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FORMULATION AND EVALUATION OF SELF EMULSIFYING DRUG DELIVARY SYSTEM FOR CANDESARTAN

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ABSTRACT

Preformulation studies were carried out for physical characteristics revealed that drug was white color crystalline powder, bitter in taste, odorless. The solubility of the drug was found freely soluble in methanol and ethanol, sparingly soluble in chloroform and slightly soluble in water. UV spectrum was found absorption maxima (λ_{max}) in scanning range of 200-400 nm was found to be at 263nm as per specification. The maximum solubility was determined in castor oil 143.63±1.51 mg/g and 122.83±2.56 mg/g of tween-80 as a surfactant phase and 178.26±2.05 mg/g of PEG-600 as a co-surfactant phase. The maximum % transmittance was found to be 87.7% at 3:2:1 (oil:surfactant:co-surfactant) ratio. Robustness to dilution was performed diluted with excess of water, standard phosphate buffer pH 6.8 and 0.1N HCl (500-900 ml) and was stored for 12 hours gives no precipitation or phase separation was found. Microscopic evaluation was performed morphology and structure of self emulsion using optical microscopy. The *in-vitro* performances of the formulation were visually assessed using the grading system. The emulsification time of SEDDS was determined as per procedure and maximum emulsification time was found in F2 formulation. The viscosities of the system were determined as such before and after dilution using Brookfield viscometer DV-E using spindle RV-6 at 100 rpm at 25±0.5^{O}C. F-2 and F-4 were the final preparations on the basis of different evaluation parameters e.g. Assessment of self emulsification were grade A for both, lesser Emulsification time 11±1.52 and 15±2.51 seconds, also lesser Turbidity (NTU) 20 & 21cps, smaller droplets of size 173 ± 2.53 & 141.7 ± 1.02 and higher drug content 95.42 ± 1.13 & 94.52 ± 1.41. Hence, **F-2 and F-4** formulations were selected for further evaluation for drug release. *In-vitro* drug Release of Candesartan SEDDS preparations were studied and

found F-2 = 94.18 and GF-4 = 91.27, were excellent preparation on the basis of drug release profile.

KEYWORD: Evaluation, Self Emulsifying Drug Delivary System, SEDDS, Candesartan.

INTRODUCTION

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development.[1] A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability.[2] Poorly soluble compound belongs to class II of BCS, also present many in vitro formulation obstacles, such as severely limited choices to delivery technologies and increasingly complex dissolution testing with limited or correlation to the *in-vivo* absorption.[3]

Self-Emulsifying Drug Delivery Systems (SEDDS) systems have the ability to emulsify in the presence of one or more surfactants in adding to oily phase.[4] The lipophilic drug is solubilize in the oily vehicle. The surfactant helps to disperse the oily vehicle in GI fluid, which leads to the formation of a micro-emulsion.[5] Advantagesof SEDDS are show the quick onset of action, Reduction in the Drug Dose, Ease of Manufacturing & Scale-up, Improves the oral bioavailability of the drug, Inter-subject and Intra-subject variability and food effects, Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.[6] No influence of lipid digestion process, Increase drug loading capacity.[7,8]

Candesartan is a BCS class II drug having low aqueous solubility and high permeability; hence its bioavailability is solubility rate limited.[9,10] Hence, the aim of the present investigation is to incorporate candesartan in self emulsifying drug delivery system and enhance the solubility, dissolution rate and avoid intra and inter subject variability of candesartan by self emulsifying drug delivery system.

MATERIAL AND METHODS

Candesartan was obtained from Cipla Pvt. Ltd. Indore (M.P.), castor oil from Finar Chemical (India) Pvt Ltd., Ahmedabad, and tween-80, PEG-600 from Hi Media Laboratories Pvt Ltd. UV- spectroscope of Systronics 2203 double beam, Bruker's FTIR spectroscopy, Zetasizer from Malvern instrument, Australia, Optical Microscope, Centrifuge and Magnetic stirrer of

Remi 2 MLH, Brookfield viscometer DV-E using spindle RV-6, Turbidimeter from Esico D-10-model 331, Japan were used.

Methods

Preformulation Study

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combination with excipients.

Physical Characteristics

A small quantity of drug powder was taken on butter paper and viewed in well-illuminated place. Very less quantity of drug was used to get taste with the help of tongue as well as smelled to get the order.

Solubility

A qualitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of drug. After each addition, the system is vigorously shaken and observed visually.

Partition Coefficient

First 25 µg/ml solution of pure drug in octanol was prepared. Then the mixture of octanol and water were mixed in ratio of 1:1. Then this mixture was mixed properly for 30 minutes. Further the mixture was allowed to stand for one hour. After this the mixture was centrifuged at 5000 rpm in 25^{O}C. Mixture was than separated & the absorbances of individual phases of water and octanol were measured by ultraviolet- spectroscopy.

Melting Point

The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

Ultra-Violet (UV) spectroscopy

Organic molecules when exposed to light in UV region they absorb light of particular wavelength depending on the type of electron transition associated with the absorption. The absorption maximum of drug was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Determination of λ_{max} of candesartan

10 mg of drug sample was weighed accurately and dissolved in 10 ml of methanol in 10 ml of volumetric flask and stock solution was prepared. 10ppm dilution was prepared and scanned from 200 – 400nm by UV spectrophotometer.

Calibration curve in pH 6.8 phosphate buffer

From stock solution various dilutions were prepared to get concentration, 0.2-2 µg/ml. The graph of concentration v/s peak area was plotted and data was subjected to linear regression analysis on the maximum absorbance (λ_{max}) 263 nm.

Infrared spectroscopy

Infra red spectrum of any compound gives information about the group present in particular compound. An Infrared spectrum of drug was taken using KBr pellets method. Various peaks in IR spectrum of pure drug were interpreted for presence of different functional group. The IR spectrum was recorded using on Bruker's FTIR spectrophotometer and presented in Figure.

Screening of the Vehicles

a. Solubility of drug in oils: Solubility of pure drug (Candesartan) was determined in different oils. Excess amount of drug was added in 2 g of selected oils (castor oil, soya bean oil, arachis oil, sesame oil, sunflower oil, cod-liver oil, olive oil, oleic acid) until saturation occurs. Higher the quantity of drug incorporated in particular oil which was then selected as oily phase for SEDDS formulation.

b. Solubility of drug in surfactants and Co-surfactants: Solubility of pure drug was estimated in different surfactant and co-surfactants. Excess amount of drug was added in 2 g of selected surfactant and co-surfactant (tween-20, tween-40, tween-80, span-20, span-80, non-ionic phenyl ethyl oxalate, PEG-400, PEG-600, Propylene-glycol), until occurs. Higher

the quantity of drug in particular surfactant and co-surfactant which was then selected as surfactant phase for SEDDS formulation.

c. Preliminary screening of surfactant: Surfactant was selected on the basis of maximum solubility of drug. Surfactant for the peroral use was screened for emulsification ability according to method. Oily phase: surfactant ration taken (1:1, 1:2, 1:3, and 2:1). The mixture was gently heated at $50^{O}C$ for mixing of the components. Then, mixture, 50 mg, was then diluted with distilled water to 50 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversion required to yield homogenous emulsion. Emulsion was allowed to stand for 2 hours and their % transmittance was evaluated by UV-spectrophotometer using distilled water as a blank. Emulsion was further observed visually for any turbidity or phase separation.

d. Preliminary screening of co-surfactant

The selected oily phase and surfactant were used for the further screening of the co-surfactant for their emulsification ability. Mixture of oily phase : surfactant : co-surfactant taken (3:2:0.5; 3:2:1 and 3:2:2). The mixture was gently heated at $50^{O}C$ for homogenization of the components. Then, mixture, 50 mg was then diluted with distilled water to 50 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversion required to yield homogenous emulsion. Emulsion was allowed to stand for 2 hours and their % transmittance was evaluated by UV-spectrophotometer using distilled water as a blank. Emulsion was further more observed visually for any turbidity or phase separation.

Formulation Development

SEDDS forms fine o/w emulsion with only gentle agitation, upon its introduction into aqueous media. Since the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous. Surfactant forms layers around emulsion droplets and reduce the interfacial energy as well as providing mechanical barrier to coalescence. The visual test measures the apparent spontaneity of emulsion formation and the series of SEDDS were prepared and observed visually.

The 1:1 Smix ratios maximum area covered by particular Smix was selected and also which indicate that the area covered the maximum numbers of formulation and further subjected to spontaneous emulsification formation and percent transmittance test.

Spontaneous emulsification method

The self emulsifying properties of the formulations were assessed by visual observation. From these isotropic mixture 50 mg was weighed respectively and diluted to 50 ml with distilled water. The self emulsifying property was assessed by visual observation at 37°C. The content was mixed with magnetic stirrer. The tendency to form emulsion was judged "good" when droplets spread in water easily and form fine emulsion and judged "bad" when there is poor or no emulsion formation with immediate coalescence of oil droplets and further evaluated to percent transmittance.

On the basis of pseudo ternary phase diagram study 1:1 Smix ratio covers the largest area thus, it was selected. From these isotropic mixtures 50 mg was weighed respectively and diluted to 50 ml with distilled water. The spontaneous emulsification property i.e. turbid or clear of formulation was assesses by visual observation at 37^{O}C.

Percentage transmittance

The self-emulsifying properties of the formulations were assessed by percentage transmittance. From these isotropic mixture 50 mg was weighed accurately and diluted to 50 ml with distilled water. The content was mixed with magnetic stirrer. The tendency to form emulsion was judged "good" when droplets spread in water easily and form fine emulsion and judged "bad" when there is poor or no emulsion formation with immediate coalescence of oil droplets and further evaluated to percent transmittance.

On the basis of pseudo ternary phase diagram study 1:1 Smix ratio covered the largest area and hence was selected. From these isotropic mixtures 50 mg was weighed respectively and diluted to 50 ml with distilled water at 45-60^{O}C. The ease of formation of emulsion was monitored by noting down the number of volumetric flask inversion required to give uniform emulsion. The resulting emulsions were allowed to stand for 2 hours and their transmittance was assessed at 638.2 nm by UV double beam spectrophotometer using distilled water as blank.

Optimization of SEDDS formulation

On the basis of spontaneous emulsification method and percentage transmittance the total 9 formulations were selected and subjected to different thermodynamic stability study.

Thermodynamic Stability Studies

The physical stability of a lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipients matrix. In addition, poor formulation physical stability can lead to phase separation of the excipients, affected not only formulation performance, but visual appearance as well. In addition, incompatibility between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

a. Heating cooling cycle

Six cycles between refrigerator temperatures $4^{O}C$ and $45^{O}C$ with storage at each temperature for not less than 48 hours was studied. Those formulations which are stable at these temperatures were subjected to centrifugation test.

b. Centrifugation test

Passed formulations were centrifuged at 3500 rpm for 30 min (Remi-12C, Japan). That formulation that passes the thermodynamics stability studies was selected for further evaluations.

Evaluation of SEDDS formulations

a. Visual observation: 50 mg of formulation was diluted with 50 ml media like water, standard phosphate buffer (pH 6.8) and acidic buffer (pH 1.2) in order to determine appearance, color, etc.

b. Robustness to dilution: These systems when diluted with excess of water, standard phosphate buffer (pH 6.8) and 0.1N HCl (500-900 ml) and stored for 12 hours yield no precipitation or phase separation and are thus, said ‘robust to dilution’

c. Microscopic evaluation: The morphology and structure of self emulsion were studied using optical microscopy. To perform the microscopic observation, emulsion formulation was diluted with water 1/100. A drop of the diluted emulsion was directly deposited on the film grid and observed after drying

d. Physical stability of SEDDS formulations: The physical stability i.e. appearance, color, and pH of resulting emulsion under different storage conditions were also studied. For pH measurement sample was allowed to equilibrate at room temperature. 9 g of water was mixed

with 1 g of sample. The oil-water mixture was swirled to facilitate emulsification. The pH of emulsified sample was recorded using pH meter.

e. Percentage transmittance: The self emulsifying properties of the formulation were assessed by percentage transmittance. From these isotropic mixture 50 mg was weighed and diluted to 50 ml with distilled water, standard phosphate buffer pH 6.8 and 0.1N HCl respectively.

The ease of formation of emulsion was monitored by noting down the number of volumetric flask inversion required to produce uniform emulsion. The resulting emulsions were allowed to stand for 2 hours and their transmittance was assessed at 638.2 nm by UV double beam spectrophotometer using double distilled water as blank.

f. Assessment of efficiency of self emulsification: The efficiency of self emulsification was assessed using a standard US pharmacopoeia XXIII dissolution apparatus type II. One g of each formulation was added drop wise to 200 ml of either 0.1N HCl or distilled water at 37^{O}C. Gentle agitation was provided by a standard stainless steel dissolution paddle at 60 rpm. The lipid based formulations were assessed visually according to the rate of emulsification and final appearance of the emulsion. The *in-vitro* performance of the formulation was visually assessed using the following grading system.

- **Grade A:** Rapidly forming emulsion having a clear or bluish appearance.
- **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Fine milky emulsion formed within 2 minutes.
- **Grade D:** Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify longer than 2 minutes.
- **Grade E:** Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

g. Emulsification time: The emulsification time of SEDDS was determined according to USP XXIII, dissolution apparatus II. 0.5 g of the SEDDS formulations were introduced into 250 ml of 0.1N HCl or distilled water in 500 ml conical flask under action of magnetic stirrer rotating at constant speed. Emulsification time was done at room temperature.

h. Turbidity measurement: Turbidity of the resultant emulsion given a nephlometric turbidity unit (NTU) was measured using turbidimeter. Turbidity measurements were performed on the emulsion stored in a screw capped sample vials. Accuracy at the lower range of turbidity is essential especially for small and diluted emulsion with high surfactant concentrations. The largest source of error at low turbidity is the stray light, that is, the light that reaches the detector due to sources other than samples turbidity. The time requires dispersing the system completely and uniformly was measured.

0.5 ml of the SEDDS formulation was introduced into 250 ml of 0.1 N HCl or distilled water in 500 ml conical flask under action of magnetic stirrer rotating at constant speed. Emulsification was done at room temperature. After 5 min, surface of emulsion was examined for turbidity using Nephlo turbidimeter. The time requires to disperse system completely and uniformly was measured.

i. Viscosity determination: The SEDDS system is generally administered in soft gelatin or hard gelatin capsules so, it should be easily pourable into capsule and such system should not be too thick to create a problem. The rheological properties of the micro/ nano emulsion are evaluated by a Brookfield viscometer, Japan. This viscosity determination confirms whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if system has high viscosity then it is w/o type of the system. The viscosity of the system was determined as such before and after dilution using Brookfield viscometer DV-E using spindle RV-6 at 100 rpm at 25±0.5^{O}C.

j. Droplet size analysis: The droplet size of the emulsion was determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a zetasizer able to measure sizes between 10 and 5000 nm. Light scattering was monitored at 25^{O}C at an angle a 90^{o} angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particles is retained even after 100 times dilution with water which proves the system compatibility with excess water.

k. Zeta potential determination: The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SEDDS formulation was measured using a zeta meter system. The SEDDS were diluted with a ratio o 1:2500 (v/v) with distilled water and mixed with magnetic stirrer.

RESULT AND DISCUSSION

Preformulation Study

Physical Characteristics: on the physical observation of pure drug Candesartan found that it was Odourless, Bitter and White crystalline powder soluble in ethanol, methanol but slightly soluble in water. Its Partition Coefficient was 1.95 and melting point was 158-162^{O}C

Ultra-Violet (UV) spectroscopy

Determination of λ_{max} of candesartan

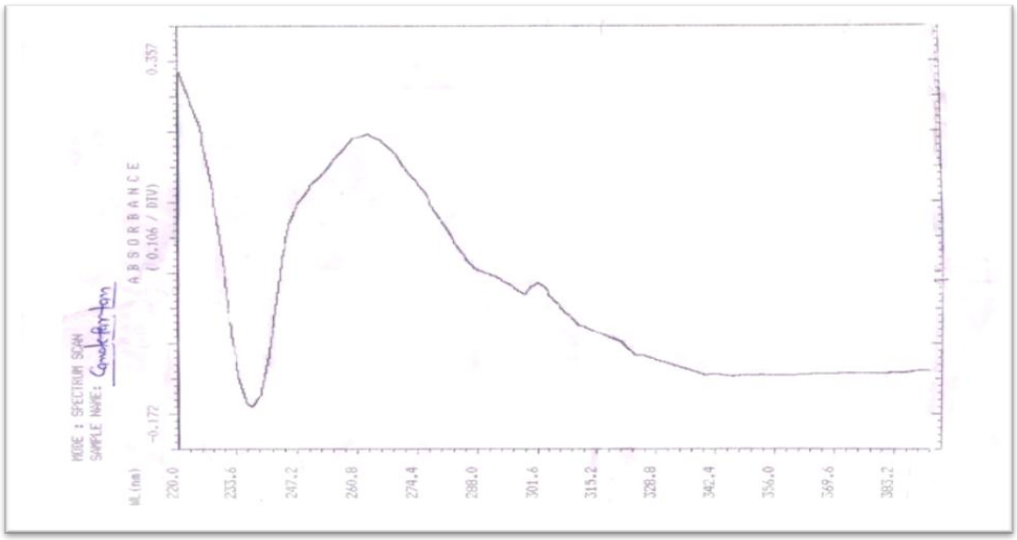

Fig: UV Spectrogram of candesartan standard drug.

Calibration curve in pH 6.8 phosphate buffer

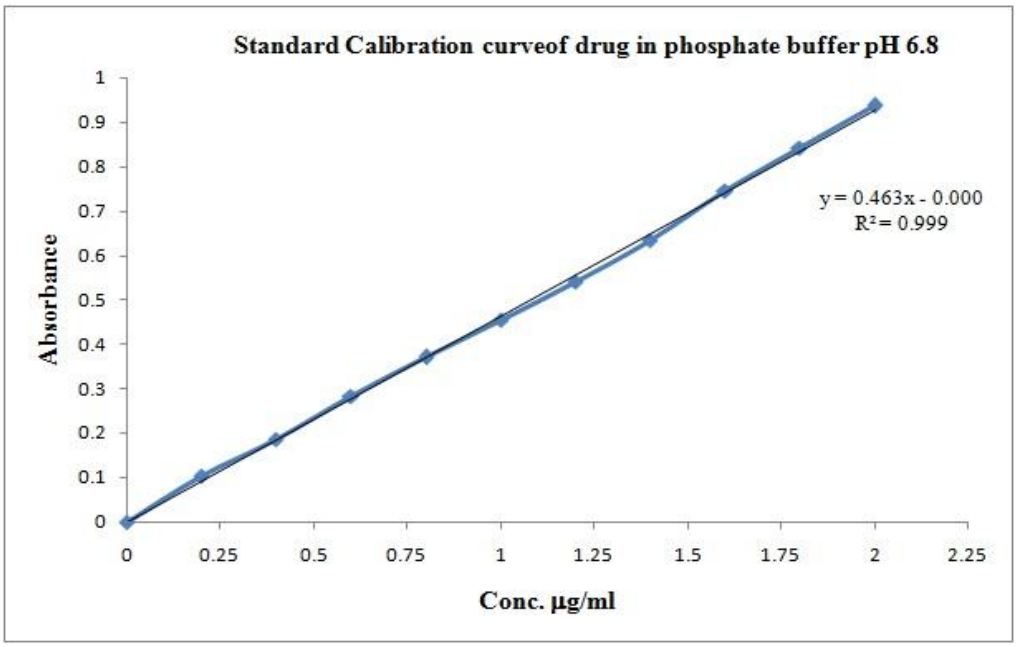

Figure 5.5 Standard curve of drug in standard phosphate buffer pH 6.8.

Screening of the Vehicles

Table 5.12: Solubility of drug in various oils, surfactants and Co-surfactants.

Oils	Solubility (mg/g)	Surfactants	Solubility (mg/g)
Castor oil	145.63 ± 1.51	Tween-20	71.7±1.53
Soyabean oil	52.08 ± 2.00	Tween-40	61.27±1.10
Arachis oil	48.47 ± 1.50	Tween-80	122.83±2.56
Sesame oil	37.43 ± 1.50	Span-20	39.36±1.76
Sunflower oil	25.26 ± 2.05	Span-80	68.13±1.45
Cod-liver oil	15.03 ± 2.01	N phenyl ethyl oxylate	112.06±1.00
Olive oil	12.3 ± 0.96	Propylene Glycol (PG)	108.3±1.93
Oleic acid	8.62 ± 0.97	PEG-400	170.73±1.55
		PEG-600	178.26±2.05

Where, value expressed as Mean ± SD, n=3

Table no.5.14: Preliminary screening of Surfactant.

Mixture	Visual observation	% Transmittance
1:1	Turbid	39.28
1:2	Transparent	50.07
1:3	Translucent	44.26
2:1	Turbid	21.79

Preliminary screening of co-surfactant

Table 5.15 Preliminary screening of co-surfactant.

Mixture	Visual observation	% Transmittance
3:2:0.5	Transparent	70.4
3:2:1	Transparent	87.7
3:2:2	Transparent	78.5

Formulation Development

Spontaneous emulsification method

Table no. 6.1: Spontaneous emulsification.

S. no.	Oil %	Smix %	Water %	Spontaneous emulsification	Percentage transmittance
1	2.430556	67.01389	30.55556	More clear	96.765
2	3.597122	68.34532	28.05755	More clear	96.509
3	5.617978	69.28839	25.09363	More clear	93.787
4	7.8125	70.3125	21.875	More clear	86.251
5	10.20408	71.42857	18.36735	Clear	76.857
6	12.76596	72.34043	14.89362	Clear	70.619
7	15.08621	71.12069	13.7931	Turbid	42.761
8	17.24138	68.96552	13.7931	Turbid	38.806
9	22.52252	67.56757	9.90991	Turbid	49.573
10	27.14932	63.34842	9.502262	Clear	70.337
11	30.837	57.26872	11.89427	Clear	70.725

12	33.78378	56.30631	9.90991	Clear	71.248
13	36.36364	54.54545	9.090909	Turbid	41.626
14	41.86047	51.16279	6.976744	Turbid	54.260
15	45.87156	45.87156	8.256881	Clear	70.012
16	52.88462	43.26923	3.846154	Turbid	40.501
17	57.69231	38.46154	3.846154	Turbid	24.304
18	62.80193	33.81643	3.381643	Turbid	28.748
19	67.96117	29.12621	2.912621	Turbid	23.950
20	72.81553	24.27184	2.912621	Turbid	19.067
21	77.6699	19.41748	2.912621	Turbid	32.996
22	82.92683	14.63415	2.439024	Turbid	37.109
23	87.80488	9.756098	2.439024	Turbid	30.688
24	91.34615	4.807692	3.846154	Turbid	44.751

Optimization of SEDDS formulation

Table 6.3: Optimized SEDDS formulation.

S. No.	Oil (%)	Smix (%)	Water (%)
1	3.597122	68.34532	28.05755
2	5.617978	69.28839	25.09363
3	7.8125	70.3125	21.875
4	10.20408	71.42857	18.36735
5	12.76596	72.34043	14.89362
6	27.14932	63.34842	9.502262
7	30.837	57.26872	11.89427
8	33.78378	56.30631	9.90991
9	45.87156	45.87156	8.256881

Thermodynamic Stability Studies: On the basis of the thermodynamic stability studies it was found that 6 formulations were passed and selected for further characterization. S. No. 2, 3, 4, 5, 7, and 9 was passed thermodynamic studies and it mentions F1, F2, F3, F4, F5, and F6 respectively.

Evaluation of SEDDS formulations

a. Visual observation

Table 6.5: Results of visual observation.

Formulation	Media	Appearance	Color
F1	Distilled water	Clear emulsion	White milky
	pH 1.2	Clear emulsion	White milky
	pH 6.8	Clear emulsion	White milky
F2	Distilled water	Clear emulsion	White milky
	pH 1.2	Clear emulsion	White milky
	pH 6.8	Bluish clear	White milky
F3	Distilled water	Clear emulsion	White milky
	pH 1.2	Clear emulsion	White milky

	pH 6.8	Bluish clear	White milky
F4	Distilled water	Clear emulsion	White milky
	pH 1.2	Slight turbid	White milky
	pH 6.8	Clear emulsion	White milky
F5	Distilled water	Clear emulsion	White milky
	pH 1.2	Slight turbid	White milky
	pH 6.8	Clear emulsion	White milky
F6	Distilled water	Clear emulsion	White milky
	pH 1.2	Slight turbid	White milky
	pH 6.8	Slight turbid	White milky

b. Robustness to dilution: all optimized formulations were subjected for Robustness to dilution found all were stable on dilution with Distilled water, 0.1N HCl and Phosphate buffer pH 6.8

c. Microscopic evaluation

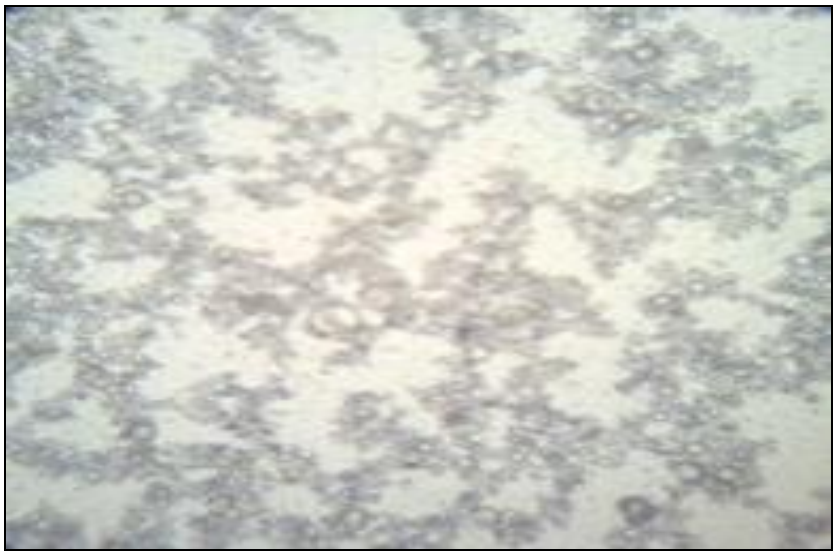

Figure no.: Microscopic evaluation.

d. Physical stability of SEDDS formulations

Table no.: Physical stability study.

Formulations	Time	Storage condition	Color	pH
F1	0 days	-	White milky	4.8
	5 days	RT	White milky	4.6
		$45^{O}C$	White milky	4.4
	15 days	RT	White milky	4.6
		$45^{O}C$	White milky	4.7
	25 days	RT	White milky	4.9
		$45^{O}C$	Turbid	4.6
F2	0 days	-	White milky	4.2
	5 days	RT	White milky	4.2

		45^{O}C	White milky	4.5
	15 days	RT	White milky	4.2
		45^{o}C	White milky	4.1
	25 days	RT	White milky	4.3
		45^{O}C	White milky	4.6
Formulations	**Time**	**Storage condition**	**Color**	**pH**
F3	0 days	-	White milky	4.9
	5 days	RT	White milky	5.1
		45^{O}C	White milky	4.9
	15 days	RT	White milky	4.8
		45^{O}C	Turbid	4.6
	25 days	RT	White milky	4.4
		45^{O}C	Turbid	4.6
F4	0 days	-	White milky	4.6
	5 days	RT	White milky	4.7
		45^{O}C	White milky	4.9
	15 days	RT	White milky	4.6
		45^{O}C	White milky	4.2
	25 days	RT	White milky	4.2
		45^{O}C	White milky	4.2
F5	0 days	-	White milky	4.2
	5 days	RT	White milky	4.5
		45^{O}C	White milky	4.2
	15 days	RT	White milky	4.8
		45^{O}C	Turbid	4.6
	25 days	RT	White milky	4.4
		45^{O}C	Turbid	4.6
F6	0 days	-	White milky	4.2
	5 days	RT	White milky	4.4
		45^{O}C	Turbid	4.3
	15 days	RT	White milky	4.4
		45^{O}C	Turbid	4.5
	25 days	RT	Turbid	4.6
		45^{O}C	Turbid	4.5

e. Percentage transmittance

Table no.: Percentage transmittance results.

Formulations	Percentage transmittance		
	Distilled water	Buffer pH 6.8	0.1N HCl
F1	97.509	91.003	95.264
F2	93.787	87.268	90.045
F3	86.251	81.028	81.000
F4	77.857	69.278	76.282
F5	73.725	71.243	73.474
F6	70.824	68.483	68.212

f. Assessment of Self Emulsification efficiency, Emulsification time, Turbidity measurement

Table no.: Assessment of self emulsification and another parameters result.

Parameters		F1	F2	F3	F4	F5	F6
Assessment of self emulsification		Grade A	Grade A	Grade B	Grade A	Grade B	Grade C
Emulsification time (Second)		20±4.04	11±1.52	21±3.60	15±2.51	24±1.73	30±2.00
Turbidity (NTU) 1000 NTU		005	011	018	028	048	068
Viscosity (cps)	Before dilution	22	20	24	21	28	31
	After dilution	10	9	12	9	13	15

Where- value expressed as Mean ± SD, (n=3)

NTU- Nephlometric turbidity unit

Droplet size analysis, Zeta potential, Poly Dispersity Index (PDI) and Drug content (%) of

Table no. 18: Characterization of selected candesartan SEDDS formulations.

Formulation Code	Droplet size (nm)	Zeta potential (mV)	Poly Dispersity Index (PDI)	Drug content (%)
F-1	231.3 ± 4.24	14.2 ± 1.42	0.402 ± 0.03	93.21 ± 1.22
F-2	173.2 ± 2.53	13.2 ± 1.45	0.329 ± 0.04	95.42 ± 1.13
F-3	183.3 ± 1.39	12.4 ± 2.66	0.424 ± 0.01	89.32 ± 2.13
F-4	141.7 ± 1.02	14.6 ± 1.37	0.299 ± 0.05	94.52 ± 1.41
F-5	243.5 ± 2.33	13.5 ± 1.86	0.443 ± 0.03	93.31 ± 2.13
F-6	212 ± 1.42	14.4 ± 0.56	0.426 ± 0.08	91.42 ± 1.53

Note: All the values are mean of triple reading ± standard deviation

Note: F-2 and F-4 were the final preparations on the basis of different evaluation parameters e.g. Assessment of self emulsification were grade A for both, lesser Emulsification time 11±1.52 and 15±2.51 seconds, also lesser Turbidity (NTU) 20 & 21cps, smaller droplets of size 173 ± 2.53 & 141.7 ± 1.02 and higher drug content 95.42 ± 1.13 & 94.52 ± 1.41. Hence, **F-2 and F-4** formulations were selected for further evaluation for drug release.

Drug Release Kinetic Models for SEDDS Emulsion

a. Zero order kinetics

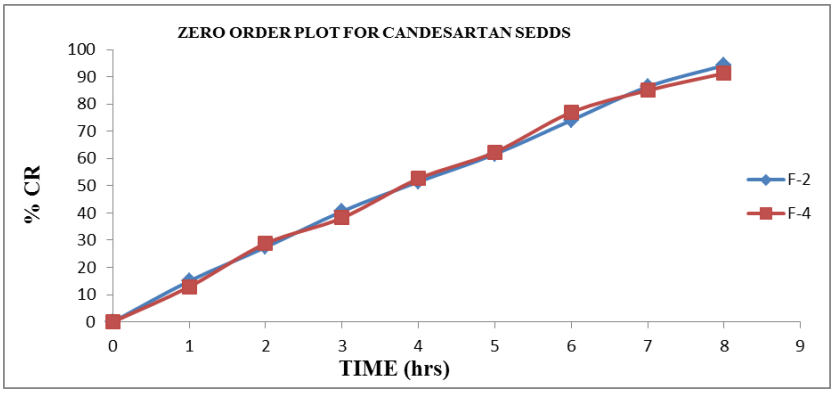

Fig. no. 6: Zero Order plots for candesartan release.

b. First order kinetics

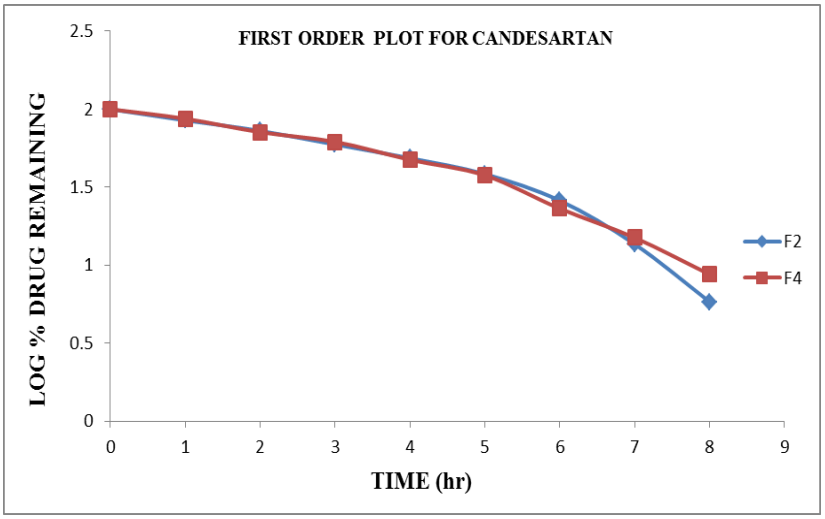

Fig. no. 7: First Order plots for Candesartan.

c. Higuchi model of drug release kinetics

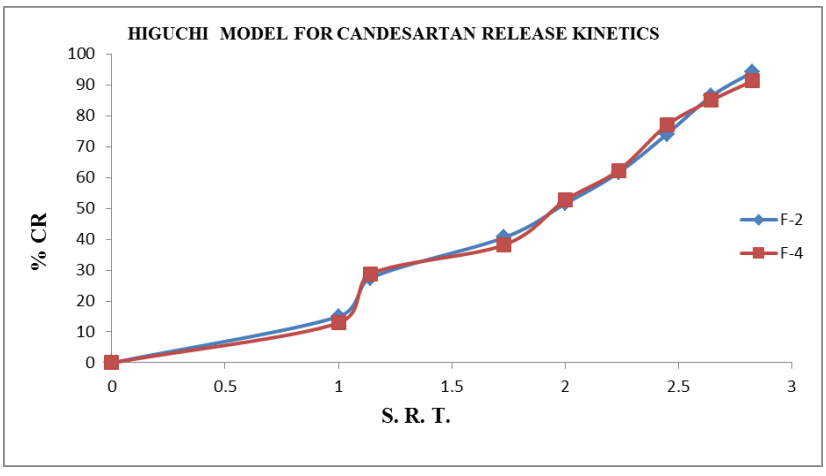

Fig. no. 8: Higuchi model plots for Candesartan.

d. Peppas model of drug release kinetics

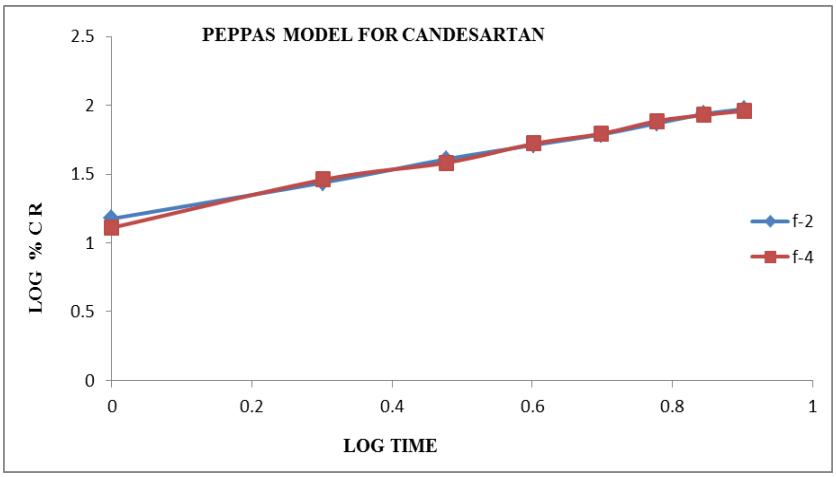

Fig. no. 9: *Peppas* model plots for Candesartan.

DISCUSSION

The present investigation was undertaken to formulate and evaluate drug in self micro emulsifying drug delivery system. Preformulation studies were carried out, the physical characteristics like organoleptic property of drug revealed white color crystalline powder, bitter in taste, odourless. The solubility of the drug was found as freely soluble in methanol and ethanol, sparingly soluble in chloroform and slightly soluble in water. The partition coefficient was found to be 1.95. The melting point was found to be in the range of 158-162^{O}C. The UV spectrum absorption maximum (λmax) on scanning from 200-400 nm was found 263 nm. The calibration curve for drug in standard phosphate buffer pH 6.8 was in the concentration range of 0.2-2.0 µg/ml and the R^2 value was calculated as 0.999. The solubility of the drug was tested in different oils, maximum solubility was determined in castor oil 143.63±1.51 mg/g and in different surfactant, maximum solubility determined 122.83±2.56 mg/g of tween-80 and 178.26±2.05 mg/g of PEG-600 as a co-surfactant phase. The maximum % transmittance was found to be 50.07 % at 1:2 (oil:surfactant ratio). The maximum % transmittance was found to be 87.7% at 3:2:1 (oil:surfactant:co-surfactant) ratio. The formation of clear transparent emulsion shows better stability whereas turbidity leads to phase separation. The spontaneous emulsification property i.e. turbid or clear of formulation was assesses by visual observation at 37^{O}C and results were shown in Table. The resulting emulsions were percentage transmittance was assessed at 638 nm by UV. The formulation was selected on the basis of 65-100% transmittances. On the basis of spontaneous emulsification method and percentage transmittance the total 9 formulation were selected and subjected to different thermodynamic stability study. By the thermodynamic stability study

six formulations were selected out of nine formulations. Visual observation was determined 50 mg of formulation was diluted with 50 ml with media like water, Standard phosphate buffer pH 6.8, pH 1.2 in order to determine appearance, color, etc. Robustness to dilution was performed diluted with excess of water, standard phosphate buffer pH 6.8 and 0.1N HCl (500-900 ml) and was stored for 12 hours gives no precipitation or phase separation was found. Microscopic evaluation was performed morphology and structure of self emulsion using optical microscopy.

The physical stability studies include appearance, color, and pH of resulting emulsion under different storage condition. The *in-vitro* performances of the formulation were visually assessed using the grading system. The emulsification time of SEDDS was determined as per procedure and maximum emulsification time was found in F2 formulation. The turbidity of SEDDS was performed determined and maximum turbidity was found in F6 formulation. The viscosities of the system were determined as such before and after dilution using Brookfield viscometer DV-E using spindle RV-6 at 100 rpm at 25±0.5^{O}C. F-2 and F-4 were the final preparations on the basis of different evaluation parameters e.g. Assessment of self emulsification were grade A for both, lesser Emulsification time 11±1.52 and 15±2.51 seconds, also lesser Turbidity (NTU) 20 & 21cps, smaller droplets of size 173 ± 2.53 & 141.7 ± 1.02 and higher drug content 95.42 ± 1.13 & 94.52 ± 1.41. Hence, **F-2 and F-4** formulations were selected for further evaluation for drug release. The smaller droplet size provides a larger interfacial surface area for drug absorption. *In-vitro* drug Release of Candesartan SEDDS preparations were studied and found F-2 = 94.18 and GF-4 = 91.27, were excellent preparation on the basis of drug release profile. Both preparations drug release data were fitted into the zero order, first order, Higuchi and peppas model of drug release kinetics.

CONFLICTS OF INTEREST

There are no conflicts of interests.

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