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Development and Optimization of Macitenan Loaded Self-Micro Emulsifying Tablets

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KEYWORDS

Macitentan, SMEDDS, Quality by Design, Solidification of SMEDDS, Tablet

ABSTRACT:

Macitentan is an orally administered endothelin receptor antagonists used for the treatment of pulmonary arterial hypertension. As it is fall under BCS class 2 medicine, its solubility and oral bioavailability are poor. Here, a self micro-emulsifying drug delivery system (SMEDDS) was developed to improve its solubility and drug dissolution. The objective of our investigation was to formulate a self micro-emulsifying drug delivery system (SMEDDS) of Macitentan using minimized quantity of oil, surfactant and co-surfactant that could improve its solubility, stability, and dissolution. The composition of optimized Liquid SMEDDS formulation by BBD, consists of Capmul PG 8® as oil, Acrysol EL135® as surfactant and Propylene Glycol as cosurfactant, containing 100 mg of Macitentan showing mean droplet size (140.52 nm), rate of self-emulsification (53 sec) and Polydispersibility index (0.394). This optimized liquid SMEDDS is converted into the tablet dosage form using solid carrier technique. Macitentan SMEDDS tablet is optimized by 32 factorial designs, has desired hardness, disintegration time and dissolution rate more than 95% within 30 min.

1. INTRODUCTION

Approximately one third of the drugs emerging from drug discovery programs are poorly water soluble, presenting the pharmaceutical scientist with several problems when developing formulations for such active pharmaceutical ingredients (API). Most of the conventional oral dosage forms are poorly water-soluble drugs. In usual solid oral drugs are mean to pass through the gastrointestinal tract which means the drug must dissolve in the GI fluids before it can be absorbed. Thus, their rate and extent of absorption is largely dependent on the rate of dissolution.[1]

Oral route has always been preferred and has dominated over other routes of administration due to its convenience, non-invasiveness, and cost effectiveness thus it become necessary that drug should have some aqueous as well as some lipid solubility for better absorption through this route.

Approximately 40% of new chemical entities exhibit poor aqueous solubility is often poor candidates for development of formulation. These drugs are classified as class 2 drugs according to Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility a high permeability.

Different formulation approaches like micronization, solid dispersion and complexation with cyclodextrins have been used but they have some disadvantages.[2] The problem with micronization is chemical/thermal stability; many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow.

Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires facilities and processes, leading to high production cost. Though traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrin techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.[3]

Use of lipid materials has been increased in the design of drug delivery systems due to its accepted nature and improving biopharmaceutical profile of the drug. Self-micro emulsifying drug delivery system (SMEDDS) is one of the most famous and commercially viable approaches. Comparative to emulsion similar products,

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the scale up to SMEDDS is easy with less manufacturing issues.

SMEDDS are isotropic mixtures of oils, solid or liquid surfactants, or instead, one or more hydrophilic solvents and cosolvents/surfactants which leads into microemulsion (ME) upon modest stirring and proper dilution in aqueous media. The resultant globules have a size almost less than 100 nm, which increases stability.[4] SMEDDS also help to reduce dosing size, better and steady absorption profile with selectivity in specific absorption window. It protects the drug from gastric conditions with less variability, high drug entrapment. It also can be sterilized easily. Oral absorption may be increased by SMEDDS, by delaying GI transit time, improving drug solubility in the lumen, increase lymphatic and enterocyte mediated permeation and enhance membrane transport.[5]

The process of self-emulsification depends on multiple factors such as the nature of oil, surfactant, and cosurfactant and on oil to surfactant ratio or oil to surfactant and cosurfactant ratio, the self-emulsification temperature, the polarity of the emulsion, and droplet size and charge. From multiple studies, it was evident that only a specific combination of drug and excipients lead to efficient self-emulsifying system.[6]

Macitentan is a medication primarily used for the treatment of pulmonary arterial hypertension (PAH). PAH is a rare and progressive condition characterized by high blood pressure in the arteries of the lungs, which can lead to heart failure and other complications. It is typically administered orally in the form of tablets and having dose of 10 mg. Clinical studies have shown that Macitentan can improve exercise capacity and quality of life in PAH patients. It has also been shown to slow down the progression of the disease.

Macitentan, as a Class II drug, has high permeability but low solubility. This classification suggests that while it can be well-absorbed through the intestinal membrane due to its high permeability, efforts may be needed to enhance its solubility to ensure efficient and consistent absorption. Pharmaceutical formulations such as SMEDDS (Self Micro Emulsifying Drug Delivery Systems) or other approaches may be employed to improve the solubility and bioavailability of Macitentan for therapeutic use in the treatment of conditions like pulmonary arterial hypertension.[1,7,8]

Evaluation Parameters:

Emulsion Appearance Qualitative grading (EAQG)[9]: It is Self-emulsification efficiency was measured by visual inspection and qualitative grading method described by Charman, W.N (9).

The emulsion was given a rating according to the appearances of emulsion as below,

Rapidly forming (<1 min) with clear or slightly bluish in appearance – A,

Rapidly forming (<1 min) with a less clear and bluish-white appearance – B,

Forming within 2 min (but more than 1 min) with bright white – C,

Takes more than 2 min with dull, greyish white emulsion – D,

Poor emulsification with large oil droplets on the surface of the water - E

Rate of Self-emulsification[9]: 1 ml of formulation was added drop wise to 200 ml of distilled water at 37°C temperature. Rotating paddle was kept at 60 RPM speed to provide gentle agitation. Time required for complete dispersion of oily media called rate of self-emulsification. It was measured visually using a stop clock.

Drug Precipitation[10]: After complete dispersion and determining the rate of emulsification and EAQG, 100 ml of final dispersion or emulsion was transferred into clean glass beaker and kept aside for visual observation for 24 hours. After 6, 12, and 24 hours the bottom of the glass beaker was observed for any sign of drug precipitation against the dark background.

Mean Droplet Diameter[11]: This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. The average droplet size and polydispersity index of SMEDDS formulation was measured by photon correlation spectroscopy that analyzes the fluctuation in light scattering due to the Brownian motion of the droplets as function of time using a Malvern Zetasizer (Nano ZS 90, Malvern instrument ltd., U.K.). Light scattering was monitored at 25°C at 90° angle. 100µl of formulation was dispersed into 100 ml of distilled water under gentle stirring in a glass beaker. Then 1ml aliquot was withdrawn and added into sample cell (1 cm2 cuvette). Each sample was analyzed in triplicate.

Polydispersity index (PDI)[12]: The polydispersity index is a measure of particle homogeneity, and it varies from 0.0 to 1.0. The closer to zero the PI value the more homogenous are the particles. An ideal SMEDDS should be widely distributed with particles less than 100 nm and so PDI should be less than 0.3 or in other words particles having size more than 100 nm should be maximum up to 23 % (12).

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Drug Content[13]: Each formulation ten tablets were powdered and weighed 100 mg and dissolved in methanol in 100 ml standard flasks, suitable dilution was prepared and analyzed at 231 nm using UV spectrophotometer using methanol as blank.

Drug content = Absorbance of sample/Absorbance of standard x 100

***In vitro* dissolution study**[14]: In this study by using Disso2000 dissolution apparatus (paddle type). 900 ml 0.1 N HCl is used as dissolution medium and the temperature at 37ºC ± 0.5ºC at 75 rpm. Samples measuring 1ml were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes intervals, replaced dissolution medium in same quantity to each jar. The collected samples were diluted to 10 ml 0.1 N HCl and analyzed at 231 nm using 0.1 N HCl as blank in UV spectrophotometer.

Hardness[15]: The hardness of tablets was determined by Monsanto hardness tester. The pressure is slowly increased to break the tablet. The value was expressed in Kg/cm^2.

Disintegration Time[15]: It was carried out at 37ºC ± 2ºC in 900 ml of distilled water as disintegration medium. The test used six tablets in each of the six tubes containing one tablet and one disk. The time in seconds for complete disintegration of the tablets was noted.

Friability[16]: The weight of 10 tablets and placed in Roche friabilator. The percentage friability was calculated by the formula:

Friability = (W1 – W2) / W1 x 100

Where, W1 - Weight of ten tablets before test, W2 - Weight of ten tablets after test

2. MATERIALS AND METHODS

➢ Materials

Macitentan was received as a gift sample. Many different oils, surfactants and co-surfactants were purchased and gifted. All excipients of tablet preparation were available at the college laboratory. All the excipients used in this study were pharmaceutical grade.

➢ Methods

Preparation of standard calibration curve of Macitentan in 0.1 N HCl

Standard calibration curve of Macitentan in 0.1 N HCL was prepared. Different concentrations of Macitentan 2, 4, 6, 8 and 10 µg/ml in 0.1 N HCl was prepared separately & absorbance of these prepared solutions were measured at the λmax of 231 nm spectrophotometrically using 0.1N HCL as reference solution.

The calibration curve of Macitentan was found to be over a concentration range 2-10 µg/ml. (R2=0.9989) the data for calibration curve is given in table 7.2 and the calibration curve is shown in figure 1.

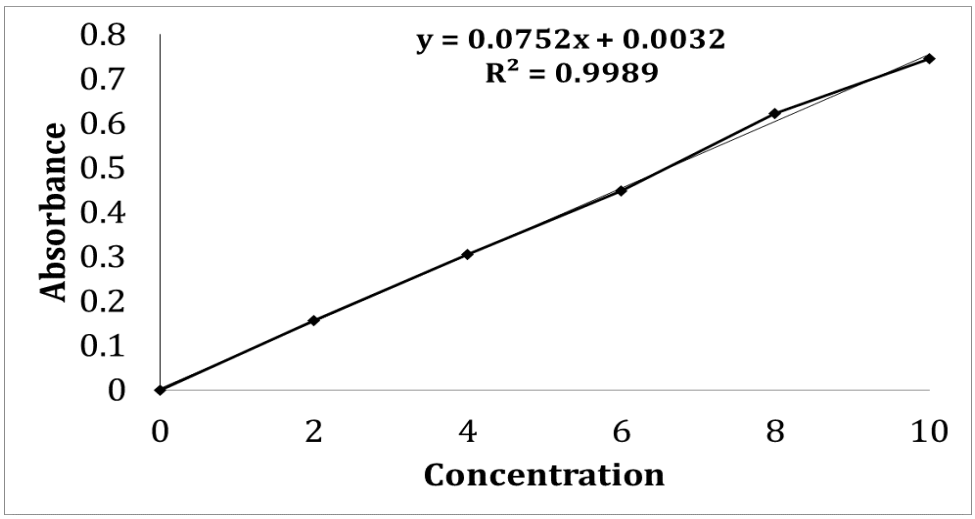

Fig 1: Calibration curve of Macitentan in 0.1 N HCl at 231 nm

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Drug-Excipient Solubility Profiling for Screening of Excipients

Solubility of Macitentan was carried out by placing excess amount of drug in to 2 ml of solvent (Oil /Surfactant/Cosurfactant) in 5 ml glass vial with rubber closer. Vial containing Drug-solvent mixture was subjected to intense sonication for 30 min with heating. The vial was kept unstirred for 48 hours to allow equilibrium in system. Supernatant was collected and centrifuged at 2000 RPM for 10 min to sediment undissolved drug present if any. 1 ml of post centrifugation supernatant was diluted up to 10 ml with methanol and evaluated by UV- Visible spectrophotometric method. This trials with different oils and surfactants are not showed here, however Capmul MCM, Capmul PG 8, Acrysol EL 135, Polysorbate 80, Polysorbate 20, Propylene glycol, Acconon MC 8, and PEG-400 shows good solubility of drug. Hence further study was conducted with selected oils and surfactants.

Preliminary Trials for Selection of Combination of Excipients

Based on the result of drug-solubility profiling and literature review, the first three solvents from each of three categories (oil, surfactant and cosurfactant) with superior solubility were selected for further study. Combinations of oil, surfactant and cosurfactant gives a total of 18 preliminary formulation trials (Table 7.5). Each trial contains an equal amount of oil, surfactant and cosurfactant, i.e., 33.33% of each component (1+1+1= 3 ml and 5 mg drug). All preliminary formulations, as described in Table 7.5, were evaluated for their self-emulsification efficiency and drug precipitation.

No	Oil	Surfactant	Cosurfactant
TM 1	Capmul MCM	Acrysol EL 135	Propylene glycol
TM 2	Capmul MCM	Acrysol EL 135	Acconon MC 8
TM 3	Capmul MCM	Acrysol EL 135	PEG-400
TM 4	Capmul MCM	Polysorbate 80	Propylene glycol
TM 5	Capmul MCM	Polysorbate 80	Acconon MC 8
TM 6	Capmul MCM	Polysorbate 80	PEG-400
TM 7	Capmul MCM	Polysorbate 20	Propylene glycol
TM 8	Capmul MCM	Polysorbate 20	Acconon MC 8
TM 9	Capmul MCM	Polysorbate 20	PEG-400
TM 10	Capmul PG 8	Acrysol EL 135	Propylene glycol
TM 11	Capmul PG 8	Acrysol EL 135	Acconon MC 8
TM 12	Capmul PG 8	Acrysol EL 135	PEG-400
TM 13	Capmul PG 8	Polysorbate 80	Propylene glycol
TM 14	Capmul PG 8	Polysorbate 80	Acconon MC 8
TM 15	Capmul PG 8	Polysorbate 80	PEG-400
TM 16	Capmul PG 8	Polysorbate 20	Propylene glycol
TM 17	Capmul PG 8	Polysorbate 20	Acconon MC 8
TM 18	Capmul PG 8	Polysorbate 20	PEG-400

Table 1: Formulations for Preliminary Trials

Development of Ternary Phase Diagram

As shown in Figure 2 and Table 2 various points from ternary plot were selected for development of Ternary Phase Diagram. Selected ternary graph points were formulated and evaluated for rate of self-emulsification and transparency. Formulations with rate of self-emulsification less than 1 min and transparency more than 90% were tagged in ternary plot. Region with self-emulsifying efficiency, thus explored, was used to determine levels of independent factors in optimization process in later part. A combination of oil, surfactant and cosurfactant were selected based on result of preliminary trials and literature review.

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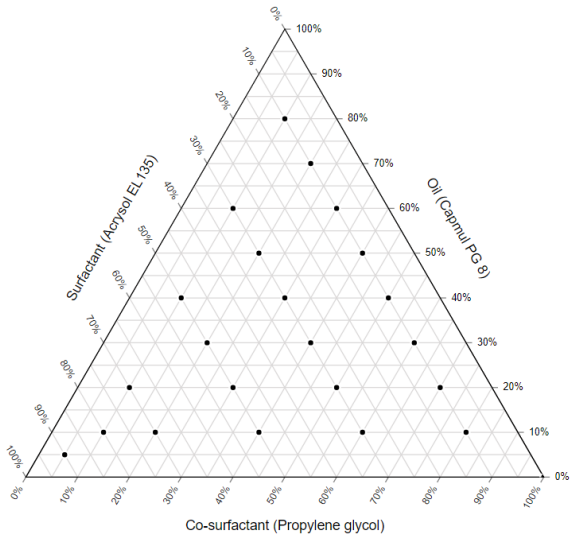

Fig 2: Ternary Plot Point Selected for Evaluation

Sr. No.	Oil	Surfactant	Co surfactant
TP 1	5	90	5
TP 2	10	80	10
TP 3	10	70	20
TP 4	20	70	10
TP 5	10	50	40
TP 6	20	50	30
TP 7	30	50	20
TP 8	40	50	10
TP 9	10	30	60
TP 10	20	30	50
TP 11	30	30	40
TP 12	40	30	30
TP 13	50	30	20
TP 14	60	30	10
TP 15	10	10	80
TP 16	20	10	70
TP 17	30	10	60
TP 18	40	10	50
TP 19	50	10	40
TP 20	60	10	30
TP 21	70	10	20
TP 22	80	10	10

Tab 2: Composition of Ternary Points (in %) Selected for Evaluation

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Preparation of Macitentan SMEDDS

Each Run point was prepared by mixing respective components in clean screw caped plastic tube of 25 ml and mixed thoroughly by vortex mixture. Each formulation contained 100 mg of Macitentan. Tubes were sonicated with heating at 37°C for 30 minutes and kept unstirred for 24 hours to attain equilibrium.

Optimization of Liquid SMEDDS by Box–Behnken design

From the preliminary trial, the formulation with Capmul PG 8®, Acrysol EL135® and Propylene Glycol shows the best transparency grading. The rest of the trials failed to qualify for further studies. So, optimization of amount of Capmul PG 8®, Acrysol EL135® and Propylene Glycol was performed employing 3^3 Full-Factorial design. Details of Independent factor, Coded and Uncoded levels, and design points are given in Table 3. Check point batches (as shown in Table 4) were prepared to evaluate predictability of optimization model. Optimized formula was revealed using Numerical Optimization Tool of SAS 9.1 program. Mean droplet size (Y1), Rate of Emulsification (Y2), PDI (Y3), Surfactant (X3) and minimum oil (X1), surfactant (X2) and co-surfactant (X3) were selected as set criteria for optimization.

All responses were fitted into model by the Design Expert software. The polynomial equation can be approximated in the following mathematical model:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_{12}X_1X_2 + B_{23}X_2X_3 + B_{13}X_1X_3 + B_{11}X_1^2 + B_{22}X_2^2 + B_{33}X_3^2$$

where Y is the measured response, B_1-B_3 are regression coefficients, and X_1, X_2, X_3 are independent factors. The model adequacy was verified by ANOVA, lack-of-fit and multiple correlation coefficient ($R2$) tests provided by the Design Expert software. Further optimization was conducted with a desirability function.

Independent Factors (Amount in ml)	**Coded level**			**Uncoded level**		
	Low	Medium	High	Low	Medium	High
X_1 = Capmul PG 8	-1	0	+1	1	2	3
X_2 = Acrysol EL 135	-1	0	+1	7	8	9
X_3 = Propylene Glycol	-1	0	+1	1.5	2.5	3.5
Dependent Factors						
Y_1 = Mean Droplet Diameter in nm						
Y_2 = Rate of self-emulsification in sec						
Y_3 = Polydispersibility Index						

Tab 3: Experimental Design Detail for Optimization of Macitentan Liquid SMEDDS

	Coded Value			Uncoded Value		
Run	X1	X2	X3	X1	X2	X3
1	-1	-1	0	1	7	2.5
2	1	-1	0	3	7	2.5
3	-1	1	0	1	9	2.5
4	1	1	0	3	9	2.5
5	-1	0	-1	1	8	1.5
6	1	0	-1	3	8	1.5
7	-1	0	1	1	8	3.5
8	1	0	1	3	8	3.5
9	0	-1	-1	2	7	1.5
10	0	1	-1	2	9	1.5
11	0	-1	1	2	7	3.5

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12	0	1	1	2	9	3.5
13	0	0	0	2	8	2.5
14	0	0	0	2	8	2.5
15	0	0	0	2	8	2.5

Tab 4: Box-Behnken Design Points

Solidification of Liquid SMEDDS:

Optimized liquid SMEDDS formulation was converted to free flowing and compressible powder by absorption with various absorbents or carriers. Three absorbents: AEROSIL® 300 (colloidal silicon dioxide), Neusilin UFL2 (Magnesium Aluminometasilicate), Syloid FP (synthetic amorphous silica) were selected as absorbent. All excipients have a high specific surface area of approximately 300 m^2/gm.

By practicing different trials with solid carriers, liquid SMEDDS and Neusilin UFL2 at the ratio of 1.4 ml:0.2 g gets optimum results of powder flow properties. After optimizing solid SMEDDS the sample was checked for content of drug, and it finds that 100 mg S-SMEDDS Powder had 5 mg of Macitentan.

Optimization of SMEDDS Tablet by 2^3 factorial design

Preliminary trials with various binders like: Microcrystalline cellulose (MCC), Emcompress®, Pregelatinized starch, lactose, mannitol, and silicified microcrystalline cellulose were performed. From the result of preliminary trials MCC, Emcompress® and Pregelatinized starch were selected for optimization purposes. 2^3 factorial design was selected as the design of experiment to keep total weight of tablet (300 mg) uniform in all run points of experiment. Details of dependent factors, their levels and independent factors are shown in Table 5.

Independent Factors (Amount)	**Coded level**		**Uncoded level**	
	Low	High	Low	High
X_1 = Amount of PVP K 30 in mg	-1	1	9	15
X_2 = Amount of Pre-gel Starch in mg	-1	1	3	9
Dependent Factors				
Y_1 = Hardness (kg/cm^2)				
Y_2 = Disintegration Time (Minutes)				

Tab 5: Details of Factors of Factorial Design

Preparation of SMEDDS Tablet

The tablet was prepared by direct compression method. Each tablet contains 200 mg SMEDDS Powder equivalent to 10 mg Macitentan. Each component of experimental run point was weight accurately for batch size of 50 tablets. All components were mixed into clean mortar and passed through 22# sieve size. After mixing, powder mixture was subjected to tablet compression unit for tablet preparation (300 mg each). Table 6 shows detailed formulation of each batch. Final check point batches were compared for dissolution test.

Batch	**MT1**	**MT2**	**MT3**	**MT4**	**MT5**	**MT6**	**MT7**	**MT8**	**MT9**
SMEDDS Powder	200	200	200	200	200	200	200	200	200
PVP K 30	12	9	15	12	9	15	9	12	15
Pregelatinized Starch	3	9	6	9	3	9	6	6	3
Emcompress®	85	82	79	79	88	76	85	82	82

Tab 6: Batches of Design

3. RESULTS AND DISCUSSION

Preliminary Trial Result for Selection of Combination of Excipients:

Trial Code	**Rate of Emulsification (Sec± SD)**	**EAQG**	**Drug Precipitation**
TM 1	48±1.4	B	No

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TM 2	31±2.45	B	Yes (after 24 hrs.)
TM 3	82±1.33	C	No
TM 4	55±3.45	B	No
TM 5	38±2.54	B	Yes (after 12 hrs.)
TM 6	101±3.22	C	No
TM 7	65±1.8	C	No
TM 8	49±1.34	B	Yes (after 6 hrs.)
TM 9	121±5.2	C	Yes (after 12 hrs.)
TM 10	**11±1.76**	**A**	**No**
TM 11	23±1.4	B	Yes (after 24 hrs.)
TM 12	58±1.56	B	No
TM 13	28±3.22	B	No
TM 14	42±4.22	B	Yes (after 24 hrs.)
TM 15	71±2.44	C	Yes (after 6 hrs.)
TM 16	81±3.22	C	No
TM 17	69±5.33	C	Yes (after 6 hrs.)
TM 18	112±6.33	C	Yes (after 6 hrs.)

Tab 7: Results preliminary trials of selected combinations.

According to the result of preliminary trial of combinations of excipients shows that TM 10 batch had optimum results for selected characteristics. Accordingly, TM 10 excipients were selected for further study.

Ternary Phase Diagram:

The ternary plots results are incorporated at the specific points as per the composition. Now, positive resulted batches were highlighted in ternary plot to understand SMEDDS area in the ternary phase diagram (Fig 3).

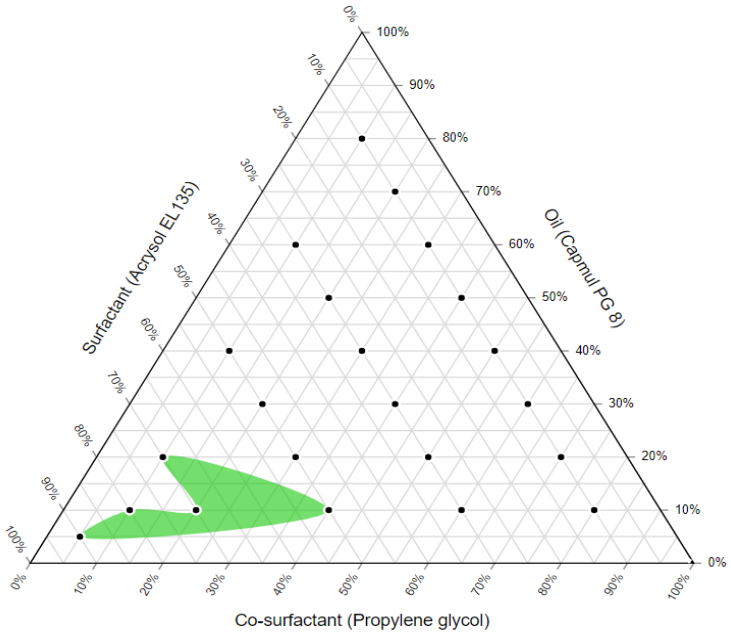

Fig 3: Ternary plot resulted area.

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Optimization of Liquid SMEDDS by Box–Behnken Design:

Based on the preliminary results and ternary phase diagram Capmul PG 8 selected as oil, Acrysol EL135® selected as surfactant and Propylene glycol selected as co-surfactant. Table 8 shows results of the batches proposed through design of experiment.

Run	Coded Value			Uncoded Value			Result		
	X_1	X_2	X_3	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	-1	-1	0	1	7	2.5	146.6	230 ± 5	0.874
2	1	-1	0	3	7	2.5	199.8	112 ± 3	0.696
3	-1	1	0	1	9	2.5	120.4	210 ± 3	0.482
4	1	1	0	3	9	2.5	128.9	58 ± 2	0.49
5	-1	0	-1	1	8	1.5	156.2	180 ± 3	0.713
6	1	0	-1	3	8	1.5	177.3	65 ± 6	0.612
7	-1	0	1	1	8	3.5	134.6	150 ± 5	0.37
8	1	0	1	3	8	3.5	179.4	50 ± 4	0.777
9	0	-1	-1	2	7	1.5	191.5	198 ± 8	0.701
10	0	1	-1	2	9	1.5	130.3	105 ± 6	0.425
11	0	-1	1	2	7	3.5	165.9	90 ± 2	0.482
12	0	1	1	2	9	3.5	127	58 ± 3	0.432
13	0	0	0	2	8	2.5	156.4	55 ± 4	0.442
14	0	0	0	2	8	2.5	155.8	56 ± 3	0.445
15	0	0	0	2	8	2.5	155.9	52 ± 6	0.496

Tab 8: Result of Experimental Design Points (n=3)

A three-factor, three-level BBD was applied to understand the effects of independent factors and to optimize three responses: Mean droplet diameter (Y1), Rate of Emulsification (Y2), PDI (Y3) of the SMEDDS formulation. The BBD matrix by run order and the observed responses or dependent variables of 15 runs is shown in Table 8. All data were explored by Design Expert®. Each response was individually fitted to a second-order quadratic model, and model significance was determined by ANOVA, lack-of-fit test, and multiple correlation coefficient (R^2) tests provided by the Design Expert software. The model P-value should be less than 0.05 for the model to best fit the quadratic model.[17] Lack-of-fit test indicates the variation of the data around the fitted model, and for the model to fit the data well, lack-of-fit should be insignificant (P-value > 0.1) relative to the pure error.[18] A model with a significant lack of- fit lacks prediction efficiency. Multiple correlation coefficient (R^2) signifies the measure of the amount of variation around the mean as explained by the model, and a value more than 0.6 is preferable and more than 0.9 is desirable. The effect of estimate of Y1, Y2 and Y3, Quadratic Equations of Y1, Y2 and Y3, and ANOVA is given in table 9, table 10 and table 11 respectively.

	Value	B0	B1	B2	B3	B12	B23	B13	B11	B22	B33
Y_1	Coefficients	156.03	15.95	-24.65	-6.05	-11.17	5.925	5.57	0.54	-7.65	5.29
	P-value	-	< 0.0001	< 0.0001	0.0002	< 0.0001	0.0010	0.0013	0.5660	0.0003	0.0019
Y_2	Coefficients	54.33	-60.63	-24.88	-25.00	-8.50	3.75	15.25	48.33	49.83	8.58
	P-value	-	0.0005	0.0206	0.0203	0.4569	0.7367	0.2078	0.007	0.0062	0.4696
Y_3	Coefficients	0.461	0.017	-0.116	-0.049	0.047	0.127	0.057	0.141	0.033	0.016
	P-value	-	0.612	0.0144	0.1818	0.3436	0.0356	0.2598	0.0284	0.5047	0.7475

Tab 9: The Effect of Estimate of Dependent Factors

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$Y_1 = 156.03 + 15.95\ X_1 - 24.65\ X_2 - 6.05\ X_3 - 11.17\ X_1 X_2 + 5.925\ X_2 X_3 + 5.57\ X_1 X_3 + 0.54\ X_1^2 - 7.65\ X_2^2 + 5.29\ X_3^2$ *(R-Square = 0.9982)*
$Y_2 = 54.33 - 60.63\ X_1 - 24.88\ X_2 - 25\ X_3 - 8.50\ X_1X_2 + 3.75\ X_2X_3 + 15.25\ X_1X_3 + 48.33\ X_1^2 + 49.83\ X_2^2 + 8.58\ X_3^2$ *(R-Square = 0.9625)*
$Y_3 = 0.461 + 0.017\ X_1 - 0.116\ X_2 - 0.049\ X_3 + 0.047\ X_1X_2 + 0.127\ X_2X_3 + 0.057\ X_1X_3 + 0.141\ X_1^2 + 0.033\ X_2^2 + 0.016\ X_3^2$ *(R-Square = 0.8798)*

Tab 10: Quadratic Equations of Dependent Factors

		DF	SS	MS	f	Significance f
Y_1	Regression	9	8300.13	922.23	316.23	< 0.0001
	Residual	5	14.58	2.91		
	Total	14	8314.71			
Y_2	Regression	9	57162.51	6351.39	14.27	0.0046
	Residual	5	2224.41	444.88		
	Total	14	59386.93			
Y_3	Regression	9	0.2895	0.0321	4.067	0.0484
	Residual	5	0.0395	0.0079		
	Total	14	0.3291			

Tab 11: ANOVA of Dependent Factors

In the ANOVA test, the significance-f value Y1, Y2 and Y3 are for mean droplet size, rate of self-emulsification and PDI respectively. As all significance-f values are less than 0.05, all responses (Y1, Y2, Y3) fitted the quadratic model well. According to values of coefficient and p-values the Polynomial Equation of dependent variables Y1, Y2 and Y3 are given in table 10. Figure 4 shows overlay contour plots for optimized value of dependent variables Mean droplet diameter (Y1), Rate of Emulsification (Y2), PDI (Y3) at optimized formulation quantity incorporated in figure.

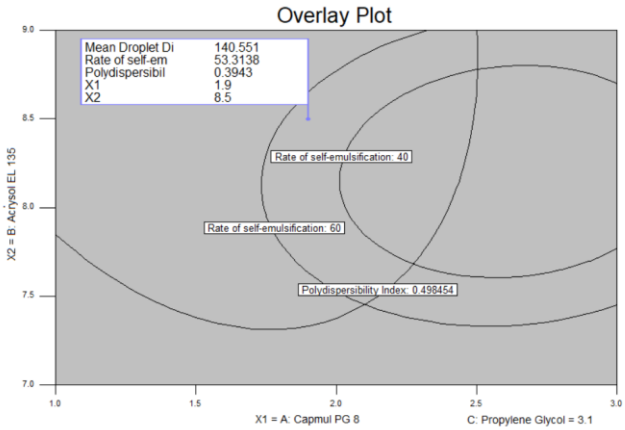

Fig 4 Overlay Contour Plot for SMEDDS

As per the desired dependent variables many batches were proposed by the software. Now to get final formulation as tablet one checkpoint batch formulation of liquid SMEDDS was used to process further studies. The check point batch have quantity of Capmul PG8 1.8 ml, Acrysol EL 135 8.4 ml and Propylene Glycol 3.4 ml with 100 mg of Macitentan. The practical and proposed values of dependent variables were checked and passed as per chi square test. This liquid SMEDDS batch was used for solidification of SMEDDS with different solid carriers at different ratios. The solid SMEDDS powder with good flow properties is used for preparation of tablet.

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Results of Optimization of SMEDDS Tablet

	Coded Value		Uncoded Value		Result Value	
Run	**X_1**	**X_2**	**X_1**	**X_2**	**Y_1**	**Y_2**
MT1	0	-1	12	3	6.8 ± 0.5	7.8 ± 1.1
MT2	-1	1	9	9	4.3 ± 0.3	4.6 ± 0.9
MT3	1	0	15	6	7.7 ± 0.1	12 ± 1.5
MT4	0	1	12	9	5.9 ± 0.3	6.5 ± 0.5
MT5	-1	-1	9	3	5.3 ± 0.4	5.9 ± 0.8
MT6	1	1	15	9	7.3 ± 0.5	10 ± 1.2
MT7	-1	0	9	6	4.8 ± 0.6	5.2 ± 0.4
MT8	0	0	12	6	6.4 ± 0.9	7.1 ± 0.9
MT9	1	-1	15	3	8.1 ± 0.57	13.5 ± 1.7

Tab 12: Result of Experimental Design Points (n=3)

A two-factor, three-level factorial design was applied to understand the effects of independent factors and to optimize two responses: Hardness in kg/cm^2 and Disintegration Time in minutes of the SMEDDS tablet. The factorial design matrix by run order and the observed responses or dependent variables of 9 runs is shown in Table 12. All data were explored by Design Expert®. Each response was individually fitted to a second-order quadratic model, and model significance was determined by ANOVA, lack-of-fit test, and multiple correlation coefficient (R^2) tests provided by the Design Expert software. The model P-value should be less than 0.05 for the model to best fit the quadratic model (17). Lack-of-fit test indicates the variation of the data around the fitted model, and for the model to fit the data well, lack-of-fit should be insignificant (P-value > 0.1) relative to the pure error (18). A model with a significant lack of- fit lacks prediction efficiency. The effect of estimate of Y_1, and Y_2, Quadratic Equations of Y_1, and Y_2, and ANOVA is given in table 13, table 14 and table 15 respectively.

	Value	B0	B1	B2	B12	B11	B22
Y_1	Coefficients	6.378	1.450	-0.450	0.050	-0.117	-0.017
	P-value	-	< 0.0001	< 0.0001	0.0138	0.0033	0.3081
Y_2	Coefficients	7.166	3.3	-1.016	-0.55	1.4	-0.05
	P-value	-	0.0002	0.0075	0.0645	0.0142	0.8658

Tab 13: The Effect of Estimate of Dependent Factors

$Y_1 = 6.37 + 1.45\ X_1 - 0.45\ X_2 + 0.05\ X_1X_2 - 0.017\ X_1^2 - 0.017\ X_2^2$ *(R-Square = 0.9999)*
$Y_2 = 7.166 + 3.3\ X_1 – 1{,}016\ X_2 - 0.55\ X_1X_2 + 1.4\ X_1^2 - 0.05\ X_2^2$ *(R-Square = 0.9942)*

Tab 14: Quadratic Equations of Dependent Factors

		DF	**SS**	**MS**	**f**	**Significance f**
Y_1	Regression	5	13.867	2.7735	7488.6	< 0.0001
	Residual	3	0.001	0.0003		
	Total	8	13.868			
Y_2	Regression	5	76.6766	15.335	103. 77	0.0015
	Residual	3	0.4433	0.147		
	Total	18	77.12			

Tab 15: ANOVA of Dependent Factors

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The ANOVA test, the significance-f value Y_1, and Y_2 are for tablet hardness and disintegration time. As all significance-f values are less than 0.05, all responses (Y_1, Y_2) fitted the quadratic model well. According to values of coefficient and p-values the Polynomial Equation of dependent variables Y_1, and Y_2 are given in table 14. Figure 5 shows overlay contour plots for optimized value of dependent variables hardness (Y_1) and disintegration time (Y_2) at optimized formulation quantity incorporated in figure.

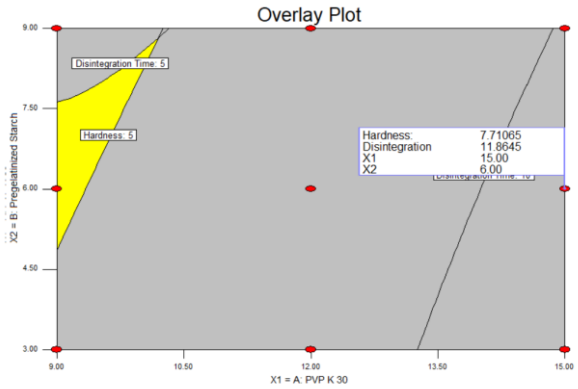

Fig 5: Overlay Contour Plot for SMEDDS Tablet

Details And Results of Check Point Batches:

Check Point Batch	Coded Level		Uncoded Level		Y1			Y2		
	X1	X2	X1	X2	Predicted	Actual	p-Value	Predicted	Actual	p-Value
MTC 1	-1	1	9.05	9	4.33	4.5 ± 0.3	0.447	4.75	4.9 ± 0.6	0.440
MTC 2	-0.75	1	9.42	9	4.54	4.5 ± 0.7		4.77	4.8 ± 0.4	
MTC 3	-0.5	1	10.49	9	5.12	5.2 ± 0.8		5.07	5.05 ± 0.3	
MTC 4	-0.5	0.25	11.07	6.97	5.77	5.8 ± 0.5		6.00	6.1 ± 0.8	

Tab 16: Details and Result of Check point batches of SMEDDS Tablet

To get desired hardness and disintegration time of SMEDDS Tablet, the software resulted in 4 checkpoint batches. The check point batches with coded level, uncoded level and results of checkpoint batches for Y1 and Y2 are given in Table 16. The values of desired levels were shown to be a p-value less than 0.5 which shows that all the check point batches give results are near and passable when compared to predicted and actual. The dissolution test results of check point batches are shown in figure 6.

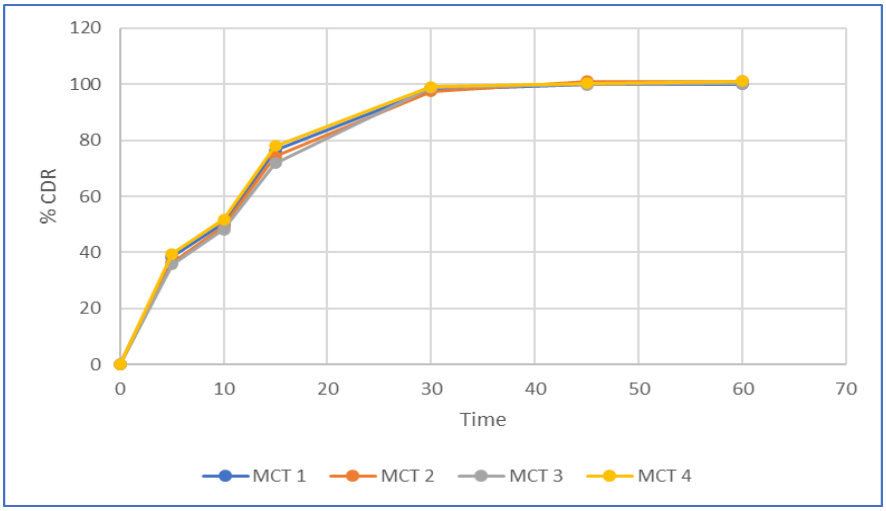

Fig 6: Dissolution of check point batches of SMEDDS Tablet

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As expected, the dissolution rate of the SMEDDS tablets was very fast (more than 95% within 30 min) at 0.5 N HCl, indicating increased solubility of Macitentan. So, all four batches of Macitentan SMEDDS tablet formulation showed significantly enhanced dissolution rate and maximum dissolution percentage. This result indicates that SMEDDS with micro-sized particle provided a large surface area, enhancing the dissolution of drug from formulation.

4. Conclusion

The self-micro emulsifying formulation of Macitentan can be developed with nano particle size. The optimized formulation of Macitentan is capable of producing micro-emulsion spontaneously having an average globule size of 140.52 nm (0.394 PDI) within less than one minute. The solid SMEDDS can be incorporated into a tablet by using solid carrier. The optimized SMEDDS tablets have good hardness and disintegration time with dissolution rate more than 95% within 30 min. However, a comprehensive in-vivo study is required to prove improvement in the oral bioavailability.

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