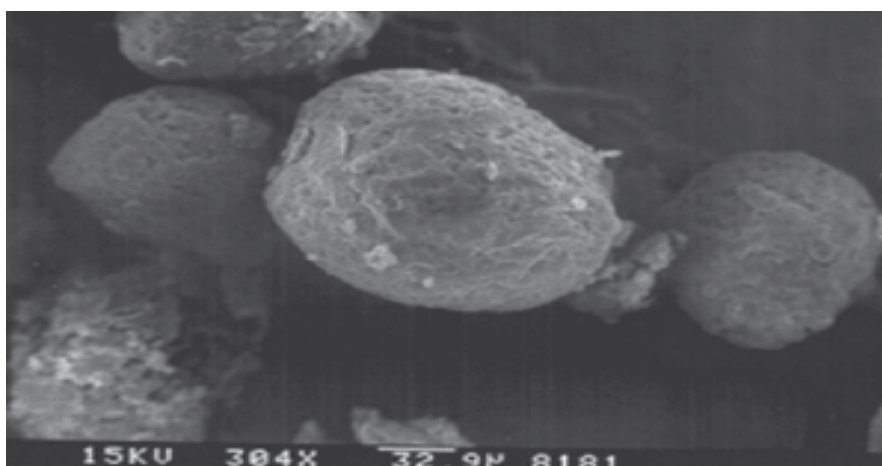


Figure 7: Scanning electron micrographs (300x) of optimized formula.

d. Stability Study

The stability studied shows that all formulations are stable at 4°C and 25°C

but at 45°C, formulations were unstable after 5 days they as indicated by physical changes in the terms of phase separations and drug precipitation.

Table 6: Visual assessment of various SMEDDS

Formulation	Grade based on visual observation	Time of emulsification in (Min:Sec)	Storage stability at 4°C after (days)			Storage stability at 25°C after (days)			Storage stability at 45°C after (days)		
			5	10	15	5	10	15	5	10	15
F-1	A	00:25	--,--		--,--	--,--		--,--	--,--		+,+
F-2	A	00:35	--,--		--,--	--,--		--,--	--,--		+,+
F-3	A	00:40	--,--		--,--	--,--		--,--	--,--		+,+
F-4	B	00:55	--,--		--,--	--,--		--,--	--,--		+,+
F-5	B	00:60	--,--		--,--	--,--		--,--	--,--		+,+

e. Dissolution Study

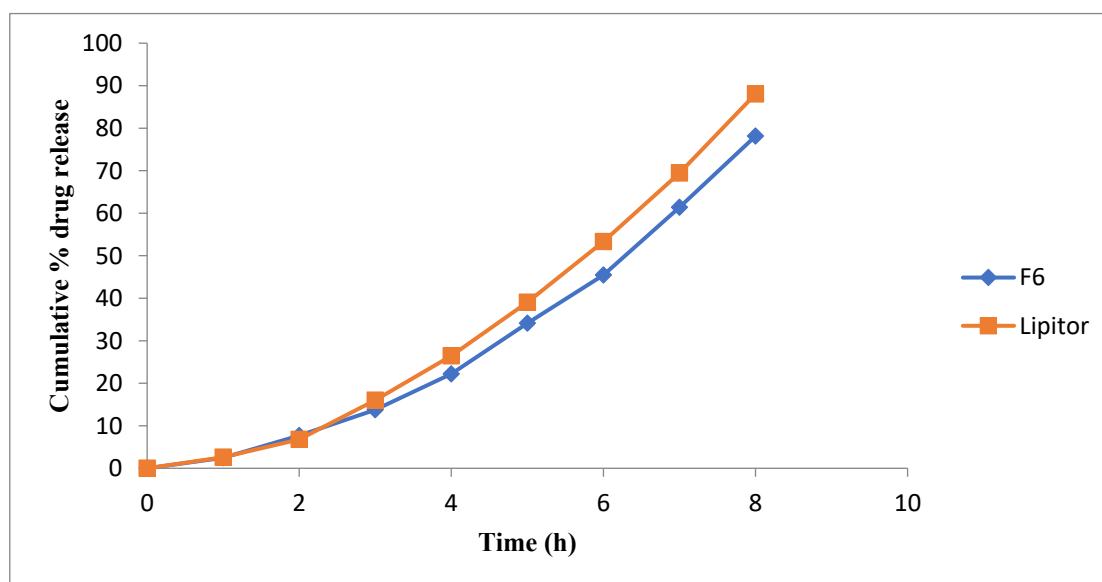


Figure 8 Comparative drug release profile of prepared self emulsifying based tablet and marketed formation Lipitor

4. DISCUSSION

The preformulation investigation of aceclofenac confirmed its crystalline, lipophilic, and poorly water-soluble nature, classifying it as a BCS Class II drug. While its permeability is favorable, solubility and dissolution remain major limitations for oral bioavailability. Drug-

excipient compatibility studies revealed no significant interactions, supporting further formulation efforts.

These findings suggest that advanced drug delivery approaches such as SMEDDS, nanoparticles, or solid dispersions are essential to enhance the solubility, dissolution rate, and therapeutic efficacy of

aceclofenac.

The self-micro-emulsifying performance of SME mixtures was evaluated using ternary phase diagrams and time taken to produce a fine nanoemulsion. The results showed that certain combinations of oil, surfactants, and co-surfactants in a certain composition range produced a fine nanoemulsion upon aqueous dilution. The emulsification efficiency of SME mixtures was tested on all six combinations, with Tween 80-PEG 400, Cremphor RH 40-PEG 400-, and Cremophor RH 40-Transcutol being the largest SME regions. The time taken for complete emulsification was also considered, with Cremophor RH 40 taking more time to emulsify than Tween 80. The Tween 80-PEG 400 mixture had the largest SME region and the least time to micro-emulsify. Drug incorporation into SMEDDS did not affect the SME performance, suggesting that the presence of drugs does not affect the self-microemulsifying property of the SME mixtures.

Tween 80-Labrafac Lipophile WL 1349-PEG 400 was chosen as a SME mixture for drug delivery, and a liquid SMEDDS formulation was prepared by dissolving 200 mg of aceclofenac drug in the optimized mixture. The Liquid SMEDDS was adsorbed onto Tween 80 US2 and subsequently solidified into a powder. Six

combinations of oil, surfactant, and cosurfactant ratios were prepared, with various km ratios evaluated. The mixtures were then mixed with oil phases to form an isotropic self microemulsifying (SME) mixture. The self-emulsifying properties of these mixtures were evaluated.

The droplet sizes of the nanoemulsion are important since it determines the rate and extent of drug releasing and absorption. The drug can diffuse faster from smaller droplets into the aqueous phase, thereby increasing the drug dissolution. Smaller droplet size presents large surface area for drug absorptions. Reduction in droplet size improved bioavailability of emulsion when compared to a coarse emulsion. Increases in surfactants concentration decreases the droplet size up to a certain size but there after anymore increase in surfactant concentration results in an increase in droplet size. The reduction in droplet size can also be attributed to the stabilization of oil droplets according to localization of surfactants monolayers at the oil-water interface. Increase in surfactants concentration causes enhanced water penetration into oil droplets leading to breakdown of oil droplets and resultant bigger droplets.

For converting a Liquid SMEDDS into the solid state, a highly porous powder with good oil adsorbing capacity is required.

Such powders can adsorb oil components of the Liquid SMEDDS and convert them into a free-flowing powder. US2 has a highly porous structure which is capable of adsorbing up to three times its weight of oil. Scanning electron microscopy reveals the morphology of solid SMEDDS. From the aceclofenac drug appeared to be made of smooth rectangular crystalline structures. Similar observations about ibuprofen micrographs were made by other researchers. Tween 80 appears to be spherical porous particles of size of 75 approximately 100 μm . Micrographs of Solid SMEDDS shows Liquid SMEDDS adsorbed onto the surface of Tween 80 particles. Since the formulation process involved facilitating adsorption through physical mixing, partially covered Tween 80 are also visible in the field of vision. Crystalline structures characteristic of solid ibuprofen was not seen in Solid SMEDDS micrographs suggesting that the drug is present in a completely dissolved state in the Solid SMEDDS

5. CONCLUSIONS

In this study, self-micro emulsifying (SME) mixtures are containing surfactant, cosurfactant and a medium chain triglyceride were been prepared and their tendency to efficiently emulsify was to evaluated. Upon aqueous dilution, such mixtures spontaneously emulsified

forming an oil-in-water nanoemulsion. This property was dependent upon the composition of the excipients as well as their individual concentration in the mixture. Excipients are evaluated for self-microemulsification were been Tween 80 and Cremophor RH 40 as surfactants, Transcutol P, Capyrol 90 and PEG 400 as cosurfactants and Labrafac Lipophile (LL) WL 1349 (a medium chain triglyceride) as an oil. All the excipients are showed a tendency to form a nanoemulsion with varying degrees of efficiency. Self-microemulsifying drug delivery system (SMEDDS) is known to improve dissolution characteristics of a poorly water-soluble drug since they maintain the drugs in a solubilized state in the GI tract. Using the optimized SME mixture, ocimum sanctum loaded Liquid and Solid SMEDDS were prepared, evaluated for their self-microemulsification tendency and characterized. The resulting microemulsions are from the trial formulations showed a droplet size of approximately 20 nm and a neutral zeta potential. Our studies indicated that SMEDDS can be potentially used for delivering poor water-soluble drug. Finally, the prepared self emulsion based solid dosage form was compared with marketed preparation Lipitor for its ability to release the drug. The cumulative % of drug release was obtained as 88.03% and 78.14%

respectively for prepared formulation when compared to market formulation Lipitor.

6. ACKNOWLEDGEMENT

Authors are thankful to Themis Medicare Pvt Ltd for providing gift sample of aceclofenac and RKDF School of Pharmaceutical Sciences, BHABHA University, Sehore, Madhya Pradesh for providing necessary facilities.

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