IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Research Article**
January 2021 Vol.:20, Issue:2


# Formulation and Evaluation of New Self-Micro-Emulsifying Mouth Dissolving Film of Azilsartan

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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**Submitted:** 05 December 2020
**Revised:** 26 December 2020
**Accepted:** 16 January 2021

HUMAN JOURNALS
**www.ijppr.humanjournals.com**

**Keywords:** Self Microemulsifying system, Mouth dissolving, Film, Azilsartan, SMEDDS, Drug Delivery System

**ABSTRACT**

**Objective**: Present research work demonstrates the formulation development and characterization of the poorly soluble drug, azilsartan into Self micro-emulsifying drug delivery system to increase its solubility and thereby dissolution rate and bioavailability. **Methods**: Self micro-emulsifying drug delivery film (SMEDF) was prepared from oil, surfactant, and co-surfactant ratio mixture. The ratio of drug to oil and the oil: surfactant and co-surfactant mixture optimized and then prepared SMEDF were evaluated for globule size, zeta potential, and percent transmittance. Many formulations-related evaluations, such as surfactant concentration, oil: surfactant ratio, the polarity of the emulsion, droplet size was studied and optimized for determining the self-emulsification ability. The optimized formulation was evaluated for folding endurance, disintegration time, globule size, and *in-vitro* drug release study, etc. **Results**: The optimized SMEDDF exhibiting good folding endurance, disintegrated within 20 seconds and immediately turned into a stable micro-emulsion when mixed with salivary fluid with globule size 22.29±4.28 nm indicating positive zeta potential and PDI near to one. *In-vitro* drug release was found to be about 99.30% after one hour at pH 8.6 buffer solution. **Conclusion**: SMEDF is a promising formulation for poorly soluble hydrophobic drugs like Azilsartan as compared with its conventional dosage form and fast dissolving tablet formulation with improved patient compliance, quick onset of action, and thus, improved drug absorption and bioavailability through the oral mucosa.

## INTRODUCTION:

Currently, fast dissolving dosage forms have started gaining popularity and acceptance as new drug delivery systems due to their unique properties.[1] They quickly dissolve and disintegrate in the mouth with salivary glands and can be administered without water, making them particularly suitable for pediatrics and geriatric patients. Fast dissolving dosage forms include tablets, films, and microspheres.

A self-micro-emulsifying drug delivery system is one of the approaches for increasing the solubility of hydrophobic drugs formulated by solubilizing in the lipid vehicles with the help of surfactants and co-surfactants ratio, which leads to an increase in solubility and absorption of the drug through the oral mucosa.

The solubility of hydrophobic drugs can be enhanced by various methods and one of them is a self-micro-emulsifying drug delivery system (SMEDDS) or self-emulsifying drug delivery system (SEDDS) as they also enhance the permeability and bioavailability of the hydrophobic drugs without going into first pass metabolism. The self-micro-emulsifying drug delivery system (SMEDDS) is the isotropic mixture and lipid-based formulations given by oral route. The hydrophobic drug which is soluble in the oil can be formulated in this technique. The mixture consists of oil which has to be in the range of less than 100 nm droplet size. The bioavailability of the hydrophobic drug will be enhanced by in situ solubilization of the drug absorbed by the lymphatic pathway. The SMEDDS will get in contact with the GIT lumen and form w/o microemulsion with the GI fluid.

The mechanism for the increase in absorption of the drug by SMEDDS is *in vivo* solubilization of drug in presence of lipid in the gastrointestinal tract (GIT) which stimulates the secretion of bile salt and biliary lipids such as phospholipids and cholesterol, lead to the formation of intestinal mixed micelles. This in turn causes enhancement in the solubilization capacity of GIT. The addition of lipid from formulation causes a further increase in solubilization capacity. An increase in gastric residence time of drug–lipid in the GIT causes a delay in gastric emptying. This enables better dissolution of drugs and improves drug absorption. Promotion of intestinal lymphatic transport of drug-lipid enhances the lymphatic transport of lipophilic drugs and enhances bioavailability via the reduction in first pass metabolism. Affecting intestinal permeability-Lipid can change the physical barrier function of the gut wall. Thus, an increase in permeability of the drug, reduced metabolism, and efflux activity of the drug. Certain surfactants and lipids show a reduction in the activity of efflux

transporters in the gut wall thus increase in absorption of the drug, e.g., Labrasol, Cremophore EL 21.

The advantages include improved bioavailability, dose reduction, decreased food effects and, reduction in irritation caused by the contact between drug and the gut wall. Formulation is simple by involving simple mixing, low energy consumption, easy manufacturing process, less time consuming, Moreover, hydrophobic drugs can be absorbed with stable plasma-time profile and drugs which can be degraded by GIT can also be used.[2]

A Self-micro-emulsifying mouth dissolving film (SMMDF) is a novel approach. SMMDF is based on SMEDDs formulated into a film that can get self-micro-emulsified in salivary fluid and dissolved in the mouth [2,3]. Thus, the SMMDF showed advantages of both the dosage forms showing greater potential with enhanced oral dissolution and bioavailability of poorly soluble drugs like Azilsartan. SMEDF get dissolved in salivary fluids within 20 minutes and form o/w microemulsion in the mouth lead to the buccal absorption eliminating the first bypass effect and improved bioavailability can be achieved.

**Composition**

Selection of surfactants are based on HLB value, if the HLB value is high then it facilitates o/w microemulsion and if HLB>12 increases the solvent capacity of the formulations in which the droplet size will be <100 cu.nm. Co-solvents and co-surfactants should be hydrophilic. The range of co-solvents and co-surfactants should be in 20-50% w/w of the formulation and always 30% w/w more than the concentration of the surfactants. The HLB value of the co-surfactants should be 10-14. Alcoholic surfactants are not used in the formulation as they cause precipitation of the drug. So, amphiphilic surfactants with HLB more than 12 are used in the concentration range between 30-60% w/w of the formulation. Lipids can further improve the bioavailability apart from solubilization of the drug by affecting drug absorption to the lymphatic circulation. They are used in the concentration of less than 20% w/w of the formulation. Drug candidates having poor water solubility, low dose, poor bioavailability, low melting point, chemically and physically stable in SMEDDS are good candidates for SMEDDS.

Mouth dissolving film is typically designed for oral administration with the user placing the strip on or under the tongue or along the inside of the cheek. As the strip forming polymer (which forms the platform for the oral film) is the most essential and major component of the

film, at least 45%w/w of polymer should generally be present based on the total weight of dry film but typically 60 to 65%w/w of polymer is preferred to obtain desired properties.[5] The polymers employed in the oral film preparation should be non-toxic and non-irritant, devoid of leachable impurities, should not retard disintegration time of the film, tasteless, should have good wetting and spreading ability, should exhibit sufficient peel, shear, and tensile strength. It should be readily available, inexpensive, should have sufficient shelf-life and should not aid in causing secondary infections in the oral mucosa or dental regions.

**Self-Micro-emulsifying Mouth Dissolving Film (SMMDF)**

Selection of a suitable self-micro emulsifying film formulation depends upon the assessment of the solubility of the drug in various components, the efficient self-micro emulsifying region as SMMDF is based on mouth dissolving film integrated with self-micro-emulsifying components. SMMDF has enormous potential for enhancing oral dissolution and bioavailability of the poorly water-soluble drug.[6] Its advantages include the quick onset of action as compared to a tablet, does not require water during administration, avoids first past metabolism, taste masking is possible by using different sweetening agents, no risk of choking, good stability& patient compliance, rapid disintegrating and dissolution, flexible and portable nature gives ease in transportation, storage, and handling.

The evaluation of SMMDF was determined by Film thickness, folding endurance, Disintegration time, *In vitro* drug release study, drug content and droplet size of the reconstituted microemulsion, morphological analysis of SMMDF by SEM (Scanning Electronic Microscopy), and solid-state characterization of SMMDF by FTIR (Fourier transformed infrared spectroscopy), DSC and XRD, etc.[7]

Azilsartan (AZL) is a novel selective angiotensin II receptor blocker used in the treatment of hypertension. It inhibits the action of angiotensin II (AT-II) by binding to and inhibiting the AT-II type 1 (AT1) re-ceptor. Azilsartan prevents the vessels from narrowing and thus helps to lower the arterial blood pressure. Azilsartan has shown pharmaceutical problems of water solubility. Because it is practically insoluble in water, the dissolution of AZL from its available dosage form after oral administration which is an important factor for its bioavailability is usually the rate-limiting step in the absorption process.

Thus, the aim of the present study was to enhance the solubility and dissolution rate of poorly water soluble Azilsartan by formulating into Self-microemulsifying mouth dissolving film

(SMMDF). SMEDDS is an isotropic thermodynamically stable solution consisting of an oil, by formulating into SMMD film it improves the stability, becomes patient convenient (bedridden patients, geriatric patients), provides fast action by providing an immediate release of the drug.[8-11]

## MATERIALS AND METHODS:

### MATERIALS:

**Azilsartan medoxomil (99 % pure) was obtained as gift sample from Xylopia, Ahmedabad. All other ingredients used were of analytical grade and obtained from Xylopia, Ahmedabad.**

### METHODS:

#### *Preparation of standard curve of drug*

In methanol: Azilsartan (10mg) was dissolved in 10 ml of methanol to obtain a solution (1000 mcg/ml). The standard solution of Azilsartan was subsequently diluted with methanol to obtain a series of dilutions containing 2,4,6,8,10,12,14,16,18,20 µg/ml concentration of the drug, respectively. The absorbance of each solution was measured against methanol as a blank.

Similarly the standard curve was taken in pH 6.8 phosphate buffer solution: Azilsartan (10mg) was dissolved in methanol to obtain a solution (1000 µg/ml). The standard solution of Azilsartan was subsequently diluted with pH 6.8 buffer to obtain a series of dilutions containing 2,4,6,8,10,12,14,16,18,20 µg/ml concentration of the Azilsartan, respectively. The absorbance of each solution was measured against 6.8 pH buffer as a blank.[12]

#### Pre-formulation studies

Pre formulation parameters like organoleptic characteristics i.e., color, odor, and taste were characterized and recorded using descriptive terminology. Derived properties like the angle of repose, bulk density, and tapped density were also performed as per the standard methods.

#### *Melting point*

The melting point was determined by the capillary method. The drug was filled in a glass capillary (sealed from one end) and it was tied with a thermometer having a capacity of

360ºC and the thermometer was kept in a water bath (heated gradually with burner). The temperature was noted down at which powder was melted.

***Standard solubility study***

Saturation solubility of Azilsartan was determined in distilled water, methanol, 0.1N HCL, and phosphate buffer (pH 6.8 and pH 7.4). All media were prepared and an excess amount of Azilsartan was added to each of them and kept in an incubator shaker at a speed of 200 rpm for 24 hours at 34ºC. After 24 hr., the solution was centrifuged at 2000 rpm for 15 min. The supernatant was diluted with the respective media solution and the absorbance was measured at 250 nm using a UV-visible spectrophotometer (V-730, JASCO, Japan) and solubility was calculated.[13]

**Excipient screening**

***Solubility study in oil***

Two ml of each component was taken in screw cap vials with a known quantity of the excess drug. A vortex mixer was used to facilitate the solubilization. Sealed vials were kept on an isothermal mechanical shaker at 40±2ºC for 72 hours. After equilibrium, each test tube was centrifuged at 6000 rpm for 20 min using a centrifuge. The supernatant was filtered through a membrane filter using a 0.45 µm filter disk. The filtered solution was appropriately diluted with methanol and UV absorbance was measured.

***Emulsification study with surfactant***

Briefly, 5 ml of surfactant was added to 5 ml of the oil phase, the mixture was heated at 50ºC for the homogenization of the components. Each mixture, 100 µl, was then diluted with 50 ml distilled water in a glass stopper conical flask. The number of flask inversions is recorded to yield homogenous emulsion. % transparency was evaluated at UV absorbance wavelength using distilled water as a blank. The emulsion was further observed visually for any turbidity or phase separation.

***Co-surfactant study***

The screenings were done based on % transmittance and ease of emulsification. Mixtures of the co-surfactant selected surfactant and the selected oil were prepared and evaluated similarly as described in the above section on surfactant.

**Drug excipient compatibility study[2]**

Azilsartan was intimately mixed with probable excipients in the formulations in the ratio as in dosage forms and filled in the glass vials. These glass vials were exposed to various storage conditions mentioned in ICH guidelines of stability study for drug substance for 1 month.

The conditions in which the mixtures are kept were controlled room temperature (CRT), 40ºC (accelerated room temperature), and 37ºC with 75% RH. For stability study, the drug was kept with each selected component and the parameters were recorded.

**Fourier transform infrared spectroscopy study[2]**

The Fourier transform infrared (FTIR) spectral data of pure AZL, physical mixture of AZL with excipients, and S- SMEDS were recorded for the determination of possible interaction between AZL and excipients by the KBr disc method using FTIR spectroscopy (Affinity-1 FTIR spectrophotometer, Shimadzu Corp., Kyoto, Japan). The sample disc was placed in the sample holder and scanned from 4000 to 400 $cm^{-1}$ at a resolution of 4 $cm^{-1}$.

**Preliminary batches**

***Selection of oil concentration:***

The optimum concentration of oil required for the formation of microemulsion different concentration of capryol 90 was used. Polymer concentration and the stirring speed was constant. The microemulsions formed were observed for their physical characteristics.

***Selection of surfactant concentration:***

Optimum concentrations of surfactant required for the formation of microemulsion different concentrations of labrasol were used. Polymer concentration and the stirring speed was constant. The microemulsion formed was observed for their physical characteristics.

***Selection of Co-surfactant concentration:***

Optimum concentrations of co-surfactant required for the formation of microemulsion different concentrations of PEG 400 were used. Polymer concentration and stirring speed were constant. The microemulsion formed was observed for their physical characteristics.

**Formulation and development[2]**

***Formulation and development of self-micro-emulsifying drug delivery system (Construction of phase diagram)***

To determine the concentration of components in the existing range of SMEDDS, the pseudo-ternary phase diagrams were constructed at ambient temperature using a water titration method. Oil, surfactant, and co-surfactant were grouped in different combinations for phase studies. Surfactant and co-surfactant ($S_{mix}$) in each group were mixed in weight ratios of 1:0, 1:1, 1:2, and 3:1 (w/w), respectively. For each phase diagram, the oil and specific $S_{mix}$ ratio (Capryol 90: PEG 400) were mixed thoroughly for 5 min in different weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different glass vials and placed in an oven at 50ºC for 1 hour then placed at room temperatures for 24 hours. Each isotropic mixture was slowly titrated with water (from 5% to 95%). The mixtures in vials were stirred on a magnetic stirrer for 2 min and allowed to equilibrate after each addition of water. The change in physical state from transparent to turbid and vice versa were visually observed and marked on the three components ternary phase diagram where each axis represented the oil, $S_{mix,}$ and water, respectively. Phase diagrams were plotted using the trial version of CHEMIX ternary plot software (CHEMIX School 7).

The turbidity of the samples indicated the formation of a coarse emulsion. A clear isotropic solution indicated the formation of a microemulsion. The formation of microemulsion was monitored visually for turbidity-transparency-turbidity. [14]

***Preparation of Azilsartan SMEDDS***

Accurately weighed quantity of surfactant & co-surfactant taken and vortexed for 5-10 minutes. The $S_{mix}$ was then placed in an oven at 50ºC for 1 hour and oil was added in each formulation with a different ratio to $S_{mix}$. Then the mixture was shaken by vortex shaker for 5-10 minutes and placed in an oven at 50ºC for 1 hour to form an isotropic mixture. Finally, the drug Azilsartan (AZL) was added to these isotropic formulations and mixed by vortex shaker until a clear solution is obtained.

***Optimization of microemulsion by D-optimal design***

D-optimal design and the desirability function were applied to optimize a self-micro emulsifying drug delivery system (SMEDDS). The optimized key parameters were the

following: oil (A), surfactant (B), and co-surfactant (C) which were identified as the independent variables affecting the globule size ($R_1$) and % transmittance ($R_2$) (dependent variables).

Three formulation variables, a surfactant mixture, and an oil mixture were included in the experimental design.

**Characterization of SMEDDS[2]**

***Visual observation, self-emulsification efficiency, and dispersibility test of SMEDDS***

Prepared formulation of SMEDDS containing drug was diluted with 250 ml of distilled water and phosphate buffer of pH 6.8 at 37ºC, mixed using vortex shaker for 5 minutes and stored for 24 hours. Finally, it was checked or observed visually for phase separation and precipitation. Those formulations exhibiting a negligible phase separation were taken for further study.

***Thermodynamic stability test***

Optimized formulations were then subjected to different thermodynamic stability study tests namely centrifugation and freeze-thaw cycles. In the centrifugation study, the formulation was added to deionized water in ratio 1:20 and centrifuged at 3500 rpm for 30 minutes, and observed for phase separation or precipitation. In the freeze-thaw cycle, the formulations which are stable under centrifugation were subjected to a freeze-thaw cycle. In this study, SMEDs were diluted with deionized water in a 1:2 ratio and subjected to two freeze-thaw cycles between -20ºC and +25ºC by storing at each temperature for 48 hrs. and samples were observed for phase separation.

***Determination of optical clarity/ Percent Transmittance study***

The optical clarity of the aqueous dispersion of SMEDDS was measured spectrophotometrically. The formulations were diluted 100 times by distilled water (1:100). The resulting microemulsion was observed for any precipitation and the percentage transmittance as a determinant of optical clarity for the prepared SMEDDS was measured at 250 nm using distilled water as blank[18].

***Determination of globule size and PDI***

Droplet size is an important factor affecting self-emulsification performance as it determines the rate and extent of drug release. Before measurement, 1 ml of each SMEDDS formulation was diluted 10 times with distilled water. The globule size and poly dispersibility index (PDI) of the formed microemulsion were determined by dynamic light scattering (DLS) using a photon correlation spectrometer (Zeta sizer, Malvern Instruments LTD, Malvern, UK), which analyses the fluctuation in light scattering due to Brownian motion of the particles. Light scattering was monitored at 25ºC at a scattering angle of 90º [19].

***Determination of Zeta potential***

The zeta potential of the diluted SMEDDS was determined using a Zeta sizer (Malvern Instruments Ltd., Malvern, UK). Samples were placed in a clear disposable cuvette and the results were recorded. The charge on emulsion droplets and their zeta potential values were obtained [39].

***Drug content uniformity study***

The percentage drug content of formulations was determined from the calibration curve by using UV. Drug loading efficiency for determining the AZL content, 1 ml of SMEDDS containing AZL was diluted with methanol in a volumetric flask and mixed well by shaking or inverting the flask 2 to 3 times. Samples were prepared in triplicate and absorbance was measured after suitable dilutions at 250 nm using a UV spectrophotometer (JASCO, V-730, Japan). The amount of AZL present in each formulation was calculated from a calibration curve[20].

***Viscosity study***

The viscosity of prepared SMEDDS was measured before and after dilution using a spindle number S31 of Brookfield viscometer (DV-II+ Pro) at 50 rpm. The viscosity determinations were carried out at 25 ± 0.5ºC[21].

***In vitro dissolution studies***

For *In vitro* dissolution/drug release studies both the formulations were filled in size "1" hard gelatin capsule and placed in the rotating basket of US-type I (USP XXIII dissolution test apparatus at 50 rpm) dissolution test apparatus in 900 ml phosphate buffer of pH 7.8 at

37±0.5ºC. *In vitro* drug release study was performed for 50 minutes. Samples were withdrawn at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 minutes time intervals and filtered through a 0.45µ filter. The samples were then analyzed using a UV spectrophotometer (JASCO V-730, Japan) at 250 nm and the concentration of the AZL was determined from the standard calibration curve[22].

**Screening of casting solvent[2,22]**

The SMEDF was prepared using the Solvent Evaporation technique with the help of the solvent casting method. For that, the film-forming polymers (0-40%), plasticizers (0-20%), sweetener (3-6%), flavors (q.s.), and saliva stimulating agents (2-6%) were screened.

One mL of SMEDS was incorporated into the film-forming polymer solution by the emulsion evaporation technique. The detailed method was described in the preparation of SMEDF.

**Preparation of SMEDF[2,22]**

The polymer HPMC (hydroxypropyl methylcellulose) E5/ HPMC E15 (10%) was stirred in methanol for 10 minutes and then citric acid was added with constant stirring in a magnetic stirrer to obtain a smooth dispersion and allowed to stand for 15 minutes to expel the entrained air bubbles. After that, saccharin and vanillin were added and stirred continuously till a clear emulsion is formed. At this stage, the SMEDS containing Azilsartan was added to obtain a homogenous mixture. The solution was stirred for 1 hour until a clear is emulsion formed. Then the solutions were poured into the petri dish and allowed to stand for 3 hours. The 2x2 size was cut out of the dried film and taken for evaluation of self-micro-emulsifying mouth dissolving film.

**Evaluation of Azilsartan self-micro-emulsifying mouth dissolving film[2,22]**

***Transparency***

Evaluated by the visual appearance of oral film and categorized in various levels such as best, good, medium, bad for transparency.

***Film thickness***

Film thickness is measured by using a micrometer screw gauge or calibrated digital vernier caliper. The thickness of the sample film was measured in ten different positions in triplicate

and the average value was calculated. This evaluation is necessary to calculate the uniformity of thickness which is directly related to the accuracy of dose in the film.

***Tensile strength*/Folding endurance**

Evaluation is done by using Tensiometer. Tensile strength is defined as the maximum stress required for the film breaking. This test is executed to measure the mechanical strength of the film. It can be calculated by the following equation:

Tensile strength = load at failure*100/ strip thickness*strip width

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times folded without breaking is noted as the value.

The surface texture was evaluated by the visual appearance of oral film and categorized in smooth to rough surface indicated by sign '+'.

***Disintegration time***

A film was placed into 2 ml of distilled water in the disintegration tester at room temperature and the time taken to get the strip disintegrated was measured as disintegration time. Time taken by the film to dissolve completely is measured as the disintegrating time[23].

***Drug content uniformity study***

Perform the drug content test to ensure the uniform distribution of the drug. Place each film unit in 10 ml of the volumetric flask containing the solvent. Obtain homogenous solution with constant stirring and filter. Determine the drug content by UV after proper filtration.

***In vitro drug release study***

Performed *in-vitro* drug dissolution of SMMDF using USP paddle apparatus at 37ºC with a stirring speed of 75 rpm in 900 ml phosphate buffer pH 6.8. Five ml of samples were withdrawn at predetermined time intervals of 2, 4, 6, 8, and 10 min and replaced with the same volume of buffer. Collected samples were taken to determine the concentration at the appropriate wavelength using a UV-visible spectrophotometer.[25-28]

## RESULTS AND DISCUSSION

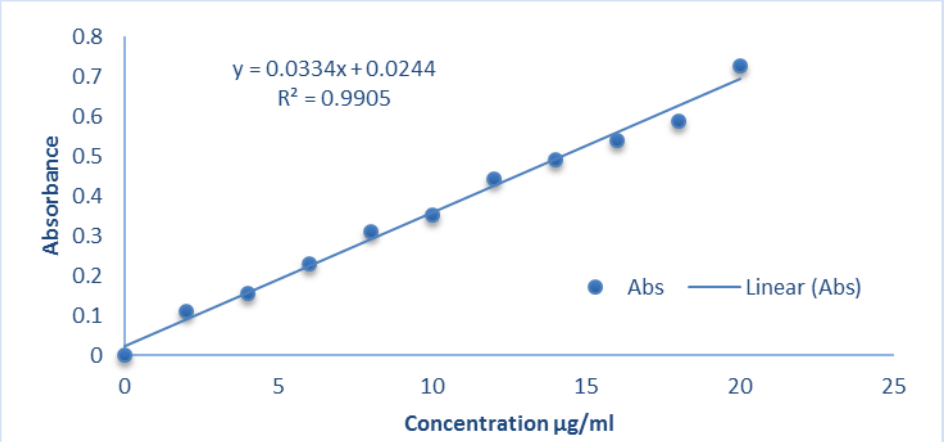



**Figure No. 1: Calibration curve of Azilsartan in pH 6.8.**

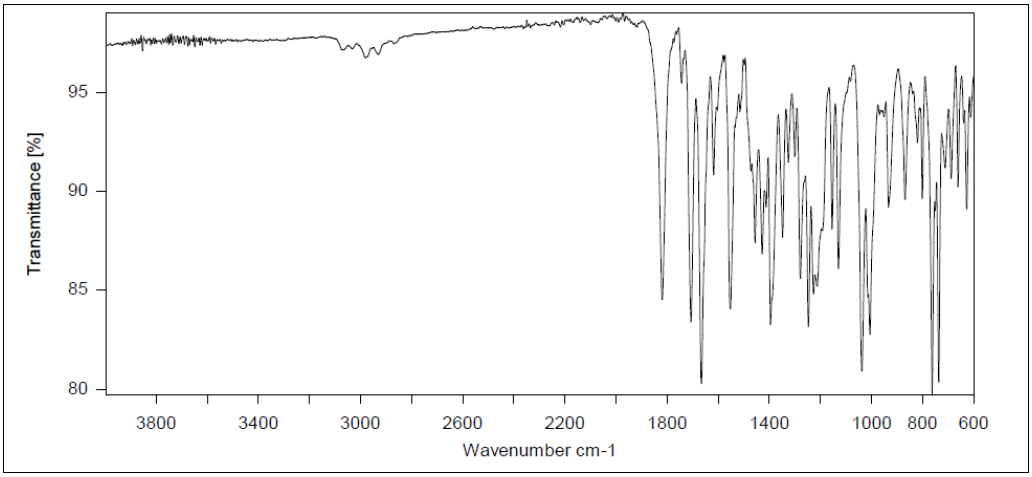



**Figure No. 2: FTIR spectra of pure Azilsartan.**

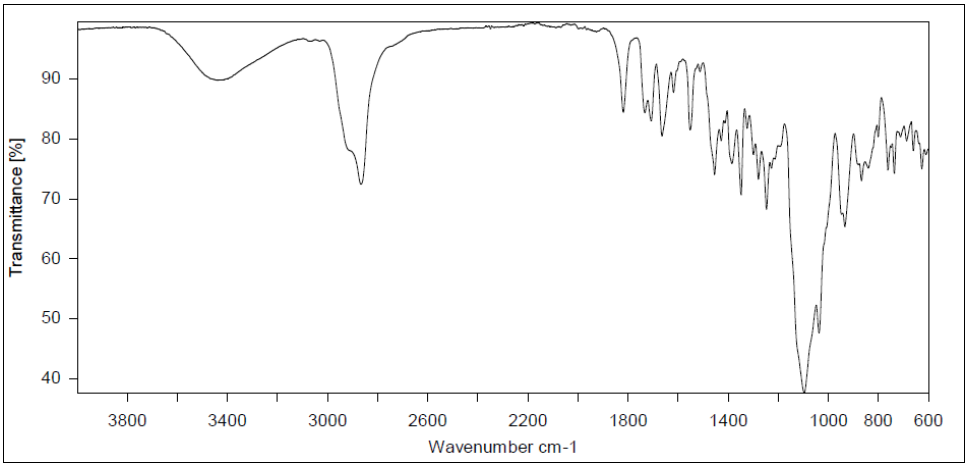


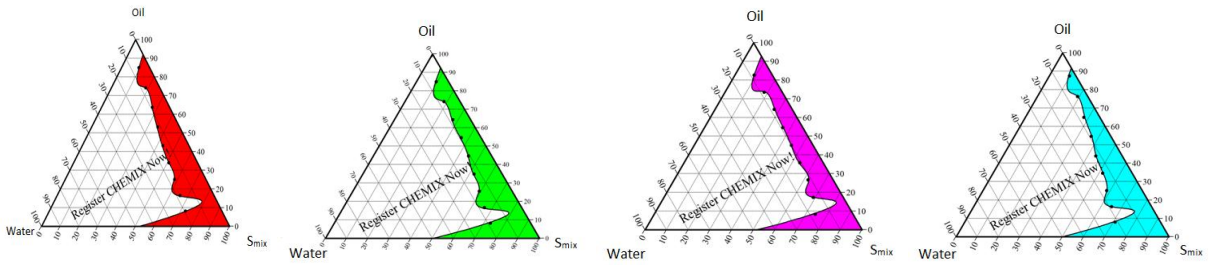

**Figure No. 3: FTIR spectra of azilsartan+SMEDDS.**

**Table No. 1: Results of Preformulation parameter**

| Functional group | Reported value | Recorded value | Drug + polymer |
|---|---|---|---|
| Carboxylic acid | 1550-1610 | 1553 | 1552 |
| Ether | 1300-1420 | 1395 | 1385 |
| Amide | 1630-1680 | 1666 | 1664 |

**Table No. 2: Drug solubility in oil, surfactant, and co-surfactant**

| Excipients | Conc | Excipients | Conc | Co-surfactant | Conc |
|---|---|---|---|---|---|
| Oleic acid | 25 mg/ml | Tween 20 | 35 mg/ml | Methanol | 45 mg/ml |
| Labrafac lipophile WL 1349 | 34 mg/ml | Labrafil M1944CS | 20 mg/ml | Transcutol P | 55 mg/ml |
| Peppermint oil | 33 mg/ml | Labrafil M2125CS | 15 mg/ml | PEG 400 | 65 mg/ml |
| Rose oil | 20 mg/ml | Cremophore ELP | 32 mg/ml | | |
| Almond oil | 15 mg/ml | Tween 80 | 40 mg/ml | | |
| Cinnamon oil | 10 mg/ml | Labrasol (selected) | 45 mg/ml | | |
| Capryol 90 (selected) | 36 mg/ml | | | | |




**(a): 1:1 ratio** **(b): 1:2 ratios** **(c): 2:1 ratio** **(d): 1:3 ratio**

**Figure No. 4: Pseudo-ternary phase diagram**

**Table No. 3: Levels of polymer for D-optimal design batches**

| INGREDIENTS | Low level | High level |
|---|---|---|
| A: Oil | 4 | 20 |
| B: Surfactant | 25 | 35.5 |
| C: Surfactant | 50 | 71 |
| A+B+C | 79 | 100 |

**Results and Discussion of SMEDDS**

**Determination of UV absorption maxima**

Standard solutions of Azilsartan with different concentrations were analyzed in the UV range 200-400 nm where maximum absorbance showed 250 nm (n=3).

**Preformulation studies**

Preformulation parameters were studied i.e., organoleptic properties, solubility, physical and derived properties indicating white crystalline powder with no characteristic odor, bitter taste, insoluble in water, 212-214℃ melting point, etc.

**Drug Excipient compatibility study**

There is no change in the parameters which were color, odor, taste, degradation, and physical change. The studies were observed for 1 month and the parameters were recorded before storage and after storage. All the mixtures showed no change in room temperature, controlled room temperature (25ºC and 60±5% RH) and with higher temperatures (45ºC and 75±5% RH). There is no color, characteristic odor, bitter taste, no degradation, and liquid taste were recorded.

FTIR study (Figure No. 2 and 3) of pure drug and drug plus polymer mixture showed that the sample of Azilsartan is pure and the formulation complies the criteria of standard value showing no interaction with the polymers under study. The peaks of carboxylic acid, ether and amide functional groups were within the reported range (Table No. 1).

Results of the solubility study from Table No. 2 indicated that the drug solubility was found highest in Capryol 90 (oil), Labrasol (surfactant), and PEG 400 (Co-surfactant) amongst all

oils, surfactants, and co-surfactants under study. So, Capryol 90, Labrasol, and PEG 400 were selected for further study.

According to the pseudo-ternary diagram (Figure No. 4), the 1:2 ratio showed maximum area coverage where the co-surfactant is double than surfactant and formed better emulsifying property at that area. So, the SMEDDS formulations have proceeded with 1:2 ratios.

Optimization of microemulsion by D-optimal design and Overlay plot was potted with the help of design expert software. The results of the mathematical analysis of the data (Table No. 5 and 6) demonstrated (Figure No. 5) showed significant interactions among the formulation variables like globule size & percentage transmittance. From equation 1 it is seen that the interaction of oil and surfactant mixture has a negative effect on globule size while oil and Co-surfactant have more effect on globule size of the formed microemulsion. While from equation 2 it is indicated that the surfactant: cosurfactant mixture has a more pronounced effect on % Transmittance of the formed microemulsion. As the concentration of Smix increased the % transmittance increased. Table No. 5 and 6 it is shown $p<0.05$ indicating the model terms are significant in the case of globule size of the formed microemulsion. Model terms are non-significant in the case of % T (Transmittance).

The equations are as follows:

Globule size ($R_1$): 0.063*A+0.043*B+0.028*C-0.146*A*B+0.0053*A*C+0.049*B*C-----(1)

% Transmittance($R_2$): 147*A+79.85B+94.42*C-85.97*A*B-52.62*A*C+47.065*B*C-----(2)

Visual observation showed that the batches SM2, SM4, SM8, SM9, and SM10 were forming clear and transparent emulsion indicating good dispersibility and self-emulsification efficiency. So, were selected for further study.

The thermodynamic stability study was done to check the phase separation of the SMEDDS. It was found that formulation batch SM2, SM4, and SM10 showed no phase separation and thus were selected for further studies.

The prepared batches (Table No. 4) of SMEDDS are evaluated from which SM10 batch was the best out of all the batches. The zeta potential of the SM10 was in the range of ±20 mv, globule size within the range of 0-5 mm, and PDI in the range of 0-1 as compared to other batches. So, SM10 was selected as the best batch of all the SMEDDS batches and hence, evaluated further for *in vitro* drug release studies.

From Figure No.6 it can be revealed that the cumulative percentage drug release of the SM10 batch was 70.5 % as compared with 40% drug release of the marketed formulation within 50 mins. Thus, the optimized batch formulation gave more drug release in 50 min as compared with the marketed formulation.

**Table No. 4: Zeta potential, globule size, PDI, % transmittance, viscosity, conductance, and drug content.**

| Batches | Zeta potential | Globule size | PDI | % Transmittance | Viscosity | Conductance | Drug content |
|---|---|---|---|---|---|---|---|
| SM1 | 5.93 | 0.1462 | 3.08 | 83.5 | 0.921 | 204 | 97.20% |
| SM2 | -0.81 | 4.95 | 0.1157 | 95.8 | 0.927 | 227 | 99.00% |
| SM3 | 0.81 | 0.0523 | 6.98 | 76.4 | 0.925 | 232 | 91.20% |
| SM4 | 10.76 | 3.53 | 0.524 | 90.2 | 0.932 | 227 | 95.60% |
| SM5 | -12.30 | 0.0594 | 11.44 | 94.8 | 0.927 | 231 | 96.40% |
| SM6 | 15.4 | 0.0422 | 14.75 | 84.1 | 0.946 | 211 | 98.80% |
| SM7 | -8.48 | 0.0594 | 8.67 | 83.2 | 0.937 | 232 | 98.20% |
| SM8 | 5.36 | 0.562 | 0.02 | 71 | 0.919 | 249 | 99.10% |
| SM9 | 2.98 | 0.332 | 0.765 | 99 | 0.921 | 241 | 92.80% |
| SM10 | 23.49 | 0.02229 | 0.143 | 98.6 | 0.939 | 231 | 99.30% |
| SM11 | -3.89 | 2.223 | 0.842 | 97 | 0.94 | 226 | 98.90% |

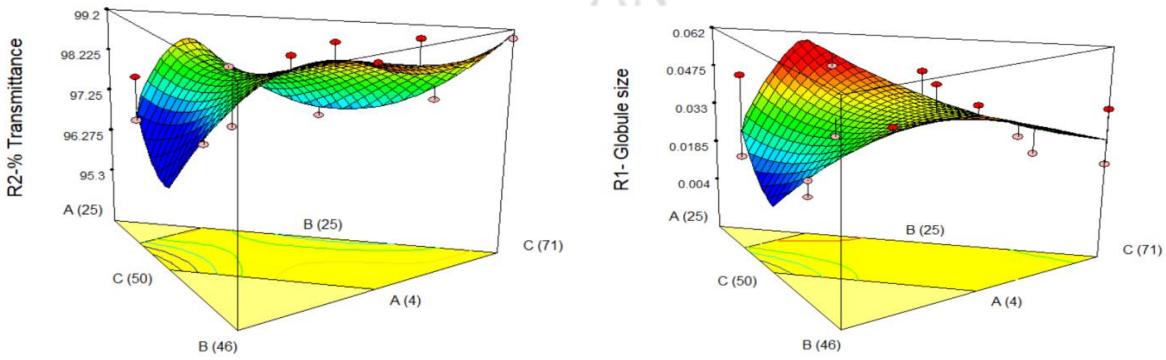



**Figure No. 5: 3D contour plot of the effect of Oil (A), Surfactant (B) & Co-surfactant(C) on % Transmittance and Globule size**

**Table No. 5: Analysis of Variance of dependent variables using D-optimal design**

| Source | SS | df | Mean Square | F Value | p-value | R - Square |
|---|---|---|---|---|---|---|
| **Globule size (R1)** | | | | | | |
| Model | 8.429111 | 6 | 1.404852 | 3.807314 | 0.0359 | 0.717371 |
| Residual | 3.320889 | 9 | 0.368988 | | | |
| Total | 11.75 | 15 | | | | |
| **%Transmittance (R2)** | | | | | | |
| Model | 0.001588 | 6 | 0.000265 | 2.060486 | 0.1584 | 0.578709 |
| Residual | 0.001156 | 9 | 0.000128 | | | |
| Total | 0.002744 | 15 | | | | |

**Table No. 6: Analysis of Variance of dependent variables**

| Source | Std. Dev.[a] | R-Square[b] | Adjusted R-Square[c] | Predicted R-Squared | PRESS[d] | |
|---|---|---|---|---|---|---|
| Globule size (R1) | | | | | | |
| Linear | 0.0142 | 0.0430 | -0.1042 | -0.5259 | 0.00418 | |
| Quadratic | 0.0110 | 0.5558 | 0.33382 | -0.2992 | 0.00356 | Suggested |
| Special Cubic | 0.0113 | 0.5787 | 0.29784 | -0.5086 | 0.00413 | |
| Cubic | 0.0119 | 0.6896 | 0.22424 | -27.0659 | 0.07700 | |
| % Transmittance(R2) | | | | | | |
| Linear | 0.6884 | 0.4756 | 0.3950 | 0.2530 | 8.77639 | Suggested |
| Quadratic | 0.7259 | 0.5515 | 0.3273 | -0.0782 | 12.6691 | |
| Special Cubic | 0.6074 | 0.7173 | 0.5289 | 0.1779 | 9.65860 | |
| Cubic | 0.3277 | 0.9451 | 0.8628 | -4.1546 | 60.5675 | Suggested |

b Percentage of Response variable variation, the higher the value the better the model fits the data.

c Percentage of Response variable variation, based on its relationship with one or more predictor variable.

a Standard Error of the Regression represents the standard distance between the data value and the fitted regression line.

d Prediction Error sum of squares the smaller the PRESS value, the better the model predictive ability.

**Table No. 7: Selected concentration of polymers**

| Polymer | | Best concentration |
|---|---|---|
| Film-forming polymer | HPMC E5 | 10% |
| Saliva stimulating agent | Citric acid | 6% |
| Sweetener | Saccharin | 4% |
| Flavor | Vanillin | q.s. |

**Dose calculation:**

Diameter = 9 cm, Radius = 4.5 cm, Area = $A = \pi r^2$ = 3.14 x $(4.5)^2$= 314 x 20.25= 63.58 $cm^2$

A Film was cut in 2x2 cm, So, 4 $cm^2$ = 40, 63.58 = ? = 63.58x40/4 = 635.85 mg drug.

So, 1 ml of SMEDDS contains 635.85 mg drug. In each 2x2 cm film – 40 mg of the drug is present.

**Table No. 8: Formulation and development of Azilsartan self-micro-emulsifying mouth dissolving film by emulsion evaporation technique.**

| Batches | Drug+ SMEDDS | HPMC E5 (%) | HPMC E15 (%) | Citric acid (%) | Saccharin (%) | Vanillin (%) |
|---|---|---|---|---|---|---|
| SM10A | 1 ml | 0.8 | - | 0.6 | 0.4 | q.s. |
| SM10B | 1 ml | 0.9 | - | 0.6 | 0.4 | q.s. |
| SM10C | 1 ml | 10 | - | 0.6 | 0.4 | q.s. |
| SM10D | 1 ml | - | 0.8 | 0.6 | 0.4 | q.s. |
| SM10E | 1 ml | - | 0.9 | 0.6 | 0.4 | q.s. |
| SM10F | 1 ml | - | 10 | 0.6 | 0.4 | q.s. |

**Table No. 9: Results for film thickness, folding endurance, disintegration time, and drug content.**

| Batches | Weight (mg) | Folding endurance | Thickness | % Drug content | Disintegration time (sec) |
|---|---|---|---|---|---|
| SM10A | 24.36±0.09 | 88.0±1.00 | 0.6±0.087 | 97.37±1.28 | 28±4.6* |
| SM10B | 35.2±1.5 | 90.6±3.57 | 0.8±0.11 | 98.34±2.46 | 26±3.6 |
| SM10C | 42.5±1.61 | 96.6±2.52 | 1.1±0.03 | 99.13±1.09 | 25±4 |
| SM10D | 44.51±1.85 | 92.33±1.82 | 1.1±0.5 | 98.03±1.64 | 35±1.7 |
| SM10E | 44±0.57 | 90.23±0.21 | 1.1±0.9 | 98.67±1.28 | 40±2.6 |
| SM10F | 48±1.00 | 89.23±1.00 | 1.1±0.99 | 99.91±2.43 | 46±3 |

*Results taken in triplicate where, n=SD

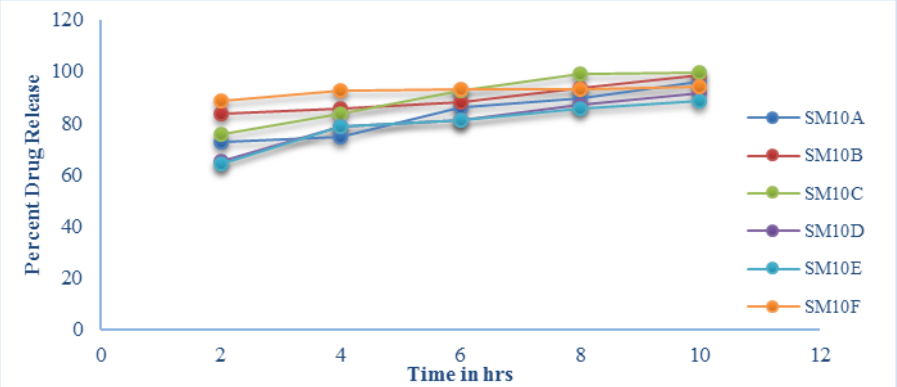



**Figure No. 6: Percentage drug release of all the formulations**

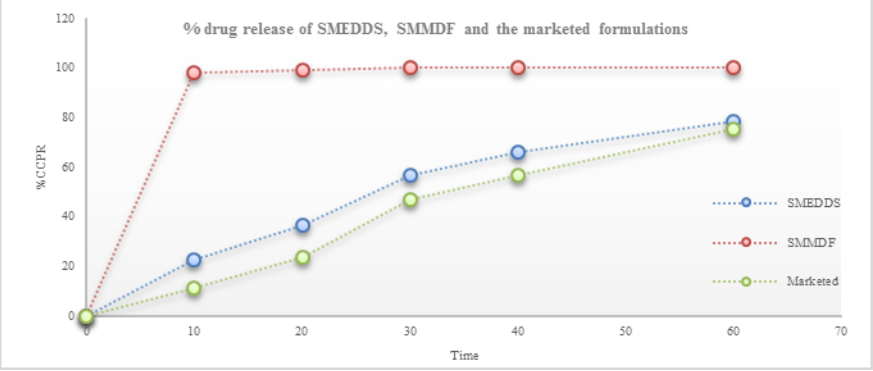



**Figure No. 7: % drug release of SMEDDS, SMMDF, and the marketed formulations.**

**Evaluation of Azilsartan self-micro-emulsifying mouth dissolving film**

HPMC was selected for the formulation of SMMDF as it showed good film-forming capacity with a 10% concentration. Citric acid (6%) was used as the saliva stimulating agent. Saccharin at 4% gives enough sweetness for the film. And vanillin as a flavoring agent to give a good fragrance and smell. (Table No. 7).

SM10A, SM10B, and SM10C showed good transparency, smooth surface, and better film-forming capacity as they are flexible (Table No. 8).

The SM10B and SM10C batch showed better results. The folding endurance of the film is higher than that of all batches which suggests that the film will not easily break. The most important evaluation is disintegration time which is especially important for the fast-dissolving film was around 25-26 sec which is less than all the batches and suggesting the film gets dissolved within 30 sec in the buccal mucosa. (Table No. 9)

SM10C showed a higher % release which is 90% in 10 min. as compared to the marketed formulation and the SMEDDS, SMMDF shows the higher and fast release of the drug within 10 minutes. (Figure No. 6 and 7)

The selected batch SM10C was transparent, flexible, and smooth. The weight of the selected film was 42.5±1.61. The folding endurance was 96.6±2.52. The thickness was 1.1±0.03. The drug content was 99.13±1.09. The disintegration time of the selected film was 25±4 which is good as compared to the conventional marketed formulation and the self-micro-emulsifying drug delivery system. All the findings suggest that the films are the promising dosage form to release the drug at a faster rate which is good for patient compliance and geriatric patients.

Stability studies of optimized batch SM10C indicated 95% w/v drug release in 10 min, 98% Transmittance, and 99.32% drug content uniformity after three months.

**CONCLUSION**

In this study, a new self-micro-emulsifying mouth dissolving film of Azilsartan was prepared by incorporating self-micro-emulsifying components with solid film carriers including HPMC and citric acid. The SMMDF was disintegrated in water within 30 sec with reconstituted microemulsion which showed that the SMMDF preserved the self-micro-emulsification performances of SMEDDS.[24-26] From these results, it was suggested that presenting Azilsartan in the form of SMMDF kept distinguished advantages of mouth

dissolving films and the absorption enhancement as high as with liquid SMEDDS. Therefore, this new SMMDF may provide a useful oral solid dosage form with patient compliance for poorly water-soluble drugs.

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