Nanotechnology Perceptions
ISSN 1660-6795
www.nano-*ntp.com*

Design And Development Of Azilsartan Medoxomil Solid Self Microemulsifying Drug Delivery System

Asha Praveen[1], Surendra Pratap Singh[1*], Sunil Kumar Shah[2], Jitendra Kumar Malik[1]

[1.] Faculty of Pharmacy, P K UniversityShivpuri (M.P.).
[2.] TIT College of Pharmacy, Bhopal, MP
*Corresponding Author**
Surendra Pratap Singh
Spspharma2001@gmail.com
Faculty of Pharmacy, P K University Shivpuri (M.P.).

Design and development of Azilsartan Medoxomil solid Self Microemulsifying drug delivery system. The selection of oil, surfactant and co-surfactant was carried out using screening study. AM is more soluble in castor oil, tween-20 and carbitol. The solubility was found to be 19.63±0.08 mg/ml, 80.56±0.125 mg/ml and 83.62±0.165 mg/ml in olive oil, tween- 80 and carbitol respectively. For the selection of the surfactant % oil solubilize in different surfactant and ease of emulsification study was carried out, in this study tween-20 highest 5.3% oil solubilize in castor oil and 9 no of flask inversion required for mix tween-20 with castor oil and % transmittance was found to be 93.2. According to that result tween 20 selected for the surfactant phase for further study. The co-surfactant selected according to the minimum amount of co-surfactant required to form clear solution and ease of emulsification, in this study the carbitol 130 (µl) required to form clear solution with castor oil and tween-20, 11 phase inversions required for mixing with castor oil and tween-20, % transmittance of that mixture 89.6 %, so carbitol was selected for the co surfactant phase. The pseudo ternary phase diagram was constructed using castor oil as oil phase, tween-20 as surfactant phase and carbitol as co-surfactant phase. For this the different three ratio 1:1, 1:2 and 2:1 surfactant and co-surfactant was selected. The different trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is 1:2 and 2:1 but stability properties are inferior at this ratio, so fixed the 1:1 ratio of surfactant and co-surfactant according to stability. The transparent emulsion was produce at the concentration of 80 mg of AM /1ml of SMEDDS formulation.

Keywords: Biopharmaceutical Classification System (BCS), Super critical fluid (SCF), Self emulsifying drug delivery systems (SEDDS**),** Azilsartan medoxomil (AM), PEG **.**

INTRODUCTION

Oral route is the easiest & most suitable way of noninvasive administration. Oral drug delivery systems being the most cost-effective have always lead the worldwide drug delivery market[1]. Conventional oral dosage forms for poorly water soluble drugs present the drug in a solid form to the gastrointestinal tract which means the drug has to dissolve in the GI fluids before it can be absorbed[2]. Thus, their rate & extent of absorption is largely dependent on the rate of dissolution. The formulation technique plays an important role in overcoming this shortcoming

of poorly water soluble drugs. According to the Biopharmaceutical Classification System (BCS) shown in Figure-1, drugs are classified on the basis of their solubility & permeability into four classes, two classes of drugs show poor aqueous solubility namely BCS II & BCS IV. BCS II drugs possess poor aqueous solubility but have good permeation properties. BCS class IV drugs are poorly water soluble & poorly permeable[3]. Developing a formulation for a class IV drug is nearly impossible unless the dose necessary is very small[5]. Most of the times, such drugs are withdrawn at its lead optimization stage of drug discovery & reworked to improve its physico-chemical properties. Developing a formulation for a drug belonging to BCS II is often challenging as it requires improved dissolution characteristics. Popular formulation techniques used for delivering a poorly water soluble drug include. pH adjustment[4], Micro-emulsion, Self-emulsifying drug delivery systems, Manipulation of solid state, Particle size reduction, Super critical fluid (SCF) process, Inclusion complexes/complexation, Co-solvency, Miceller solubilization, Hydrotrophy, Solid Dispersions, Nano-suspension, Floating Granules, Cryogenic techniques, Nano-crystallization.

In recent years, much attention has turned to lipid-based formulations with the aim of improving the oral bioavailability of poorly water soluble drugs. Lipid-based formulations encompass a diverse group of formulations, very different in physical appearance, ranging from a simple tri-glyceride vehicle to more sophisticated formulations such as Self emulsifying drug delivery systems (SEDDS)[5].

MATERIAL AND METHOD

Fourier transforms infrared spectroscopic studies (FTIR)

FTIR spectra for drug alone and with excipients were performed using a FTIR spectrophotometer with KBR pellets to study drug-excipients and excipient-excipient compatibility. Drug excipient interaction was analysed by performing infrared spectroscopy using FTIR (Bruker, Mumbai).

The FTIR studies were carried out by the pressed pellet technique using a KBr press in which the KBr was taken and kept in a hot air oven for two hours for the discard any moisture. The above dried KBr was taken for the preparation of pellets of drug, and the selected formulations. The pellet was prepared by taking drug: KBr in 1: 100 ratios. The prepared pellet was placed in the sample holder and kept in the instrument to confirmation the FTIR peaks[6].

Analytical Method development

Method was performed by UV Spectrophotometer.

Determination of λ_{max}

The Standard drug solution concentration of 10 µg/ml was preparing following media**,**

- ✓ Methanol
- ✓ 0.1 N HCl

The Solution was scanned in UV visible spectrophotometer in wavelength 200-400 nm. From this scan, the peak of maximum absorbance as identified (λ_{max}) in each media and used for further analysis

Standard calibration curve of Azilsartan medoxomil (AM) in various solvents

Preparation of Standard calibration Curve for AM in Methanol[7]

Weighed precisely 10 mg of Azilsartan medoxomil and placed in 100 ml of volumetric flask and volume was made up to the mark with methanol. Aliquots were taken from prepared stock solution and were appropriately diluted to prepare 2, 4, 6, 8…. 18 µg/ml and then absorbance were taken at 257 nm, keeping methanol as a blank solution.

Preparation of Standard Curve for AM in 0.1 N HCl

Weighed accurately 10 mg of Azilsartan medoxomil and placed in 100 ml of volumetric flask and volume was made up to the spot with 0.1 N HCl. Aliquots were taken from prepared stock solution and were appropriately diluted to prepare 5, 10, 15, …. 40µg/ml and then absorbance were taken at 257 nm, keep 0.1 N HCl as blank solution.

Screening study

Solubility of drug in the various oils, surfactants and co-surfactants

Screening of excipients can be done by determining the equilibrium solubility of Azilsartan medoxomil in different oils, surfactants and co-surfactants[8]. Excessive amount of Azilsartan medoxomil was added to 2 ml of each excipients. Both components were mixed in a vial for 5 min using vortex mixer (REMI, Mumbai, India). The mixtures in vials were shaken at 25 ±1.0ºC for 72 hour using controlled temperature mechanical shaker. The mixtures centrifuged using R-4C DX Laboratory Centrifuge (REMI, Mumbai, India) at 8000 rpm for 25 minutes at 25 ±1.0ºC. The supernatant was filtered through membrane filter by using 0.45 μmfilter disk. Filtered solution was appropriately diluted by methanol, and UV absorbance was measured at 257 nm. Concentration of dissolved drug was determined by using standard equation.

Screening of Oils

The oils in which the solubility of drug was more were selected for further study.

Screening of Surfactants

Surfactants were selected based on the following criteria.

Based on ability to solubilize the drug

The surfactant which could solubilized highest amount of AM was considered.

Based on % oil solubilize in different surfactants

Surfactants were screened as per their ability to from microemulsion, like Tween 20, Tween 80, Cremophor EL, Captex 355, Labrafac PG. on behalf of this surfactant solution was prepared in concentration like 15% wt/v. 2.5 ml of this solution was taken and 4 µl of oil was added with vigorous vortexing. If a one-phase clear solution was obtained, the addition of oil was repeated until the solution became like cloudy[9].

Based on ease of emulsification

Different surfactants were screened for emulsification capability of the selected oil phase. Surfactant selection was performed on the basis of % transparency and ease of emulsification. In brief, 300 µl of the surfactant was added to 300 µl of selected oil phase. The mixture was gently heated at 50^0 c for homogenization of the components. 50 µl of the mixture was diluated with distilled water to 50 ml in a to volumetric flask. Ease of emulsification was evaluator by the number of flask inversions required to yield a homogenous emulsion[10]. The emulsion was allowed to stand for 2 hours and their % transparency or transmittance was determined at

650 nm by a double-beam UV spectrometer using distilled water as a blank. The emulsion was further more observed visually for any turbidity and phase separation[11].

Screening of Co-surfactants

The co-surfactants namely, PEG-400, Transcutol, Propylene Glycol, Carbitol were subjected to the following mentioned tests and the best co-surfactant which satisfied all the criteria was selected.

Based on solubility of drug

The co-surfactant which could solubilize highest amount of AM was considered.

Based on ability to form clear solution

The co-surfactant was added to get more efficient self-micro emulsion systems. The screening of the co-surfactant was performed as follows. After mixing 80 µl of surfactant with 200 µl oil phase, the surfactant/oil mixture was diluated to 400 µl by using distilled water. 20 µl of the once mentioned resultant solution was titrated with increasing amount of co-surfactant until the system turned clear and the amount of co-surfactant used was recorded as a minimum amount[12].

Based on ease of emulsification

Different co-surfactants were screened for emulsification ability of the selected oil phase and surfactant. Co-surfactant selection easy performed on the basis of % transparency & ease of emulsification. The procedures carried out are as follows .

Briefly, 200 µl of the surfactant was added in to 100 µl of each co-surfactant. Then 300 µl of selected oil phase was added to the mixture. The mixture was smoothly heated at 50^0 c for homogenization of the components[13]. 50 µl of the mixture was diluated with distilled water to 50 ml in volumetric flask. Ease of emulsification was judged by the number of flask inversions required to yield to become homogenous emulsion. The emulsion was allowed to stand for 2 hours and their % transparency or transmittance was evaluated at 650 nm by a double-beam UV spectrometer using distilled water as a blank. The emulsions were furthermore observed visually for any turbidity and phase separation[14].

Construction of pseudo ternary phase diagram

Surfactant (Tween 20) and co-surfactant (Carbitol) were mixed (Smix) in special volume ratios (1:1, 2:1, 1:2). For each phase diagram, oil (Castor oil) and specific surfactant/co-surfactant (Smix) ratio were mixed thoroughly with different volume ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different glass vials. Pseudo ternary phase diagrams were developed using the aqueous titration method. Slow titration with the aqueous phase was performed for each mixture of oil and Smix individually. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% time intervals[15]. The calculation for the addition with aqueous phase was done by calculating the % of each component of the microemulsion present at each 5% addition. The advantage of this system is that the scale-up of the proportions is easy, as the system is thermodynamically stable. After each 5% addition of the aqueous phase to the oil: Smix mixture, visual observation was made and recorded. Through visual observation, the following categories were assigned: (1) Transparent and make flowable: Oil/water microemulsions; (2) Transparent gel: Microemulsion gel; (3) Milky or cloudy: Emulsion; (4) Milky gel: Emulgel.

In a similar, calculations for the other ratios of oil and S mix were also done. For each Smix ratio, a separate phase diagram was constructed, and for each phase diagram visual observations were recorded. The pseudo ternary phase diagram Figure-6.3was constructed by using CHEMIX software based on the visual observations noted[16].

Effect of drug on phase diagram

The experiment was carried out to investigate the effects of AM on the SMEDDS. The formulation amount of AM was added to the boundary formulations of the self microemulsifying domain of ternary phase diagrams. The self-microemulsifying system performance was visually assessed after infinite dilution using purified water.

Formulation Development

Optimization of Formulation Variables:

Mainly 3 formulation variable that effect on self-microemulsifying properties and solubility[17]. Concentration of oil, surfactant and co-surfactant were taken as critical formulation variables have major impact on the self-emulsification and solubility of drug. Quantitative aspects of the effects and relationships among various formulation parameters affecting solubility of drug are investigated using response surface (RSM). To revision this, we performed, "Box Behnken Design" (BBD) used for optimization of formulation parameters known to affect their result. The BBD is a popular for RSM because it requires only two-levels of each and every process factor and only a fraction of all the possible combinations[18].

In this design, the experimental region is assumed to be a cube, and experiments are performed at points corresponding to midpoint of each edge and replicated experiments at the center of this multidimensional dice.

This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models. The complete design consisted of 17 experimental run that included 12 single run and 5 replications run at the center point.

The Design Expert (Version 9, State Ease Inc., USA) program was used for design of experiment and analysis of this second-order model & for drawing of three dimensional response surface and contour plots. Table shows dependent and independent variables of BBD and table matrix of BBD of formulation variables[19].

Table: Dependent and independent variables of BBD:

Independent variable	Variable level	
	Low (-1)	**High (+1)**
Oil (ml) A	1	9
Surfactant (ml) B	0.5	4.5
Co-surfactant (ml) C	0.5	4.5

Dependent variables	Self-Emulsification Time (Sec) % Transmittance (%) % cumulative Drug Release (%)

Preparation of liquid SMEDDS

A series of SMEDDS formulations were prepared by oil (Castor oil), Surfactant Tween 20) and Co-surfactant (Carbitol) as shown in Table 5.5. In all the formulations, the level of Azilsartan medoxomil (AM) was set aside constant (i.e. 20 mg). The amount of SMEDDS should be such that it should solubilize the drug (single dose) completely [104]. The Azilsartan medoxomil (20 mg) was added in the mixture. Next the components were mixed by gentle stirring and mixing, and heated at 40˚C.The mixture was stored at room temperature until used. So, prepared SMEDDS was the concentrate of oil, surfactant, co-surfactant and drug[20].

Table: Matrix of Box-Behnken Design for formulation parameters

S. No	Std.	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)
1	8	1	AMB1	9	2.5	4.5
2	17	2	AMB2	5	2.5	2.5
3	16	3	AMB3	5	2.5	2.5
4	10	4	AMB4	5	4.5	0.5
5	15	5	AMB5	5	2.5	2.5
6	1	6	AMB6	1	0.5	2.5
7	3	7	AMB7	1	4.5	2.5
8	13	8	AMB8	5	2.5	2.5
9	9	9	AMB9	5	0.5	0.5
10	4	10	AMB10	9	4.5	2.5
11	6	11	AMB11	9	2.5	0.5
12	7	12	AMB12	1	2.5	4.5
13	2	13	AMB13	9	0.5	2.5
14	14	14	AMB14	5	2.5	2.5
15	12	15	AMB15	5	4.5	4.5
16	5	16	AMB16	1	2.5	0.5
17	11	17	AMB17	5	0.5	4.5

Evaluation of liquid SMEDDS formulation

Dispersibility Test

The dispersibility test of SMEDDS is carried out to evaluate its capability to disperse into emulsion and the size of resulting globules to categorize them as SMEDDS. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). 1 ml of every formulation is added to 500 ml of water at 37 ± 0.5 ºC and the paddle is rotated at 50 rpm[21]. Then titration

with water the SMEDDS formulation forms a mixture or gel which is of different type depending upon which the in vitro performance of formulation can be assessed.

Robustness on dilution

Robustness to dilution was conducted by diluting liquid SMEDDS formulation, 100 and 1000 times with various media like distilled water and 0.1 N HCl and verify out any phase separations or precipitation of drug even after 12 hrs of storage space, that formulation is considered as robust to dilution[22].

Emulsification time

The emulsification time was monitored by visually analyze the disappearance of SMEDDS and the final appearance of the microemulsion in triplicate. A visual test to evaluate the self-emulsification properties of SMEDDS formulation was performed by visual evaluation as previously reported. In this method, a predetermined volume of formulation 1 ml was introduced into 300 ml of water in a glass beaker that was maintained at 37^{o}C, and the contents mixed gently using a magnetic stirrer. The time to emulsify spontaneously and progress of emulsion droplets were observed.

Percentage Transmittance

The % transmittance of the liquid SMEDDS after the 100 times dilution with distilled water measured at 650 nm using UV visible double beam spectrophotometer keeping water as with blank Solution[23].

Drug Content

AM from SMEDDS formulation was extracted in methanol using sonication method. The solutions were filtered, using Whatman paper. The methanolic extract was analyzed for the AM content spectrophotometrically (UV-1800, Shimadzu, Japan) at 257 nm using standard curve.

In-vitro Dissolution Study

The quantitative in vitro dissolution studies are carried out to by dialysis bag method. The SMEDDS formulation was instilled in Dialysis beg equal to 20 mg AM and one end was tied with thread and was placed in 900 ml of 0.1 N HCL as dissolution medium at 37±0.5˚C. The revolt speed of paddle was maintained at a rate of 100 rpm. Samples (5ml) were withdrawn at regular time intervals (0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 min.) and aliquot amount of 0.1 N HCL was replaced. The samples were analyzed for the drug content using UV spectroscopic method at 257nm

Thermodynamic stability studies

The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can direct to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. as well the incompatibilities between formulation & gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies[24].

- **Heating cooling cycle:** - Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with coverage at each temperature

for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.

- **Centrifugation:-** Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. That formulation that doesn't confirm any phase separation is taken for the freeze thaw stress test.
- **Freeze thaw stress cycle:-** Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours. Those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispensability test for assessment of self-emulsification efficiency[25].

Viscosity

The viscosities were measured to determine rheological properties of formulations. Brookfield DV-11+ Pro viscometer at 30˚C with a 62 spindle at 5 rpm was used to serve this purpose

Globule size measurement

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The emulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette and the globule size of the emulsion was determined via a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90°at 25°C.

Poly Disparity Index (PDI):

PDI value from 0.0 to 0.5 indicates that the uniformity of oil globules is more. So emulsion is more uniform. Poly disparity index was determined by Malvern ZetasizerNS90.

Zeta Potential:

Zeta potential was determined by Malvern Zetasizer. Zeta potential shows an electric charge there on the oil globule. Since zeta potential we can conclude that whether emulsion is stable or not. If zeta potential is not reliable then separation occurs in emulsion[26].

Preparation of Solid Self Microemulsifying Drug Delivery System

The Solid-SMEDDS prepared with lyophilization technique. Mannitol used as the cryoprotectant. Mannitol used in different ratio by means of liquid SMEDDS to optimize the formulation. The 1%, 1.5%, 2% & 2.5% w/v Mannitol (1, 1.5, 2 and 2.5 gm mannitol/ 100 ml liquid SMEDDS) mixed in liquid SMEDDS. The mixture was solidified in lyophilizer at -50 ^{0}C, and Lyophilization was performed at -75°C temperature and 50 mm-Hg vaccum pressure. Prepared lyophilized powder was evaluated[27]

Evaluation of Solid SMEDDS Formulation

Characterization of Solid SMEDDS Formulation

Drug Content

Required quantity of freeze dried powder equivalent to 20 mg of Azilsartan medoxomil (AM) was diluted by using Methanol up to 100 ml. Withdraw 1 ml of above solution and again diluted up to 10 ml with methanol and measured the absorbance at 257 nm using UV spectrophotometer[28].

Zeta Potential

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. From zeta potential we can conclude that whether emulsion is stable or not. If zeta potential is not reliable then separation occurs in emulsion..

Globule Size

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The emulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette & the globule size of the emulsion was determined via a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90°at 25°C.

Poly Dispersity Index

PDI value from 0.0 to 0.5 indicates that the uniformity of oil globules is more. So emulsion is more consistent. Poly dispersity index was determined by Malvern Zetasizer NS90.

Self-emulsification time of powder

It was measured by added a water slowly in self-emulsified freeze dried powder and measure the time (sec) until the emulsion was formed.

In-Vitro Dissolution Study

In vitro drug release studies from Solid SMEDDS were performed by means of USP Type I dissolution apparatus with number of paddle rotations set to 50 rpm. The dissolution medium consisted of 900 ml of 0.1N HCL maintained at 37 ±0.5°C. The freeze dried powder containing 20 mg of Azilsartan medoxomil put it in capsule and it was introduced into the dissolution medium[29].

At predetermined time intervals 5ml of aliquot was withdrawn, filtered using 0.45µm syringe filter and an equivalent volume of fresh dissolution medium was immediately added. An amount of drug released was estimated by measuring absorbance @ 257 nm using a UV spectrophotometer. The dissolution reading was carried out with similar procedure as mentioned above for plain drug and marketed tablet with aim of comparison study[30].

RESULT AND DISCUSSION

Fourier Transform Infrared spectroscopic studies (FTIR):

FTIR study was done for the identification of the drug and excipients and to study drug - excipients and excipients - excipients compatibility. FTIR spectra of drug and final freeze dried powder mixture are shown in figure 3 and 4 respectively. The spectral elucidations for drug alone and with freeze dried powder mixture are shown in table 1.

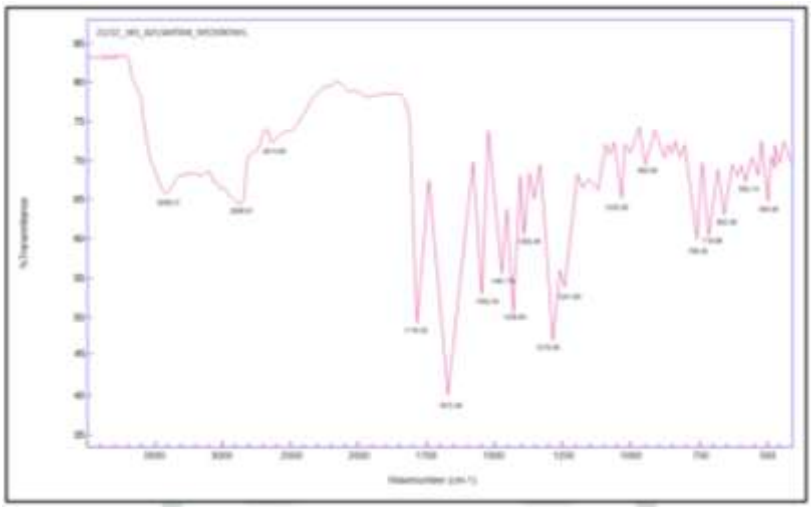


Figure 1: FTIR Spectra of Azilsartan Medoxomil (AM)

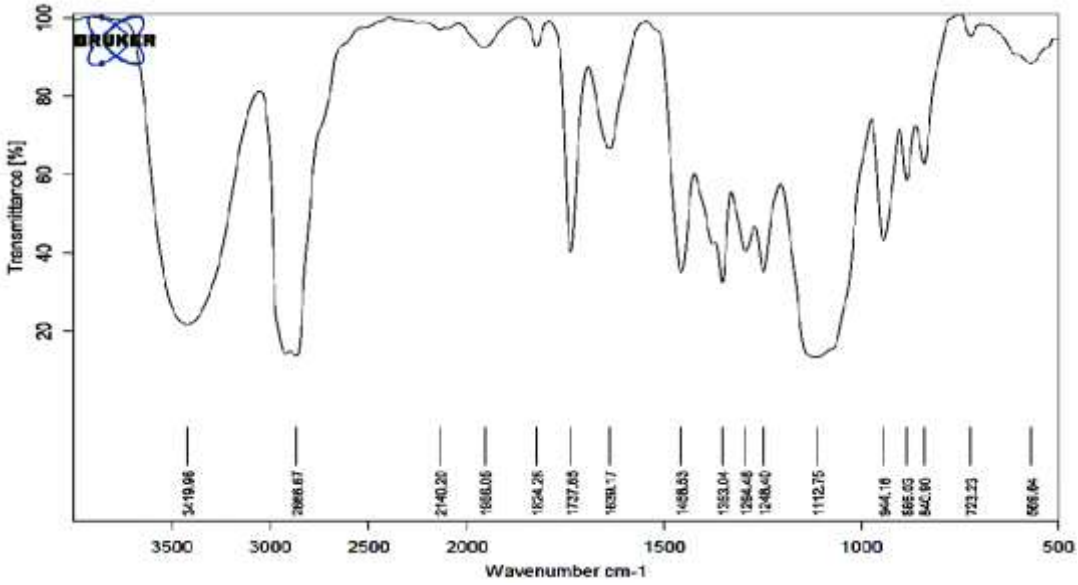


Figure 2: FTIR Spectra of Final freeze dried powder of AM

Table 1: FTIR peaks

Principle Peaks(cm-1)	Functional group stretching	Wave number (cm^{-1})	freeze dried powder of Azilsartan Medoxomil (AM) Wave number (cm^{-1})

	C=O stretching (carboxyl group)	1776.3	2866
	C–O stretching	1280.7, 1309	1458 and 1639
	C–O–C stretching	1083.9	1737
	N–H bending (amine group)	1467	1112
	C–H bending (out-of-plane)	761.8	1294
	C=N stretching	1691.5	3419
	C-H Aromatic	761.8	

Frequencies of principle peaks in FTIR spectra of physical mixture of drug with other excipients were nearly similar to the frequency of principle peaks present in FTIR spectra of pure drug[31]. So, these results revealed that the drug was compatible with excipients and neither drug decomposition nor drug-excipients and excipients-excipients interactions occurred in the formulation.

Analytical Method Development:
Determination of λ_{max}

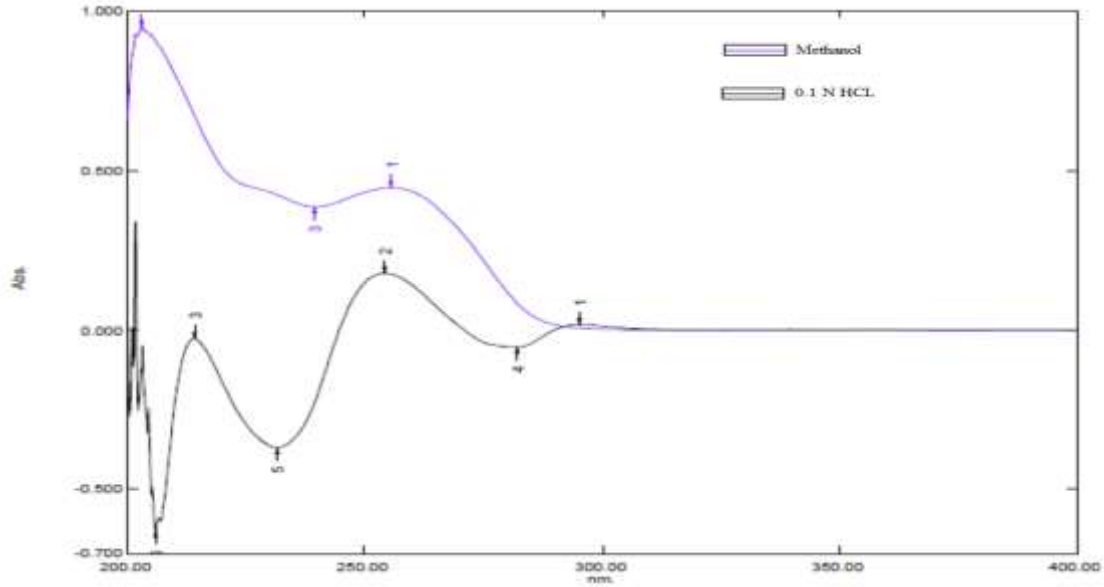


Figure 3: Overlay spectra

The standard drug solution of 10 µg/ml concentration was scanned in UV visible in the range of 200-400 nm. From this scanned spectra, the peak of maximum absorbance was identified (λ_{max}) at m 239-259 nm in both methanol and 0.1 N HCl media.

Calibration curve of Azilsartan Medoxomil in methanol

A standard curve of Almesartan Medoxomil(AM) in methanol was analyzed in the range of 2-18 µg/ml. The selected range of AM was found to be linear. A regression coefficient (R^2) at 248 nm was found to be 0.996.

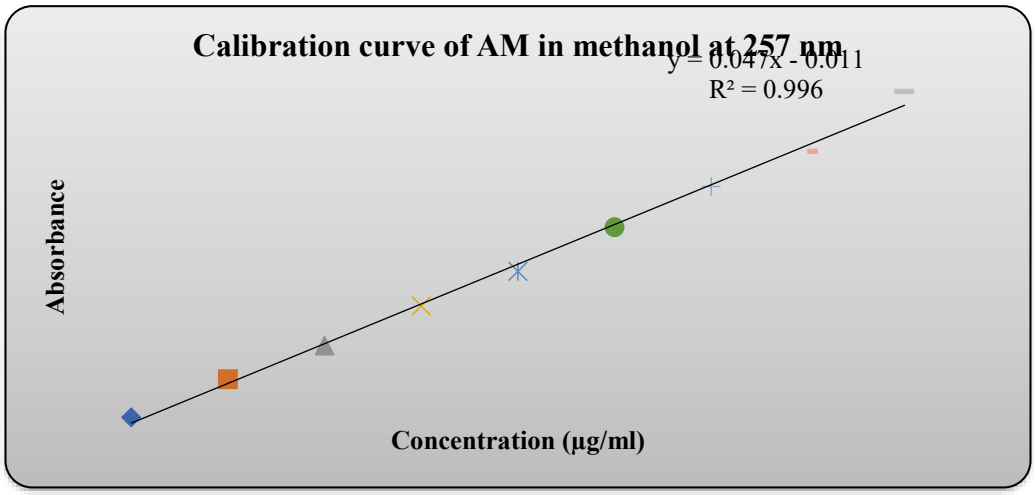


Figure 4: Calibration curve of Azilsartan medoxomil in methanol

Calibration curve of Azilsartan medoxomil in 0.1 N HCL

A standard curve of Azilsartan medoxomil in 0.1 N HCL was analyzed in the range of 5-40 µg/ml. The selected range of AM was found to be linear. A regression coefficient (R^2) at 248 nm was found to be 0.999.

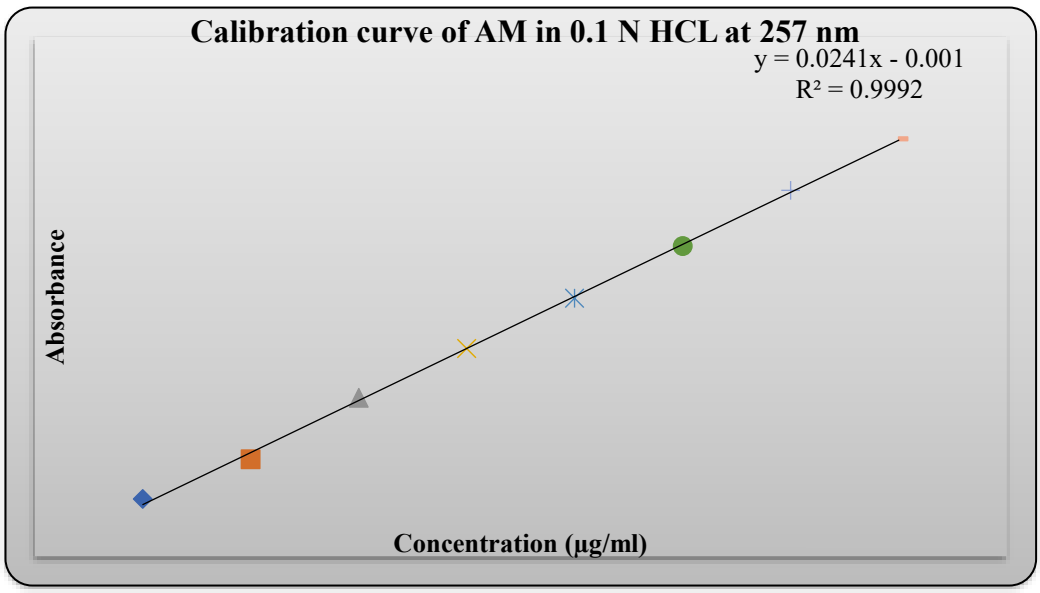


Figure 5: Calibration curve of Azilsartan medoxomil in 0.1 N HCL

Standard curves of Azilsartan medoxomil in methanol and 0.1 N HCL were analyzed in the range of 2-18 µg/ml and 5-40 µg/ml respectively. The selected range of AM was found to be linear. Regression co-efficient at 248 nm were found to be 0.996 and 0.999 respectively[32]. Regression co-efficient for the drug in methanol and in 0.1 N HCL was found to be near to one and in the linearity range. This standard concentration method obeys Beers law and found to be suitable for the determination of drug content and In vitro drug release study.

Screening Study

Screening study was performed for selection of oil, surfactant and co-surfactant for development of formulation by preparing saturated solution of drug in oil, surfactant and co-surfactant[33].

Screening of Oils (Based on solubility of drug)

Table 6: Solubility study in different oils

Sr No	Oils	Solubility (mg/ml)
1	Castor Oil	19.23±0.08
2	Olive Oil	12.37±0.28
3	Oleic Acid	8.45±0.24
4	Labrafil M 1944	7.84±0.23
5	Labrafac CC	9.54±0.21

*Mean ± SD, n=3

The solubility of the drug was tested in different oils phases and maximum solubility was determined in castor oil 19.63±0.08 mg/ml and was selected as oily phase for SMEDDS formulation.

Screening of Surfactants (Based on solubility of drug)

Table 7: Solubility study in different Surfactants

S. No	Surfactants	Solubility (mg/ml)
1	Tween 20	80.56±0.125
2	Tween 80	34.62±0.202
3	Cremophor EL	38.60±0.259
4	Labrafac PG	41.61±0.271
5	Captex 355	27.52±0.231

*Mean ± SD, n=3

The solubility of the drug was tested in different surfactants phases and maximum solubility was determined in tween 20 is 80.56±0.125 mg/ml and was selected as surfactant phase for SMEDDS formulation.

Based on % oil solubilize in different surfactants

Table 8: % oil solubilize in different surfactants

S.No.	Surfactants	% oil solubilize
1	Tween 20	5.4%
2	Tween 80	2.3%
3	Cremophor EL	3.3%
4	Labrafac PG	1.5%
5	Captex 355	1.3%

*Mean ± SD, n=3

Results inferred that the oily phase Castor oil exhibited the highest 5.3% solubilize with Tween 20. The mentioned results suggested the use of Castor oil as an oily phase with Tween 20 as a surfactant for further study

Based on ease of emulsification

Table 9: Number of flask inversion and % transmittance oil and different surfactant combination

S. No.	Surfactants	No. of flask inversions	% Transmittance at 650 nm
1	Tween 20	8	93.1
2	Tween 80	13	86.6
3	Cremophor EL	17	63
4	Labrafac PG	23	34.8
5	Captex 355	22	26

Results inferred that the oily phase Castor oil exhibited the highest emulsification efficiency with Tween 20 for the homogenous emulsion formation. On the other hand, Castor oil showed poor emulsification properties with other surfactants employed, requiring a higher number of flask inversions. The aforementioned results suggested the use of Castor oil as an oily phase with Tween 20 as a surfactant for further study.

Screening of Co-surfactants

Based on solubility of drug

Table 10: Solubility study in different Co-surfactants

S. No	Co-surfactants	Solubility (mg/ml)
1	PEG-400	42.60±0.31

2	Transcutol	73.55±0.23
3	Propylene Glycol	12.73±0.63
4	Carbitol	82.63±0.16

*Mean ± SD, n=3

The solubility of the drug was tested in different Co-surfactants phases and maximum solubility was determined in Carbitol is 83.62±0.165 mg/ml and was selected as Co-surfactant phase for SMEDDS formulation.

Based on ability to form clear solution

Table 11: Minimum amount of co-surfactant required to form clear solution

S. No.	Co-surfactants	Minimum co-surfactant required for clear solution (µl)
1	PEG-400	150
2	Transcutol	117
3	Propylene Glycol	140
4	Carbitol	104

Results inferred that the co-surfactant phase Carbitol exhibited the minimum amount of co-surfactant required to form clear solution with castor oil as oily phase and tween 20 as a surfactant phase in combination. The mentioned results suggested the use of Carbitol as a Co-surfactant phase with Castor oil as an oil and Tween 20 as a surfactant for further study

Based on ease of emulsification

Table 12: Number of flask inversion and % transmittance oil, surfactant and different co-surfactant combination

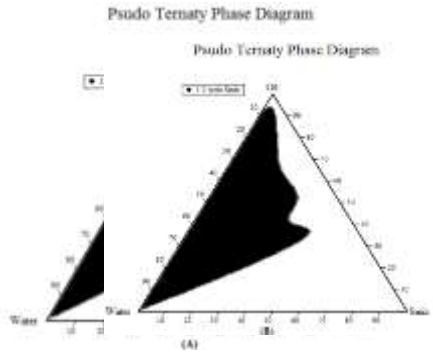
S. No	Co-surfactants	No. of phase inversions	% Transmittance at 650 nm
1	PEG-400	24	31.5
2	Transcutol	14	76.8
3	Propylene Glycol	27	64.4
4	Carbitol	11	88.5

Results inferred that the oily phase Castor oil and surfactant phase Tween 20 exhibited the highest emulsification efficiency with Carbitol as co-surfactant for the homogenous emulsion formation. On the other hand, Castor oil and Tween 20 showed poor emulsification properties with other co-surfactants employed, requiring a higher number of flask inversions. The aforementioned results suggested the use of Castor oil as an oily phase and Tween 20 as a surfactant with Carbitol as a co-surfactant phase for further study[33].

Construction of pseudo ternary phase diagram

Constructing phase diagrams is time consuming, particularly when the aim is to accurately delineate a phase boundary. Care was taken to ensure that observations are not made on metastable systems, although the free energy required to form a microemulsion is very low, the formation is thermodynamically spontaneous. The relationship between the phase behavior of a mixture and its composition can be captured with the aid of a phase diagram. Castor oil (oil), Tween 20 (surfactants) and Carbitol (co-surfactant) were put in different groups based on the ratio of surfactant to co-surfactant (1:1, 1:2, 2:1) under test to study the phase diagrams in detail[34].

From the trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is higher than 1:2 but stability properties are inferior at this ratio. Fixing the surfactant/co-surfactant ratio at 1:1 is a better choice from the stability point of view.



(A)

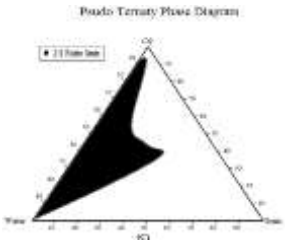


Figure 6: (A) Surfactant/co-surfactant 1:1, (B) surfactant/co-surfactant 1:2 and (C) surfactant/co-surfactant 2:1. Pseudo ternary phase diagram of the system, Castor oil, Tween 20: Carbitol, and water

Effect of drug on phase diagram

Effect of drug on the phase diagram is shown in table 13. The drug was incorporated in the formulation gradually and the emulsion was visually assessed. The results concluded that the transparent emulsion was produce at the concentration of 80 mg of AM/1ml of SMEDDS formulation. After 80 mg precipitation of AM occurs. So, results show that 80mg of AM loaded in 1ml of SMEDDS formulation.

Table 13: Effect of Drug on Phase Diagram

Amount of drug	Visual inspection
10mg	Transparent
20mg	Transparent
30mg	Transparent
40mg	Transparent
50mg	Transparent
60mg	Transparent
70mg	Transparent
80mg	Transparent
90mg	Precipitation
100mg	Precipitation

Formulation Development
Optimization of Formulation variables:

Mainly 3 formulations variables that affect on self-microemulsifying properties and solubility.

1. Concentration of oil
2. Concentration of surfactant
3. Concentration of Co-surfactant

All the batches were analyzed using the Design Expert 9 software. Box Behnken statistical design with 3 factors, 2 levels was prepared by Design expert 9 with 5 center point and 17 runs was selected for the optimization study. The optimization design consists of a set of points lying at the midpoint of each edge.

Optimization of oil, surfactant and Co-surfactant concentration:
Matrix of Box-Behnken Design for formulation parameters and its evaluation:
For optimization of formulation parameters such as concentration of oil, surfactant and co-surfactant was carried out by evaluating emulsification time, % transmittance and % cumulative drug release. Matrix of Box-Behnken Design for formulation parameters and its evaluation[35].

Table 14: Matrix of Box-Behnken Design for formulation and its evaluation

Sr No	Std	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)	Emulsification time (Sec)	% Transmittance (%)	% CDR (%)
1	8	1	AMB 1	9	2.5	4.5	46±5.28	80.96±1.76	92.1±0.028
2	17	2	AMB 2	5	2.5	2.5	64±42	74.82±1.07	68.52±0.024

3	16	3	AMB 3	5	2.5	2.5	65±5.55	75.82±1.26	66.16±0. 021
4	10	4	AMB 4	5	4.5	0.5	86±2.60	59.15±0.90	52.35±0. 022
5	15	5	AMB 5	5	2.5	2.5	63±2.60	74.83±1.07	69.74±0. 026
6	1	6	AMB 6	1	0.5	2.5	50±3.35	88.12±0.76	80.6±0.0 29
7	3	7	AMB 7	1	4.5	2.5	37±3.65	91.27±0.99	86.41±0. 032
8	13	8	AMB 8	5	2.5	2.5	64±44	75±1.11	69.52±0. 026
9	9	9	AMB 9	5	0.5	0.5	90±42	43.05±0.79	50.1±0.0 26
1 0	4	10	AMB 10	9	4.5	2.5	67±2.54	62.9±0.88	63.35±0. 018
1 1	6	11	AMB 11	9	2.5	0.5	112±2.60	32.06±0.51	44.08±0. 028
1 2	7	12	AMB 12	1	2.5	4.5	18±2.64	99.07±0.23	99.53±0. 015
1 3	2	13	AMB 13	9	0.5	2.5	83±2	51.48±0.47	68.82±0. 030
1 4	14	14	AMB 14	5	2.5	2.5	64±2.64	76.83±1.07	70.58±0. 028
1 5	12	15	AMB 15	5	4.5	4.5	23±2.64	95.35±0.77	96.62±0. 011
1 6	5	16	AMB 16	1	2.5	0.5	73±3.50	64.13±0.74	61.10±0. 028
1 7	11	17	AMB 17	5	0.4	4.4	38±3.62	90.8±1.82	94.35±0. 028

Statistical Analysis:

For optimization Box-Behnken design was employed to study the effect of independent variables (i) oil (ml) (A), (ii) surfactant (ml) (B) and (iii) co-surfactant (ml) (C) on dependent variable (Y1) emulsification time, (Y2) % transmittance and (Y3) % cumulative drug release. All the batches were prepared according to the design. All the batches were analyzed using the design expert 9 software. The software itself suggests Quadratic Model and also gave model equation for dependent variables. The ANOVA of emulsification time, % transmittance and % cumulative drug release.

Response 1 – Emulsification Time

Emulsification time from the batch AMB1 to AMB17 of emulsion varied from 18±2.64 sec to 112±3.60 sec. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect (P<0.05) on emulsification time.

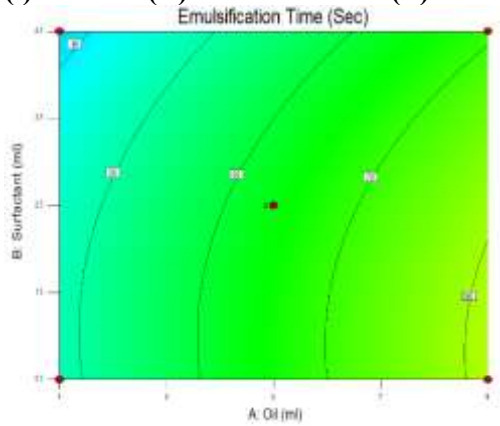
Polynomial Equation for Emulsification Time:

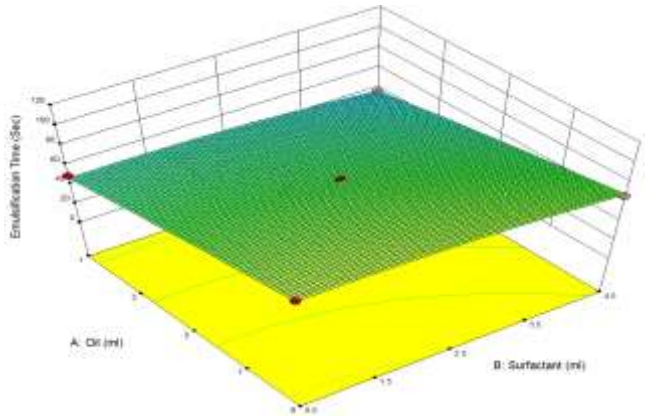
Emulsification time = +63.80 + 16.25 × A - 5.75 × B - 29.25 × C - 0.50 × AB - 3.00 × AC - 2.50 × BC -1.15 × A^2 - 3.65 × AMB2- 0.65 × C^2

Table 15: ANOVA of Emulsification Time

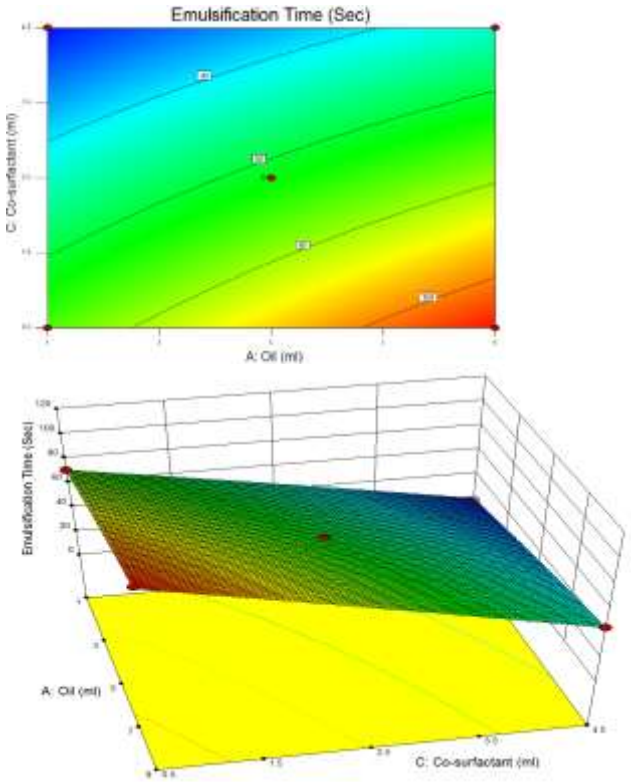
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	9350.75	9	1038.96	299.24	<0.0001	Significant
Lack of Fit	21.54	3	7.15	10.25	0.0229	Significant
Pure Error	2.70	4	0.70	-	-	
Cor Total	9375.05	16	-	-	-	
R-Squared		**0.9975**				
Adj R-Squared		**0.9942**				
Pred R-Squared		**0.9627**				

(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and co-surfactant (C)



(iii) Surfactant (B) and Co-surfactant (C)

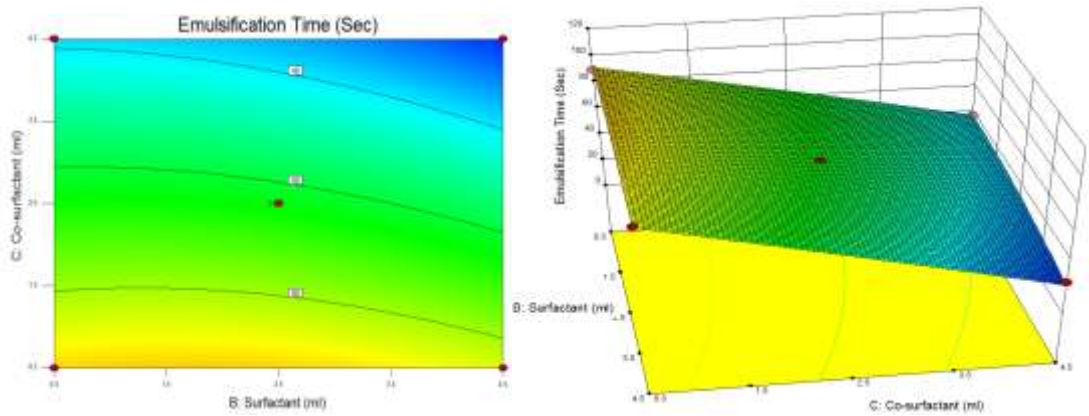


Figure 7: Contour plot and Response surface of emulsification time (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Transmittance

% Transmittance from the batch AMB1 to AMB17 of emulsion varied from 32.06±0.51 % to 99.08±0.23 %. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect ($P<0.05$) on % transmittance.

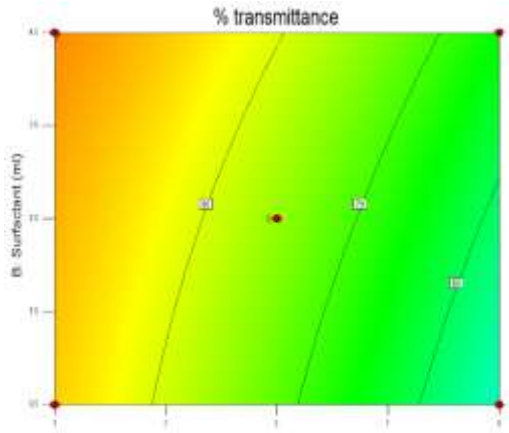
Polynomial Equation for % Transmittance:

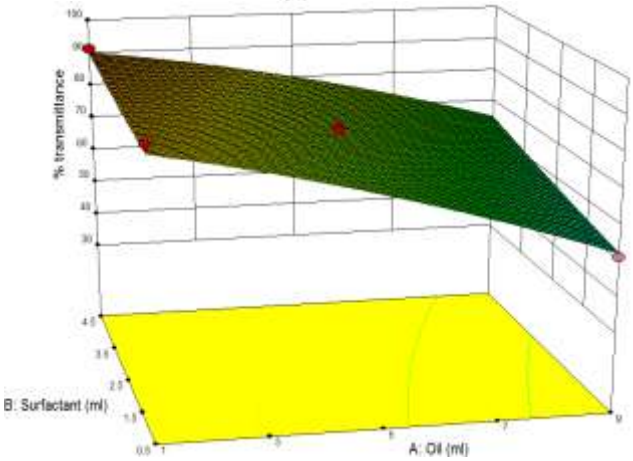
% Transmittance = $+75.25 - 14.40 \times A + 4.40 \times B + 20.98 \times C + 2.07 \times AB + 3.49 \times AC - 2.89 \times BC - 2.52 \times A^2 + 0.51 \times AMB2 - 3.87 \times C^2$

Table 16: ANOVA of % Transmittance

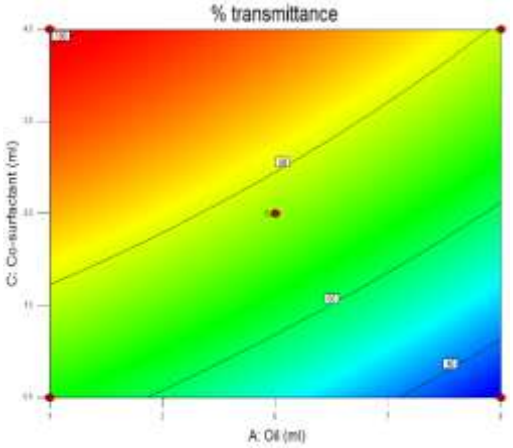
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	5527.29	9	614.15	122.52	< 0.0001	Significant
Lack of Fit	32.10	3	10.72	14.28	0.0132	Significant
Pure Error	3.00	4	0.75	-	-	
Cor Total	5562.38	16	-	-	-	
R-Squared		**0.9936**				
Adj R-Squared		**0.9855**				
Pred R-Squared		**0.9067**				

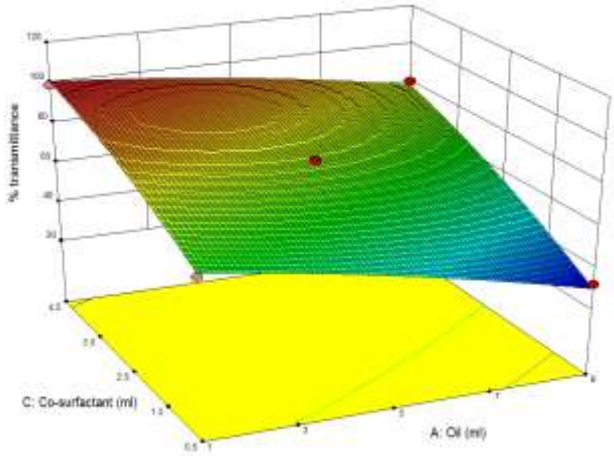
(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and Co-surfactant (C)





(iii) Surfactant (B) and Co-surfactant

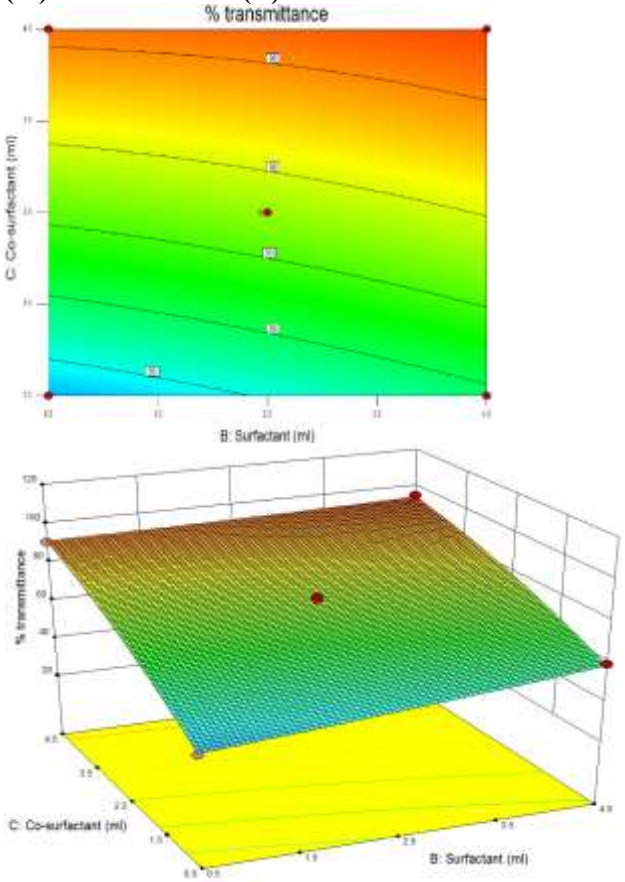


Figure 8: Contour plot and Response surface of % transmittance (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Cumulative Drug Release

% Cumulative drug release from the batch AMB1 to AMB17 of emulsion varied from 44.08±0.028 % to 99.43±0.015 %. From the P-value, it was concluded that the effect of oil (A), surfactant (B) and co-surfactant (C) had the prominent effect ($P<0.05$) on % cumulative drug release.

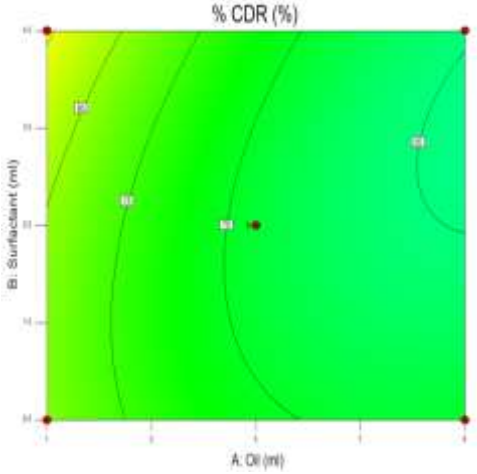
Polynomial Equation for % Cumulative Drug Release:

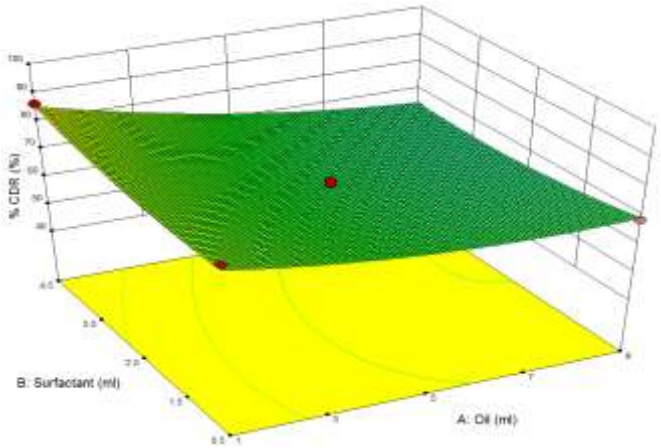
% Cumulative Drug Release = $+68.90 - 7.37 \times A + 0.66 \times B + 21.90 \times C - 2.80 \times AB + 2.45 \times AC - 0.078 \times BC + 3.42 \times A^2 + 2.49 \times AMB2 + 1.88 \times C^2$

Table 17: ANOVA of % Cumulative Drug Release

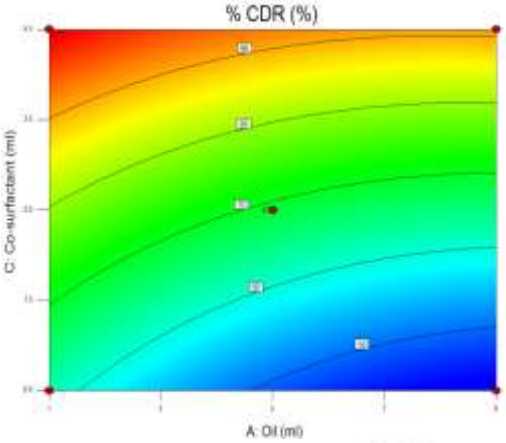
Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	
Model	4431.18	9	492.38	121.33	< 0.0001	Significant
Lack of Fit	17.82	3	5.50	1.92	0.2663	Not Significant
Pure Error	11.61	4	2.80	-	-	
Cor Total	4450.60	16	-	-	-	
R-Squared		0.9936				
Adj R-Squared		0.9854				
Pred R-Squared		0.9357				

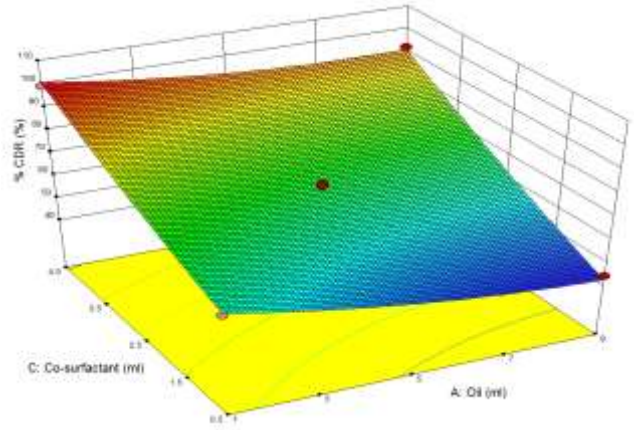
(i) Oil (A) and Surfactant (B)





(ii) Oil (A) and Co-surfactant (C)





(iii) Surfactant (B) Co-surfactant (C)

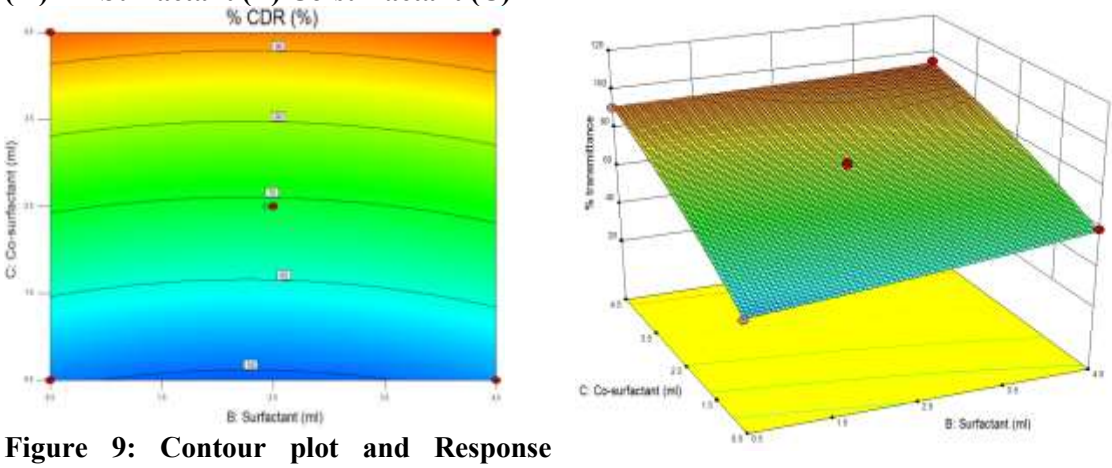


Figure 9: Contour plot and Response surface of % cumulative drug release (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Discussion:

The effect of oil (A), surfactant (B) and co-surfactant (C) on emulsification time (Sec), % transmittance (%) and % cumulative drug release are shown in figure 16 to 18 in the form of response surface plots and contour plots.

A mean level of surfactant (B) and co-surfactant (C) on emulsification time was found to be increased from 18±2.64 sec to 112±3.60 sec, % transmittance was found to be decreased from 99.08±0.23% to 32.06±0.51%, % cumulative drug release was found to be decreased from 99.43±0.015% to 44.08±0.028%, when increasing in oil (A) from 1 ml to 9 ml.

A mean level of oil (A) and co-surfactant (C) on emulsification time was found to be decreased from 112±3.60 sec to 18±2.64 sec, % transmittance was found to be increased from 32.06±0.51% to 99.08±0.23%, % cumulative drug release was found to be increased from 44.08±0.028% to 99.43±0.015%, when increasing in surfactant (B) from 0.5 ml to 4.5ml.

A mean level of oil (A), surfactant (B) on emulsification time was found to be increased from 112±3.60 sec to 18±2.64 sec, % transmittance was found to be increased from 32.06±0.51% to 99.08±0.23%, % cumulative drug release was found to be increased from 44.08±0.028% to 99.43±0.015%, when increasing in co-surfactant (C) from 0.5 ml to 4.5ml.

Evaluation of liquid SMEDDS Formulation

Dispersibility Test

Table 18: Dispersibility tests of Box-Behnken Design formulation

S. No	Batch No	Dispersibility Grade	
		Distilled Water	0.1 N HCl
1	AMB1	Grade A	Grade A

2	AMB2	Grade B	Grade B
3	AMB3	Grade B	Grade B
4	AMB4	Grade D	Grade D
5	AMB5	Grade B	Grade B
6	AMB6	Grade B	Grade B
7	AMB7	Grade B	Grade B
8	AMB8	Grade B	Grade B
9	AMB9	Grade D	Grade D
10	AMB10	Grade C	Grade C
11	AMB11	Grade D	Grade D
12	AMB12	Grade A	Grade A
13	AMB13	Grade C	Grade C
14	AMB14	Grade B	Grade B
15	AMB15	Grade A	Grade A
16	AMB16	Grade C	Grade C
17	AMB17	Grade A	Grade A

When infinite dilution is done to microemulsion formulation, there is every possibility of it to phase separate leading to precipitation of a poorly soluble drug as microemulsion are formed at a particular concentration of oil, surfactant, co-surfactant and water. For oral microemulsions the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC. In the present study, we used distilled water and 0.1 N HCl as a dispersion medium because it is well reported that there is no significant difference in the microemulsions prepared using nonionic surfactants, dispersed in either water or simulated gastric or intestinal fluid. Formulations that passed Dispersibility test in Grade A and B were taken for further study, as Grade A and B formulations will remain as microemulsions when dispersed in GIT. All the formulation that were falling in Grade C and D of Dispersibility tests were discarded for further study.

Robustness on dilution

Table 19: Robustness on dilution of Box-Behnken Design formulation

S. No	Batch No	Dispersibility Grade	
		Distilled Water	0.1 N HCl
1	AMB1	Stable, No precipitation	Stable, No precipitation
2	AMB2	Stable, No precipitation	Stable, No precipitation
3	AMB3	Stable, No precipitation	Stable, No precipitation
4	AMB4	Stable, No precipitation	Stable, No precipitation
5	AMB5	Stable, No precipitation	Stable, No precipitation
6	AMB6	Stable, No precipitation	Stable, No precipitation
7	AMB7	Stable, No precipitation	Stable, No precipitation

8	AMB8	Stable, No precipitation	Stable, No precipitation
9	AMB9	Stable, No precipitation	Stable, No precipitation
10	AMB10	Stable, No precipitation	Stable, No precipitation
11	AMB11	Stable, No precipitation	Stable, No precipitation
12	AMB12	Stable, No precipitation	Stable, No precipitation
13	AMB13	Stable, No precipitation	Stable, No precipitation
14	AMB14	Stable, No precipitation	Stable, No precipitation
15	AMB15	Stable, No precipitation	Stable, No precipitation
16	AMB16	Stable, No precipitation	Stable, No precipitation
17	AMB17	Stable, No precipitation	Stable, No precipitation

The prepared formulation diluated when 100 times with distilled water and 0.1 N HCL were found to be stable without any precipitation.

Emulsification Time

Self-emulsification time was measured using stop watch. It was measure by adding water in liquid SMEDDS and measured time for formed an emulsion. The formulation AMB12 has less self-emulsification time was found to be 18±2.64 second as compared as other formulation. Result of self-emulsification time is shown in table

% Transmittance

The clarity of microemulsions was checked by transparency, measured in terms of transmittance (%T). SMEDDS forms o/w microemulsion since water is external phase. Formulation AMB12 has % transmittance value greater than 99%.These results indicate the high clarity of microemulsion. In case of other systems %T values were about 80% suggesting less clarity of microemulsions. This may be due to greater particle size of the formulation. Due to higher particle size, oil globules may reduce the transparency of microemulsion and thereby values of %T.

Drug Content

Table 20: Drug Content of Box-Behnken Design formulation

S. No	Batch No	Drug Content
1	AMB1	90.72±0.012
2	AMB2	93.57±0.0154
3	AMB3	95.50±0.0145
4	AMB4	83.79±0.0298
5	AMB5	96.23±0.021
6	AMB6	94.82±0.018
7	AMB7	97.62±0.011
8	AMB8	94.40±0.016
9	AMB9	88.01±0.020
10	AMB10	89.29±0.011
11	AMB11	83.82±0.029
12	AMB12	99.01±0.009

13	AMB13	94.06±0.016
14	AMB14	92.78±0.019
15	AMB15	98.86±0.013
16	AMB16	90.24±0.017
17	AMB17	93.78±0.019

*Mean ± SD, n=3

Drug content was measured using UV spectrophotometer at 257 nm. Drug content was measured using linearity equation of methanol. The formulation AMB12 has maximum drug content of liquid SMEDDS was found to be 99±0.009 % of optimized batch.

Time (min)	**Batch No**							
	AMB1	**AMB2**	**AMB3**	**AMB4**	**AMB5**	**AMB6**	**AMB7**	**AMB8**
0	0	0	0	0	0	0	0	0
5	10.35±0.025	6.65±0.018	5.88±0.016	3.70±0.012	6.23±0.018	13.65±0.027	8.64±0.023	5.36±0.017
10	17.35±0.038	17.33±0.025	12.56±0.027	8.95±0.017	15.00±0.027	22.95±0.025	21.70±0.022	14.50±0.014
15	23.32±0.031	25.59±0.027	21.01±0.021	19.47±0.024	23.57±0.035	29.10±0.025	31.11±0.029	25.62±0.022
20	32.86±0.021	34.05±0.026	30.04±0.030	26.85±0.020	32.73±0.034	38.59±0.031	43.97±0.018	33.54±0.019
25	43.82±0.025	40.10±0.029	41.02±0.029	32.00±0.019	37.01±0.028	47.88±0.027	54.15±0.034	39.52±0.025
30	61.62±0.028	47.57±0.027	48.20±0.029	37.37±0.024	43.83±0.025	58.58±0.034	65.09±0.021	46.88±0.018
35	74.43±0.036	55.52±0.024	53.60±0.038	41.17±0.029	55.13±0.029	69.85±0.028	73.54±0.027	53.43±0.028
40	87.64±0.028	62.07±0.023	60.47±0.024	45.42±0.020	61.36±0.027	76.78±0.038	84.49±0.035	63.16±0.025
45	92.41±0.029	68.52±0.024	66.16±0.021	52.36±0.022	69.74±0.027	80.53±0.029	86.41±0.031	69.53±0.025

Table 21: In-vitro drug release of batch AMB9 to AMB17

Table 21: In-vitro drug release of batch AMB9 to AMB17
*Mean ± SD, n=3

Dissolution studies were performed for the SMEDDS formulations in 0.1 N HCL. The maximum drug release of batch no AMB12 was 99.43±0.015 % within the 45 min in case of SMEDDS.

Time (min)	Batch No								
	AMB9	**AMB10**	**AMB11**	**AMB12**	**AMB13**	**AMB14**	**AMB15**	**AMB16**	**AMB17**
0	0	0	0	0	0	0	0	0	0
5	3.84±0.014	4.62±0.011	4.25±0.010	15.15±0.021	4.39±0.020	8.09±0.022	13.08±0.012	8.11±0.024	10.59±0.021
10	8.95±0.018	11.12±0.022	9.84±0.022	30.12±0.017	10.57±0.024	14.56±0.024	28.28±0.015	15.38±0.029	21.19±0.030
15	13.23±0.021	19.75±0.019	13.87±.013	45.13±0.018	18.75±0.033	24.88±0.026	41.70±0.012	24.74±0.023	30.38±0.024
20	22.37±0.020	27.94±0.018	17.00±0.020	56.25±0.012	26.53±0.026	33.16±0.029	54.47±0.018	28.48±0.011	42.75±0.021
25	28.78±0.022	34.64±0.029	20.14±0.026	73.67±0.018	32.92±0.030	39.45±0.027	71.93±0.012	35.65±0.025	52.97±0.022
30	31.55±0.015	41.81±0.023	24.84±0.013	85.61±0.018	36.69±0.027	45.71±0.022	81.98±0.015	43.03±0.020	65.57±0.023
35	40.93±0.013	50.21±0.024	32.22±0.019	96.21±0.016	47.67±0.022	53.20±0.025	92.61±0.023	49.68±0.026	78.56±0.026
40	45.41±0.013	55.67±0.020	39.38±0.025	99.24±0.005	52.86±0.026	62.30±0.025	95.65±0.018	59.04±0.028	91.95±0.024
45	50.10±0.024	63.45±0.016	45.08±0.027	99.43±0.015	68.83±0.020	70.59±0.038	96.60±0.012	61.11±0.027	94.35±0.028

Conclusion

Azilsartan medoxomil (AM) is a novel selective angiotensin II receptor blocker USFDA approved drug for the treatment of hypertension. It is the prodrug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite Azilsartan medoxomil is a poorly water soluble drug due to this poor solubility the oral bioavailability of is about 26% in healthy humans. The selection of oil, surfactant and co-surfactant was carried out using screening study. AM is more soluble in castor oil, tween-20 and carbitol. The solubility was found to be 19.63±0.08 mg/ml, 80.56±0.125 mg/ml and 83.62±0.165 mg/ml in olive oil, tween- 80 and carbitol respectively. For the selection of the surfactant % oil solubilize in different surfactant and ease of emulsification study was carried out, in this study tween-20 highest 5.3% oil solubilize in castor oil and 9 no of flask inversion required for mix tween-20 with castor oil and % transmittance was found to be 93.2. According to that result tween 20 selected for the surfactant phase for further study. The co-surfactant selected according to the minimum amount of co-surfactant required to form clear solution and ease of emulsification, The pseudo ternary phase diagram was constructed using castor oil as oil phase, tween-20 as surfactant phase and carbitol as co-surfactant phase. For this the different three ratio 1:1, 1:2 and 2:1 surfactant and co-surfactant was selected. The different trial has shown that the emulsifying effect is good if the ratio of the surfactant to the co-surfactant is 1:2 and 2:1 but stability properties are inferior at this ratio, so fixed the 1:1 ratio of surfactant and co-surfactant according to stability. The transparent emulsion was produce at the concentration of 80 mg of AM /1ml of SMEDDS formulation. After 80 mg precipitation of AM occurs.

REFERENCE

1. Bayomi MA, Abanumay KA, Al-Angary AA. Effect of inclusioncomplexation with cyclodextrins on photostability of nifedipine insolid state. Int J Pharm. 2002;243:107–117.
2. Kim DW, Kwon MS, Yousaf AM, et al. Comparison of a solidSMEDDS and solid dispersion for enhanced stability and bioavail-ability of clopidogrel napadisilate. Carbohyd Polym. 2014;114:365–374.
3. Bhagwat DA, D'Souza JI. Development of Solid Self Micro Emulsifying Drug Delivery System with Neusilin US2 for Enhanced Dissolution Rate of Telmisartan. Int J Drug Dev & Res. 2012; 4:398-407.
4. Ponnaganti H, Abbulu K. Enhanced Dissolution of Repaglinide: SMEDDS Formulation and In-vitro Evaluation. Research J. Pharm. and Tech. 7(11): Nov. 2014 Page 1246-1252.
5. Kanaujiya AK, Shah SK, Dubey BK, Basedia DB ., Formulation and characterization of rifaximin colon targeting nanosponges, Biochemical & Cellular Archives, 2024: 3569
6. Khansili A, Bajpai M. Formulation, Evaluation and Characterization of Solid Self-Micro Emulsifying Drug Delivery System (Solid SMEDDS) containing Nifedipine. Research J. Pharm. and Tech. 6(3): March 2013; Page 278-284
7. Bhagwat DA, D'Souza JI. Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier. Int Curr Pharm J. 2012; 1: 414-19.
8. Bandivadekar MM, Pancholi SS, Shelke N. Preparation and characterization of solid SMEDDS by adsorbent techniques to improve dissolution profile of poorly aqueous soluble drug Ramipril. Int Res J Pharm. 2011; 2: 85-90.
9. More HN, Hajare AA. Practical physical pharmacy. Career Prakashan, Nashik. 2010;

2nd ed: pp. 129-131.
10. Aulton ME. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone. 1988; 2nd ed: pp. 133-134.
11. Sravanthi N, Alekhya I, Reddy V. Formulation and Evaluation of Mouth Dissolving Tablets of Clozapine by Direct Compression Method. Research J. Pharm. and Tech. 2017; 10(8): 2543-2550.
12. Thakur VS, Tiwari A,Dubey BK, Basedia DK, Patel MK, Shah SK, Development and evaluation of floating nanosponges of captopril, The International journal of analytical and experimental modal analysis 2024;16(2):135-149
13. Panigrahi R, Chowdary KA, Mishra G, Bhowmik M, Behera S. Formulation of fast dissolving tablets of Lisinopril using combination of synthetic superdisintegrants. Asian J. Pharm. Tech. 2012; 2(3): 94-98.
14. Madoria N, Maheshwari Y. Formulation, Optimization and Characterization of Fast Dissolving Tablet of Celecoxib. Research J. Pharm. and Tech. 2012; 5(8): 1085-1088.
15. Banker GS, Anderson NR. Tablet. In: Leon Lachman, HA Lieberman, JL Kanig, The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Mumbai. 1990; 3rd ed: pp. 296-302.
16. Indian Pharmacopoeia Government of India, Ministry of Health and Family Welfare. The controller of publications. New Delhi, 1996; Vol-II, 734-6.
17. Gupta S, Chavhan S, Sawant KK. Self-nanoemulsifying drug delivery system for adefovir dipivoxil: Design, characterization, in vitro and ex vivo evaluation. Colloids and Surfaces A: Physicochem Eng Aspects. 2011; 392: 145-55.
18. Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm. 2010; 66: 227-43.
19. Tianshu L, Yinghua S, Dawei D, Qi Z, Rui F, Zhonggui H, Jing W. Study on Enhanced Dissolution of Azilsartan-Loaded Solid Dispersion, Prepared by Combining Wet Milling and Spray-Drying Technologies. AAPS Pharm Sci Tech. 2017; 18:473-80.
20. Skoog AS, Holler JF, Timothy AN. Principle of Instrumental Analysis. Coles: Thomson Books. 2003; 1st ed: pp. 300-325.
21. Nazzal S., Khan M. A. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters, International Journal of Pharmaceutics. 2006; 315: 110-121.
22. Ray S, Joy M, Sa B, Ghosh S, Chakraborty J. pH dependent chemicalstability and release of methotrexate from a novel nanoceramic car-rier. RSC Adv. 2015;5(49):39482–39494.
23. Na YG, Byeon JJ, Wang M, et al. Strategic approach to developing aself-microemulsifying drug delivery system to enhance antiplateletactivity and bioavailability of ticagrelor. Int J Nanomedicine.2019;14:1193–1212.
24. Hwang I, Kang CY, Park JB. Advances in hot-melt extrusion tech-nology toward pharmaceutical objectives. J Pharm Investig. 2017;47(2):123–132.
25. Madhav KV, Kishan V. Self microemulsifying particles of loratadinefor improved oral bioavailability: preparation, characterization and invivo evaluation. J Pharm Investig. 2018;48(4):497–508.
26. Zhao J, Xie P, Ye C, et al. Outside-in synthesis of mesoporous silica/molybdenum disulfide

nanoparticles for antitumor application. ChemEng J. 2018;351:157–168..
27. Rahman MA, Mujahid M, Hussain A, Iqbal Z. Development andpharmacokinetic evaluation of spray-dried self-nanoemulsifyingdrug delivery system of sertraline. J Pharm Investig. 2017;47(4):325–333.
28. Rashid R, Kim DW, Yousaf AM, et al. Comparative study on solidself-nanoemulsifying drug delivery and solid dispersion system forenhanced solubility and bioavailability of ezetimibe. Int JNanomedicine. 2015;10:6147–6159.13.
29. Rawat PK, Tyagi CK, Shah SK, Pandey AK Formulation, characterization and in vitro evaluation of famciclovir loaded solid lipid nanoparticles for improved oral absorption, JPRI, 2020;32(29): 1-17.
30. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug deliv-ery systems. Eur J Pharm Sci. 2000;11:S93–S98.24.
31. Gursoy RN, Benita S. Self-emulsifying drug delivery systems(SEDDS) for improved oral delivery of lipophilic drugs. BiomedPharmacother. 2004;58:173–182.
32. Onoue S, Uchida A, Kuriyama K, et al. Novel solid self-emulsifyingdrug delivery system of coenzyme Q 10 with improved photochemi-cal and pharmacokinetic behaviors. Eur J Pharm Sci. 2012;46:492–499.
33. Nazzal S, Smalyukh I, Lavrentovich O, Khan MA. Preparation and invitro characterization of a eutectic based semisolid self-nanoemulsi-fied drug delivery system (SNEDDS) of ubiquinone: mechanism andprogress of emulsion formation. Int J Pharm. 2002;235:247–265.16.
34. Oh DH, Kang JH, Kim DW, et al. Comparison of solid self-micro-emulsifying drug delivery system (solid SMEDDS) prepared withhydrophilic and hydrophobic solid carrier. Int J Pharm.2011;420:412–418.
35. Balakrishnan P, Lee B-J, Oh DH, et al. Enhanced oral bioavailabilityof dexibuprofen by a novel solid self-emulsifying drug deliverysystem (SEDDS). Eur J Pharm Biopharm. 2009;72:539–545.