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Formulation and optimization of Ambrisentan self-micro emulsifying drug delivery system (SMEDDS) tablet by wet granulation

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ABSTRACT

Ambrisentan is an orally administered endothelin receptor antagonists used for the treatment of pulmonary hypertension. As it is fall under BCS class 2 medicine, its solubility, stability and oral bio availability 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 Ambrisentan using minimized quantity of oil, surfactant and co-surfactant that could improve its solubility, stability, and dissolution. The composition of optimized formulation consists of Maisine CC as oil, Acrysol EL 135 as surfactant and Capryol PGMC as cosurfactant, containing 200 mg of Ambrisentan showing mean droplet size (155.12 nm), rate of self-emulsification (56 sec) and Polydispersibility index (0.331). This optimized liquid SMEDDS is used as a liquid component in wet granulation and prepare tablet of Ambrisentan having 5 mg strength. A prepared tablet is evaluated further for tablet evaluation tests and dissolution. This research results in good dissolution and stability.

Keywords: Ambrisentan, SMEDDS, Factorial Design, Wet granulation, SMEDDS-Tablet

INTRODUCTION

SMEDDS, which stands for Self-Emulsifying Drug Delivery System, is a specialized formulation approach used in the field of pharmaceuticals and drug delivery. It is designed to enhance the solubility and bioavailability of poorly water-soluble drugs, making it easier for the body to absorb and utilize them effectively. This technology is particularly valuable for drugs with low solubility, as they often have limited therapeutic efficacy when administered in traditional dosage forms [1].

The key concept behind SMEDDS is the creation of a stable, isotropic (uniformly dispersed) mixture of a lipophilic drug, lipids, surfactants, and co-surfactants. When this mixture encounters gastrointestinal fluids, it spontaneously forms fine oil-in-water emulsions or microemulsions. These emulsified drug particles have a significantly larger surface area than the original drug, which facilitates faster and more efficient drug absorption in the gastrointestinal tract [2,3].

In summary, SMEDDS is a promising drug delivery system that addresses the challenge of delivering poorly water-soluble drugs. Its ability to enhance solubility, promote absorption, and provide formulation flexibility makes it a valuable tool in pharmaceutical development, potentially leading to more effective and efficient drug therapies [4].

Ambrisentan is a medication used to treat pulmonary arterial hypertension (PAH). PAH is a rare but serious condition characterized by high blood pressure in the arteries of the lungs, which can lead to heart failure and other complications. Ambrisentan belongs to a class of drugs known as endothelin receptor antagonists (ERAs) and is specifically classified as a selective endothelin-A (ET-A) receptor antagonist [5].

Ambrisentan works by blocking the effects of endothelin, a substance in the body that causes blood vessels to narrow. By selectively inhibiting the endothelin-A receptors, Ambrisentan relaxes

the blood vessels in the lungs, reducing pulmonary arterial pressure and making it easier for the heart to pump blood through the lungs. It is typically administered orally in the form of tablets, usually once daily [6].

Ambrisentan is an important treatment option for individuals with pulmonary arterial hypertension, and its use should be carefully managed by healthcare professionals to optimize its benefits while minimizing potential side effects and risks. Patients should consult their healthcare provider for specific information regarding the use of Ambrisentan, as individual circumstances may vary. It is fall under BCS class 2 medicine. Accordingly, this drug having low solubility and high permeability [6,7].

Drugs classified as BCS Class 2 have low aqueous solubility but high permeability across biological membranes. In other words, they don't readily dissolve in water but can easily pass through the intestinal membrane into the bloodstream. The challenge with drugs in this class primarily lies in their low solubility. Because they have difficulty dissolving in the gastrointestinal fluids, their absorption can be limited, leading to poor bioavailability. Bioavailability refers to the fraction of the administered drug that reaches the systemic circulation unchanged and is available to produce a therapeutic effect improves the bioavailability of BCS Class 2 drugs, various formulation strategies may be employed [3,4]. These can include the use of pharmaceutical excipients, such as surfactants or co-solvents, to enhance solubility. Additionally, technologies like nanosuspensions, solid dispersions, and lipid-based delivery systems (like SMEDDS mentioned earlier) may be utilized to address solubility and absorption issues [8].

MATERIALS AND METHODS

Evaluation Parameters:

Emulsion Appearance Qualitative grading (EAQG)

It is Self-emulsification efficiency that 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

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 [11].

Polydispersity index (PDI)

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].

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 263.5 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 5 M acetate buffer pH 5.0 is 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 pH 5.0 and analyzed at 263.5 nm using pH 5.0 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

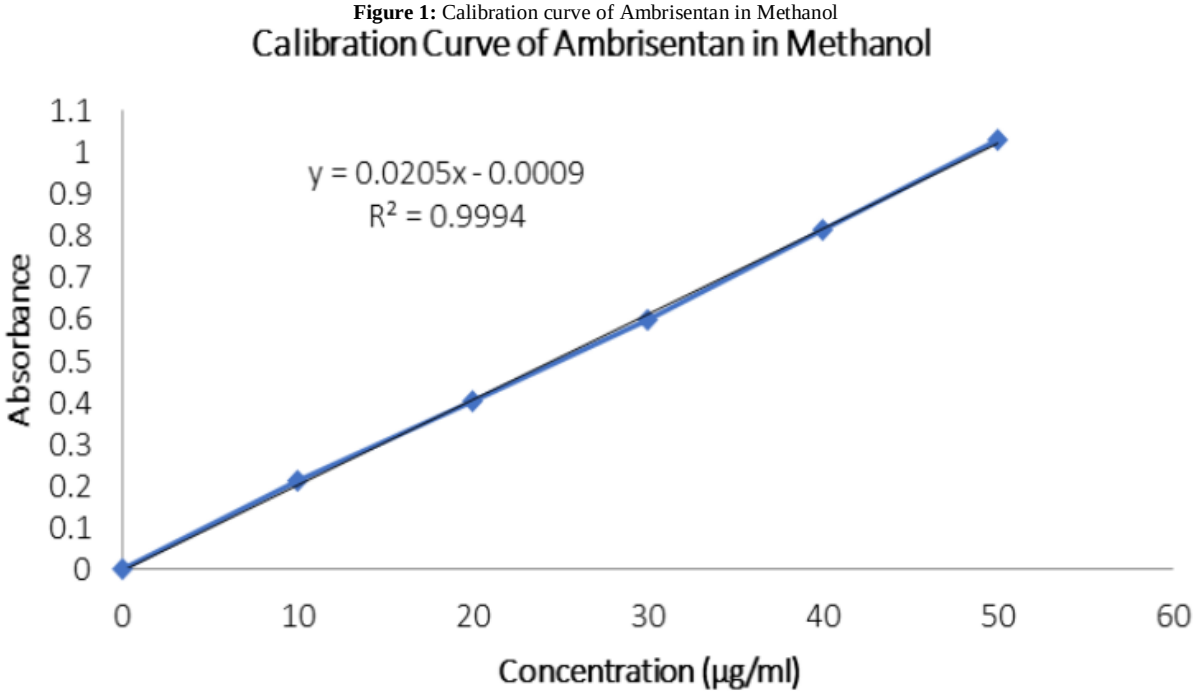
Where, W1 - Weight of ten tablets before test, W2 - Weight of ten tablets after test

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

Preparation of standard calibration curve of Ambrisentan in Methanol

Standard calibration curve of Ambrisentan in Methanol was prepared. Different concentrations of Ambrisentan 10, 20, 30, 40, and 50 µg/ml in Methanol was prepared separately & absorbance of these prepared solutions were measured at the λ_{max} of 263.5 nm spectrophotometrically using Methanol as reference solution. The calibration curve of Ambrisentan was found to be over a concentration range 10-50 µg/ml. (R^2=0.9994) The calibration curve is shown in Figure. 1.

Figure 1: Calibration curve of Ambrisentan in Methanol



Drug-Excipient Solubility Profiling for Screening of Excipients

Solubility of Ambrisentan 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 combination was subjected to intense sonication for 30 min with heating. The vial was kept unstirred for 48 hours which allowed equilibrium in system. Supernatant was collected plus centrifuged at 2000 RPM for 10 min to sediment undissolved drug particles presents, if any. 1 ml of post centrifugation supernatant was diluted up to 10 ml with methanol and evaluated by UV- Visible spectrophotometric method.

Preliminary Trials for Selection of Combination of Excipients

Based on the results 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 (2^3) of oil, surfactant and cosurfactant gives a total of 18 preliminary formulation trials (Table 1). Each trial contains an equal amount of oil, surfactant and cosurfactant, i.e., 33.33% of each component (1+1+1= 3 ml and 200 mg drug). All preliminary formulations, as described in Table 1, were evaluated for their self-emulsification efficiency and drug precipitation.

Table 1: Formulations for Preliminary Trials

Batch	Rate of Emulsification (sec ± SD)	EAQG	Drug Precipitation
TA1	8±1.56	A	No
TA2	21±2.6	A	No
TA3	42±5.1	C	Yes (after 12 hrs.)
TA4	65±4.6	B	No
TA5	68±2.5	C	Yes (after 12 hrs.)
TA6	91±8.5	C	No
TA7	45±1.5	B	No
TA8	39±3.2	B	Yes (after 6 hrs.)
TA9	75±5.4	C	Yes (after 6 hrs.)
TA10	19±1.4	A	No
TA11	44±4	B	No
TA12	58±5.7	B	No
TA13	58±3.7	B	No
TA14	52±6.28	B	No
TA15	61±4.04	B	Yes (after 6 hrs.)
TA16	89±2.9	C	Yes (after 12 hrs.)
TA17	96±8.4	C	Yes (after 6 hrs.)
TA18	98±6.8	C	Yes (after 6 hrs.)

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. Certain ternary graph points were formulated and evaluated for rate of self-emulsification and transparency. Formulations which have rate of self-emulsification less than 1 min and transparency beyond 90% were tagged in ternary plot. Region with self-emulsifying efficiency, accordingly explored, was used to determine levels of independent factors in optimization procedure in later part. A combination of three phases i.e., oil, surfactant and cosurfactant were chosen based on the result of preliminary trials and literature review.

Figure 2: Ternary Plot Point Selected for Evaluation

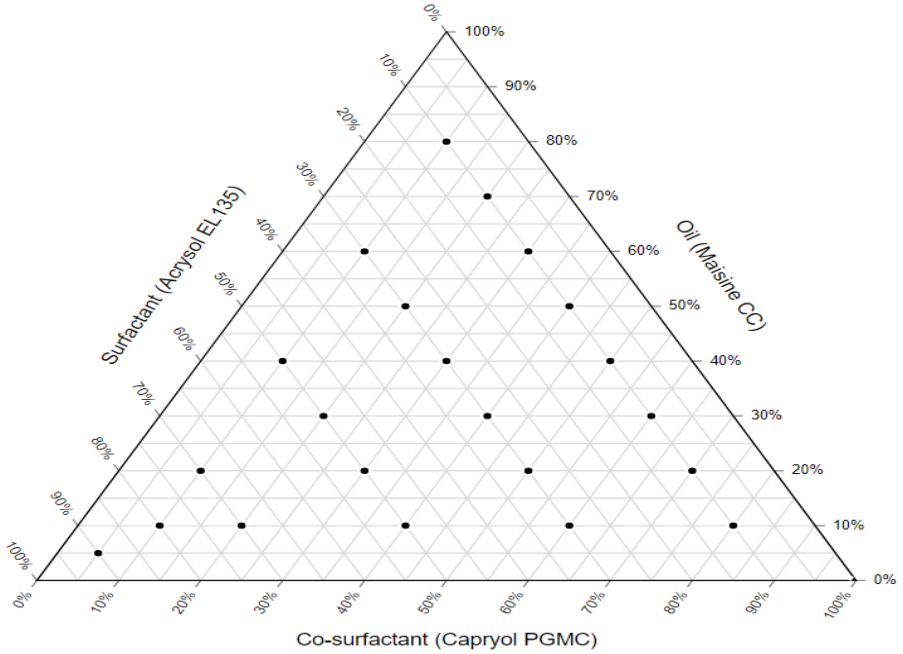


Table 2: Composition of Ternary Points (in %) Selected for Evaluation

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

Preparation of Ambrisentan 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 200 mg of Ambrisentan. 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 of Maisine® CC, Acrysol EL135® and Capryol® PGMC shows the clearest transparency grading. The rest of the trials failed to qualify for further studies. So, optimization of amount of Maisine® CC, Acrysol EL135® and Capryol® PGMC 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 software. 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 (*R*2) tests provided by the Design Expert software. Further optimization was conducted with a desirability function.

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

Independent Factors (Amount in ml)	Coded level			Uncoded level		
	Low	Medium	High	Low	Medium	High
X1 = Maisine® CC	-1	0	+1	1	2.5	4
X2 = Acrysol EL 135®	-1	0	+1	5	7	9
X3 = Capryol® PGMC	-1	0	+1	2	3	4

Dependent Factors: Y1 = Mean Droplet Diameter in nm, Y2 = Rate of self-emulsification in sec, Y2 = Rate of self-emulsification in sec

Table 4: Box-Behnken Design Points

	Coded Value			Uncoded Value		
Run	X_1	X_2	X_3	X_1	X_2	X_3
1	0	1	-1	2.5	9	2
2	0	-1	1	2.5	5	4
3	-1	0	1	1	7	4
4	0	1	1	2.5	9	4
5	0	0	0	2.5	7	3
6	0	0	0	2.5	7	3
7	1	0	1	4	7	4
8	1	-1	0	4	5	3
9	1	1	0	4	9	3
10	0	-1	-1	2.5	5	2
11	-1	-1	0	1	5	3
12	0	0	0	2.5	7	3
13	-1	1	0	1	9	3
14	-1	0	-1	1	7	2
15	1	0	-1	4	7	2

Preparation of SMEDDS granules by wet granulation

The preparation of Ambrisentan SMEDDS batch formulation was done according to the quantities stated in optimized batch. However, to prepare 40 tablets of each 5 mg Ambrisentan tablet, weighed amounts of oil, surfactants, and co-surfactant were mixed with 200 mg Ambrisentan and prepared liquid SMEDDS using same process. After which lactose was added as solid carrier/ adsorbent and binder and was properly mixed to form a wet mass. The wet mass was sieved using 800µm sieve. The granules were dried, and dry sieving was done using 600 µm sieve, and then dried again in an oven 60°C. In dried granules Disintegrant (starch), glidant (talc) and lubricant (Mg. stearate) were added to the granules. Prepared granules were evaluated for flow property or pre-formulation studies. These granules were compressed to prepared tablet. Prepared tablets were evaluated for drug content, dissolution, hardness, disintegration time and friability.

RESULTS AND DISCUSSION

Preliminary Trials for Selection of Combination of Excipients

According to results of table 6, batch TA1 shows good results of rate of self-emulsification, EAQG and drug precipitation. So, now further study was done using oil, surfactant and co-surfactant as used in batch TA1.

Drug-Excipient Solubility Profiling for Screening of Excipients

Table 5: Results of solubility of drug in excipients

Excipient	Solubility (mg/ml ± SD)
Capmul-MCM (Glyceryl Caprylate)	91.5
Capmul-PG8 (Propylene Glycol Monocaprylate)	78.6
Captex 355 (Medium chain triglycerides)	85.1
Captex 100 (Medium chain triglycerides)	82.4
Maisine® CC (Glyceryl monolinoleate)	226.6
Peceol™ (Glyceryl monooleate)	191.2
Labrafac™ PG (Propylene glycol dicaprylocaprate)	68.3
Acrysol EL135® (Castor oil derivative)	212.4
Acrysol K140® (PEG-40 Hydrogenated Castor Oil)	56.9
Acconon MC 8® (PEG-8 Caprylic/Capric Glycerides)	179.7
Propylene glycol	95.4
PEG-400	148.9
SPAN 80® (Sorbitan Monooleate)	163.7
Lauroglycol™ FCC (Propylene glycol monolaurate)	108.2
Lauroglycol™ 90 (Propylene glycol monolaurate)	99.9
Capryol® PGMC (Propylene glycol monocaprylate)	119.6

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 (Figure 3)

Table 6: Results preliminary trials of selected combinations.

Batch	Rate of Emulsification (sec± SD)	EAQG	Drug Precipitation
TA1	**8±1.56**	**A**	**No**
TA2	21±2.6	A	No
TA3	42±5.1	C	Yes (after 12 hrs.)
TA4	65±4.6	B	No
TA5	68±2.5	C	Yes (after 12 hrs.)
TA6	91±8.5	C	No
TA7	45±1.5	B	No
TA8	39±3.2	B	Yes (after 6 hrs.)
TA9	75±5.4	C	Yes (after 6 hrs.)
TA10	19±1.4	A	No
TA11	44±4	B	No
TA12	58±5.7	B	No
TA13	58±3.7	B	No
TA14	52±6.28	B	No
TA15	61±4.04	B	Yes (after 6 hrs.)
TA16	89±2.9	C	Yes (after 12 hrs.)
TA17	96±8.4	C	Yes (after 6 hrs.)
TA18	98±6.8	C	Yes (after 6 hrs.)

Optimization of Liquid SMEDDS and Box–Behnken design

Based on the results Maisine® CC selected as oil, Acrysol EL135® selected as surfactant and Capryol® PGMC selected as co-surfactant. Table 7 shows results of the batches proposed through design of experiment.

Figure 3: ternary plot resulted area.

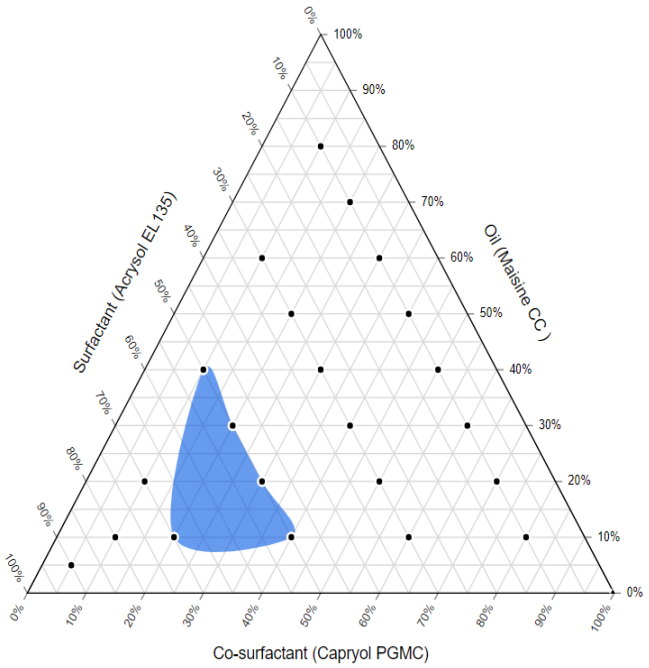


Table 7: Result of Experimental Design Points (n=3).

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	0	1	-1	2.5	9	2	176.03	91 ± 3	0.523
2	0	-1	1	2.5	5	4	185.2	98 ± 4	0.511
3	-1	0	1	1	7	4	164	65 ± 7	0.464
4	0	1	1	2.5	9	4	159.23	58 ± 5	0.343
5	0	0	0	2.5	7	3	149.08	52 ± 1	0.321
6	0	0	0	2.5	7	3	152.51	51 ± 3	0.338
7	1	0	1	4	7	4	188.03	143± 8	0.536
8	1	-1	0	4	5	3	198.74	163 ± 2	0.558
9	1	1	0	4	9	3	181.06	102 ± 9	0.448
10	0	-1	-1	2.5	5	2	177.89	103 ± 14	0.441
11	-1	-1	0	1	5	3	184.12	75 ± 3	0.311
12	0	0	0	2.5	7	3	150.3	50 ± 6	0.346
13	-1	1	0	1	9	3	143	54 ± 4	0.377
14	-1	0	-1	1	7	2	156.32	56 ± 5	0.382
15	1	0	-1	4	7	2	189.77	134 ± 11	0.498

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 7. 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 was given in table 8 and ANOVA is given in table 9.

Table 8: Effect of estimate of Y1, Y2 and Y3

Value	Y1		Y2		Y3	
	Coefficients	P-value	Coefficients	P-value	Coefficients	P-value
B0	150.33	-	51	-	0.335	-
B1	13.63	0.001	36.5	0.0002	0.0633	0.0089
B2	-10.63	0.0032	-16.75	0.0065	-0.0163	0.3346
B3	-0.25	0.9054	-2.5	0.5324	0.0013	0.9377
B12	6	0.0873	-10	0.1165	-0.044	0.0964
B23	-2.25	0.4623	0	1	-0.011	0.6312
B13	-6.25	0.0781	-7	0.2419	-0.0625	0.0337
B11	13.08	0.0067	29.75	0.0029	0.052	0.068
B22	13.08	0.0067	17.75	0.0231	0.0365	0.1643
B33	10.83	0.0143	18.75	0.0189	0.083	0.0139

Table 9: ANOVA of Y1, Y2 and Y3

		DF	SS	MS	f	Significance f
Y1	**Regression**	9	4183.02	464.78	14.5319	0.0044
	Residual	5	159.92	31.983		
	Total	14	4342.93			
Y2	**Regression**	9	18584.8	2064.98	18.5533	0.0025
	Residual	5	556.5	111.3		
	Total	14	19141.3			
Y3	**Regression**	9	0.0938	0.0104	5.623	0.0359
	Residual	5	0.0093	0.0019		
	Total	14	0.1031			

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 below. Figure 4, 5 and 6 shows contour plots of dependent variables mean droplet diameter (Y1), Rate of Emulsification (Y2), PDI (Y3) respectively.

Results of SMEDDS Tablet

As per the desired dependent variables two check point batches were proposed by the software. Now to get final formulation as tablet checkpoint batches formulation of liquid SMEDDS were used as wet part in wet granulation technique. The detailed tablet formulation of check point batches ASC1 and ASC2 has been given in table 10. The evaluation parameters of ASC1 and ASC2 are given in table 11. The dissolution profile as time vs. % drug release is shown in figure 7.

Figure 4: Contour plot of Y1

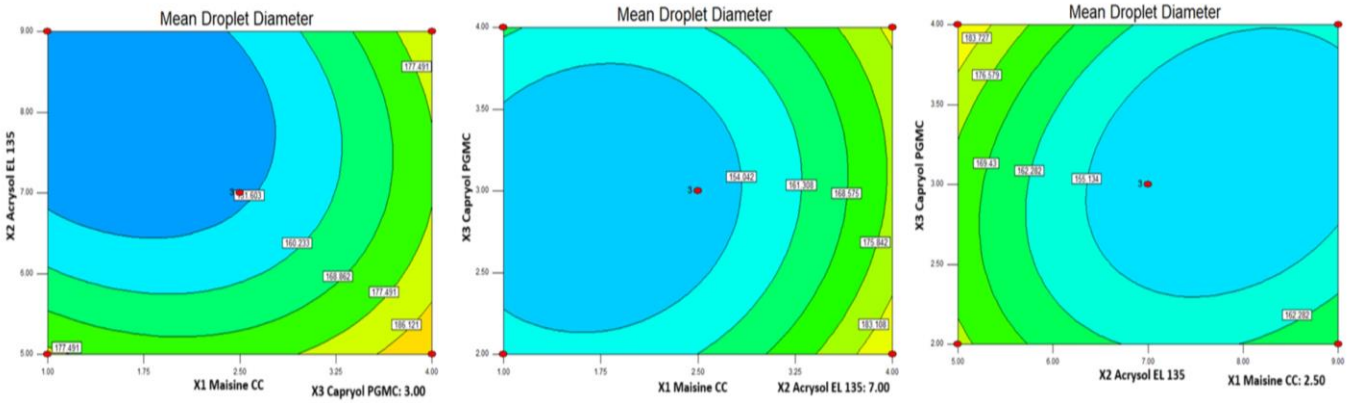


Figure 5: Contour plot of Y2

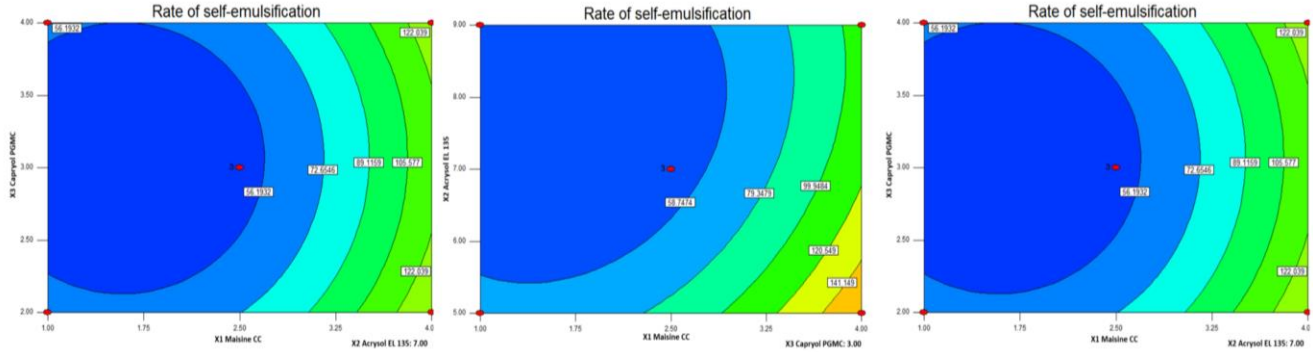


Figure 6: Contour plot of Y3

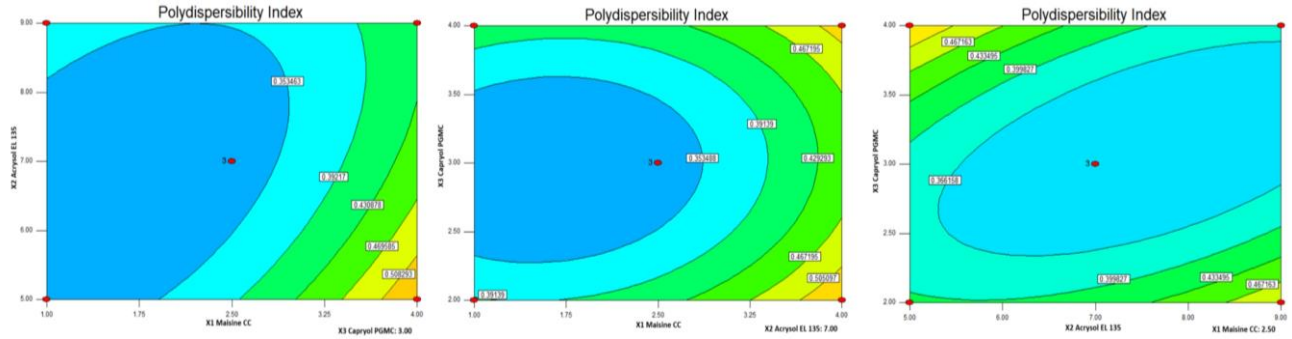


Table 10: Formulation of tablets

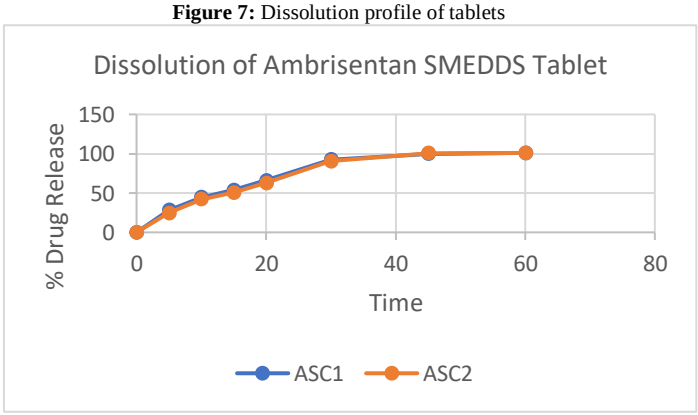
Ingredients	Batch	
	ASC1 (40)	ASC2 (40)
Maisine CC	1 ml (980 mg)	1.5 ml (1413 mg)
Acrysol EL 135	6.25 ml (6614.5 mg)	7.5 ml (7950 mg)
Capryol PGMC	2.25 ml (2260 mg)	2.75 ml (2750 mg)
Lactose	q. s.	q. s.
Starch	420 mg	640 mg
Magnesium stearate	70 mg	80 mg
Total weight of Batch	14400 mg	18000 mg
Total Weight per Tablet	360 mg	450 mg

Table 11: Evaluation parameters of tablets

Evaluation Parameters	ASC1	ASC2
Weight Variation (n=20)	359 ± 1.52 mg	449.5 ± 1.83 mg
Hardness (n=3)	5.7 ± 0.3 kg/cm^2	5.2 ± 0.8 kg/cm^2
% Friability (n=20)	0.28 ± 0.02	0.32 ± 0.04
Disintegration time (n=6)	4.88 ± 0.38 minutes	5.61 ± 0.17 minutes
Drug content (n=3)	4.96 ± 0.18 mg	4.92 ± 0.27 mg

As expected, the dissolution rate of the SMEDDS tablets was very fast (more than 80% within 30 min) at pH 5.0, indicating increased solubility of Ambrisentan. So, both ASC1 and AC2 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.

Figure 7: Dissolution profile of tablets



CONCLUSION

In this study of Ambrisentan, the properties of three independent variables of Ambrisentan loaded SMEDDS amount of Maisine® CC (X1), amount of Acrysol EL135® (X2) and amount of Capryol® PGMC (X3) on mean droplet diameter, rate of self-

emulsification and PDI were appraised by three-factor, three level BBD. The significant impact of partnership effects and quadratic effects of independent variables upon dependent variables was shown by BBD. The optimal formulation presents responses close to the predicted values. In-vitro drug dissolution studies showed quicker drug dissolution rate for the Ambrisentan SMEDDS tablet formulation as listed in marketed preparation. Both the optimized tablet formulation ASC1 and ASC2 gives desirable characteristics however as ASC1 has less quantity of surfactant and co-surfactant, it is superior choice for further studies. This study also signals that BBD can facilitate in-depth evaluation of the inherent correlation between the formulation variables and the desired responses, and the optimization of SMEDDS formulation for approach to quality by design. This study also shows that wet granulation technique shows optimum benefits in solidification of SMEDDS and convert into solid oral dosage form.

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