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Research Article

DEVELOPMENT AND EVALUATION OF POORLY AQUEOUS SOLUBLE DRUG RACECADOTRIL BY USING SOLID SELF MICRO EMULSIFYING DRUG DELIVERY APPROACH

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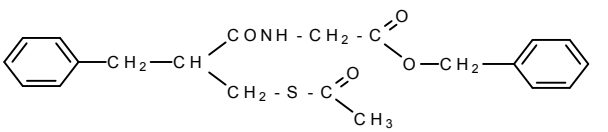
ABSTRACT
The objective of present work was to develop solid self-micro emulsifying drug delivery system (SMEDDS) of Racecadotril. Design of SMEDDS formulations helps to improve the oral absorption of highly lipophilic compounds. For formulation of stable SMEDDS, micro emulsion region was identified by constructing Pseudo ternary phase diagram of selected oil surfactant co-surfactant using water titration method. Stable SMEDDS was prepared at ratio of 4:6 using combination of Capryol 90 and Captex 200 (1:1), Cremophore EL and Transcutol (km 2:1) and evaluated for all parameter of liquid SMEDDs. Using aerosil 200, liquid SMEDDS converted into Solid SMEDDS by using adsorption to solid carrier technique. Prepared S-SMEDDS evaluated for micro meretics properties, drug content, dispersibility test, self micro emulsification time, globule size, transparency test, *In vitro* drug release and in vivo study on male wistar albino rats. From result it showed that drug releases from S- SMEDDS formulations were found to be significantly higher as compared with that of pure drug, and marketed formulation and from *in vivo* study it was found that S-SMEDDS showed lower frequency, Stool volume and wet diarrheal drops as compared to L-SMEDDS, Plain Drug and marketed formulation. Thus study concluded with S-SMEDDS provides useful solid dosage form to improve solubility and dissolution rate of Racecadotril and concomitantly bioavailability.
Keywords: Racecadotril, S-SMEDDs, L-SMEDDs, bioavailability, *In vitro* release, *in vivo* release, adsorption technique.

INTRODUCTION

Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects.[1] The most frequent causes of low oral BA is attributed to poor solubility and low permeability.[2] The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality.[3] The major advantages of this technology are its general applicability to most drugs and its simplicity. This is the case of class II drug, e.g. Racecadotril (according to the Biopharmaceutical drug Classification System BCS).[4-7] In recent years, Up to 40 % of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra- and inter subject variability, and lack of dose proportionality.[8-10] Self micro emulsifying drug delivery system (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, that have a unique ability of forming fine oil-in-water (o/w) MEs upon mild agitation followed by dilution in aqueous media, such as GI fluids.[11] SMEDDS formulation having transparent and/ or bluish appearance, with particle size in range of 1 to 100 nm.[12,13] The used of SMEDDS to improve the bioavailability of poorly water soluble drugs was first reported in 1982 by Pouton.[14-18] After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets.[19-21] Racecadotril is an anti diarrheal drug which acts as a peripherally acting enkephalinase inhibitor indicated primarily in the treatment of diarrhea. Racecadotril is rapidly converted in the body to thiorphan[22,23]. The anti secretory mechanisms are independent of effects on intestinal motility, differentiating this compound from μ- opiate receptor agonists like loperamide and diphenoxylate.



Chemical Structure of Racecadotril

The solubility of RACE in aqueous medium is very low. Absolute bioavailability of the RACE is very low and biological half-life is 3 hours that results into poor bioavailability after oral administration. Hence it is necessary to increasing aqueous solubility and dissolution of RACE[22,23]. Aerosil 200 is sub microscopic fumed silica with a particle size of about 15 nm. It exhibit high adsorbing capacity and can be used to convert SMEDDS to S-SMEDDS. Hence in this study S-SMEDDS of RACE was prepared using aerosil 200 by adsorption technique for enhancement of dissolution rate.[14-16,24].

MATERIALS AND METHODS

Materials

RACE (assigned purity 99.8 %) was procured as a gift sample from Symed Laboratories Ltd. Hyderabad, India. Polyglycolyzed glycerides (Capryol 90, Capmul MCM, Captex 200, Captex 355) were gifted from Gattefosse Pvt Ltd. Labrafac PG; and Labrafill, Cremophor RH40 and Cremophore EL were gifted from (BASF Ltd, Mumbai, India), Transcutol, Lutrol 400 and Oleic acid, propylene glycol and polyethylene glycol 400 (PEG 400) were purchased from PC Drug Center Co, Ltd. (Bangkok, Thailand). Ethyl oleate was purchased from Sigma Aldrich (Buchs, Switzerland). Labrafac CC, Lauroglycol FCC, Lauroglycol 90, Labrafil M2125 CS, and Plurol oleique were obtained from Gattefosse (Mumbai, India). Aerosil 200 was from Fugi Silysia Chemical Ltd. (Aichi, Japan). Hard gelatin capsules (size 00) were from Capsugel (Bangkok, Thailand).

Acetonitrile and methanol were purchased from Loba chemicals (Hyderabad, India). All other chemicals were of analytical grade.

Solubility Studies of Racecadotril in different Vehicles
Solubility Studies
The solubility of Racecadotril in various vehicles, including oils, surfactants and co surfactants was determined by the shake flask method. An excess amount of Racecadotril was added to each cap vial containing 2 ml of the vehicles. After sealing, the mixture was vortexed at a maximum speed for 10 minutes in order to facilitate proper mixing of Racecadotril with the vehicles. Mixtures were then shaken in a water bath shaker maintained at room temperature until equilibrium (48 h). The mixtures were then centrifuged at 5000 rpm for 10 minutes. The supernatants were collected into glass vials and diluted approximately by methanol; the concentration of Racecadotril in the solution was assayed by UV spectroscopy (Shimadzu 1600, Japan) at 231 nm[25] as shown in Table 1, 2, 3 resp.

Surfactant Emulsification study
Different surfactants were screened for its emulsification ability selected in oil phase. Surfactant selection was done on the basis of % transparency and ease of emulsification. Briefly 500 uL of surfactant was added to 500 uL of oil phase. The mixture was heated at 50^0c for homogenization of components. Each mixture 100 uL was diluted with 50 ml D.W in glass conical flask, ease of emulsification was judge by no. of flask inversion required to yield homogeneous emulsion. % transparency evaluated using UV, and emulsion observed visually for turbidity or phase separation.[26]

Co surfactant Emulsification study
The screening was done on the basis of % transparency and ease of emulsification. Mixtures of the co surfactant, selected surfactant, and the selected oil were prepared and evaluated in similar fashion as described in surfactant emulsification study.[26]

Construction of pseudo-ternary phase diagrams (Phase Diagram Study)
The phase diagrams of oil, surfactant: co-surfactant and water were developed using water titration method. The mixture of oil and surfactant: co-surfactant at certain weight ratios were diluted with water in a drop wise manner. For each phase diagrams at specific ratio of surfactant: co-surfactant, 1:1, 1:2 and 2:1 (w/w) (Figure 1, 2 and 3) transparent mixtures of oil ranging from 20 % to 30 % and drug was formed under the mixing by magnetic stirring. Then each mixture was titrated with water and visually observed for phase clarity and flow ability. After the identification of micro emulsion region in phase diagrams, the micro emulsion formulation were selected at desired component ratio.[32]

Preparation of liquid SMEDDS
Racecadotril was incorporated in oil phase, warmed on water bath at 40°C. Surfactant, and co surfactant measured separately and mixed with previously prepared oil phase. The resulting mixture is vortexed till drug is completely solubilized. The resulting solution was kept at room temperature until used. See Table 4.

Preparation of solid SMEDDS using adsorption to solid carrier
Aerosil 200 (5.0 g) used as a solid carrier, for conversion of liquid SMEDDS to Solid. The conversion process involved addition of liquid formulation (10 g) onto carriers under continuous mixing in a blender, sieved after mixing. The powder was dried and filled directly into capsules.

Characterizations of Liquid SMEDDS
Particle Size Analysis using Motic microscope
Particle size of liquid SMEDDS was measure using motic microscope. Particle size was measured from captured image in micron meter and converted it in nanometer.

Determination of % Drug Content
The dispersed systems of Racecadotril were assayed spectrophotometrically for the drug content at the wave length 233 nm with proper dilution of formulations taking acetate buffer pH 1.2 a blank.

Stability Study by Visual Assessment
Shelf life as a function of time and storage temperature was evaluated by visual inspection of the SMEDDS system at different time period. Racecadotril SMEDDS was diluted with purified distilled water and to check the temperature stability of samples, they were kept at two different temperatures as (refrigerator, room temperature) for two months and observed for any evidences of phase separation, flocculation or precipitation.

***In Vitro* drug release of SMEDDS**
The release of drug from liquid S(M)EDDS formulations and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. The dissolution media is Acetate buffer pH 1.2, Water and 0.1N Hcl. (900 ml) and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined intervals 5, 10, 15, 20, 30 and 45, 60, 90 minutes and filtered through 0.45-µm pore size membrane filters. The removed volume was replaced each time with 5 ml of fresh medium. The amount of drug dissolved was determined using an UV Spectroscopy method.

Dye Solubilization test
Dye solubilization test so as to confirm the oil in water nature of SMEDDS a water soluble dye Eosin was sprinkled onto the surface of prepared micro emulsion and observed for spontaneous dispersion.

Cloud point measurement
Liquid SMEDDS was diluted with distilled water in the ratio of 1:250, placed in a water bath and its temperature was increased gradually. Cloud point was measured as the temperature at which there was a sudden appearance of cloudiness visually.

% Transmittance
1 mL of Liquid SMEDDS was diluted to 100 mL distilled water and observed for any turbidity and % transmittance was measured at 650 nm using UV- Visible spectrophotometer (Shimadzu-1800, Japan) against distilled water as a blank.

Robustness to dilution
Robustness to dilution was studied by diluting Liquid SMEDDS to 50, 100 and 1000 times with water, buffer pH

1.2 and buffer pH 7.5. The diluted SMEDDS were stored for 12 h and observed for any signs of phase separation or drug precipitation.

***In Vivo* study of Liquid SMEDDS**

Created five groups for study the effect of prepared formulation on animal as showed in Table 5: [27-31]

Six groups each containing 6 male wistar rats were used to test solution as shown in the Table 5. Weight of animals was maintained in the range of 150-180 g.

Induction of Diarrhea

1 ml of castor oil by the oral rout was given for the induction of diarrhea.

Experimental Procedure

1 ml of castor oil was given to rats for inducing diarrhea 1 h before starting experiment.

Group 1 served as control given with vehicle, group 2 received racecadotril formulation served as standard, group 3 was formulation of prepared liquid SMEDDS and 4 group was of prepared solid SMEDDS and group 5 was of plain racecadotril and group 6 was of marketed formulation, 1 h before castor oil administration. Followed by dose of 10 mg kg^{-1}.

Rats were be fasted during experiment

Formulation administered by oral route by mixing formulation with 0.5 % Carboxy methyl cellulose.

The numbers of both wet and dry diarrheal droppings was counted every hour for a period of 4 h mean of the positive control group.

Rats were place on filter paper in the cage to calculate stool volume. And determined the frequency and duration of diarrhea and finally compared Liquid and Solid SMEDDS to that of plain drug and marketed formulation of racecadotril.

Characterizations of Solid SMEDDS

Micro meritic properties of S-SMEDDS

Prepared S-SMEDDS was evaluated for micro meretic properties such as angle of repose, bulk and tapped density, compressibility index and Hausner ratio. (Table 12) [21,22]

Determination of drug content

Drug content was estimated by extracting Racecadotril from S-SMEDDS. In brief S-SMEDDS was dissolved in sufficient quantity of methanol. Solution was sonicated for 10-15 minutes for extraction of the Racecadotril in methanol and filtered. The absorbance of filtrate was read at 233 nm on UV- Visible Spectrophotometer (Shimadzu-1800, Japan).

Reconstitution properties of S-SMEDDS

Dilution study by visual observation

S-SMEDDS (100 mg) was introduced into 100 mL of double distilled water in a glass beaker that was maintained at 37ºC and the contents mixed gently using a magnetic stirrer. The tendency to emulsify spontaneously and progress of emulsion droplets were observed with respect to time. The emulsification ability of S-SMEDDS was judged qualitatively "good" when clear micro emulsion formed and "bad" when there was turbid or milky white emulsion formed after stopping of stirring.

% Transmittance

It was determined as described in Liquid SMEDDS

FTIR study of S-SMEDDS

FTIR spectrum was recorded for RACE, Liquid SMEDDS, S-SMEDDS using FTIR spectrophotometer see Table 6, 7.

Dissolution studies of Solid SMEDDS

The release of drug from solid S(M)EDDS formulations filled in capsules and pure drug was determined using a US Pharmacopoeia Type II dissolution apparatus. The dissolution media Acetate buffer pH 1.2, D.W and 0.1 N Hcl (900 ml) and temperature of the dissolution medium was maintained at 37^0C operated at 50 rpm. A 10 ml sample of medium was withdrawn at predetermined intervals 5, 10, 15, 20, 30 and 45, 60, 90 minutes and filtered through 0.45-µm pore size membrane filters. The amount of drug dissolved was determined using UV spectro photometry.

XRD (X-Ray diffraction) studies

XRPD diffractograms of drug, placebo (Oil surfactant, co-surfactant are mixed according to the ratio's of finalized formulation of S(M)EDDS without drug) and solid SMEDDS formulations were recorded using a Bruker D8 advanced Diffractometer with a Cu line as the source of radiation. Standard runs using a 40-kv voltage, a 40-mA current, and a scanning rate of 0. 0.02° min^{-1} over a 20 range of 3-40° was used.

DSC of S-SMEDDS

Physical state of RACE in S-SMEDDS was characterized using differential scanning calorimeter. Thermo grams of RACE, and S-SMEDDS were obtained using differential scanning calorimeter.

Scanning Electron Microscopy

A concentrated aqueous dispersion of nanoparticles was finely spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with a gold layer (20 nm thick). The surface morphology of the nanoparticles was observed by SEM using a JSM-6400 scanning electron microscope.

***In Vivo* study of S-SMEDDS**

In vivo study of S-SMEDDS was carried out using male wistar albino rats, details of procedure is explained in section of characterization of vivo study of liquid SMEDDS.

RESULT AND DISCUSSION

Solubility Studies

The aqueous solubility of Racecadotril was found to be 0.29 mg/ml, which is in agreement with the available literature. The solubility of Racecadotril was determined in various oils, surfactants and co-surfactant. Among oils, Captex 200 showed 144 mg/ml and Capryol 90 (118.13 mg/ml) showed highest solubility. From all surfactants Cremophore EL (169.65 mg/ml) showed highest solubility. For co surfactants, Transcutol, solubility was found to be 98.78 mg/ml. Based on solubility study Capryol 90, captex 200, Cremophore EL, Transcutol are selected as oil, surfactant and co-surfactant respectively (see Figure 4-6)

Construction of Pseudo ternary phase diagram

Micro emulsion region is identified by constructing Pseudo ternary phase diagram of selected oil (Captex 200, Capryol 90) surfactant (Cremophore EL) Co-surfactant (Transcutol) using water titration method, at different Km ratio and optimized Km ratio is 2:1 as shown in Table 8 and Figure 3

Table 1: Solubility of Racecadotril in oils

Oils	Concentration mg/ml	Oils	Concentration mg/ml
Captex 200	144 ± 0.5	Ethyl oleate	117.90 ± 0.4
Captex 355	110 ± 0.6	Oleic acid	110.2
Capryol 90	121 ± 1	Seasome oil	95.132 ± 0.41
Capmul MCM	118.20 ± 0.90	Labrafil Lipophile 1349	87.89 ± 0.5
Castor oil	114.81 ± 0.144	Maisine	89.90 ± 0.133
Gelucire	89 ± 1	Water	0.290
Olive oil	99.78 ± 1.55		

Table 2: Solubility of Racecadotril in Surfactants

Surfactant	Concentration mg/ml	Surfactant	Concentration mg/ml
Tween 20	144.5 ± 0.2	Labrafil	39.89 ± 1.2
Tween 80	118.19 ± 0123	span 80	38.56 ± 0.566
Cremophore EL	169.65 ± 0.245	Water	0.290
Cremophore RH 40	77.75 ± 2		

Table 3: Solubility of Racecadotril in Various Co –Surfactant

Co- Surfactant	Concentration mg/ml	Co- Surfactant	Concentration mg/ml
Polypropylene Glycol	89 ± 2.44	Ethanol	45.67 ± 2.42
PEG 400	75 ± 1.23	Transcutol	98.78 ± 0.289
Carbitol	68.90 ± 0.998	Water	0.290
PEG 600	36.67 ± 4.22		

Table 4: Liquid SMEDDS Formulation

Ratio	Drug (mg)	Oils (ml)	Surfactant (ml)	Co surfactant (ml)	Km ratio	Results
4:6	150	Cap 90 and Cap 200 (1:1)	Cremophore EL	Transcutol	2:1	Transparent ME
4:6	150	Cap 90 and Cap 200 (1:1)	Tween 20	Polypropylene glycol	2:1	Transparent ME
1:9	150	Capryol 90	Tween 20	Polypropylene glycol	4:5	Transparent ME
1:9	150	Captex 200	Tween 20	Transcutol	4:5	Transparent ME

Table 5: No of group for *in vivo* study

No. of groups	No. of animals	No. of groups	No. of animals
1.Control group	6	4. Solid SMEDDS	6
2. Standard group	6	5.Plain Drug	6
3. Liquid SMEDDS	6	6.Marketed Formulation	6

Table 6: Characteristics IR peaks of Racecadotril

Functional group	Frequency (cm^{-1})
NH	3300 cm^{-1} (stretch)
C-O-C	1760 cm^{-1} (stretch)
C-H	2900 cm^{-1} (bending)
C=0	1740 cm^{-1}
C-S	645cm^{1} (stretch)

Table 7: IR peaks of S-SMEDDS of Racecadotril

Functional group	Frequency (cm^{-1})
NH	3286.11 cm^{-1} (stretch)
C-O-C	1733.69 cm^{-1} (stretch)
C-H	2932,23 cm^{-1} (bending)
C=0	1452.12 cm^{-1}
C-S	957.68cm^{1} (stretch)

Table 8: Pseudo ternary phase diagram consisting of Combination of Oils Capryol 90 and Captex 200, Surfactants Cremophore EL, Co surfactants Transcutol with S/C ratio 2:1

Smax ratio	Oils	S/C	Aqueous Phase	Oils:S/C
2:1	20	60	20	2:6
	30	30	40	3:3
	30	45	25	3:4.5
	5	90	5	5:9

Table 9: Formulation ingredients

Ratio	Drug (mg)	Oils (ml)	Surfactant (ml)	Co surfactant (ml)	Km ratio	Results
4:6	150	Cap 90 and Cap 200 (1:1)	Cremophore EL	Transcutol	2:1	Transparent ME
4:6	150	Cap 90 and Cap 200 (1:1)	Tween 20	Polypropylene glycol	2:1	Transparent ME
1:9	150	Capryol 90	Tween 20	Polypropylene glycol	4:5	Transparent ME
1:9	150	Captex 200	Tween 20	Transcutol	4:5	Transparent ME

Table 10: Percentage drug content of the formulations

Formulation	S1	S2	S3	S4
%Drug Content	99.08	90.82	95.41	91.13

Table 11: Kinetic study of liquid SMEDDS in acetate buffer pH 1.2

Model	Equation	R^2
Zero order	0.895 + 58.	0.429
First order	0.001 + 1.911	0.670
Higuchi	0.877 + 1.946	0.694
Hixson Crowell	0.000x + 3.557	0.132

Table 12: Micro meretics properties of S-SMEDDS

Parameters	Angle of Repose (degree)	LBD (g/ml)	TBD (g/ml)	Carr's Index (%)	Hausner Ratio
Observation	27.63 ± 0.04	0.54 ± 0.12	0.65 ± 0.47	16.92 ± 0.31	1.20 ± 0.06

Table 13: Percentage drug content of the S-SMEDDs formulations

Formulation	S-SMEDDS 1	S-SMEDDS 2	S-SMEDDS 3	S-SMEDDS 4
%Drug Content	63.07	73.33	98.18	96.36

Table 14: Diarrheal Frequency of Rats /h

Groups	Frequency /H (Mean ± SEM)					
	1 h	2 h	3 h	4 h	5 h	6 h
Normal	0.5 ± 0.2236	0.5 ± 0.2236	0.5 ± 0.2236	0.5 ± 0.2236	0.5 ± 0.2236	0.33 ± 0.2108
Control	7.83 ± 0.3073	7 ± 0.4472	5 ± 0.4472	2.83 ± 0.1667	1.5 ± 0.2236	1 ± 0.00
Plain	7.333 ± 0.2108	6 ± 0.00	5.33 ± 0.2108	3.5 ± 0.2236	1.33 ± 0.2108	1 ± 0.00
Marketed	7.66 ± 0.333##	5.5 ± 0.2236**	3.5 ± 0.2236*	1.5 ± 0.2236***	1.33 ± 0.2108	0.5 ± 0.2236
Liq. SMEDDS	7.66 ± 0.333###	4 ± 0.000***,##	2 ± 0.4472***	0.166 ± 0.1667***	0.33 ± 0.2108**	0.166 ± 0.1667**
S-SMEDDS	5.33 ± 0.2108***	2.83 ± 0.3073***,###	0.33 ± 0.2108***	0.166 ± 0.1667***	0.16 ± 0.1667**	0.166 ± 0.1667**

Table 15: Stool volume per h

Groups	Stool volume /H (Mean ± SEM)					
	1 H	2 H	3 H	4 H	5 H	6 H
Normal	0.15 ± 0.02236	0.16 ± 0.0244	0.03 ± 0.02108	0.2 ± 0.1612	0.1 ± 0.03651	0.0633 ± 0.03073
Control	1.65 ± 0.06708	1.6 ± 0.1225	0.75 ± 0.06708	0.55 ± 0.02236	0.31 ± 0.004472	0.225 ± 0.0118
Plain	1.45 ± 0.022**	0.86 ± 0.02449***	0.7 ± 0.04472	1.05 ± 0.06708*	0.5 ± 0.04472***	0.116 ± 0.01667*
Marketed	1.4 ± 0.04472***	0.76 ± 0.02449***	0.6 ± 0.02582	0.85 ± 0.02236	0.316 ± 0.01667	0.05 ± 0.02236***
Liq. SMEDDS	1.35 ± 0.02236***	0.54 ± 0.02449***	0.43 ± 0.02108***,#	0.1833 ± 0.1641###	0.016 ± 0.01667***,###	0.0166 ± 0.01667***
S-SMEDDS	0.766 ± 0.2108***,###	0.36 ± 0.02449***,###	0.05 ± 0.02236***,###	0.05 ± 0.02236*,###	0.033 ± 0.02108***,###	0.03330 ± 0.02108***

Table 16: Wet diarrheal droppings of Rats /H

Groups	Wet diarrheal dropping /H (Mean ± SEM)					
	1 H	2 H	3 H	4 H	5 H	6 H
Normal	0.33 ± 0.2108	0.5 ± 0.2236	0.166 ± 0.1667	0 ± 0.00	0 ± 0.00	-
Control	11.5 ± 0.2236	12.5 ± 1.118	6.5 ± 1.118	13 ± 0.4472	7.5 ± 1.118	-
Plain	11.5 ± 0.2236	8.5 ± 0.2236***	12.5 ± 1.118***	9 ± 0.4472***	6 ± 0.8944	-
-Marketed	10.5 ± 0.2236	7.5 ± 0.02236***	8.5 ± 0.2236	3 ± 0.4472***	1.5 ± 0.2236***	-
Liq. SMEDDS	10.5 ± 0.2236	4.5 ± 0.02236***,##	4 ± 0.4472###	0.1666 ± 0.1667***,###	0.00 ± 0.00***	-
S-SMEDDS	5 ± 0.03651***,###	3 ± 0.4472***,###	0.166 ± 0.1667***,###	0.1666 ± 0.1667***,###	0.00 ± 0.00***	-

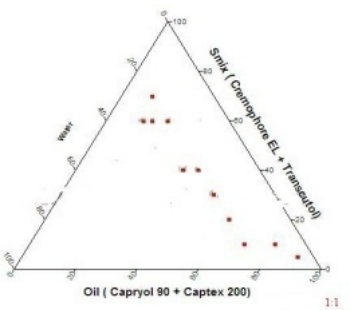


Figure1. Pseudo-ternary phase diagrams indicating the efficient self-micro emulsification region (S/CoS = 2:1 (w/w) the red area represents o/w micro emulsion existence range, the white area represents coarse emulsion range

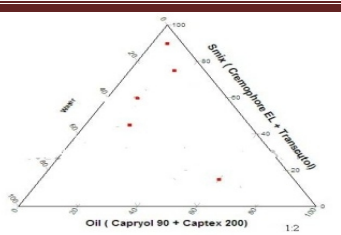


Figure 2: Pesudo ternary phase diagram with S/C diagram with S/C ratio 1:1 ratio 1:2

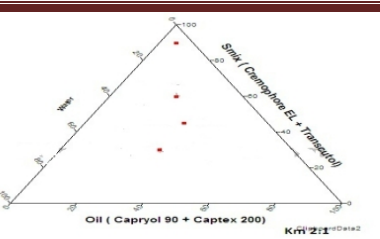


Figure 3: Pseudo ternary phase diagram with S/C ratio 2:1

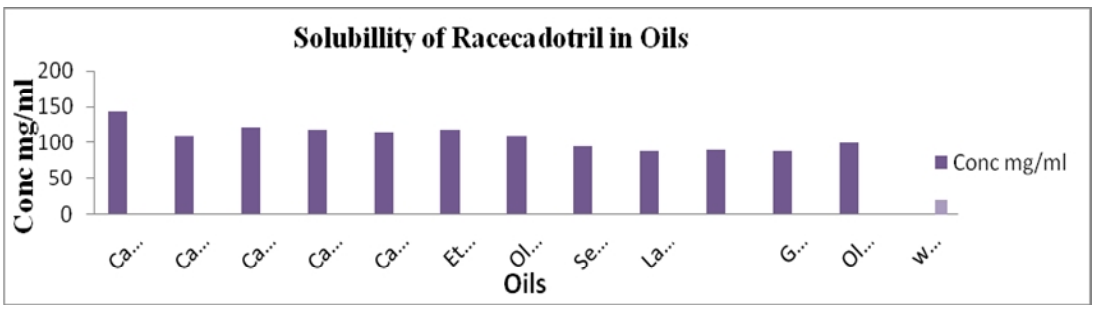


Figure 4: Solubility of Racecadotril in Oils

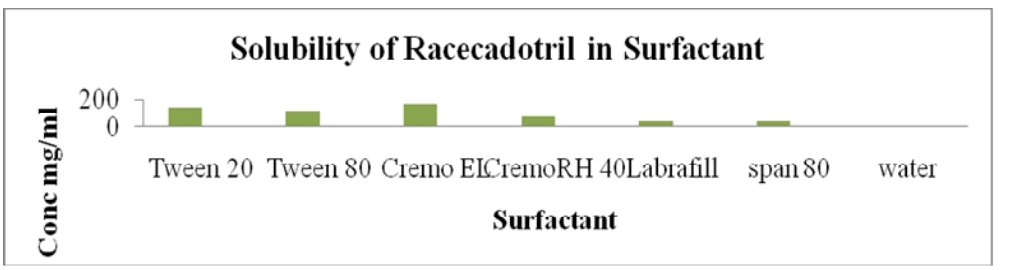


Figure 5: Solubility of Racecadotril in Surfactant

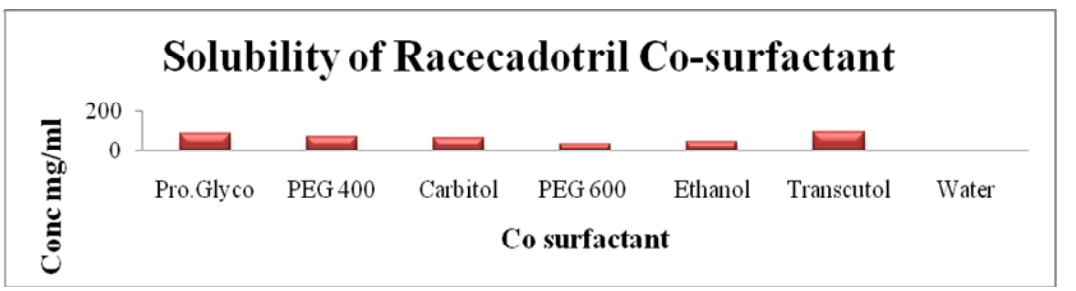


Figure 6: Solubility of Racecadotril in Co-Surfactant

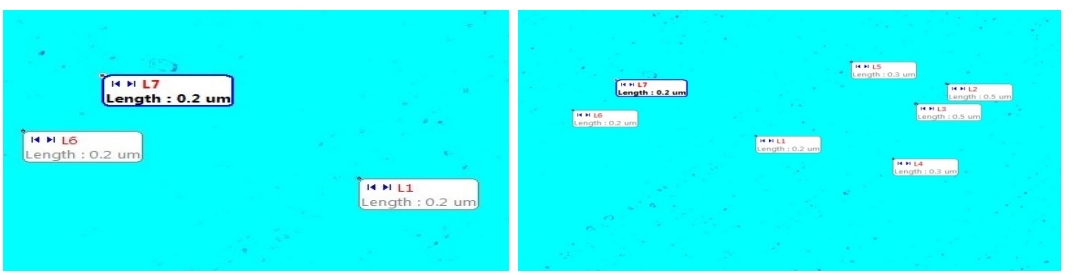


Figure 7: Particle size of L-SMEDDS by Motic

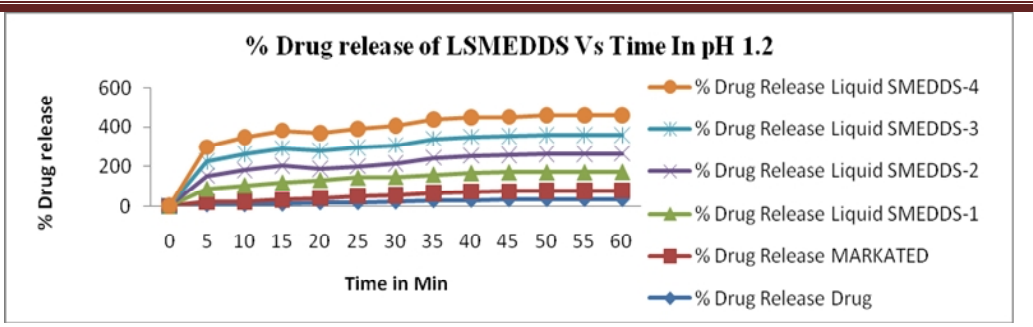


Figure 8: *In Vitro* drug release in Acetate buffer pH 1.2

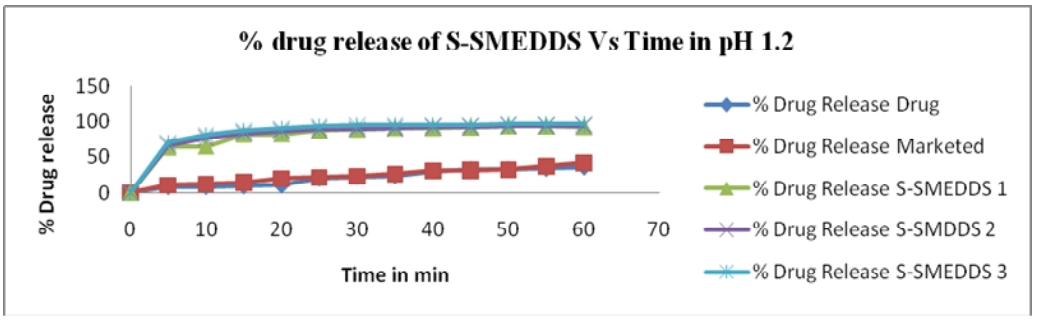


Figure 9: *In Vitro* drug release of S-SMEDDS in Acetate buffer pH 1.2

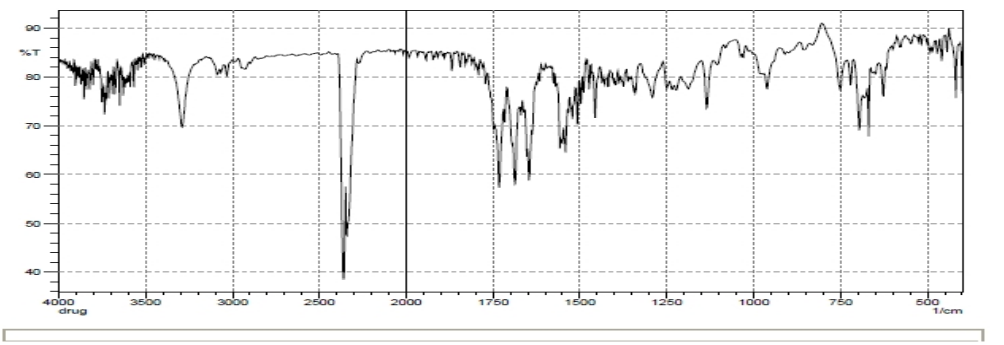


Figure 10: FTIR spectrum of Racecadotril

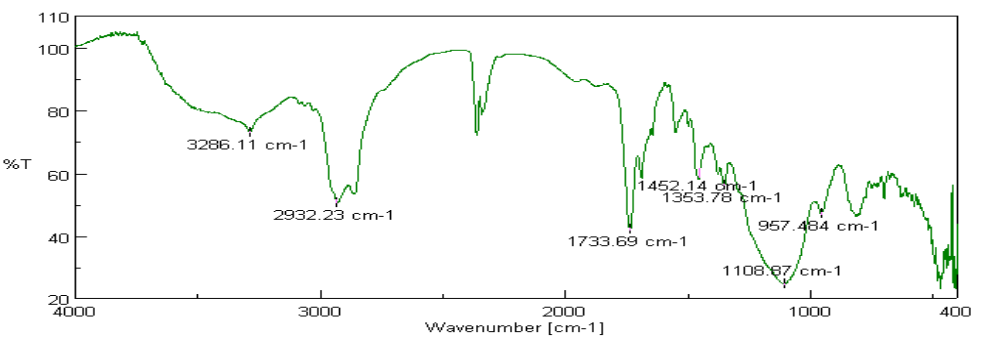


Figure 11: FTIR spectrum of Solid SMEDDS of Racecadotril

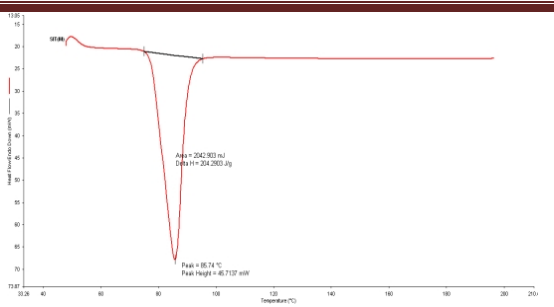


Figure 12: DSC thermo gram

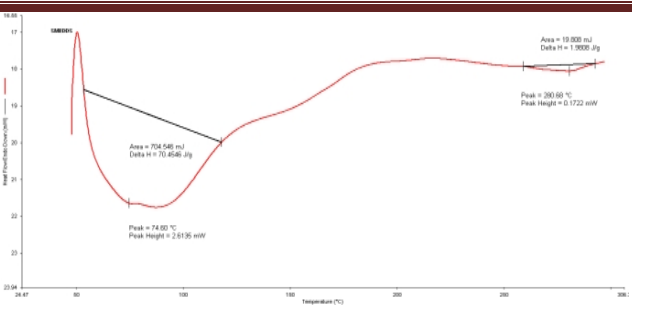
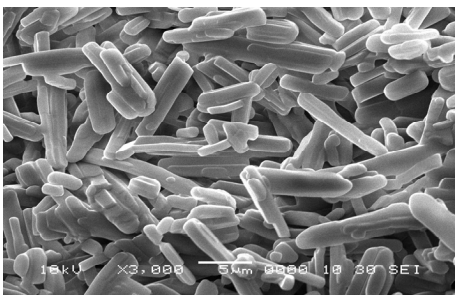
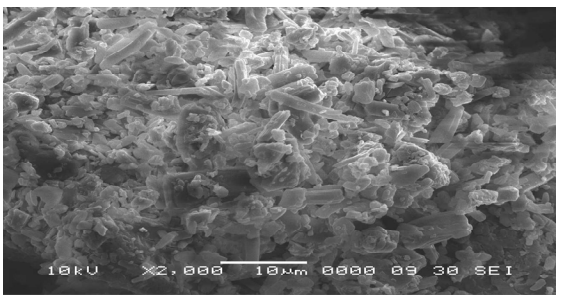


Figure 13: DSC thermo gram of S-SMEDDS of Racecadotril



a) SEM Images of RACE



b) SEM Images of S-SMEDDS of RACE

Figure 14: SEM images of S-SMEDDS

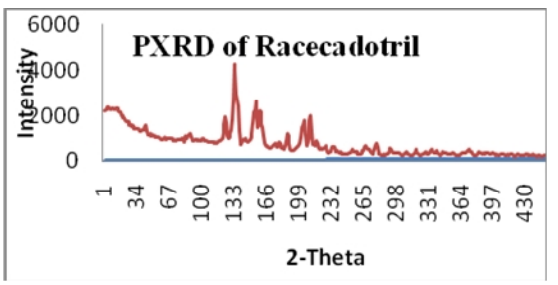


Figure 15: PXRD of Racecadotril

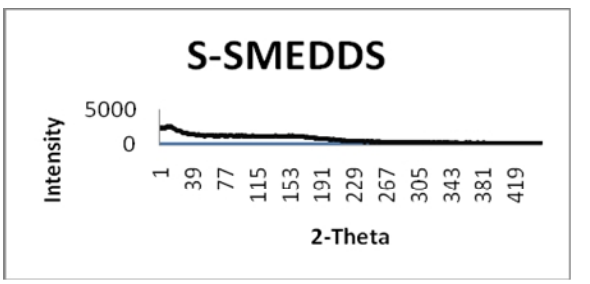


Figure 16: PXRD of Racecadotril S-SMEDDS

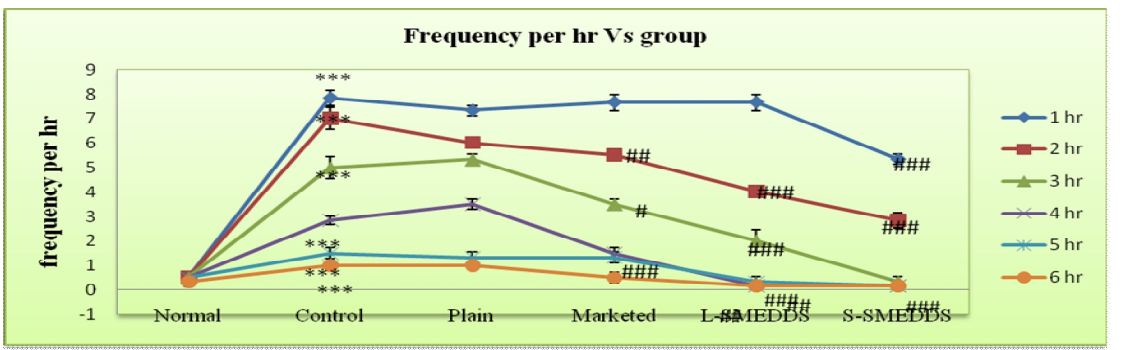


Figure 17: Diarrheal Frequency of Rats /h

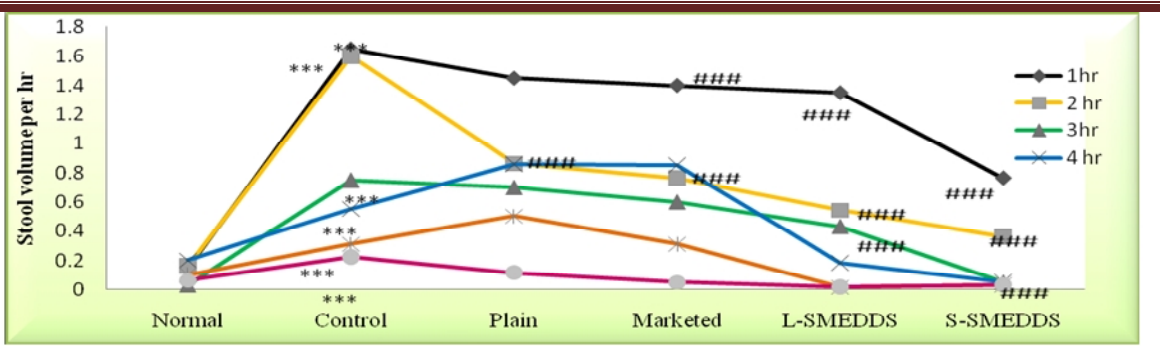


Figure 18: Stool volume per h

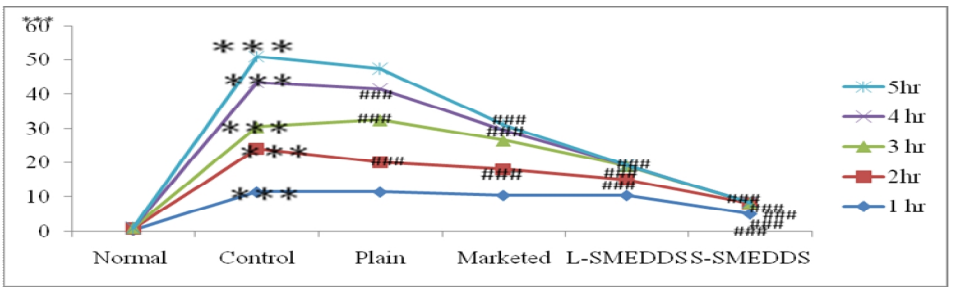


Figure 19: Wet diarrheal droppings of Rats /H

Formulation development

From Various formulations of liquid SMEDDS optimized batch found to be of Oil /S/c ratio 4:6 and Km ratio 2:1 (Table 8) compromising combination of Capryol 90, Capex 200, Cremophore EL and Transcutol.

Characterizations of liquid SMEDDS

Liquid SMEDDS is evaluated for Drug Content, I.R, Phase separation and self micro emulsifying time, Particle size, robustness to dilution, Dissolution study in D.W, acidic buffer PH 1.2 and compared it with Plain drug and marketed formulation of Racecadotril.

Particle Size of Liquid SMEDDS: - 0.1 -0.2 um see Figure 7

Determination of % Drug Content

Percent drug content of liquid SMEDDS was found to be 99.08 (Table 10)

Dye Solubilization test

Eosin dye was easily sprinkled on micro emulsion area and showed good spontaneous dispersion.

Self micro emulsification time

Racecadotril liquid SMEDDS self emulsify within 2-3 minutes.

Stability Study by Visual Assessment

No phase separation and/or precipitation were observed after period of two months. By visually assessing, it was observed that Liquid SMEDDS shows transparency after period of two months.

***In Vitro* drug release**

In vitro drug release of Liquid SMEDDS was found higher in acetate buffer pH 1.2 compare to Distilled water and 0.1 N HCl. Among various batches of liquid SMEDDS of acetate buffer pH 1.2 (Figure 8) LS 4-showed good *in vitro* releases as compare to other batches and that of marketed formulation and plain, drug RACE.

Kinetic Study

The optimized formulation of Liquid SMEDDS followed Higuchi model. (Table 11)

Characterizations of S-SMEDDS

Micro meretics properties of S-SMEDDS as shown in Table 12

Percent Transparency

Showed transparency when 0.1 g of S-SMEDDS was dissolved in 100 ml of D.W and also 100 ml of 0.1 N HCL.

Percent Drug Content

Percent drug content of S-SMEDDS was found to be 98.18, see Table 13

Self Micro emulsification time

Prepared S-SMEDDS micro emulsify within 2 to 3 minutes when added in to 10 ml or 100 ml of D.W

***In vitro* Drug Release of S-SMEDDS**

In vitro drug release of Solid SMEDDS was found higher in acetate buffer pH 1.2 compare to Distilled water and 0.1 N HCl. Among various batches of S-SMEDDS of acetate buffer, S-SMEDDS 3 -showed good *in vitro* release (Figure 9) as compare to other batches and that of marketed formulation and plain, drug RACE.

FTIR spectrum see Figure 10, 11
Differential scanning calorimetric Analysis (DSC) see Figure 12, 13

Scanning electron microscopy
The surface morphology of the drug, S-SMEDDS was determined by using of Scanning Electron Microscopy, see Figure 14

Powder X- Ray diffraction studies (PXRD)
PXRD studies for drug and S-SMEDDS were carried out. Racecadotril was found to be crystalline in nature, as shown in Figure 15 indicated by numerous peaks at 129^0, 145^0, 161^0, 193^0, 209^0

***In vivo* Study of SMEDDS**
All the studies were carried out in accordance with the guidelines given by the Indian Council for Medical Research and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India) and the Institutional Animal Ethical Committee approved the study (Approval No.: 1036/a /07/CPCSEA/IAEC/12-13/D-8)

Frequency per h, see Table 14 and Figure 17
Results are expressed as mean $\pm$ SEM. Comparison between the groups was made by one way analysis of variance (ANOVA) followed by Tukey's test @,* ,#-P<0.05, **,##-P<0.01, ***,###-P<0.001; **, ##= Highly Significant, ***,### = Extremely Significant,*= control Vs test (L-SMEDDS and S-SMEDDS) group, #-Test (Liquid SMEDDS and Solid SMEDDS) Vs Std (marketed)

Stool volume per h, see Table 15, Figure 18
Wet diarrheal droppings of Rats /h (see Table 16, Figure 19), From *in vivo* study it concluded that prepared S-SMEDDS showed decreased in diarrheal frequency, stool volume and wet diarrheal drop at 5 and 6^{th} h compared to other formulation like control group, L-SMEDDS, Marketed formulation, Plain drug.

CONCLUSION

The present research work could be summarized as successful development and evaluation of solid self micro emulsifying drug delivery system for Racecadotril. The prepared formulation contain higher proportion of oil (Capryol 90 and Captex 200 40 % w/w) and also with higher proportion of surfactants (Cremophore EL, 40 % w/w) and low proportion of co surfactant (Trancutol 20 % w/w). It showed good self emulsifying efficiency and percentage transmittance value is close to 100 %, it indicates clear micro emulsion is formed. Solid-SMEDDS of Racecadotril was prepared by adsorption to solid carrier technique, using water-soluble Aerosil 200 as solid carrier. The solid SMEDDS consisted of well-separated spherical particles and maintained the rapid self-micro emulsifying ability as that of liquid SMEDDS. This solid self micro emulsifying system enhance solubility and dissolution rate which may improve therapeutic performance. Hence study concluded that S-SMEDDS provide a useful solid dosage form for poorly water-soluble drug such as Racecadotril for enhanced bioavailability.

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