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IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF CANDESARTAN BY EMPLOYING SOLID DISPERSION TECHNIQUE USING VARIOUS METHODS

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ABSTRACT

***Objective**: The objective of the study was to improve the solubility and dissolution rate of Candesartan by employing solid dispersion technique using various methods. **Methods:** A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The angle of repose of API powder is determined by the funnel method. Solid dispersions of Candesartan were prepared with PEG 8000. In-vitro release studies were carried out using dissolution test apparatus USP Type II. A fourier transform infrared spectrophotometer equipped with spectrum v2.19 software by KBR pellet method was used to study the non thermal analysis of drug excipients (binary mixture of drug: excipient) compatibility. **Results:** Standard graph for the Candesartan drug was done in buffer solution. The percent drug release from various Tablets was found in the range of 46.9% to 92.21% within 60 minutes, whereas the pure drug exhibited only 22.4 % to 30 % within 2 hours. The Formulations SD13, SD14 which are prepared by Melting method with Poloxamer released 80.08%, 91.21% respectively at the time point of 60mins in 6.8 pH phosphate buffer. **Discussion:** A marked improvement in dissolution rates of Candesartan was observed with SD6, SD10, SD16 prepared by solvent evaporation method and SD4, SD14 are prepared by Fusion method and SD2, SD8 and SD12 are prepared by physical mixture method. **Conclusion:**. The overall results showed that dissolution rate of Candesartan were considerably improved when formulated as solid dispersions.*

KEY WORDS

Solid dispersion, Candesartan, Excipients, Fusion method.

INTRODUCTION

Solubility is a measure of the maximum amount of solute that can be dissolved in a given amount of solvent to form a stable solution. Stable solution is solution that becomes saturated and the dissolved solute is in equilibrium with the excess un-dissolved solute[1]. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

Solubilization is the process by which the apparent solubility of a poor water soluble substance is increased. The three approaches in overcoming the bioavailability problems due to such causes are:

Pharmaceutical Approach which involves modification of formulation, manufacturing, process or the physicochemical properties of drugs without changing the chemical structure.

Pharmacokinetic Approach in which the pharmacokinetics of drugs is altered by modifying its chemical structure.

Biological Approach where by the route of drug administration may be changed such as changing from oral to parenteral route.

Solid dispersions are generally prepared by solvent or co-precipitation method where by both the guest solute and the solvent are dissolved in a common volatile liquid solvent. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier.

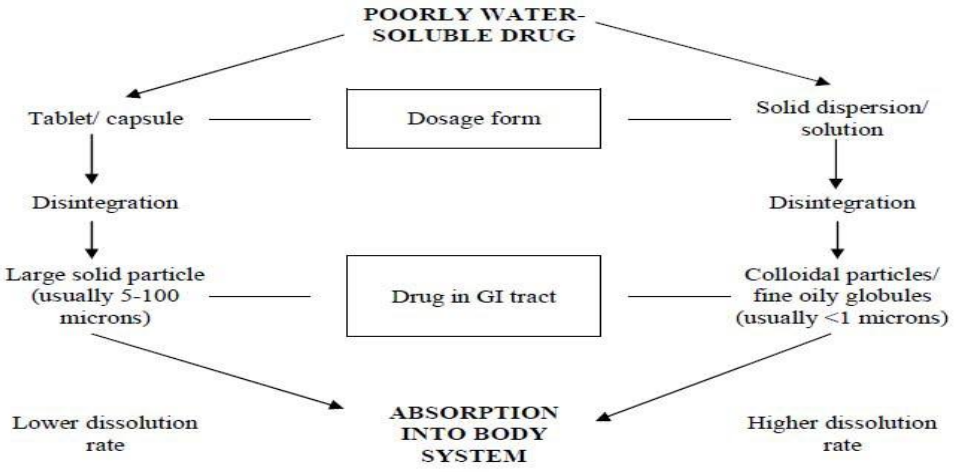

Figure 1: A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

Methods of preparing solid dispersions:

1) Fusion Process; 2) Solvent Process; 3) Fusion Solvent Method; 4) Supercritical Fluid Process.

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability limited its use in commercial dosage forms for poorly water soluble drugs. Successful development of solid dispersion systems for preclinical and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points.

Applications of solid dispersion:

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

MATERIALS & METHODS

Methods of Preparation of Candesartan Solid Dispersion:

A) Preparation of Candesartan Solid Dispersions with PEG 8000:

Solid dispersions of Candesartan were prepared with PEG 8000. The methods used for the preparation of Candesartan with PEG are physical mixture[51], solvent evaporation method[52, 53] and fusion method[54].

Table 1: Variables

Variables	(1:2)	(1:4)
Candesartan(mg)	100	100
PEG 8000(mg)	200	400

I) Physical Mixture:

The physical mixtures were prepared by weighing the calculated amount of Candesartan and the carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures was passed through 44-mesh sieve and stored in desiccators until used for further studies.

II) Solvent Evaporation Method:

The required amount of Candesartan and the carrier were dissolved in sufficient volume of Methanol with continuous stirring. The solvent was then completely evaporated at 45ºC with continuous stirring to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies

III) Fusion Method:

Accurately weighed amount of carrier was melted in a porcelain dish at 55-63^0 C and to this calculated amount of Candesartan was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized passed through 44mesh sieve and stored in desiccators until used for further studies.

B) Preparation of Candesartan Solid Dispersions with PVP K30:

Solid dispersions of Candesartan were prepared with PVP K30. The methods used for the preparation of these solid dispersions were physical mixture and solvent evaporation method[55]. PVP containing solid dispersions were not prepared by the melt method, because PVP melts at 150ºC and degrades before its melting point.

Table 2: Variables

Variables	(1:1)	(1:4)
Candesartan(mg)	100	100
Pvp k-30(mg)	100	400

I) Physical Mixture:

The physical mixtures were prepared by weighing the calculated amount of Candesartan and the carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures was passed through 44-mesh sieve and stored in desiccators until used for further studies.

II) Solvent Evaporation Method:

The required amount of Candesartan and the carrier were dissolved in sufficient volume of Methanol with continuous stirring. The solvent was then completely evaporated at 45º C with continuous stirring to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in dessicator until used for further studies.

Preparation of Tablets containing solid dispersions of Candesartan:

Solid dispersions were prepared by solvent Evaporation, Fusion, and Physical mixture methods. Candesartan dose was taken as 16 mg. polymers such as PEG 8000, PVP k30 and Poloxamer 338 were selected as carriers. Drug and polymers were taken in different ratios as stated in the above formulation chart. The prepared solid dispersions were passed through the sieve no 44 to get uniform sized particles. The solid dispersions were mixed with required quantities of diluent, lubricant and glidant. The blend was evaluated for pre compression parameters.

Table 3: Different formulations of Candesartan in weight ratios

Drug to Carrier	Method	Drug to carrier Ratio	Formulation code
Drug: PEG	Physical mixture	1:2,1:4	SD1,SD2
Drug: PEG	Melting method	1:2,1:4	SD3,SD4
Drug: PEG	Solvent evaporation	1:2,1:4	SD5,SD6
Drug: PVP	Physical mixture	1:1,1:4	SD7,SD8
Drug: PVP	Solvent evaporation	1:1,1:4	SD9,SD10
Drug : Poloxomer338	Physical mixture	1:2, 1:4	SD11,SD12
Drug : Poloxomer338	Melting method	1:2, 1:4	SD13,SD14
Drug : Poloxomer338	Solvent evaporation	1:2, 1:4	SD15,SD16

Evaluation test for tablets:

A) Thickness:

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

B) Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

C) Friability:

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([w_o - w] / w_o) \times 100$$

Where; w_O = weight of the tablet at time zero before revolution; w = weight of the tablet after 100 revolutions.

D) Hardness:

Pfizer Hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded.

E) Physical Appearance:

All the batches of Candesartan solid dispersions were evaluated for color and appearance.

F) In-vitro- Dissolution test of Candesartan tablets:

In-vitro release studies were carried out using dissolution test apparatus USP Type II

Dissolution Conditions:

Apparatus : USPII apparatus (Paddle)

Dissolution Medium : 900ml of pH 6.8 phosphate buffer[57]

Temperature : 37±0.5^{0}c

Rotating speed : 50rpm

Sample time intervals : 0, 15, 30, 45, 60 mins.

Detection : UV-Visible spectrophotometer at λmax 255nm

The sample was withdrawn at predetermined time points and was analyses spectrophotometrically at 255nm for Candesartan. Each preparation was tested and then means values were calculated.

G) Determination of Candesartan Drug Content:

Tablets were weighed individually, Pulverized and diluted to 250ml with sufficient amount of 6.8 pH phosphate buffer. After that an aliquot of the filtrate was diluted and analyzed Spectrophotometrically (pg instrument T_{80} model UV/VIS spectrophotometer, Japan) at 255nm.from that drug content was calculated.

H) Solubility study of candesartan:

The most widely used approach to study inclusion complex is the phase solubility method described by Higuchi and Connors, which examines the effect of a solubilizer, i.e., the drug being solubilized.

The solubility of Candesartan in various carriers was carried out and the solubility was determined. Phase solubility[48] studies on Candesartan with different carriers like PVP, PEG 8000 and ploxomer338 were performed by the method described by Higuchi and Connors. Excess amount of Candesartan (10 mg) was added to 25 ml of buffer solution (pH 6.8) containing various concentrations of carriers (0, 0.25, 0.50, 0.75, 1.00 and 1.25% w/v). The suspensions were shaken for 3 hours on a rotary flask at 37±1ºC and filtered through a whattman filter paper. The filtrate so obtained was analyzed spectrophotometrically at 255nm and corresponding concentrations of the drug were computed from the standard curve. The apparent solubility constant (Kc) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the phase-solubility diagram using following equation.

$$Kab = \frac{\text{slope}}{\text{So}(1 - \text{slope})}$$

The slope is obtained from the initial straight line portion of the plot of Candesartan against solid dispersion concentration, and S0 is the equilibrium solubility of Candesartan in buffer solution.

RESULTS AND DISCUSSION

CHARACTERIZATION OF CANDESARTAN:

The characterization of drug was carried out by conducting various physicochemical tests including melting point determination, spectral analysis such as UV spectrum and IR Spectrum for pure Candesartan.

Melting point:

The melting point was found to be in the range of 183-185^{0}C.

UV Spectroscopy:

UV absorption spectrum showed λ_{max} to be 255nm. The graph of absorbance vs concentration for pure Candesartan was found to be linear in the concentration range of 0-25 µg/ml at 255 nm.

Table 4: Wavelength of maximum absorption λ_{max} in different solvents.

S.NO	Solvent	λ_{max}
1	Methanol	255nm
2	6.8 phosphate buffer	255nm

STANDARD CALIBRATION OF CANDESARTAN:

Standard Calibration Curve of Candesartan in 6.8pH Phosphate buffer:

Standard graph for the Candesartan drug was done in buffer solution. Table No. 5 shows the concentrations of Candesartan in buffer solution and the respective absorbance. The Figure no. 2 shows the standard graph of Candesartan in buffer solution.

Table 5: Calibration Data of Candesartan in pH 6.8 Buffer Solution At λmax 255nm

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.162
3	10	0.329
4	15	0.463
5	20	0.592
6	25	0.763

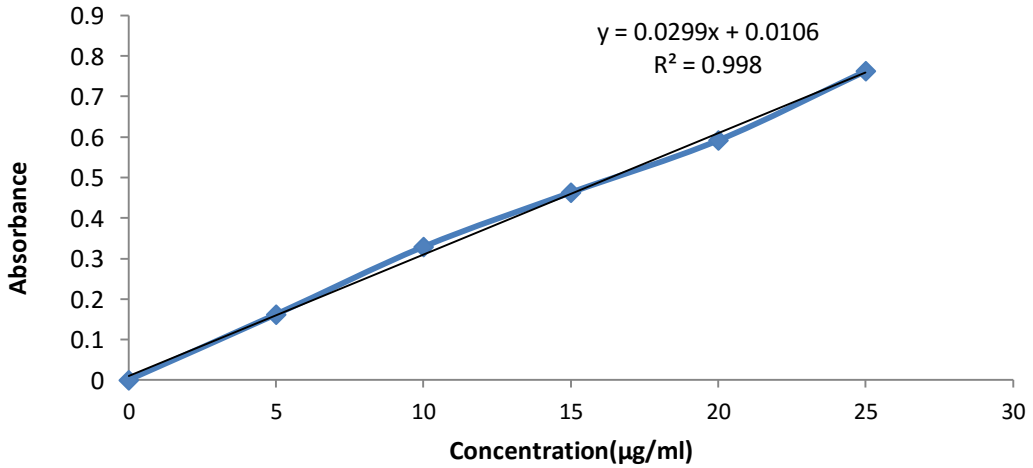

Fig 2: Standard Calibration Curve for Candesartan in 6.8pH phosphate Buffer Solution

Standard Calibration Curve of Candesartan in methanol:

Standard graph for the Candesartan drug was done in Methanol Table no 6 Shows the concentrations of Candesartan in Methanol and the respective absorbance. The Figure no 3 shows the standard graph of Candesartan in Methanol.

Table 6: Calibration Data of Candesartan in Methanol at λmax 255 nm

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.175
3	10	0.346
4	15	0.501
5	20	0.669
6	25	0.832

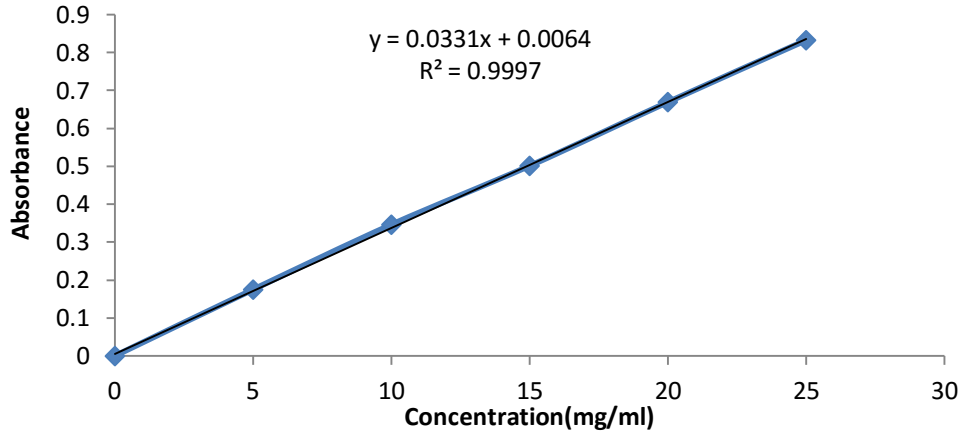

Fig 3: Standard Calibration Curve for Candesartan in Methanol

CHARACTERIZATION OF POWDERS:

FT-IR spectroscopy:

To study the possible interactions between the CDS, PEG 8000, PVP, POLOXAMER 338 in solid state, IR spectra of drug and solid dispersions are compared. The IR spectra of drug, polymers, SDs are shown in Figures 6 to 9.

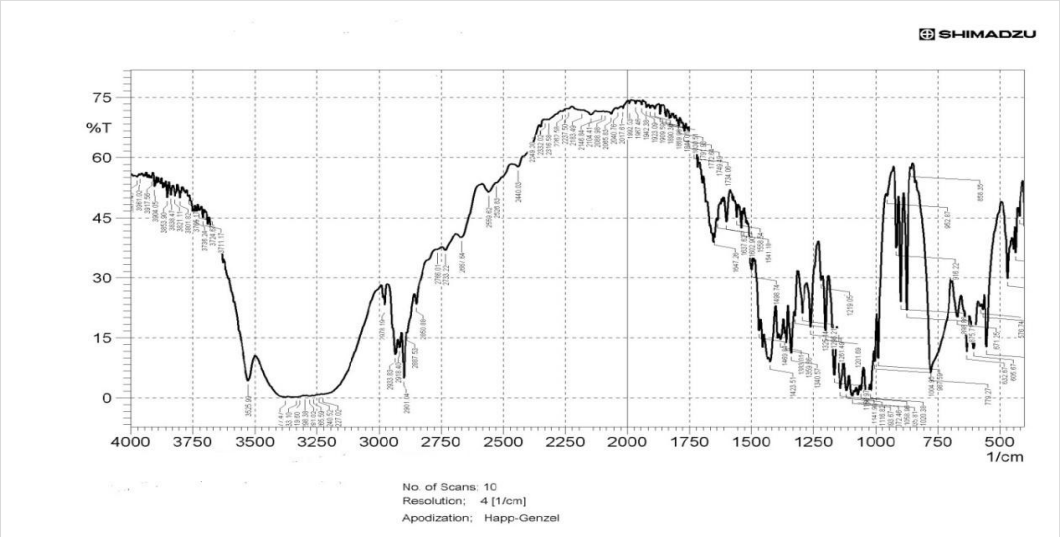

Fig 4: FT-IR spectra of pure Candesartan

Table 7: FT-IR spectra of pure Candesartan, polymer Poloxamer, Formulation

Functional Groups	Drug Candesartan	Polymer Poloxamer	Formulation	Stretching or deformation
O-H	3369.73	3440.82	3439.69	Stretching
C-H(alkanes)	3134.96	2877.52	3370.05	Stretching
C=C(alkenes)	1275.27	1636.77	1673.70	Stretching
C-N	1079.81	-	1107.39	Stretching
C-O	1346.23	1350.28	1348.46	Stretching

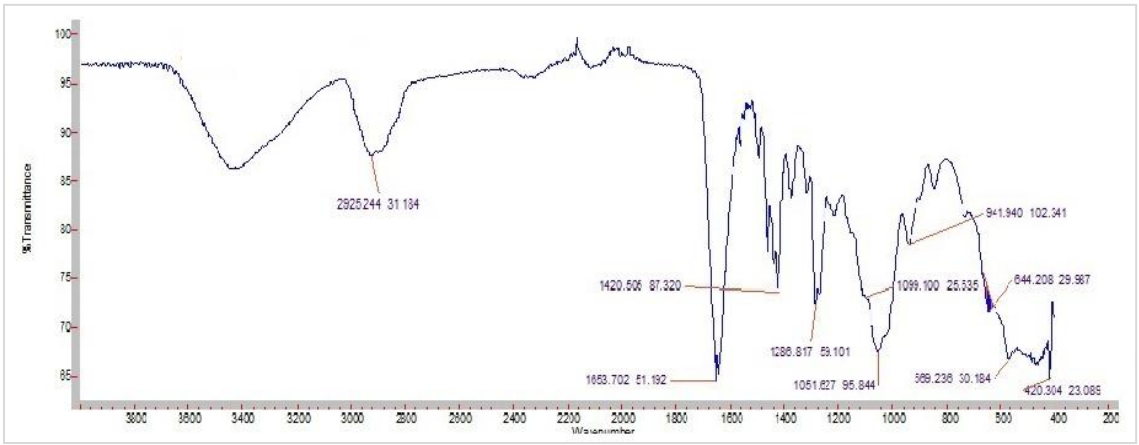

Fig 5: FT-IR spectra of pure Candesartan, polymer Poloxamer, By Melting method

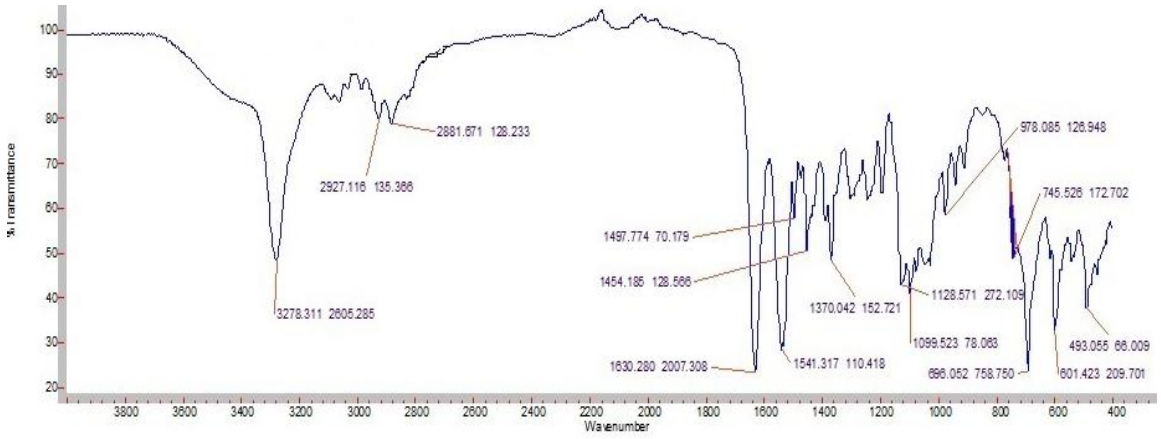

Fig 6: FT-IR spectra of pure Candesartan, polymer PEG 8000, By Solvent Evaporation Method

Table 8: FT-IR spectra of pure Candesartan, polymer PEG 8000, Formulation

Functional Groups	Drug Candesartan	Polymer PEG 8000	Formulation	Stretching or deformation
O-H	3369.73	3440.82	3369.73	Stretching
C-H(alkanes)	3134.96	2877.52	3289.26	Stretching
C=C(alkenes)	1275.27	1636.77	1673.95	Stretching
C-N	1079.81	-	1110.20	Stretching
C-O	1346.23	1350.28	1344.43	Stretching

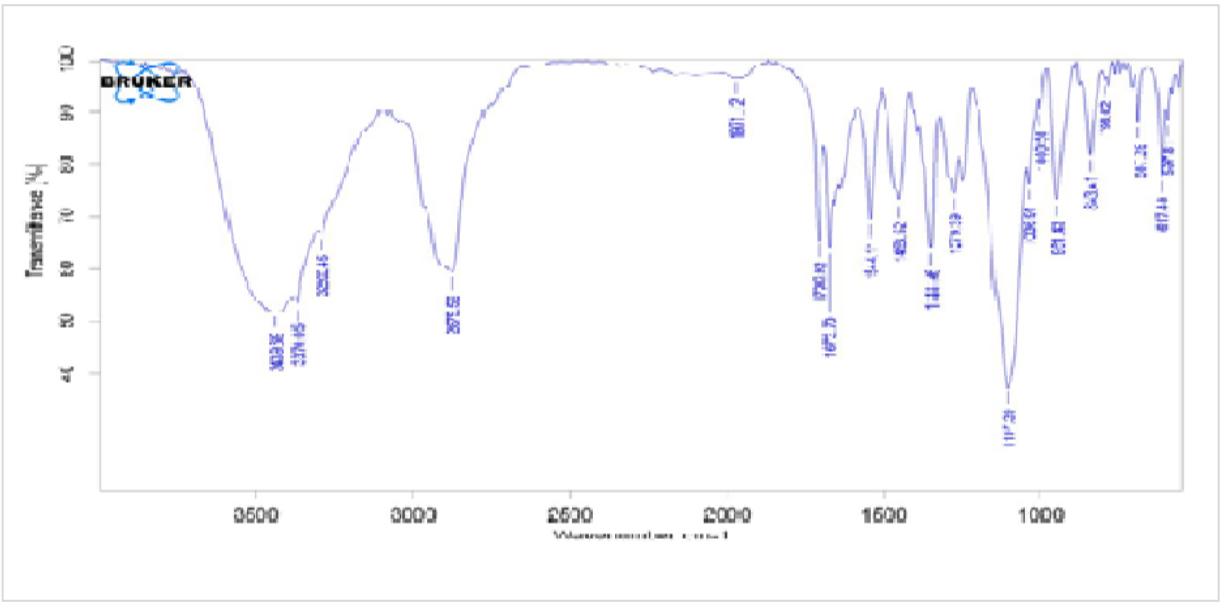

Fig 7: FT-IR spectra of pure Candesartan, polymer PVP K30, By Solvent

Evaporation Method

Table 9: FT-IR spectra of pure Candesartan, polymer PVP K30, Formulation

Functional Groups	Drug Candesartan	Polymer PVP K30	Formulation	Stretching or deformation
O-H	3369.73	3440.82	3443.52	Stretching
C-H(alkanes)	-	2877.52	2877.52	Stretching
C=C(alkenes)	1644.09	1636.77	1644.09	Stretching
C-N	1337.45	-	1337.45	Stretching
C-O	1067.58	1054.16	1067.58	Stretching

Evaluation and Characterization of Candesartan Complexes:

In the present work Formulations of Candesartan were prepared with PEG 8000, PVP K30 and Poloxamer 338 by physical mixture, solvent evaporation and fusion method. The complexes were prepared in different molar ratios of drug and carrier PEG (1:2, 1:4), PVP (1:1, 1:4), and poloxamer (1:2, 1:4) respectively. The prepared complexes were subjected to evaluation studies.

Table 10: In-Vitro Drug Release of Solid Dispersions of PEG 8000

Time in min	PHYSICAL MIXTURE PEG 8000 (%)		FUSION METHOD PEG 8000 (%)		SOLVENT EVAPORATION PEG 8000 (%)	
	SD1	SD2	SD3	SD4	SD5	SD6
0	0	0	0	0	0	0
15	20.9	25.4	23.14	27.34	34.56	43.16
30	32.9	37.28	40.85	41.1	50.47	61.27
45	41.43	50.14	55.5	55.3	61.37	62.61
60	46.9	57.8	64.5	65.71	65.10	**67.97**

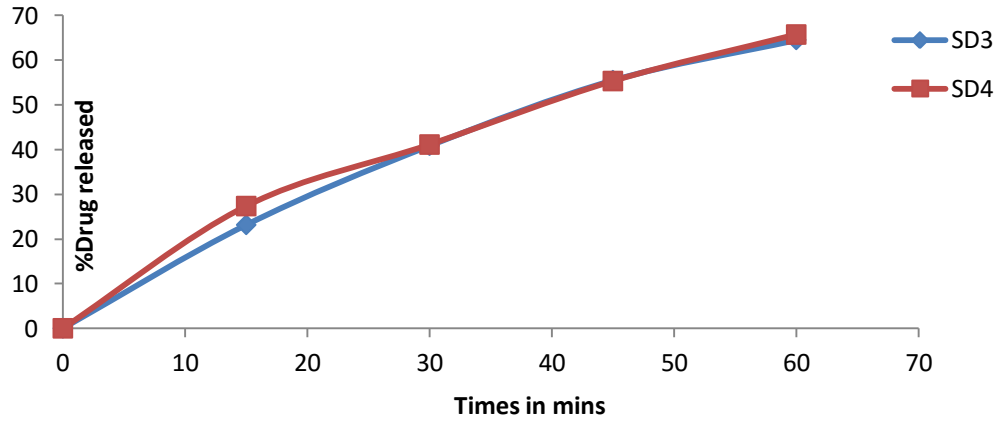

Fig 8: Dissolution profile of solid dispersions of PEG 8000(melting method) in pH 6.8 Phosphate buffer

The Formulations SD3, SD4 which are prepared by Fusion method with PEG 8000 released 64.5%, 65.71% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD3, SD4. Formulation SD4 (1:4) shows maximum release at the time point of 60mins.

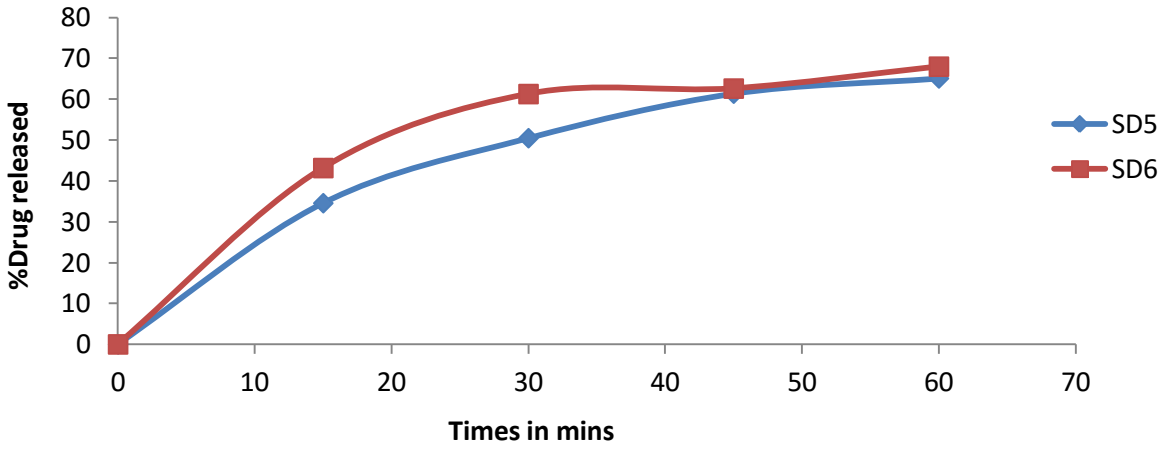

Fig 9: Dissolution profile of solid dispersions of PEG 8000 (solvent evaporation) in pH 6.8 Phosphate buffer

The Formulations SD5, SD6 which are prepared by Solvent evaporation method with PEG 8000 released 65.10%, 67.91% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD5, SD6. Formulation SD6 (1:4) shows Maximum release at the time point of 60mins.

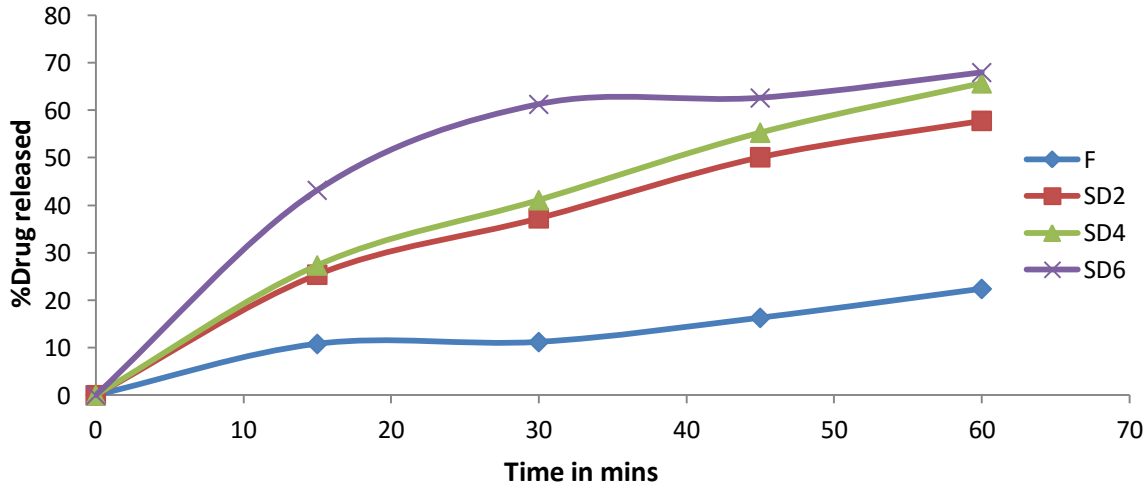

Fig 10: Comparison Dissolution profile of SD2, SD4 and SD6 with pure drug in pH 6.8 Phosphate buffer

Among the all formulations from SD1 to SD6 which are prepared with PEG 8000 by using different ratios of drug to polymer by different methods. The formulation SD6 (solvent evaporation, 1:4) showed highest release.

Table 11: In-Vitro Drug Release of Solid Dispersions of PVP K30

Time in min	PHYSICAL MIXTURE PVP K30 (%)		SOLVENT EVAPORATION PVP K30 (%)	
	SD7	SD8	SD9	SD10
0	0	0	0	0
15	27.03	28.39	34.08	38.1
30	40.2	49.141	57.13	60.82
45	43.48	60.02	67.28	72.01
60	48.64	65.07	76.34	**82.34**

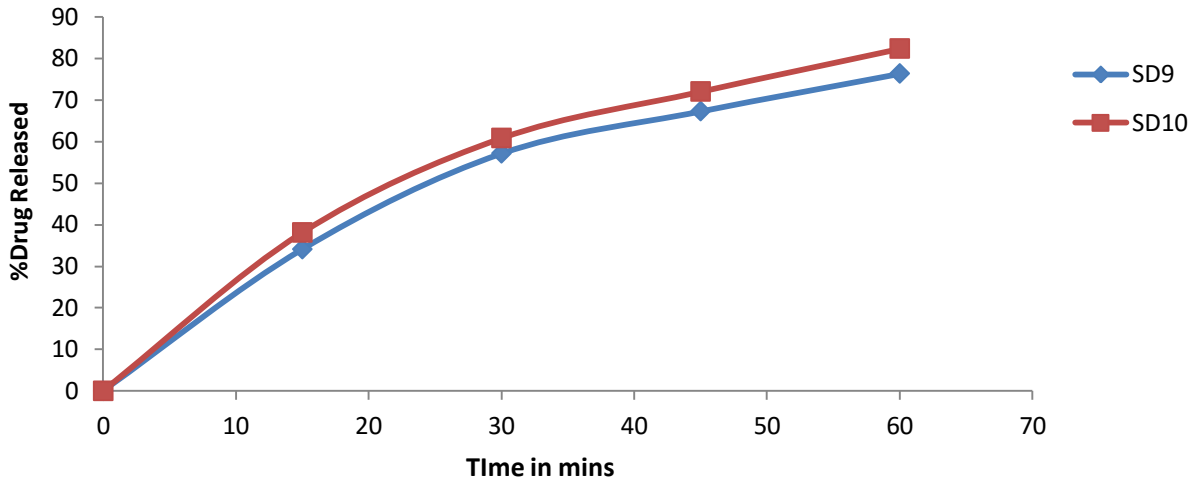

Fig 11: Dissolution profile of Drug Release of Solid Dispersions of PVP K30 (Solvent Evaporation) in pH 6.8 Phosphate buffer

The Formulations SD9, SD10 which are prepared by solvent Evaporation method with PVP K30 released 76.34%, 82.34% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD9, SD10. Formulation SD10 (1:4) shows maximum release at the time point of 60mins.

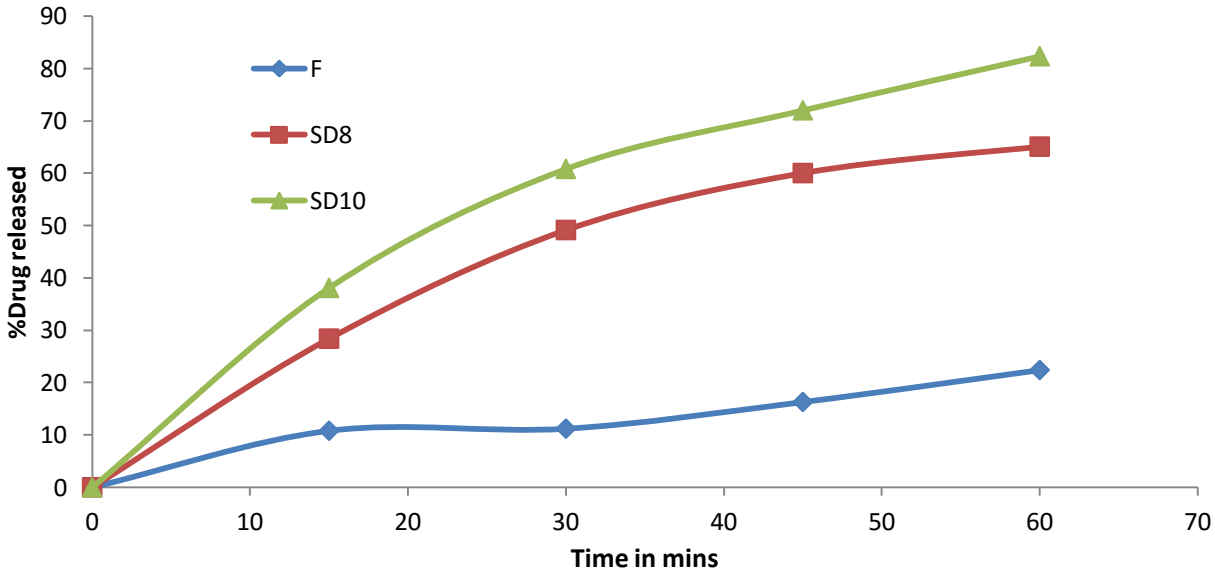

Fig 12: Comparision Dissolution profiles of SD8, SD10 with pure drug in pH 6.8 Phosphate buffer

Among the all formulations from SD7 to SD10 which prepared with PVP K30 by using different ratios of drug to polymer by different methods. The formulation SD10 (Solvent evaporation1:4) showed highest release.

Table 12: In-Vitro Drug Release of Solid Dispersions of Poloxamer

Time in min	PHYSICAL MIXTURE PXM (%)		FUSION METHOD PXM (%)		SOLVENT EVAPORATION PXM (%)	
	SD11	SD12	SD13	SD14	SD15	SD16
0	0	0	0	0	0	0
15	34.58	40.16	40.08	48.2	41.4	48.73
30	57.03	66.37	71.4	78.58	74.8	79.12
45	61.249	72.31	80.04	84.39	81.04	86.1
60	63.84	74.89	80.08	91.21	83.2	**92.21**

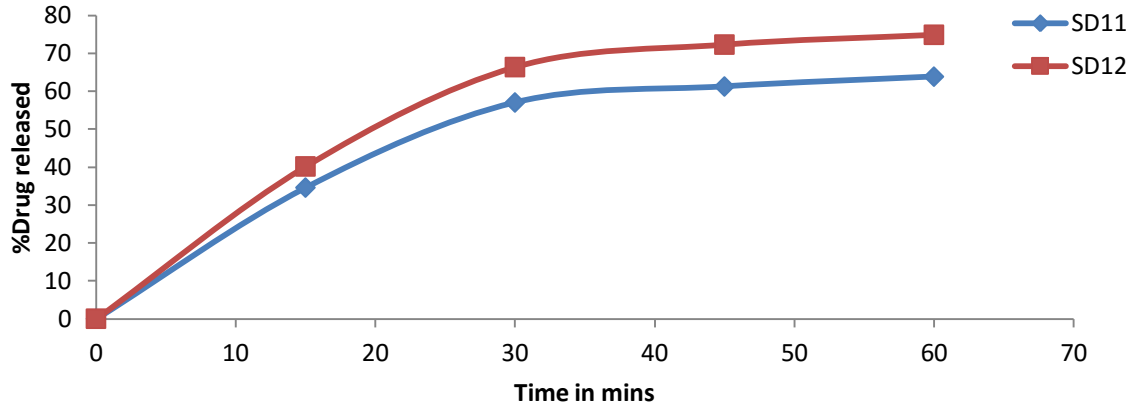

Fig 13: Dissolution profile of Solid Dispersions Poloxamer (Physical Mixture) in pH 6.8 Phosphate buffer

The Formulations SD11, SD12 which are prepared by physical mixture method with Poloxamer released 63.84%, 74.89% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD11, SD12 . Formulation SD12 (1:4) shows maximum release at the time point of 60mins.

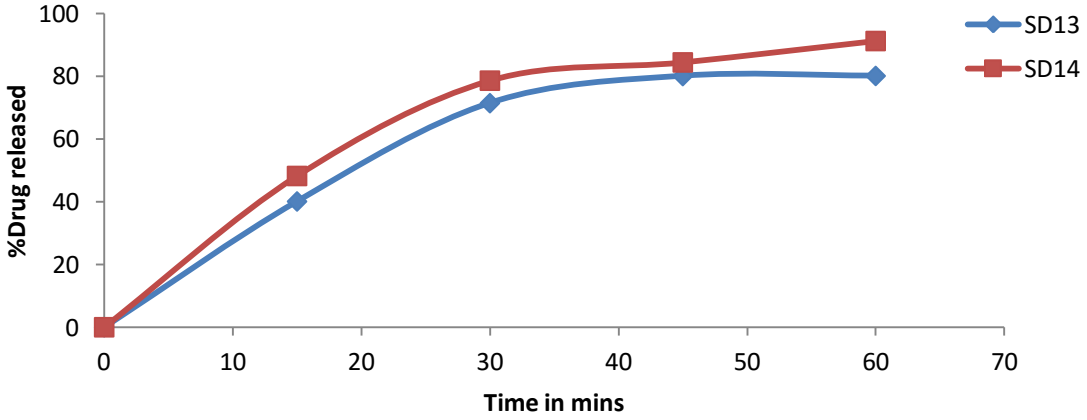

Fig 14: Dissolution profile of Solid Dispersions of Poloxamer (melting method) in pH 6.8 Phosphate buffer

The Formulations SD13, SD14 which are prepared by Melting method with Poloxamer released 80.08%, 91.21% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD13, SD14, Formulation SD14 (1:4) shows maximum release at the time point of 60mins.

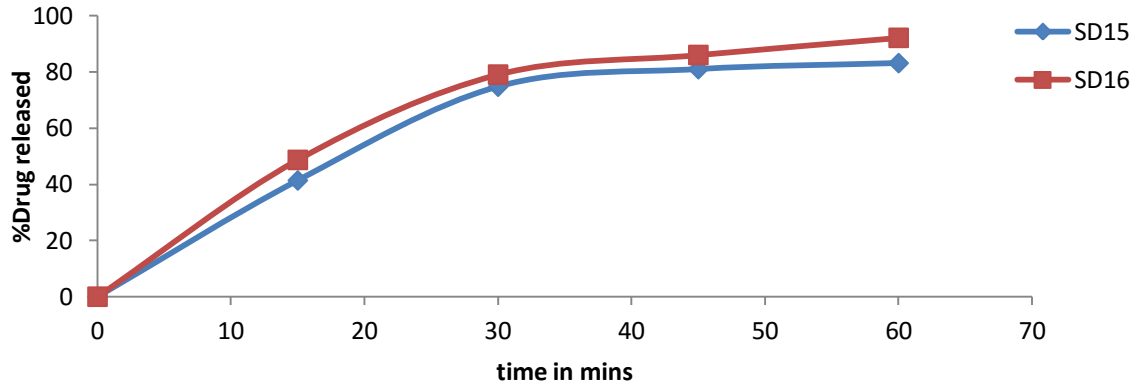

Fig 15: Dissolution profile of Solid Dispersions of Poloxamer (Solvent Evaporation method) in pH 6.8 Phosphate buffer

The Formulations SD15, SD16 which are prepared by Solvent evaporation method with Poloxamer released 83.2%, 92.21% respectively at the time point of 60mins in 6.8 pH phosphate buffer. Among the two formulations i.e., SD15, SD16. Formulation SD16 (1:4) shows maximum release at the time point of 60mins.

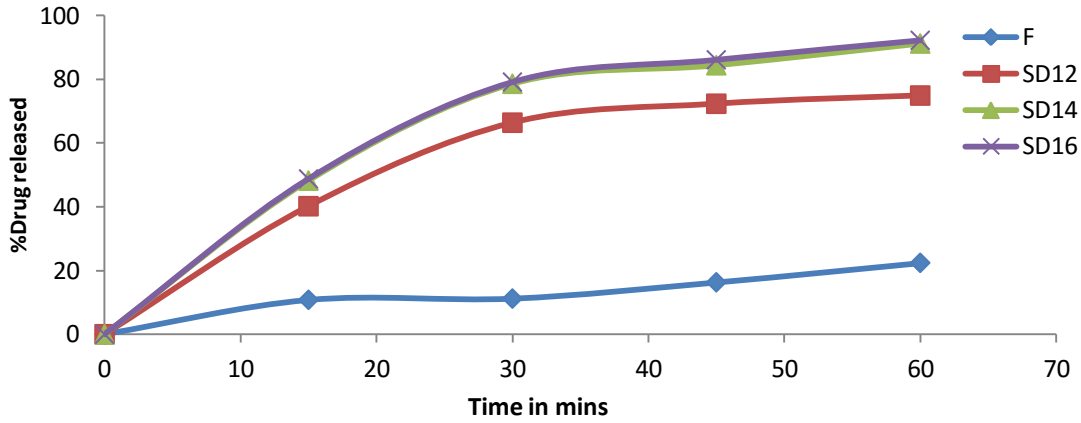

Fig 16: Comparision Dissolution profiles of SD12, SD14 and SD16 with pure drug in pH 6.8 phosphate buffer

Among the all formulations from SD11 to SD16 which are prepared with Poloxamer by using different ratios of drug to polymer by different methods. The formulation SD16 (solvent evaporation, 1:4) showed highest release.

CONCLUSION

Solubility studies showed that the solubility of Candesartan increased linearly as a function of concentration of carrier (PEG, PVP and Poloxamer). The Drug dissolution rate higher in SDs prepared by Melting method, solvent evaporation at 1:4 drug to carrier ratio compared to 1:2 in case of poloxamer. In the case of SDs prepared by using PVP, PEG8000 the higher dissolution rate was found at 1:4 drug to carrier ratio by solvent evaporation method 1:2 and other methods. The overall results showed that dissolution rate of Candesartan were considerably improved when formulated as solid dispersion.

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