Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

Characterization and Development of SMDDS to Enhance Solubility of Azilsartan Medoxomil

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(Received: 25 October 2025 Revised: 27 November 2025 Accepted: 16 December 2025)

KEYWORDS

SMEDDS, Box-Behnken design, Azilsartan Medoxomil, Phase diagram, Design Expert

ABSTRACT:
Enhance Solubility of Azilsartan Medoxomil SMDD formulations are isotropic mixture of oil, surfactant and co-surfactant. The Azilsartan medoxomil is lipophilic in nature. The oil, surfactant and co-surfactant were selected on the basis of solubility and emulsification ability. Castor oil tween 20 and carbitol were selected on the basis of solubility and emulsification ability. AM was formulated as a SMEDDS in an attempt to increase its solubility. The pseudo ternary phase diagram was constructed by using 1:1, 1:2 and 2:1 ratio of surfactant and co-surfactant with oil and distilled water. By this pseudo ternary phase diagram 1:1 ratio of surfactant and co-surfactant was more stable and good emulsification ability. The Box-Behnken design used for the statistical optimization of SMEDDS formulation using 3 factors and 2 levels and evaluated 3 response parameters emulsification time, % transmittance and % cumulative drug release. In this Box-Behnken design run total 17 batches with 5 center points, out of this batch B12 has good emulsification time 18±2.64sec, good % transmittance 99.08±0.23% and % cumulative drug release 99.43±0.015% within 45 min. The solid-SMEDDS prepared by using 2% w/v mannitol as cryoprotectant by lyophilization technique. This freeze dried powder has a good flow property. The in vitro dissolution study of freeze dried powder compared with plain drug and marketed tablet. The freeze dried powder shown 99.28±0.013% drug release within 45 min, while plain drug showed only 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min. The in vitro dissolution studies indicate that formulation of AM in the form of freeze dried powder of SMEDDS enhances the dissolution properties.

INTRODUCTION

Approximately, 40% of the new drugs in development today are practically water insoluble and associated with poor bioavailability [1]. It is very difficult to convert into solid complex form with improved solubility by using aqueous solvent. Lipid based formulation approaches, particularly the Self Microemulsifying Drug Delivery System (SMEDDS), are well known for their potential as alternative approach for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability[2]. SMEDDS is isotropic mixture of oil, surfactant and co-surfactant, when this mixture comes in contact with the gastrointestinal fluids and upon mild agitation it forms fine droplets of oil in water type of emulsion. The optimization of the SMEDDS formulation by changing the ratio of oil to the surfactant and surfactant to the co-surfactant[3], which increased the solubility as well as the bioavailability of drug, so the SMEDDS approach used for enhancement of the solubility of drug so increase the rate and extent of dissolution due to that the bioavailability of drug also increases. Acceptability and stability of Solid-SMEDDS is good as compare to liquid or semi-liquid preparation as per PSAR reports[4].

Self-microemulsifying drug delivery system (SMEDDS) is an isotropic mixture of oils, surfactants, or alternatively, one or more hydrophilic solvents or surfactants, upon mild agitation followed by dilution in aqueous media, including gastrointestinal fluids[5], this system can form fine droplets of oil-in-water (O/W) microemulsions. The resultant small droplet size provides a large surface area for drug release and absorption. The solubility of AM is enhancing by self

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

microemulsifying drug delivery system[6]. The SMEDDS formulations screening by pseudo ternary phase diagram by changing the ratio of surfactant and co-surfactant and develop stabilize system.

The stabilize SMEDDS system is screening by Box-Behnken design contain with 3 factors, 2 levels is preparing by Design expert 9 software.For optimization of formulation parameters such as concentration of oil, surfactant and co-surfactant are carry out for evaluating response parameters emulsification time, % transmittance and % cumulative drug release[7]. These optimize formulations then converting in to liquid SMEDDS to solid-SMEDDS with addition of cryoprotectant by lyophilization technique. This solid-SMEDDS formulation is then optimizing by change in the concentration of cryoprotectant for good evaluation properties[8].

MATERIAL AND METHOD

Fourier transforms infrared spectroscopic studies (FTIR)

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[9].

Analytical Method development

Method was performed by UV Spectrophotometer.

Determination of λ_{max}

The Standard drug solution concentration of 10 µg/ml was preparing Methanol and 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[10].

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

Preparation of Standard calibration Curve for AM in Methanol

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[11].

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[12].

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[13]. 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[14].

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

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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[15].

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[16]. 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[17].

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[18].

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[19]. 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[20].

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 solubilit. 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[21].

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.

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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[22].

Table 1 : 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). 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. 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[23].

Table 2: 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

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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. 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[24].

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 37ºC, 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.

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[25].

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.

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

- **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.

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 Zetasizer NS90.

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[26].

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[27].

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

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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[28].

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[29].

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.

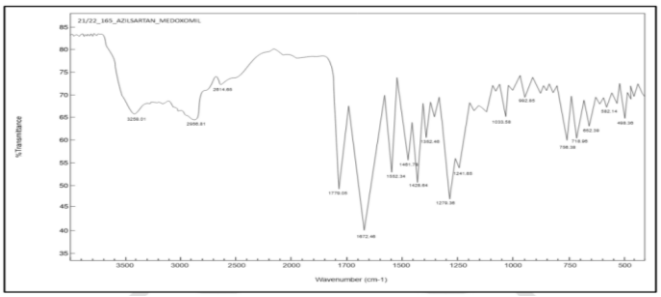

Figure 1: FTIR Spectra of Azilsartan Medoxomil (AM)

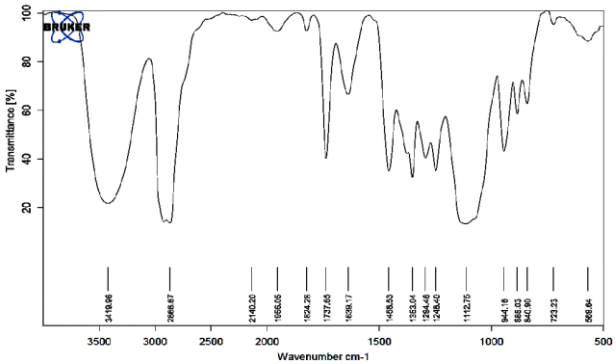

Figure 2: FTIR Spectra of Final freeze dried powder of AM

Table 1: FTIR peaks

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

Journal of Chemical Health Risks

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Analytical Method Development:

Determination of λ_{max}

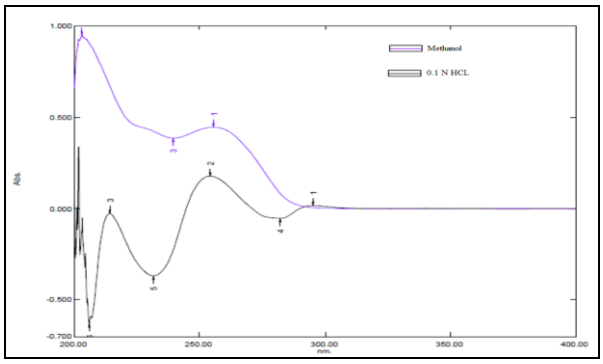

Figure 3: Overlay spectra

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.

Table 4: Calibration curve of Azilsartan medoxomil in methanol

Concentration (µg/ml)	Absorbance			Mean Absorbance ± SD
	I	II	III	
2	0.097	0.095	0.096	0.096±0.0010
4	0.187	0.184	0.188	0.186±0.0021
6	0.265	0.268	0.264	0.266±0.0021
8	0.359	0.361	0.36	0.360±0.0010
10	0.443	0.44	0.441	0.441±0.0015
12	0.546	0.549	0.544	0.546±0.0025
14	0.642	0.641	0.643	0.642±0.0010
16	0.726	0.726	0.724	0.725±0.0012
18	0.867	0.868	0.866	0.867±0.0010

*Mean ± SD, n=3

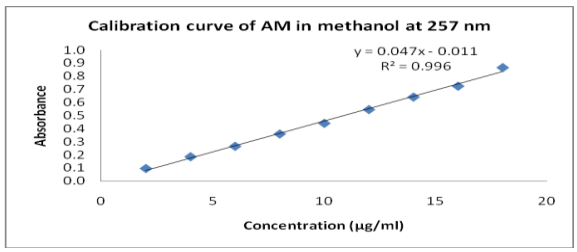

Figure 4: Calibration curve of Azilsartan medoxomil in methanol

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.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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

Concentration (µg/ml)	Absorbance			Mean Absorbance ± SD
	I	II	III	
5	0.132	0.13	0.134	0.132±0.0022
10	0.223	0.224	0.224	0.224±0.0005
15	0.364	0.366	0.364	0.366±0.0014
20	0.477	0.482	0.479	0.479±0.0014
25	0.596	0.587	0.596	0.596±0.0020
30	0.717	0.718	0.715	0.717±0.0031
35	0.846	0.845	0.844	0.845±0.0014
40	0.965	0.963	0.965	0.964±0.0010

*Mean ± SD, n=3

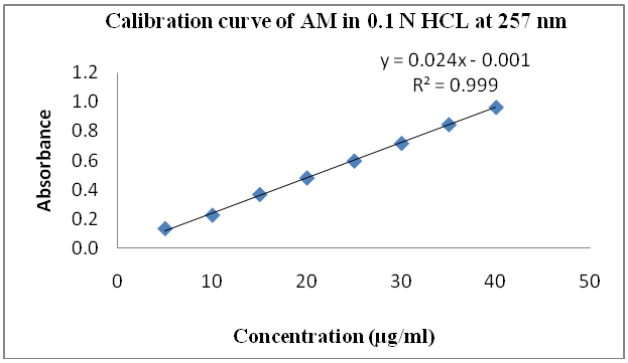

Figure 5: Calibration curve of Azilsartan medoxomil in 0.1 N HCL

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. 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[30].

Screening of Oils
Based on solubility of drug

Table 6: Solubility study in different oils

S. 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. The solubility of different oils are shown in table 21 and figure 8.

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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

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

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.

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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

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

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.

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.

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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.

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

S. No.	Std	Run	Batch No	Oil (ml)	Surfactant (ml)	Co-surfactant (ml)	Emulsification time (Sec)	% Transmittance (%)	% CDR (%)
1	8	1	B_1	9	2.5	4.5	46±5.28	80.96±1.76	92.1±0.028
2	17	2	B_2	5	2.5	2.5	64±42	74.82±1.07	68.52±0.024
3	16	3	B_3	5	2.5	2.5	65±5.55	75.82±1.26	66.16±0.021
4	10	4	B_4	5	4.5	0.5	86±2.60	59.15±0.90	52.35±0.022
5	15	5	B_5	5	2.5	2.5	63±2.60	74.83±1.07	69.74±0.026
6	1	6	B_6	1	0.5	2.5	50±3.35	88.12±0.76	80.6±0.029
7	3	7	B_7	1	4.5	2.5	37±3.65	91.27±0.99	86.41±0.032
8	13	8	B_8	5	2.5	2.5	64±44	75±1.11	69.52±0.026
9	9	9	B_9	5	0.5	0.5	90±42	43.05±0.79	50.1±0.026
10	4	10	B_{10}	9	4.5	2.5	67±2.54	62.9±0.88	63.35±0.018
11	6	11	B_{11}	9	2.5	0.5	112±2.60	32.06±0.51	44.08±0.028
12	7	12	B_{12}	1	2.5	4.5	18±2.64	99.07±0.23	99.53±0.015
13	2	13	B_{13}	9	0.5	2.5	83±2	51.48±0.47	68.82±0.030
14	14	14	B_{14}	5	2.5	2.5	64±2.64	76.83±1.07	70.58±0.028
15	12	15	B_{15}	5	4.5	4.5	23±2.64	95.35±0.77	96.62±0.011
16	5	16	B_{16}	1	2.5	0.5	73±3.50	64.13±0.74	61.10±0.028
17	11	17	B_{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 are shown in table.

Response 1 – Emulsification Time

Emulsification time from the batch B1 to B17 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.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

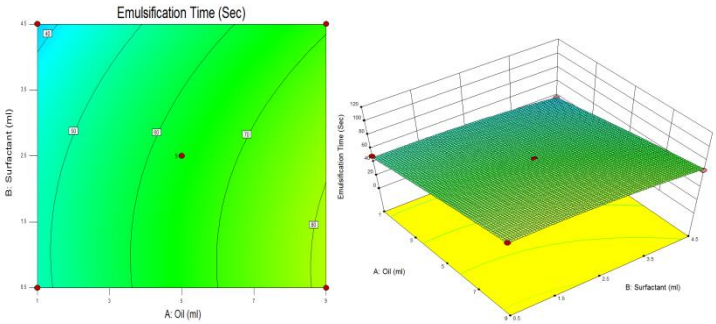
Polynomial Equation for Emulsification Time:

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 × B^2- 0.65 × C^2

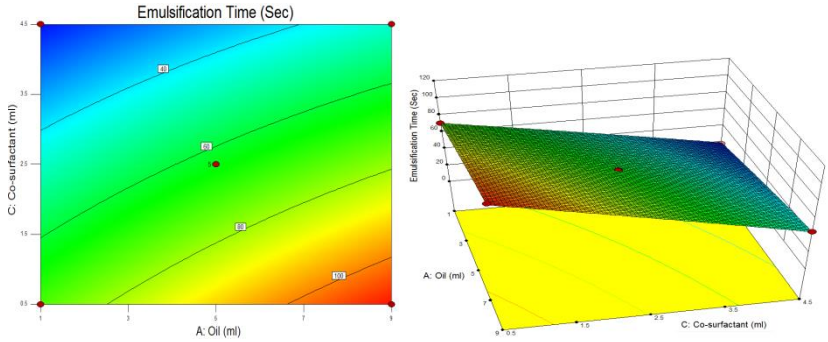
Table 15: ANOVA of Emulsification Time

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)

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

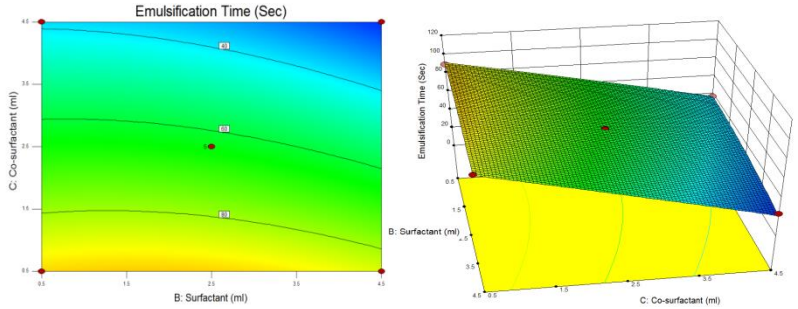


Figure 6: Contour plot and Response surface of emulsification time (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Transmittance

% Transmittance from the batch B1 to B17 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.

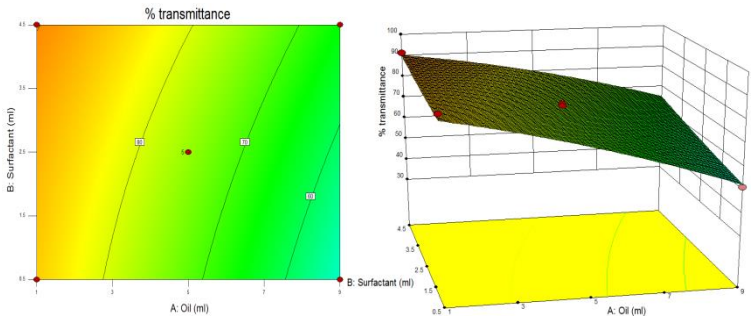
Polynomial Equation for % Transmittance:

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

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)



Journal of Chemical Health Risks

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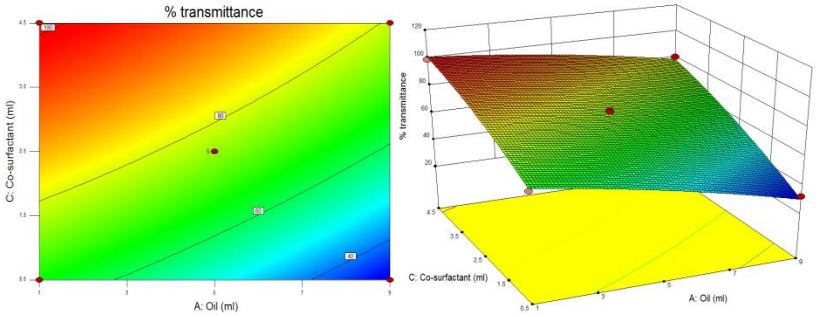
JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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



(iii) Surfactant (B) and Co-surfactant

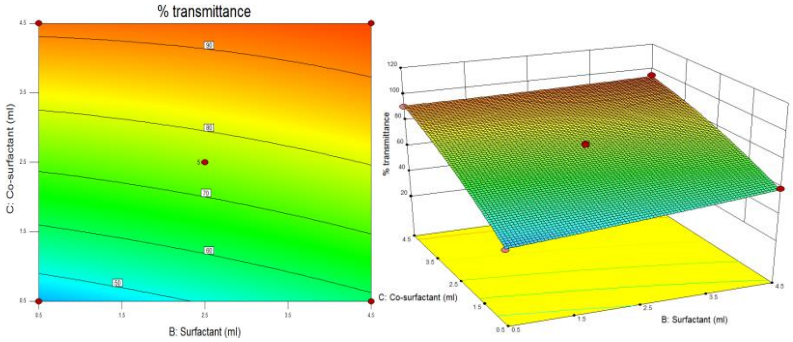


Figure 7: Contour plot and Response surface of % transmittance (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

Response 2 – % Cumulative Drug Release % Cumulative drug release from the batch B1 to B17 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 = $+68.90 - 7.37 \times A + 0.66 \times B + 21.90 \times C - 2.80 \times AB + 2.45 \times AC - 0.078 \times BC + 3.42 \times A^2 + 2.49 \times B^2 + 1.88 \times C^2$

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				

Journal of Chemical Health Risks

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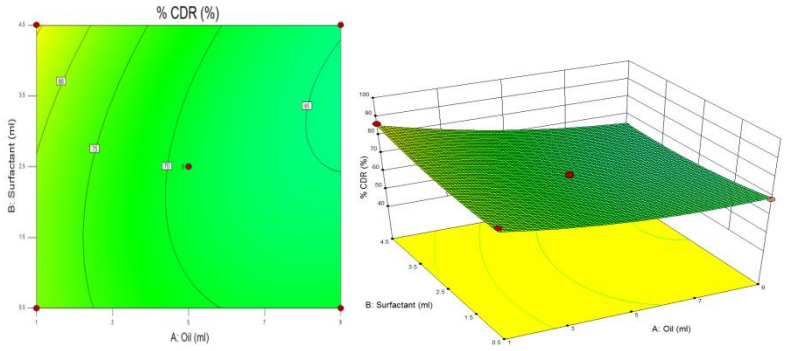
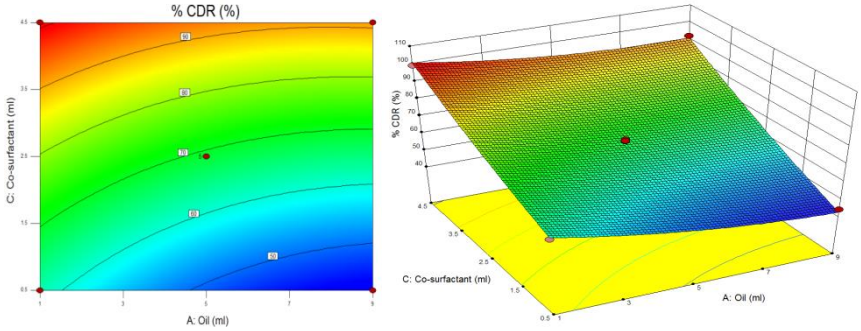
JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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



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



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

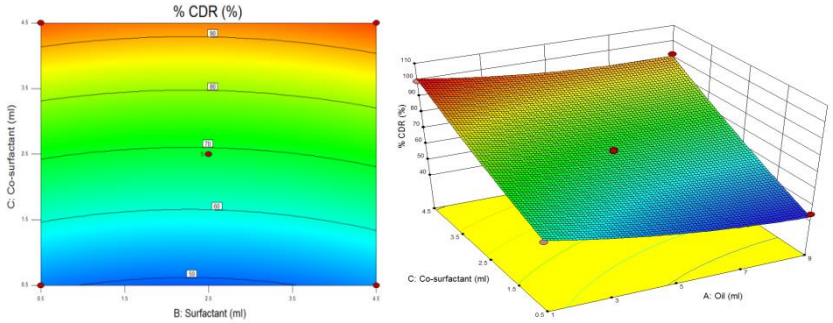


Figure 8: Contour plot and Response surface of % cumulative drug release (i) Effect of Oil (A) and surfactant, (B) (ii) Effect of Oil (A) and Surfactant (B) (iii) Effect of Surfactant (B) and Co-surfactant (C)

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 [31].

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.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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 Solid SMEDDS Formulation

Solid State characterization

Bulk Density

Table 18: Bulk Density of freeze dried powder

S. No.	Weight of Powder (mg)	Volume of Powder (ml)	Bulk Density (mg/ml)	Avg±SD
1	15	26	0.58	0.59±0.012
2	15	25	0.61	
3	15	25	0.61	

*Mean ± SD, n=3

Bulk density of optimized freeze dried powder was measured by direct filling of self-emulsified freeze dried powder in measuring cylinder. Bulk density was found to be 0.59±0.012**.**

Tapped Density

Table 19: Tapped Density of freeze dried powder

S. No.	Weight of Powder (mg)	Volume of Tapped Powder (ml)	Tapped Density (mg/ml)	Avg±SD
1	15	21	0.65	0.68±0.03
2	15	22	0.67	
3	15	23	0.71	

*Mean ± SD, n=3

Tapped density of optimized freeze dried powder was measured of self-emulsified freeze dried powder by 100 times mechanical tapping. Tapped density was found to be 0.68±003

Carr's Index and Hausner's ratio

Table 20: Carr's Index and Hausner's ratio of freeze dried powder

Sr No.	Tapped Density (mg/ml)	Bulk Density (mg/ml)	Carr's Index	Avg±SD	Hausner's ratio	Avg±SD
1	0.65	0.57	17.14	14.80±2.76	1.12	1.14±0.03
2	0.68	0.61	11.76		1.13	
3	0.71	0.61	15.49		1.18	

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

*Mean ± SD, n=3

Carr's Index and Hausner's of optimized freeze dried powder was measured of self-emulsified freeze dried powder was found to be 14.80±2.76 and 1.14±0.03 respectively.

Angle of Repose

Table 21: Angle of Repose of freeze dried powder

Sr No.	Height of Pile (cm)	Radius of Pile (cm)	Angle of Repose (θ)	Avg±SD
1	1.7	4.2	24.48	24.91±1.25°
2	1.5	3.4	23.93	
3	1.8	4.2	26.32	

*Mean ± SD, n=3

Angle of repose of optimized freeze dried powder was found to be 24.91±1.25°. Result of angle of repose of freeze dried powder.

Characterization of Solid SMEDDS Formulation

Drug Content

Drug content was measured using UV spectrophotometer at 257 nm. Drug content was measured using linearity equation of methanol. The drug content of self emulsified freeze dried powder was found to be 96.15±0.15% of optimized batch.

Zeta Potential

Zeta potential was determined by Malvern Zetasizer NS90. Zeta potential shows an electric charge present on the oil globule. Zeta potential of optimized freeze dried powder was found to be -22.5 mv.

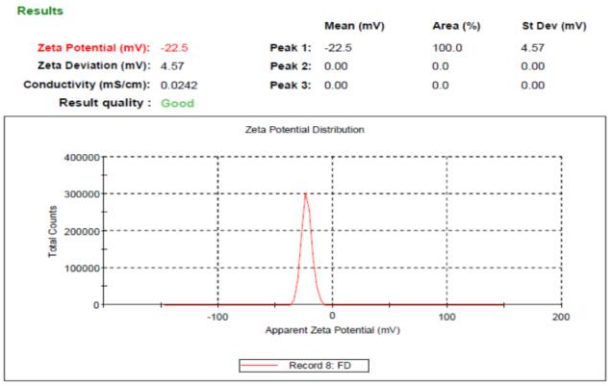


Figure 9: Zeta potential of Freeze Dried Powder

Globule Size

The globule size of the emulsion was measured by Malvern Zetasizer NS90. The globules size of optimized freeze dried powder was found to be 98.24 nm.

Poly Disperbility Index

Poly dispersity index of the emulsion was measured by Malvern Zetasizer NS90. PDI of optimized freeze dried powder was found to be 0.304. Result of freeze dried power was shown in figure 24 and table 48.

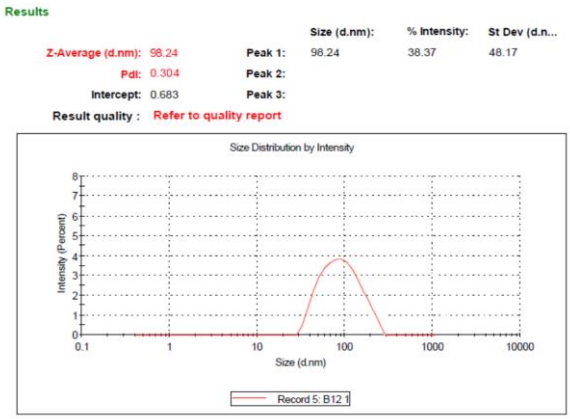


Figure 10: Droplet size and PDI of Freeze Dried Powder

Self emulsification time of powder

Self-emulsification time was measured using stop watch. It was measure by adding water in self-emulsified freeze dried powder and measured time for formed an emulsion. The self-emulsification time was found to be 20±3.60 second. Result of self-emulsification time is shown in table 48.

Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

In vitro Drug release

Table 22: in vitro drug release of freeze dried power

Sr No	Time (Min)	Plain Drug	Marketed Formulation	% CDR of 2% w/v mannitol freeze dried powder
1	0	0	0	0
2	5	1.31±0.009	3.38±0.017	12.73±0.021
3	10	5.05±0.014	7.50±0.016	27.22±0.017
4	15	14.06±0.025	14.05±0.019	41.71±0.027
5	20	21.19±0.024	21.94±0.019	54.23±0.011
6	25	25.12±0.012	27.65±0.011	71.08±0.024
7	30	28.69±0.015	35.26±0.018	79.98±0.023
8	35	31.87±0.022	44.53±0.012	90.08±0.020
9	40	34.69±0.030	51.00±0.017	97.73±0.014
10	45	37.88±0.025	58.21±0.015	99.28±0.013

*Mean ± SD, n=3

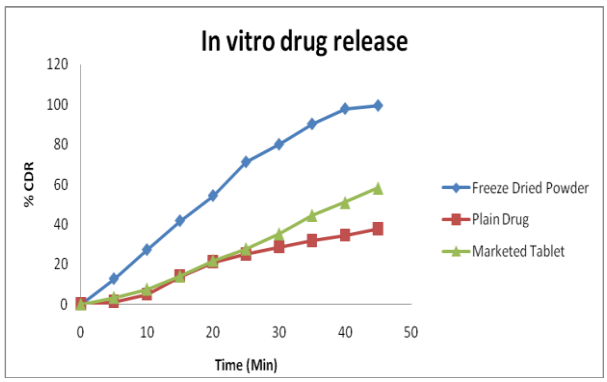

Figure 11: In vitro drug release of freeze dried powder, Plain drug and Marketed Tablet

Dissolution studies were performed for the Solid-SMEDDS freeze dried powder in 0.1 N HCL There is about 99.28±0.013% of the drug is released within 45 min in freeze dried Solid-SMEDDS, while plain drug showed only 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min. The *in vitro* dissolution studies indicate that formulation of AM in the form of freeze dried powder of SMEDDS enhances the dissolution properties[32].

Optimized freeze dried powder formulation and its evaluation

Table 23: Optimized freeze dried powder formulation and its evaluation results

Sr No	Parameters	Inference
1	Composition of batch	Drug (AM): 20 mg + Oil: 1 ml + Surfactant: 2.5 ml + Co-surfactant: 4.5 ml + Mannitol: 2 % w/v
2	Bulk Density (mg/ml)	0.58±0.012
3	Tapped Density (mg/ml)	0.66±0.03
4	Carr's Index (%)	14.80±2.75
5	Hausner's ratio	1.14±0.03

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

6	Angle of Repose (θ)		24.91 ± 1.25^0
7	Zeta Potential (mv)		-22.5
8	Globule Size (nm)		97.24
9	Poly Disperbility Index (PDI)		0.304
10	Emulsification Time (Sec)		20±3.60
11	Drug Content (%)		96.15±0.14
12	In vitro drug release (%)	Freeze Dried Powder	99.28±0.012
		Plain Drug	36.88±0.025
		Marketed Tablet	58.32±0.014

*Mean ± SD, n=3

Azilsartan medoxomil (AM) is a novel selective angiotensin II receptor blocker USFDA approved drug for the treatment of hypertension. It is the pro-drug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite Azilsartan. AM is a poorly water soluble drug is due to this poor solubility the oral bioavailability of is about 26% in healthy humans. Self-microemulsifying drug delivery system (SMEDDS) is an isotropic mixture of oils, surfactants, or alternatively, one or more hydrophilic solvents or surfactants, upon mild agitation followed by dilution in aqueous media, including gastrointestinal fluids, this system can form fine droplets of oil-in-water (o/w) microemulsions. The resulting small droplet size provides a large surface area for drug release and absorption.

FTIR study was performed to verify compatibility of drug-excipients and excipient-excipients. Drug was compatible with all excipients. Calibration curve was taken using methanol at 257 nm and 0.1 N HCL. R^2 value was found to be 0.996 and 0.999 for methanol and 0.1 N HCL respectively.

The selection of oil, surfactant and co-surfactant was carried out by means of screening study. The first solubility study was carried out of oil, surfactant and co-surfactant with Azilsartan medoxomil drug. 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 maximum 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. 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 for further study. According to this screening study castor oil, tween-20 and Carbitol was selected for the formulating SMEDDS.

The pseudo ternary phase diagram was constructed by using castor oil as oil phase, tween-20 as surfactant phase and carbitol as co-surfactant phase. On behalf of 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.

Formulation development the Box-Behnken statistical design used. Box Behnken statistical design with 3 Independent factors, 2 levels was prepared by Design expert 9 with 5 center point and 17 runs was selected for the optimization study. For optimization of formulation parameters such as concentration of oil, surfactant and co-surfactant was carried out by evaluating 3 response parameters emulsification time, % transmittance and % cumulative drug release by Box-Behnken statistical design. According to Box-Behnken statistical design batch B_{12} has a best emulsification time 18±2.64 sec, good % transmittance 99.08±0.23 % and good in vitro % cumulative drug release after 45 min was found to be 99.43±0.015 %. 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.

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

The SMEDDS formulations were further evaluated, the batch B_1, B_{12}, B_{15} and B_{17} has a disperbility grade A expects other batches. According to the robustness on dilution study all batches are be stable without any precipitation diluated when 100 times with distilled water and 0.1 N HCL. The highest amount of drug content of batch B_{12} was found to be 99±0.009 %. The maximum drug release of batch no B_{12} was 99.43±0.015 % within the 45 min in case of SMEDDS.

The batch B1, B_{12}, B_{15} and B_{17} was passed the thermodynamic stability whereas other batch failed the thermodynamic stability. According to thermodynamic stability passed 4 batches was evaluated for the zeta potential, globule size, poly disperbility index and viscosity. These 4 batches were tested in malvern zetasizer NS90 the batch B_{12} has best result compare to other 3 batches. The zeta potential droplet size, globule size and poly disperbility index of batch B_{12} was found to be -27.5 mv, 98.28 nm and 0.243 respectively**.** The solid-SMEDDS formulation prepared by lyophilization technique. Mannitol used as cryoprotectant for the solid-SMEDDS formulation. The composition of batch AM 20 mg, Oil 1 ml, surfactant 2.5 ml co-surfactant 4.5 ml and mannitol used in different ratio for preparation of solid-SMEDDS. The mannitol 2% w/v mannitol used as cryoprotectant gives the best result. The solid state characteristics of freeze dried powder bulk density, tapped density, carr's index, hausner's ratio and angle of repose was found to be 0.59±0.012, 0.68±0.03, 14.80±2.76, 1.14±0.03 and 24.91±1.25° correspondingly. The drug content of freeze dried powder was found to be 96.15±0.15%. The emulsification time of freeze dried powder was found to be 20±3.60 sec. The zeta potential, droplet size and poly disperbility index of freeze dried powder was found to be - 22.5 mv, 98.4 nm and 0.304 respectively**.** The cumulative drug release of freeze dried powder within 45 min was found to be 99.28±0.013%, while plain drug showed just 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min.

CONCLUSION

SMEDDS formulations are isotropic mixture of oil, surfactant and co-surfactant. The Azilsartan medoxomil is lipophilic in nature. The oil, surfactant and co-surfactant were selected on the basis of solubility and emulsification ability. Castor oil tween 20 and carbitol were selected on the basis of solubility and emulsification ability. AM was formulated as a SMEDDS in an attempt to increase its solubility. The pseudo ternary phase diagram was constructed by using 1:1, 1:2 and 2:1 ratio of surfactant and co-surfactant with oil and distilled water. By this pseudo ternary phase diagram 1:1 ratio of surfactant and co-surfactant was more stable and good emulsification ability. The Box-Behnken design used for the statistical optimization of SMEDDS formulation using 3 factors and 2 levels and evaluated 3 response parameters emulsification time, % transmittance and % cumulative drug release. In this Box-Behnken design run total 17 batches with 5 center points, out of this batch B_{12} has good emulsification time 18±2.64sec, good % transmittance 99.08±0.23% and % cumulative drug release 99.43±0.015% within 45 min. The solid-SMEDDS prepared by using 2% w/v mannitol as cryoprotectant by lyophilization technique. This freeze dried powder has a good flow property. The in vitro dissolution study of freeze dried powder compared with plain drug and marketed tablet. The freeze dried powder shown 99.28±0.013% drug release within 45 min, while plain drug showed only 37.88±0.025 % and marketed formulation showed only 58.31±0.015 % dissolution at the end of 45 min. The *in vitro* dissolution studies indicate that formulation of AM in the form of freeze dried powder of SMEDDS enhances the dissolution properties.

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Journal of Chemical Health Risks

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JCHR (2025) 15(6), 2932-2954 | ISSN:2251-6727

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