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Development of Aceclofenac Solid Self-Emulsifying Drug Delivery Systems

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ABSTRACT

Aceclofenac is NSAIDs used for the diagnosis of analgesic, antipyretic, rheumatoid arthritis, gout. The solubility of Aceclofenac was 50mg/ml in water. Because of poor aqueous solubility drug has low oral bioavailability (50-60%). Within present research one effort was made to create the SMEDDS of Aceclofenac which increases the solubility and bioavailability of drug. Twenty seven formulations of liquid SMEDDS were formulated with different concentrations of oleic acid, Chremophore RH 40 and PEG 400. The surfactant and co-surfactant mixture (S_{mix}) ratio has been selected based upon the self emulsification region found in Pseudo ternary phase diagram. Among different ratios of S_{mix} i.e., F1 (1:1), F2 (1:2), F3 (2:1), formulations 1:2 ratio of S_{mix} was selected to prepare Liquid SMEDDS. Among three formulations S1 is showing good results and *in-vitro* drug release studies are showing more liner and highest percentage release of drug of 98.15 at the end of 60min. Drug release mechanism was found to be zero-order based on the results of various kinetic models.

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INTRODUCTION

Self-Micro-Emulsifying drug delivery system is the latest and innovative approaches have been interested in significant interest like an effective means for improving solubility, dissolution rate and oral bioavailability poorly soluble drugs [1]. Lipid-based drug delivery systems having the capacity for improving solubility and these leads to the improving the rate and extent of drug absorption. Generally SMEDDS are prepared as liquid formulations and liquid formulation and filled into soft gelatin capsules but Complexation and the gelatine shell problems are the major drawbacks for this formulation. So to overcome these problems solid SMEDDS can be prepared. SMEDDS are isotropic mixture of Oil, hydrophilic surfactant and co-surfactant and solubilised drug. This formulation spontaneously from fine oil-in-water microemulsion upon dilution with water under the conditions of gentle agitation [2].

MATERIALS AND METHODS

Aceclofenac was gift sample from Lee pharma Ltd, MCC, Aerosil 200, oleic acid, Chremophore RH 40, PEG 400 was found Merck Pvt. Ltd. All abundant chemical as well as chemical agent utilized in this study are of analytical grade.

Methodology

FTIR Studies

An infrared (IR) spectrum was obtained using the KBr pellet press technique (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 $cm^{-1}$and the resolution was 1 cm^{-1}. FTIR absorption spectra were taken for pure drug sample, optimized liquid SMEDDS and Solid SMEDDS formulation [3].

Formulation Development

Aceclofenac SMEDDS were prepared through using water titrimetric technique.

Preliminary Studies

Before trying to construct the phase diagram graph the solubility of drug in variety oils, surfactants and co-surfactants have been did check and depending on the outcomes excipients have been selected [4].

Screening of Oils

Solubility studies were carried out using screw capped vials containing 5 ml of oil. To this excess amount of Aceclofenac was added. The suspension of vehicles is mixed in a magnetic stirrer continuously by increasing the temperature until drug dissolves for 48 hrs. Then the mixture was centrifuged at 5000 rpm for 15 min. Then filter the answer and diluted to methanol and evaluated by UV spectrophotometer again for diluted drug at 276 nm against methanol using it as a blank [5].

Preparatory of Liquid SMEDDS

The phase diagrams seem to have been designed at distinct km values and indeed the km value at elevated microemulsion is acquired was chosen for preparation of liquid SMEDDS. Preparation was ready through using oleic acid as oil phase, Chremophore RH 40 as surfactant and PEG 400 as co-surfactant (1:2). In all formulations Aceclofenac (100mg) kept constant. Accurately weighed oil, surfactant and co-surfactant were taken into glass vials according to their ratios. The amount of Aceclofenac should be such that it should be solubilise completely. The components were mixed in a magnetic stirrer and heated at 60^{o}C in a water bath Aceclofenacwas completely dissolved. Then the mixture was sealed and stored in a room temperature for further use [6].

Evaluation Tests for Liquid SMEDDS

Self-Emulsification Time

0, 5 ml of multiple option was positioned in 400 ml of liquid and components were blended to magnetic stirrer. Inside this quirkiness of emulsifying, scattering and evident stability, clarity have been evaluated. The optimized batch is emulsifying agent into transparent, clear as well as shows no indication of instability for twenty four hours [7].

Cloud Point Measuring System

Dilute the microemulsion preparation to 50 ml of liquid in flask and put on the steam bath with slowly increasing the temp till the diluted preparation aspects to cloudy.

It would provide the knowledge regarding stability of microemulsion there as body temp [8].

Zeta Potential and Globule Size Determination

The zeta potential of optimized microemulsion formulation was determined using nano zeta sizer. From this zeta sizer Charge on emulsion droplets and their mean zeta potential value ($\pm$ SD) were obtained [9].

Drug Content

It is assayed spectrophotometrically for the drug content at the wavelength 276 nm with proper dilution of formulations taking 0.1N HCl as blank. It will give the % content uniformity of the optimized microemulsion formulation [9].

Dispersibility Test

Aceclofenac SMEDDS (approximately 0.2 ml) was diluted with 100 ml of distilled water and gently stirred with a magnetic stirrer by maintaining temperature at 37$\pm$ 0.5^{0}C.

Grade I: Rapidly trying to form microemulsion, getting real.

Grade II: Quickly trying to form gently clear emulsion to have bluish white appearance.

Grade III: Fine creamy emulsion founded inside of 2 minutes.

Grade IV: Grayish white emulsion to have slightly sticky looks and gradually emulsify.

Grade V: Poor or negligible emulsifying with huge oil aggregates located on the surface [10].

% Transmission Test

The SMEDDS were reconstituted with distilled water, formed micro emulsion was noticed visually for just any sediment on after % transmittance had been assessed at 650 nm utilizing UV-vis spectrophotometer on that pure water as a blank [10].

The research were arrived at the conclusion it after 100 times samples were diluted.

Surface Morphology

To evaluate the surface morphology and size of the particles of a SMEDDS had been did check by Scanning Electron Microscope [11].

Thermodynamic Stability Studies

Mainly determined the physical stability of the emulsion.

Freeze Thaw Cycle

The preparation was kept at refrigerator temp (4^0C) and 45^0C for 48 hours. This repeat the test to six cycles. The preparations were stable at all these temp further exposed into centrifugation test [12].

Centrifugation

The formulations passed test in freeze thaw cycle storage between 21^0C and 25^oC for 48 hours and these are subjected to the centrifugation at 3500 rpm for 30 min and observe the formulations shows no phase separation [13].

Conversion of Liquid SMEDDS into Solid SMEDDS

The solid carriers used in the adsorption consisting of substances that gives the great surface morphology with good disintegration specific properties. The solid carriers include Micro Crystalline Cellulose (MCC) and colloidal silicon dioxide (Aerosil 200).

The 95% of adsorption will observe with these carriers. Solid SMEDDS were prepared using different ratios of MCC and Aerosil 200 like (1:1, 1:2, 2:1). And the optimized ratio of MCC and Aerosil 200 was 1:1 in which is used to prepare the S-SMEDDS. By using 1:1 ratio good absorption, good flow properties were observed and it requires small amount of sample.

The conversion of S-SMEDDS includes adding the optimisation liquid preparation into the solid carriers under constant mixing to form smooth dough [14]. The start preparing dough was managed to pass into the sieve no 80 to form particles. The particles have been dried a drying oven.

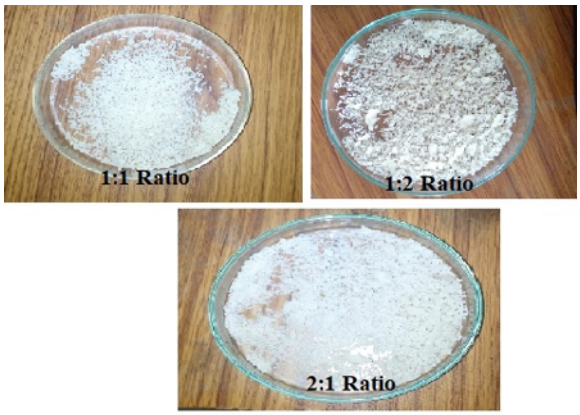

Figure 1: Solid SMEDDS Containing 1:1, 1:2 and 2:1 Ratio of Adsorbent Mixture (MCC and Aerosil 200)

Evaluation Tests for Solid SMEDDS

% Practical Yield

$$Percentage \quad Yield = \frac{\frac{Amount\ of\ solid\ SMEDDS\ obtained\ (g)}{Theoretical\ amount\ (g)}}{} \times 100$$

Drug Content

Precise number of S-SMEDDS conceivably similar to 15mg of drug taken into consideration and diffused in 100 ml of AR grade ethanol and ultrasonication for 10 min after which intensity was firm by ultraviolet-visible there as 276 nm [15].

$$Percentage\ Yield = \frac{Practical\ Drug\ Content}{Theoretical\ drug\ content} \times 100$$

Micromeritic Properties of S-SMEDDS

Bulk Density = Weight of powder / Volume of powder

Tapped Density = Weight of powder/ Tapped volume of powder

Carr's index (%) = tapped density-bulk density/tapped density $\times$ 100

Hausner's ratio = Tapped Density/Bulk Density

Angle of repose: Tan θ = h/r [16].

Reconstitution Properties of S-SMEDDS

Zeta Potential

This mixture was put inside a Zeta cell in the Zeta sizer and the Zeta potential of a formulation has been determine [17].

Scanning Electron Microscope

Surface topography of the solids SMEDDS were inspected by SEM regression.

Drug Content

Solid-SMEDDS usually contains Aceclofenac, each similar to 10 mg was scattered in recently asked of methanol. The mixture was mixed gently to dissolve the drug in methanol, centrifuge tube at 3000 rpm for 15 min utilizing 12^oC micro centrifuge to completely separate the undiluted excipients. The supernatant was appropriately diluted and evaluated UV spectrophotometer at 276 nm to use the Shimazdu UV-visible spectrophotometer [18].

In-vitro Drug Release Kinetics

Release of drug studies that once solid SMEDDS have been performed using dissolution apparatus II with 900 mL of 0.1 N HCl as a medium at 37 $\pm$ 0.5^0C. The efficiency of the paddle was adjusted to 100 rpm. Aceclofenac-loaded solid SMEDDS and 100 mg of pure Aceclofenac the S-SMEDDS were placed in a dissolution apparatus and withdraw the 5 ml of sample at predetermined time intervals 5, 10, 15, 30, 45 and 60 min. The sample was analyzed by

UV spectrophotometer at 276 nm. The obtained dissolution data were fitted into zero order and first-order kinetic models to know the drug release mechanisms [19].

RESULTS AND DISCUSSION

FTIR Studies

The physicochemical compatibility of the drug, optimized liquid SMEDDS, solid SMEDDS were developed through FTIR studies [Figure 1, Figure 2, Figure 3 and Figure 4]. In the physical mixture of Aceclofenac, the major peaks belonging to the drug functional groups were obtained almost at the same wave numbers. Finally by observing the peaks we concluded that obtained drug sample was pure and there is no interaction between drug and excipients [Table 1].

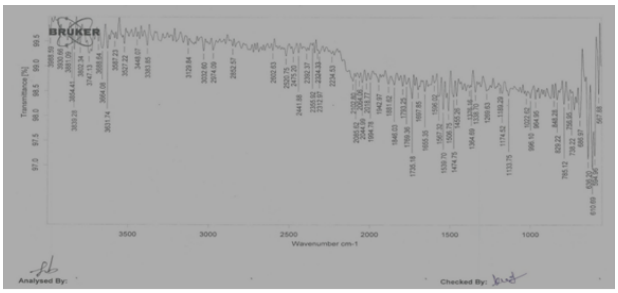

Figure 2: FTIR Spectra for Aceclofenac Pure Drug

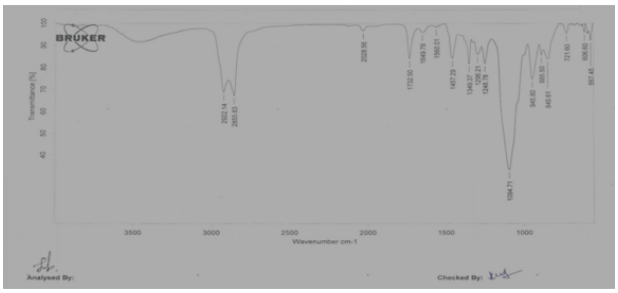

Figure 3: FTIR Spectra for Liquid SMEDDS

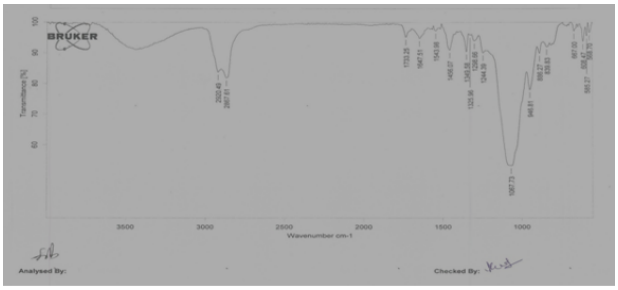

Figure 4: FTIR Spectra for Solid SMEDDS

Formulation Development

Liquid SMEDDS were prepared by constructing ternary phase diagram. Oil, S_{mix} (surfactant and co-surfactant) has been selected based on solubility studies. Based on the results of solubility studies were selected. And ratios of surfactant and co-surfactant were selected. Optimized ratios were selected for preparing for liquid SMEDDS. Among all the solubility studies we have selected the oleic acid (55 ± 6.69) as oil and Chromophore RH 40 (44±5.9) as surfactant and co-surfactant as PEG 400 (99±5.69).

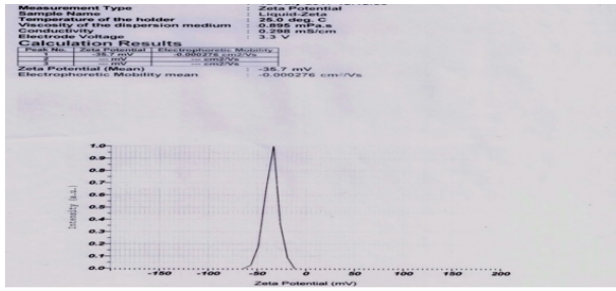

Figure 5: Zeta Potential for Liquid SMEDDS

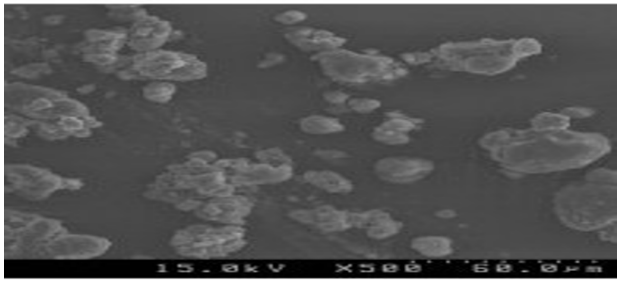

Figure 6: SEM Image for Liquid SMEDDS

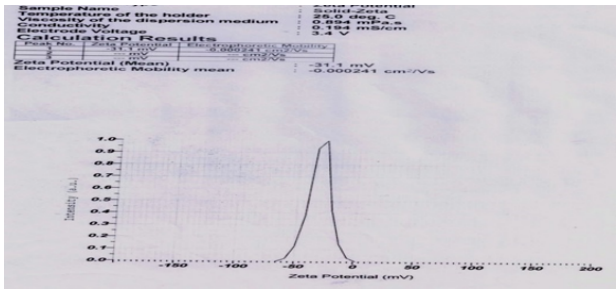

Figure 7: Zeta Potential for Solid SMEDDS

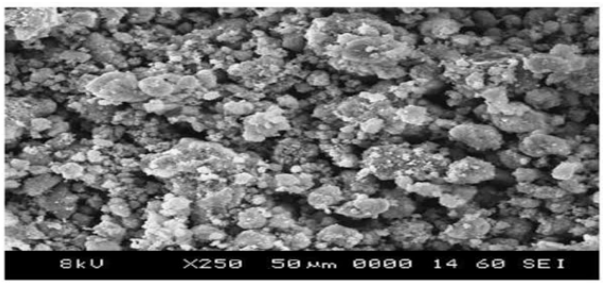

Figure 8: SEM Image for Solid SMEDDS

Preparation of Liquid SMEDDS

The liquid SMEDDS were prepared by using Chromophore RH 40 (3ml) and PEG 400 (6ml) as the

Table 1: Interpretation of FTIR Spectra of Aceclofenac Pure Drug and Liquid, Solid SMEDDS

S.No.	Functional Group	Frequency Range in cm^{-1}	Observed Frequency in cm^{-1}
1	Aromatic secondary N-H	3300-3500	3383.85
2	Aliphatic C-H	2850-3000	2974.09
3	Asymmetric o=c-o	1200-1700	1506.75
4	CN	1080-1360	1338.70
5	Aromatic C-Cl	600-800	686.97
6	Aromatic C-C	1400-1600	1539.70
7	Metallic salt Na+	1440-14600	1455.26

Table 2: Evaluation of Aceclofenac Solid SMEDDS

S.No.	Formulation code	Percentage Practical Yield	Percentage Drug Content	Drug Content
1	S1	92.69%	98.69%	97.65%
2	S2	90.55%	95.55%	93.51%
3	S3	89.46%	94.69%	85.69%

Table 3: Micromeritic Evaluation S-SMEDDS

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose	Hausner's Ratio	Carr's Compressibility Index
S1	0.45±0.01	0.56±0.02	28.6±0.03	1.25±0.02	19.6±0.01%
S2	0.33±0.03	0.52±0.03	25.8±0.01	1.28±0.01	26.8 ±0.02%
S3	0.23±0.01	0.48±0.01	30.1±0.02	1.26±0.03	26.8 ±0.03%

Table 4: Release Order Kinetics of Solid SMEDDS

Formulation Code	R^2 Values	
	Zero Order Kinetics	First Order Kinetics
S1	0.98	0.793
S2	0.958	0.953
S3	0.959	0.981

Smix combination and oleic acid (1ml) as oil. Accurately weigh the Aceclofenac (100mg) was placed in a beaker surfactant and co-surfactant was added to solubilise the drug. Then oil was added thoroughly mixed by gentle stirring and sonicated by 15 min to form homogenous mixture.

Evaluation Tests for Liquid SMEDDS

Test for Self Emulsification

It mainly measures the clarity, stability spontaneous emulsification. The above formulation shows the transparent, clear and shows no signs of instability for 24 hours.

Cloud Point Measurement

It will provide the knowledge regarding steady state of micro emulsion at body temp. The prepared formulation shows the cloudiness shows at 110^{o}C. It is stable at body temperatures.

Drug Content

It will show the % content uniformity of the optimized micro emulsion formulation. The prepared formulation for drug content was 96.6%.

Zeta Potential and Globule Size

From this zeta seizer charge on emulsifiers particles and their mean zeta potential worth (± SD) have been obtained [Figure 5]. The formulation having zeta potential within the limits. Zeta potential for formulation -35.7mv.

Dispersibility Test

Aceclofenac SMEDDS (approximately 0.2 ml) was diluted with 100 ml of distilled water gently stirred with a magnetic stirrer maintain temperature as 37± 0.5.

% Transmission Test

It was measured by directly taking absorbance of the dilute SMEDDS. Besides signifying clarity of the formulation, percentage transmittance was closer to 100%, it indicates the particle size in nanometres range. In this study the formulation % transmittance was found to be 99.6.

Scanning Electron Microscope

Morphology and particle size of the formulation should evaluated by SEM [Figure 6]. Morphology and particle size were observed within the range the diameter of the particle 60μm.

Emulsification Efficiency

It is mainly checked by magnetic stirrer at low speed at temperature 37 ± 0.5^0C the resultant formulation shows the clarity, and transparency at body temperature.

Thermodynamic Stability Studies

Mainly determined the physical stability of the emulsion. By conducting freeze thaw test and by centrifugation all the formulations were found to be stable no signs of phase separation.

Conversion of Liquid SMEDDS into Solid SMEDDS

The liquid SMEDDS containing 1:2 ratio of S_{mix} showed good results and hence used for preparing solid SMEDDS. For preparing solid SMEDDS different combinations of MCC and Aerosil (1:1, 1:2, 2:1) S1, S2, S3 were used.

The S-SMEDDS were prepared by the addition of the MCC and Aerosil with continuous stirring to form smooth dough. This smooth dough was managed to pass through sieve no 45 to form particles and finally filled into the capsules.

Evaluation Tests for Solid SMEDDS

Percentage practical yield, Percentage drug content was determined for all 3 ratios of adsorbent mixtures and values [Table 2].

Micromeritic Properties of S-SMEDDS

Bulk Density, Tapped Density, Angle of repose, Hauser s ratio, Carr's compressibility index was determined for all 3 ratios of adsorbent mixtures and values [Table 3].

Reconstitution Properties of S-SMEDDS

Zeta Potential

The S-SMEDDS were diluted with a ratio of 1:10000 (v/v) and mix 1 min with a cyclone mixture.

This mixture was placed in a Zeta cell in the Zeta seizer. Zeta potential of the formulation -31.1mv [Figure 7].

Scanning Electron Microscope

To evaluate the surface topography of the solid SMEDDS by SEM. This one was done by SEM diameter of the particulate was 50 μm [Figure 8].

Release Kinetics

The obtained dissolution data were fitted into zero order and first order kinetic models [Table 4].

CONCLUSION

SMEDDS are the very novel and promising approaching for improvement the solubility preceded by bioavailability of the poorly soluble drugs. By this study it was concluded that the Aceclofenac was suitable for formulating into SMEDDS. All the three formulations show good result for flow properties, SEM and zeta potential, drug content. Among three formulations S1, S2, are follows Zero order where as S3 follows first order. All the three formulations shows more than 90% drug release within 60 min. Hence S-SMEDDS were for the challenging approach for enhancing solubility of Aceclofenac.

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Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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