IJPSR (2022), Volume 13, Issue 7 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 October 2021; received in revised form, 08 December 2021; accepted, 06 January 2022; published 01 July 2022

DESIGN AND EVALUATION OF CANDESARTAN CILEXETIL SOLID DISPERSION INCORPORATED IN HARD GELATIN CAPSULE

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Keywords:

Candesartan cilexetil, Solid dispersion, Kneading method, Solvent evaporation method, Microwave method, Dissolution rate, PVP K 30, Hydroxypropyl beta-cyclodextrin, FTIR, XRD

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ABSTRACT: Candesartan cilexetil is widely used for the treatment of hypertension. Candesartan cilexetil is a pro-drug administered orally, rapidly converted to its active metabolite candesartan during absorption in the gastrointestinal tract. Candesartan cilexetil is a BCS II drug that is practically insoluble in the water of 0.00771 mg/ml & it has a low dissolution rate, hence; to improve dissolution rate & bioavailability, solid dispersion of Candesartan cilexetil were prepared by kneading method, solvent evaporation method & Microwave method in 1:0.5, 1:1 & 1:1.5 ratios of Candesartan cilexetil and hydroxy propyl beta-cyclodextrin /PVP K 30. Further, the SDs were filled into empty hard gelatin capsules with excipients like starch (8%), lactose, talc & Aerosil by manual capsule filling method. The formulated solid dispersions were evaluated for drug content and *in-vitro* dissolution studies. Accelerated stability studies was conducted for the optimized SD formulations, the optimized drug & carrier SD were confirmed & characterized by FT-IR. The drug content of the prepared Candesartan cilexetil SD formulations was found to be range from 94.35±0.95% to 98.44±0.56%.XRD studies showed that the drug exists in an amorphous state as there was no drug peak in the formulation. The solid dispersion of Candesartan cilexetil prepared by kneading method with HPβCD (1:1.5) showed a maximum drug release of 94.05±0.11% compared to other solid dispersion formulations. It is concluded that the dissolution rate of Candesartan cilexetil can be improved by the solid dispersion method.

INTRODUCTION: The biopharmaceutics classification system: The BCS is a framework for classifying drug substances based on their aqueous solubility and intestinal permeability. The oral route of drug administration is the preferred method for administering the drug for systemic effects. The absorption of the drug from the gastrointestinal tract like dissolution rate, intrinsic solubility, *etc*. taken to improve. The drug substances are categorized into four classes based on their solubility BCS takes into account the three *in-vitro* parameters namely, solubility, permeability and dissolution, according to which the drugs can be categorized into the following four classes [1]. Class I- High solubility-High permeability, Class II- Low solubility-High permeability Class, III- High solubility-Low permeability Class IV- Low solubility-low permeability Classes II- the drug of this class have a high absorption number but a low dissolution number [2]. The bioavailability of these products is limited by their salvation rates [3]. It can class be increased by solid dispersion [4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(7).2856-69

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(7).2856-69

Solid Dispersion (SDs) [5]: Solid products consist of two different components, a hydrophilic matrix and a hydrophobic drug. The drug particles can be dispersed molecularly, in amorphous particles (clusters) or crystalline particles.

Polymers are used to create the matrix, and their selection is based on many factors, including physicochemical (*e.g.,* drug-polymer miscibility and stability) and pharmacokinetic (*e.g.,* rate of absorption) constraints [6].

MATERIALS AND METHODOLOGY:

Materials: Candesartan cilexetil obtained from Apotex research Pvt Ltd., Bangalore, Hydroxy propyl β cyclodextrin, Lactose, Aerosil (Colloidal silicon dioxide), Capsules- Ce chem Pharmaceuticals, Bangalore. Polyethylene glycol 6000, Starch, Methanol, - SD fine chemicals, Bangalore. Talc- Thermo fisher scientific India Pvt, Bangalore.

Methodology:

Preformulation Studies: The following preformulation studies were performed for Candesartan cilexetil [7].

Physical Appearance: The appearance of the API was done by visual observation.

Determination of Solubility: Solubility of Candesartan cilexetil was performed in solvents like water, ethanol, methanol and phosphate buffer.

Determination of Melting Point: The melting point of Candesartan cilexetil is determined by the Capillary fusion method.

Standard calibration curve of candesartan cilexetil in 0.1M Sodium hydroxide [8]. Accurately weighed 100 mg of candesartan cilexetil and transfer into a 100 ml volumetric flask containing 50 ml of 0.1M NaOH, dissolved. Sonication of the solution was done, and the final volume was adjusted to 100 ml to give the stock solution of 1000 µg/ml concentration. 10 ml of the resulting solution was placed in 100 ml volumetric flask and volume adjusted with 0.1M NaOH to give solution of 100 µg/ml. Aliquots of 100 µg/ml solution were diluted with 0.1 M NaOH to give final concentrations of 4, 8, 12, 16, 20, 24, 28 µg/ml of Candesartan cilexetil were prepared, and absorbance was measured at 251 nm against blank using double beam UV-VIS spectrophotometer (1700, Shimadzu, Japan). Drug excipient compatibility studies [9]. Drug polymer interactions were studied by FT-IR spectroscopy.1-2mg of Candesartan cilexetil alone, a mixture of drug and polymer was weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was taken, and it was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet prepared was from 450-4000cm-1 was recorded. [10]. Equipment Details-Jasco FTIR 6100, Japan

Method of Preparation of Candesartan Cilexetil Solid Dispersion:

Preparation by Kneading Method [11]: The required amount of candesartan cilexetil and carrier (Hydroxy propyl β cyclodextrin / PVP K30) in 1:0.5, 1:1 and 1:1.5 ratios were wet with sufficient volume of methanol and kneaded thoroughly for 30 minutes in a glass mortar. The homogenous paste formed. The slurry was dried in a hot air oven for 40ºC for 24 hrs. and the dried complex was pulverized into a fine powder, passed through sieve no 60, and stored in an air-tight container. The formulations are summarized in table no 1

Solvent Evaporation Method [11]: Different preparations of Candesartan cilexetil with hydroxyl propyl β cyclodextrin/PVP K-30 were prepared in the drug to carrier ratios of 1:0.5, 1:1, 1:1.5 respectively using methanol as a common solvent respectively for the preparation of SD, firstly drug was dissolved in solvent (methanol). Then a polymer was dissolved in a solvent with continuous stirring using a mechanical stirrer.

The solvent was allowed to evaporate on a water bath at 45±5°C. After complete evaporation, the solid mass was further dried in a vacuum desiccator for 12 h. The dried solid mass was pulverized with a mortar and pestle and then sieved through a 60 mesh sieve. The formulations are summarized in table no1.

Microwave Method: An accurate place solid dispersion was then grounded in a glass mortar and then passed microwave activated solid dispersion in 1:0.5, 1:1. 1:1.5 ratio of the formulation was obtained by microwave irradiation. A fixed amount of physical mixture (*i.e*., 1 gram) was taken into a glass beaker and subjected to microwaves for 2 minutes at the chosen power of 600 W in a domestic microwave oven. Only one beaker at a time was placed inside the microwave oven through mesh sieve 60 to get uniform particle size; the formulations are summarized in **Table 1.**

TABLE: 1 FORMULATION OF CANDESARTAN CILEXETIL SD CAPSULES CONTAINING HPBCD AND PVP K 30 BY KNEADING METHOD, SOLVENT EVAPORATION METHOD, MICROWAVE METHOD

Ingredient	SD1 (1:0.5)	SD2 (1:1)	SD3 (1:1.5)	SD4 (1:0.5)	SD5 (1:1)	SD6 (1:1.5)	SD7 (1:0.5)	SD8 (1:1)	SD9 (1:1.5)	Category
Candesartan Cilexetil	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	active ingredient
HP β CD	4 mg	8 mg	24 mg	_	_	_	4 mg	8 mg	24 mg	enhance the aqueous solubility
PVP K 30	_	_	_	4 mg	8 mg	24 mg	_	_	_	enhance the aqueous solubility
Starch (8%)	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	Disintegrant
Lactose	163 mg	159 mg	143 mg	163 mg	159 mg	143 mg	163 mg	159 mg	143 mg	Diluents
Aerosil (1.25%)	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	anticaking agent
Talc (0.76%)	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	capsule lubricant
Total capsule weight	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	
Ingredient	**SD10 (1:0.5)**	**SD11 (1:1)**	**SD12 (1:1.5)**	**SD13 (1:0.5)**	**SD14 (1:1)**	**SD15 (1:1.5)**	**SD16 (1:0.5)**	**SD17 (1:1)**	**SD18 (1:1.5)**	**Category**
Candesartan Cilexetil	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg	active ingredient
HP β CD	_	_	_	4 mg	8 mg	24 mg	_	_	_	enhance the aqueous solubility
PVP K 30	4 mg	8 mg	24 mg	_	_	_	4 mg	8 mg	24 mg	enhance the aqueous solubility
Starch (8%)	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	Disintegrant
Lactose	163 mg	159 mg	143 mg	163 mg	159 mg	143 mg	163 mg	159 mg	143 mg	Diluents
Aerosil (1.25%)	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	3.1 mg	anticaking agent
Talc (0.76%)	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	1.9 mg	capsule lubricant
Total capsule weight	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	

Formulation Procedure of Candesartan Cilexetil: Respective quantities of candesartan cilexetil solid dispersion mixture with (hydroxyl propyl β cyclodextrin/PVP k-30), lactose and aerosil are sifted through # 20 mesh and blend the mixture for 5 minutes in the blender.

To the above blend, add talc and again blend the mixture for 5 minutes in blender and sifted through #20 mesh. Finally, the solid dispersion blends are filled into capsules by the manual capsule filling method.

Pre-Filling Parameters [13]: Bulk Density (D_b), Tapped Density (D_t), Carr's index (or) % compressibility, Hausner's ratio: [71] Was performed to check the flow properties of powder summarized in **Table 4.**

Evaluation of Capsules [13, 14]:

Content Uniformity test: Drug Content: The SD formulations prepared were assayed for drug content by dissolving a specific amount of SD in 10ml of distilled water.

The solutions were filtered and were further diluted such that the absorbance falls within the range of the standard calibration curve. The absorbance of solutions was determined at 251nm [15] refer **Table 2** and **Fig. 1** refer **Table 2** and **Fig. 9.**

% Drug Content = (Actual amount of drug in SD / Theoretical amount of drug in SD) × 100

FTIR Studies: FTIR studies were done to check the compatibility of drug and excipients summarized in **Table 5** and **Fig. 2, 4, 5,** and **6.**

Weight Variation test: To perform this test, 20 units were individually weighed at random and average weight was determined. There should not be more than 2 of the individual mass deviate from the average weight by more than the percentage deviation, and none deviate by more than twice that percentage. They are summarized in **Table 4.**

Lock Length and Thickness of Capsule: It was tested by using vernier calipers Summarized in **Table 4.**

Disintegration: The disintegration test is a method to evaluate the rate of disintegration of solid dosage forms (capsules or tablets) Summarized in **Table 4.**

Aqueous Solubility Studies [16]: The solubility of a pure drug and its solid dispersion was determined in distilled water. Drug and all SD formulations equivalent to 10mg were taken. To this, 10ml of distilled water was added in a 100ml stoppered volumetric flask and shaken for 25 hrs at room temperature on a magnetic stirrer.

The samples were protected from light by wrapping the flask using aluminium foil. After 24 hrs, samples were filtered through Whatman filter paper no.42 and aliquots were suitably diluted and assayed spectrophotometrically at 251nm. They are summarized in **Table 4** and **Fig. 7** and **8.**

***In-vitro* Dissolution Studies [17, 18]:** Dissolution test was carried out in USP apparatus (rotating basket method). The samples were placed in hard gelatin capsules. 900 ml of pH 6.8 phosphate buffer was used as dissolution media at 37±0.5 ^{o}C and maintaining stirring speed at 50 rpm. The samples were drawn at 10, 20, 30, 40, 50 & 60. min Fresh volume of the dissolution medium was replaced with the withdrawn volume to maintain the sink conditions. Samples were withdrawn and analyzed in the wavelength 251nm in UV spectrophotometer. Summarized in **Table 6** and **Fig. 10, 11, 12, 13, 14, 15** and **16.**

X-Ray Powder Diffraction Studies [19, 20]: X-ray powder diffraction patterns were used to detect the possible polymorphic transition during the crystallization process. X-ray powder diffraction was obtained at room temperature (25 °C), giving 15 minutes exposure time by using Bruker$_a$ XS D8 Advance diffractometer (Cu Kά source λ = 1.5418 Å). The scanning rate was 0.2^0/min, and the diffraction angle (2θ) was 0–80°. Refer **Table 7** and **Fig. 17, 18,** and **19.**

Stability Studies [21, 22]: The capsules were packed by 30 counts by using HDPE containers, induction sealed with adsorbent cotton. To determine the change in *in-vitro* release profile on storage, stability study of batch SD3 was carried out at 25^{o}C ± 2°C/60% ± 5% RH for 2 weeks, and at 40 ± 2°C/75 ± 5% RH. 30 capsules were packed in Alu-Alu Blisters / HDPE containers induction sealed with adsorbent cotton and kept at above-specified conditions in stability chamber for three months. Samples were evaluated after 1st, 2nd, and 3rd months for drug content as well as subjected for the *in-vitro* drug release study. The *in-vitro* dissolution studies were carried out for three months at the interval of one month. The sample was withdrawn at various intervals and evaluated for change in *in-vitro* drug release pattern and percent drug content. **Refer Table 8, 9** and **Fig. 20, 21.**

RESULTS:

Pre-Compression Evaluation Parameters: Physical appearance, the physical appearance of the drug was examined by organoleptic properties, and results are obtained as Color: White Powder, Odor: No Characteristic, State: Fine Powder. Solubility studies of the pure drug: Candesartan cilexetil was Practically In-Soluble in water, Sparingly Soluble in methanol, soluble in ethanol, DMF, DMSO, Slightly Soluble in 0.1N Hcl, pH 6.8 Buffer, pH 7.4 buffer. This was confirmed by observing the solubility studies of Candesartan cilexetil practically. Melting point: The Melting of Candesartan cilexetil was found to be 165 ^{o}C.

UV-spectrum of Candesartan Cilexetil in 0.1 M NAOH:

TABLE 2: CALIBRATION CURVE DATA OF CANDESARTAN CILEXETIL

Concentration in mcg/ml	Absorbance at 251 nm
0	0
4	0.099
8	0.2
12	0.304
16	0.399
20	0.506
24	0.61
28	0.704

Drug Excipient Compatibility Studies:

TABLE 3: IR INTERPRETATION

Functional group	Type of Vibration	Observed Characteristic Absorptions (cm^{-1}) Pure drug	Observed Characteristic Absorptions (cm^{-1}) physical mixture of candesartan cilexetil and HPβCD	Observed Characteristic Absorptions (cm^{-1}) physical mixture of Candesartan cilexetil and PVP K 30	Observed Characteristic Absorptions (cm^{-1}) SD3 formulation prepared by kneading method	Observed Characteristic Absorptions (cm^{-1}) SD6 formulation prepared by kneading method
Aromatic C-H	Stretching	2941.47cm^{-1}	2931.80cm^{-1}	2939.52cm^{-1}	2939.52cm^{-1}	2931.80cm^{-1}
-C=O (Ketone group)	Stretching	1752.39cm^{-1}	1753.29cm^{-1}	1751.36cm^{-1}	1749.44cm^{-1}	1743.65cm^{-1}
-C-O (Carbonyl group)	Stretching	1241.88cm^{-1}	1259.52 cm^{-1}	1240.23 cm^{-1}	1240.23cm^{-1}	1259.52cm^{-1}
O-substitution	Bending	748.93cm^{-1}	750.31cm^{-1}	740.67 cm^{-1}	742.59cm^{-1}	767.67cm^{-1}
C-N	Stretching	1613.74cm^{-1}	1658.78 cm^{-1}	1656.85cm^{-1}	1612.49 cm^{-1}	1658.78cm^{-1}
Inter molecular hydrogen bonding OH	Stretching	3451.36cm^{-1}	3263.56cm^{-1}	3385.07cm^{-1}	-	3325.28cm^{-1}

Pre-Filling Parameters (Micromeritic Properties) and Post Filling Parameters:

TABLE 4: MICROMERITIC PROPERTIES OF CANDESARTAN CILEXETIL SD MIXTURES AND POST FILLING PARAMETERS OF CANDESARTAN CILEXETIL SD FORMULATION

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Angle of Repose (Θ)	Hausner's ratio	Average weight of empty capsule (mg) & SD (mg)***	Weight of empty gelatin capsules (mg)	Weight of SD filled	Weight variation (mg) 7.5%	Locked length of capsules (mm)**	Thickness of capsules (mm)**	Disintegration (sec)*
Pure Drug	0.348	0.543	35.91	$46^{o}1'$	1.560	-	-	-	-	-	-	-
SD1	0.496	0.621	20	$32^{o}88'$	1.252	261	60	201	1±0.02	18.5±0.01	5.9±0.01	130
SD2	0.495	0.582	14.94	$26^{0}52'$	1.175	262	60	202	2±0.16	18.4±0.02	5.8±0.01	140
SD3	0.492	0.546	9.89	$29^{0}32'$	1.109	259	60	199	-1±0.32	18.6±0.03	6.0±0.02	130
SD4	0.493	0.586	15.87	$31^{0}70'$	1.188	261	60	201	1±0.01	18.5±0.11	5.9±0.01	130
SD5	0.495	0.582	14.94	$32^{0}00'$	1.175	263	60	203	3±0.91	18.27±0.26	6.0±0.01	130
SD6	0.495	0.596	16.9	$28^{0}89'$	1.204	259	60	199	-1±0.32	18.6±0.32	6.0±0.02	133
SD7	0.425	0.519	18.11	$28^{0}14'$	1.221	261	60	201	1±0.56	18.6±0.01	6.0±0.01	140
SD8	0.416	0.529	21.36	$32^{0}2'$	1.271	261						
SD9	0.433	0.546	20.69	$32^{0}90'$	1.260	259						
SD10	0.422	0.518	18.53	$31^{0}70'$	1.227	261						
SD11	0.418	0.518	19.3	$31^{0}67'$	1.239	261						
SD12	0.361	0.437	13.96	$30^{0}08'$	1.210	259						
SD13	0.497	0.571	12.95	$28^{0}17'$	1.148	261						
SD14	0.493	0.593	16.8	$27^{0}61'$	1.202	262						
SD15	0.495	0.576	20.22	$32^{0}45'$	1.163	261						
SD16	0.491	0.591	16.9	$29^{0}05'$	1.203	259						
SD17	0.496	0.583	14.92	$29^{0}11'$	1.175	259						
SD18	0.49	0.59	16.94	$27^{0}8'$	1.204	261						

60	201	2±0.64	18.5±0.01	6.0±0.01	140
60	199	-1±0.87	18.6±0.01	5.9±0.02	135
60	201	1±0.15	18.6±0.02	5.9±0.01	130
60	201	1±0.59	18.6±0.01	6.0±0.01	150
60	199	-1±0.23	18.5±0.01	5.9±0.02	140
60	201	1±0.84	18.4±0.01	6.0±0.01	145
60	202	2±0.75	18.5±0.13	5.8±0.03	142
60	201	1±0.54	18.5±0.02	6.0±0.01	141
60	199	-1±0.31	18.4±0.01	6.0±0.02	130
60	199	-1±0.65	18.4±0.15	5.9±0.01	135
60	201	1±0.354	18.6±0.02	6.0±0.02	140

*mean (n=3), **mean±Standard deviation (n=10),***mean ±Standard deviation (n=20)

Solid Dispersions:

TABLE 5: AQUEOUS SOLUBILITY STUDIES OF CANDESARTAN CILEXETIL – HPBCD FORMULATIONS AND PVP K 30 FORMULATION AND REPRESENTATION OF DRUG CONTENT OF CANDESARTAN CILEXETIL SD FORMULATIONS

SL. no.	Formulation code	Aq. Solubility mg/ml	% Drug Content*
1	SD1	0.712	97.63±0.12
2	SD2	0.821	96.14±0.32
3	SD3	0.948	98.44±0.56
4	SD4	0.432	97.12±0.98
5	SD5	0.521	95.43±0.11
6	SD6	0.651	96.48±0.65
7	SD7	0.324	96.69±0.78
8	SD8	0.439	94.35±0.95
9	SD9	0.562	96.12±0.35
10	SD10	0.218	95.43±0.65
11	SD11	0.329	95.98±0.55
12	SD12	0.46	97.46±0.24
13	SD13	0.181	95.12±0.18
14	SD14	0.126	95.52±0.96
15	SD15	0.363	97.42±0.66
16	SD16	0.12	96.72±0.44
17	SD17	0.16	97.00±0.59
18	SD18	0.185	94.21±0.35

*mean ±S.D (n=3)

TABLE 6: DISSOLUTION STUDIES IN COMPARISON WITH PURE DRUG AND SD FORMULATIONS

Time (Min)	%CDR									
	Pure Drug*	SD1*	SD2*	SD3*	SD4*	SD5*		Pure Drug*	SD1*	
0	0	0	0	0	0	0	0	0	0	
10	15.00± 0.45	25.31± 0.12	27.28± 0.55	30.96± 0.87	24.26± 0.35	26.32± 0.16	10	15.00± 0.45	25.31± 0.12	
20	22.65± 0.68	36.12± .15	39.58± 0.47	45.35± 0.23	35.23± 0.25	37.82± 0.51	20	22.65± 0.68	36.12± 0.15	
30	28.73± 0.25	55.26± 0.85	59.11± 0.70	66.00± 0.39	53.62± 0.19	57.69± 0.47	30	28.73± 0.25	55.26± 0.85	
40	31.85± 0.67	70.33± 0.45	73.00± 0.54	78.13± 0.79	68.83± 039	71.00± 0.54	40	31.85± 0.67	70.33± 0.45	
50	33.79± 0.71	79.91± 0.48	81.35± 0.69	86.76± 0.48	76.12± 0.25	80.16± 0.36	50	33.79± 0.71	79.91± 0.48	
60	36.55± 1.021	86.32± 0.62	91.56± 0.67	94.05± 0.11	83.42± 0.65	89.87± 0.98	60	36.55± 1.021	86.32± 0.62	
Time (Min)	**SD9***	**SD10***	**SD11***	**SD12***	**SD13***	**SD14***	**SD15***	**SD16***	**SD17***	**SD18***
0	0	0	0	0	0	0	0	0	0	0
10	29.38± 0.14	23.22± 0.23	25.23± 0.78	28.91± 0.12	22.89± 0.65	24.9± 0.31	28.00± 0.14	21.61± 0.11	23.00± 0.58	25.63± 0.55

20	42.02± 0.24	32.63± 0.45	34.63± 0.98	40.89± 0.41	30.73± 0.87	33.72± 0.64	36.39± 0.71	29.00± 0.32	32.92± 0.47	34.62± 0.35
30	62.14± 0.35	49.12± 0.54	55.12± 0.57	60.43± 0.32	48.32± 0.56	55.00± 0.48	58.31± 0.64	46.19± 0.14	52.16± 0.24	57.61± 0.34
40	75.12± 0.89	64.36± 0.36	69.38± 0.14	73.91± 0.87	61.77± 0.78	65.98± 0.12	71.92± 0.32	59.42± 0.28	62.91± 0.58	66.61± 0.25
50	82.19± 0.14	74.13± 0.11	76.52± 0.38	82.00± 0.23	72.47± 0.64	75.39± 0.33	78.00± 0.12	64.16± 0.47	68.63± 0.35	72.12± 0.65
60	90.39± 0.78	79.63± 0.17	84.32± 0.24	86.91± 0.14	75.69± 0.53	80.16± 0.47	82.43± 0.74	71.36± 0.25	75.12± 0.19	80.31± 0.87

*mean±Standard deviation (n=3)

TABLE 7: X-RAY DIFFRACTION INTERPRETATION

Samples	Degree (2θ)
Candesartan cilexetil	5^o, 10^o,18^o
Hydroxyl propyl beta-cyclodextrin	No prominent peaks
Formulation SD3	12^o, 16^o, 22^o

Stability data of Candesartan Cilexetil SD Capsules (Formulation SD3):

TABLE 8: STABILITY RESULTS OF CANDESARTAN CILEXETIL CAPSULES (SD3) AT 25 °C

S. no.	Test	Initia		25° ± 2°C / 60% ± 5% RH
				2 weeks /15 days
1	Description	White to half white color		No changes
2	Drug Content (%)*	98.44±0.56		97.63±0.12
3	Dissolution*	Time in Min	%DR (Avg)	% DR (Avg)
		0	0	0
		10	30.96±0.87	29.63±0.19
		20	45.35±0.23	44.32±0.63
		30	66.00±0.39	65.12±0.91
		40	78.13±0.79	77.36±0.68
		50	86.76±0.48	85.19±0.52
		60	94.05±0.11	93.21±0.82
4	Thickness (mm) **	6.0±0.02		6.0±0.01
5	Disintegration (sec) *	130		128
6	Lock length (mm) **	18.6±0.03		18.5±0.02

TABLE 9: STABILITY RESULTS OF CANDESARTAN CILIXETIL SD CAPSULES (SD3) AT ACCELERATED CONDITIONS

S. no.	Test	Initial		40° ± 2° C/75% ±5% RH		
				1 Month	2 Month	3 Month
1	Description	White to half white color		No change	No change	No change
2	Drug content (%)*	98.44±0.56		97.43±0.19	97.00±0.29	96.43±0.96
3	Dissolution*	Time in Min	%DR (Avg)	%DR (Avg)	%DR (Avg)	% DR (Avg)
		0	0	0	0	0
		10	30.96±0.87	30.52±0.31	29.92 ±0.16	29.00± 0.81
		20	45.35±0.23	45.00±0.82	44.12±0.93	43.72±0.63
		30	66.00±0.39	59.96±0.43	59.00±0.63	58.17±0.98
		40	78.13±0.79	78.00±0.62	77.69±0.53	77.00±0.49
		50	86.76±0.48	86.64±0.42	84.98±0.92	83.00±0.19
		60	94.05±0.11	93.33±0.18	92.69±0.84	92.00±0.36
4	Thickness (mm) **	6.0±0.02		6.00±0.12	5.9±0.98	5.9±0.36
5	Disintegration (sec) *	130		126	123	118
6	Lock length (min) **	18.6±0.03		18.6±0.22	18.5±0.13	18.5±0.68

**mean ± Standard deviation (n=10), *mean ± Standard deviation (n=3)

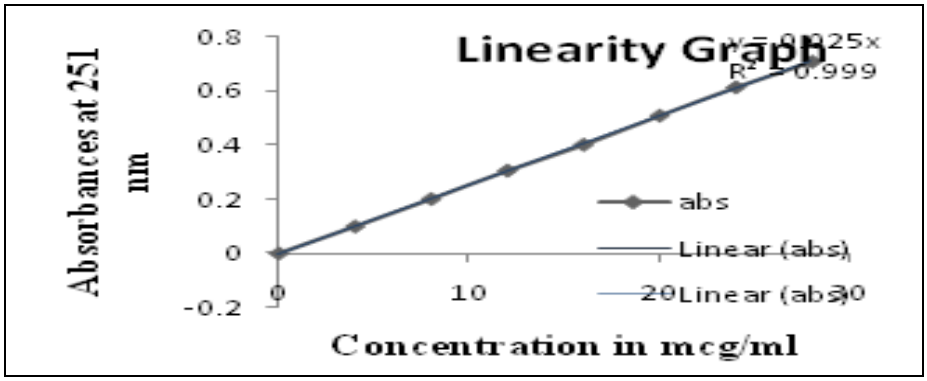

FIG. 1: CALIBRATION CURVE OF CANDESARTAN CILEXETIL AT 251 nm

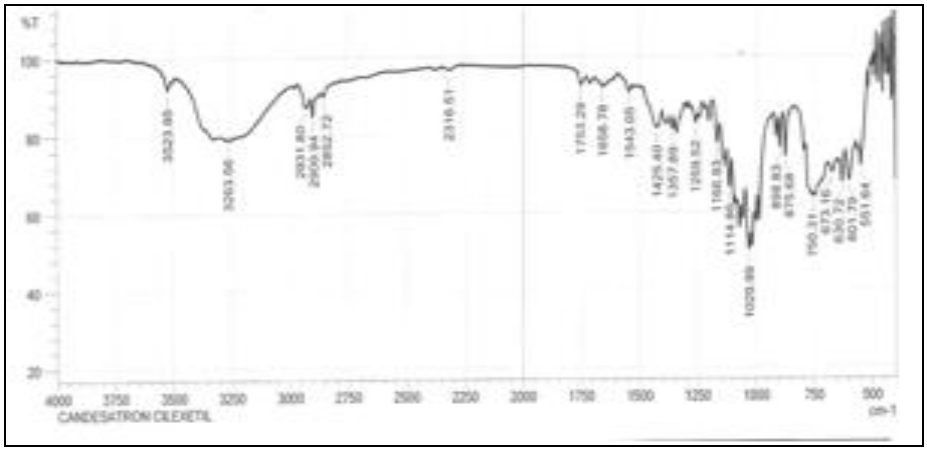

FIG. 2: FT-IR OF PURE DRUG

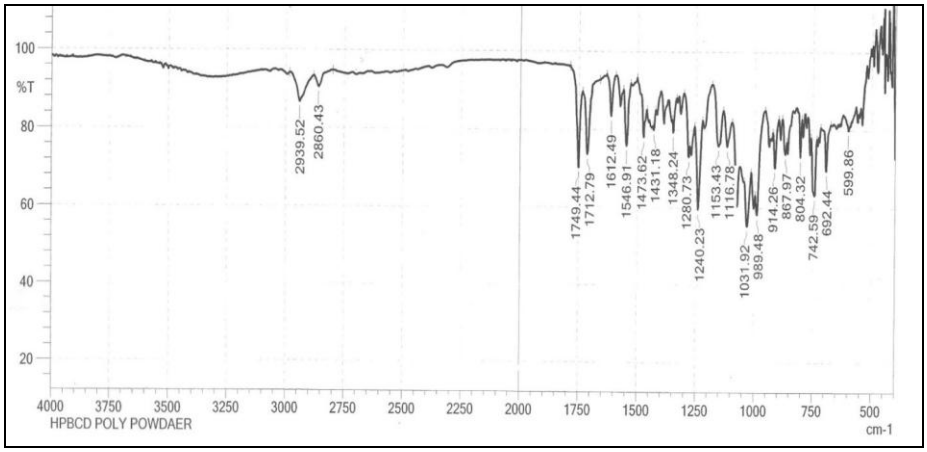

FIG. 3 : FTIR OF FORMULATION SD6 BY KNEADING METHOD

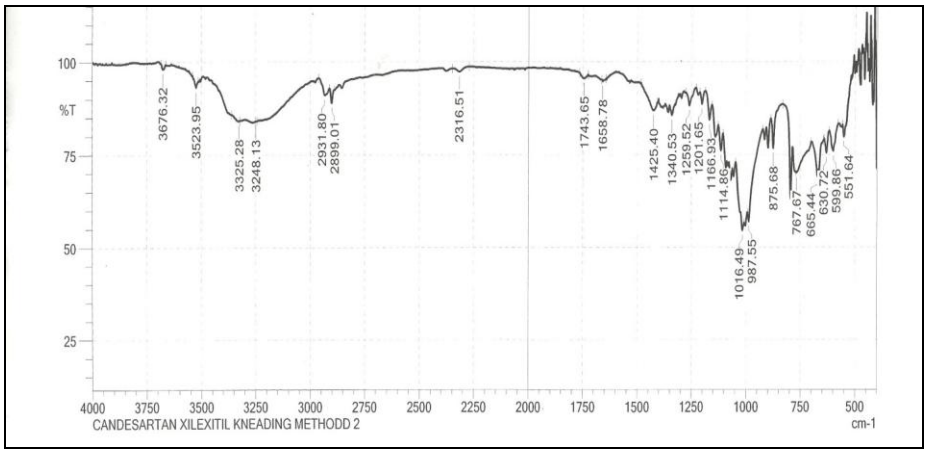

FIG. 4: FTIR SPECTRA OF FORMULATION SD3 BY KNEADING METHOD

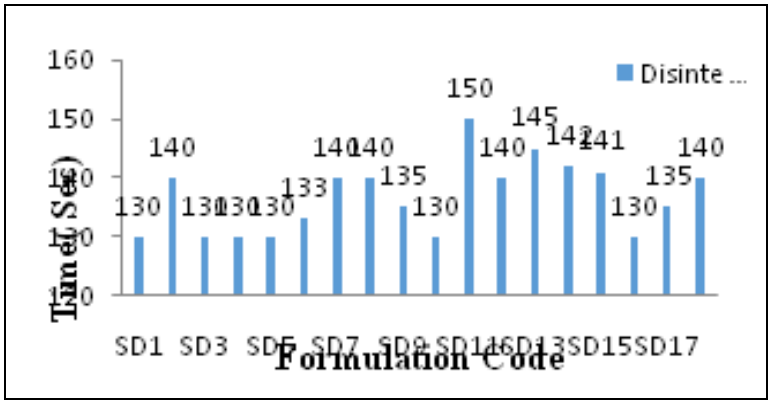

FIG. 5: DISINTEGRATION STUDIES OF ALL CANDESARTAN CILEXETIL SD FORMULATIONS

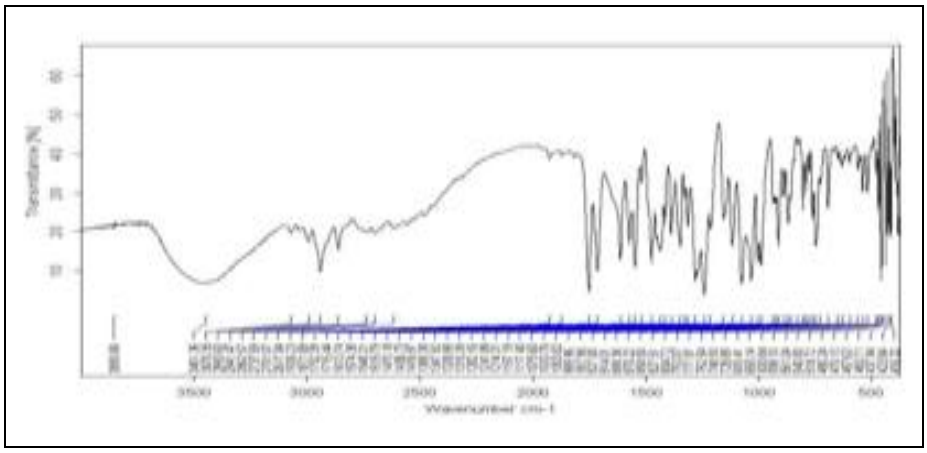

FIG. 6: FTIR SPECTRA OF PHYSICAL MIXTURE OF CANDESARTAN CILEXETIL AND HPBC

Aqueous Solubility Studies:

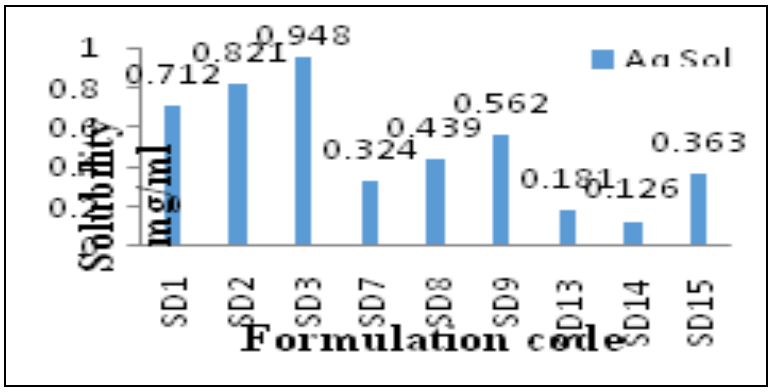

FIG. 7: AQUEOUS SOLUBILITY STUDIES OF

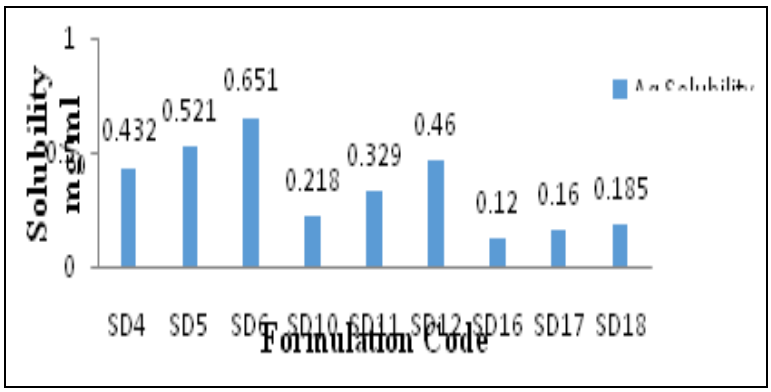

FIG. 8: OF AQUEOUS SOLUBILITY STUDIES OF CANDESARTAN CILEXETIL-CANDESARTAN CILEXETIL-HPBCD SD FORMULATIONS

PVP K 30 SD Formulation:

Drug Content Estimation:

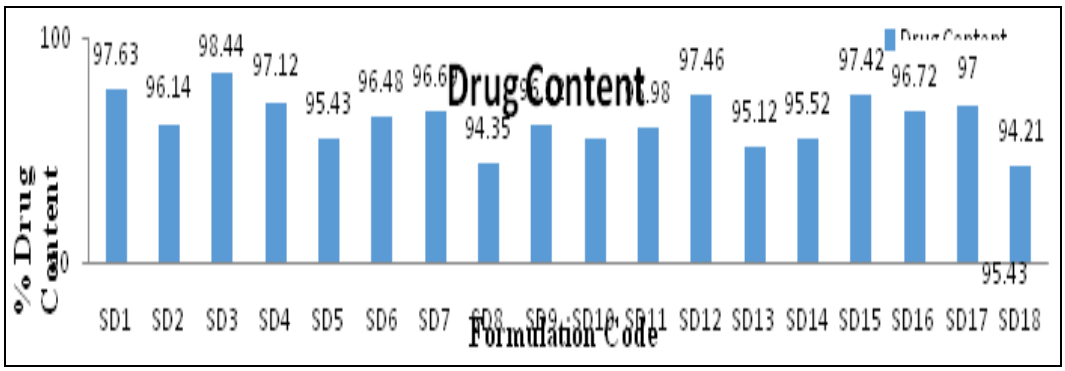

FIG. 9: DIAGRAMMATICAL REPRESENTATION OF DRUG CONTENT STUDIES OF CANDESARTAN CILEXETIL SD FORMULATIONS

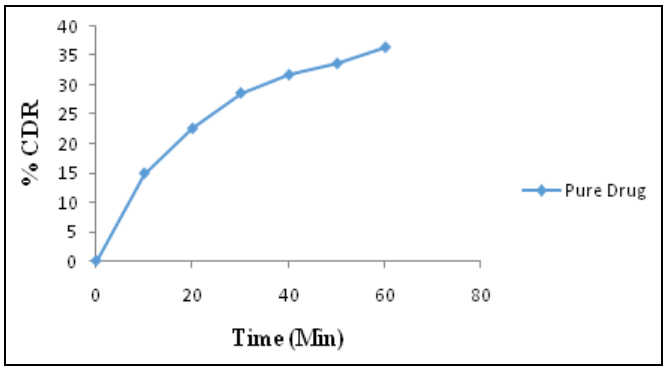

FIG. 10: DISSOLUTION DATA OF CANDESARTAN CILEXETIL IN PH 6.8 PHOSPHATE BUFFER

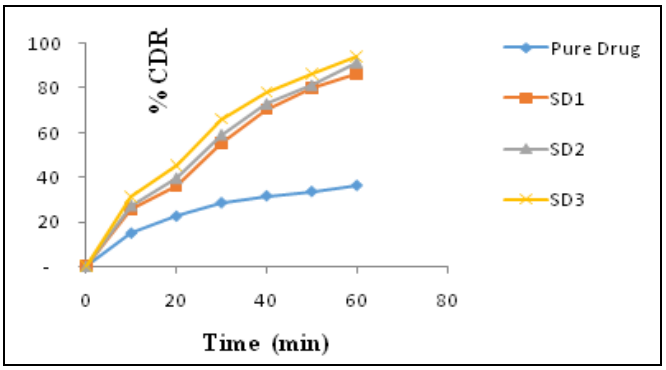

FIG. 11: DISSOLUTION DATA OF CANDESARTAN CILEXETIL- HPBCD BY KNEADING METHOD

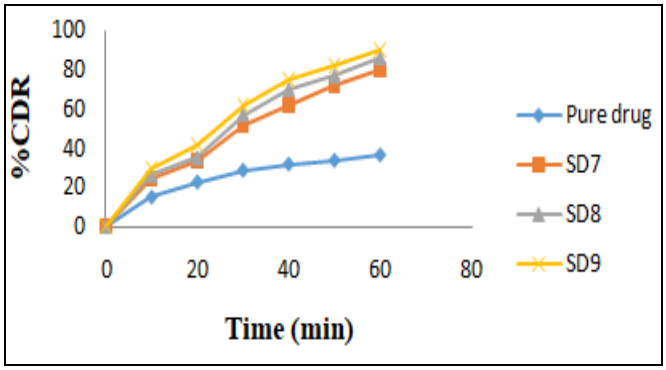

FIG. 12: DISSOLUTION DATA OF CANDESARTAN CILEXETIL HPBCD INCILEXETIL

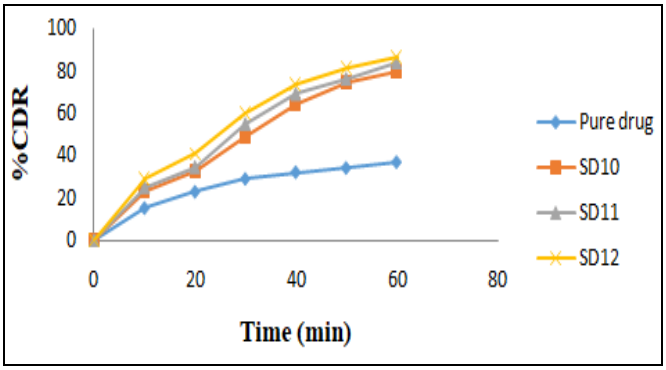

FIG. 13: DISSOLUTION DATA OF CANDESARTAN PVP K 30 BY SOLVENT EVAPORATION METHOD

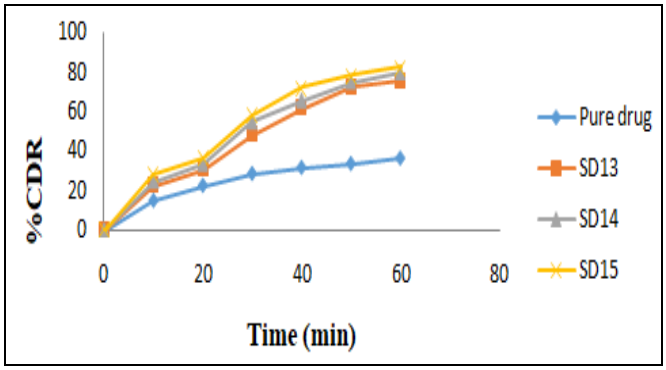

FIG. 14: DISSOLUTION DATA OF CANDESARTAN CILEXETIL PVP K 30 BY MICROWAVE METHOD

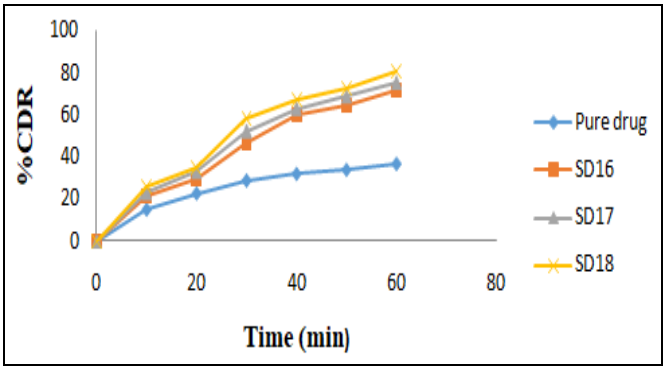

FIG. 15: DISSOLUTION DATA OF CANDESARTAN CILEXETIL HPBCD BY MICROWAVE METHOD

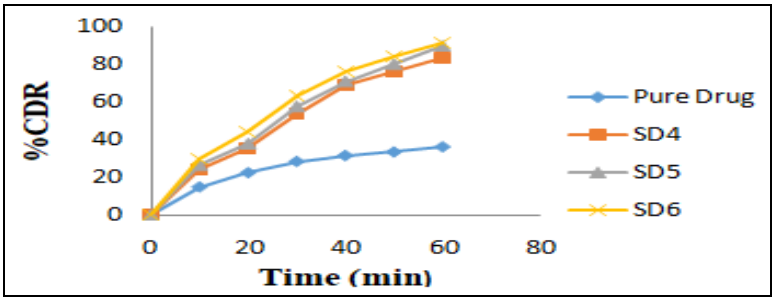

FIG. 16: DISSOLUTION DATA OF CANDESARTAN CILEXETIL -PVP K 30 BY KNEADING METHOD

X Ray Powder Diffraction Spectroscopy:

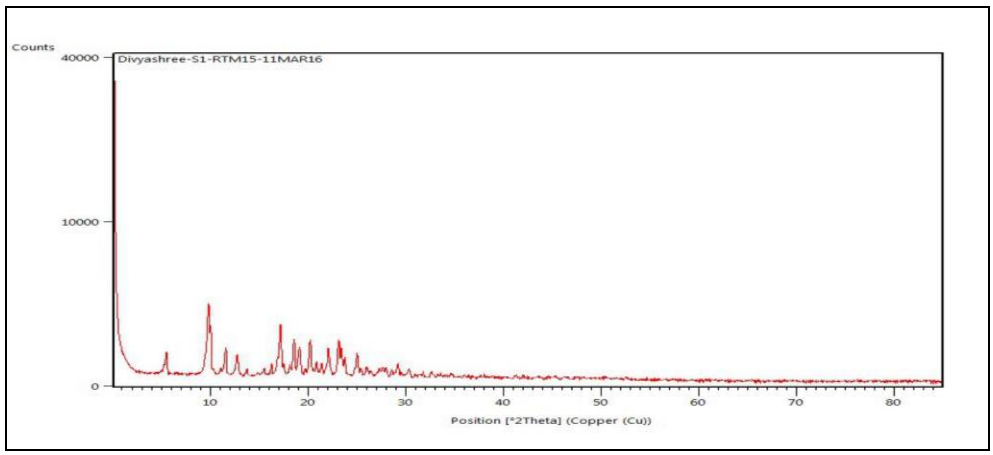

FIG. 17: X RAY POWDER DIFFRACTION OF CANDESARTAN CILEXETIL

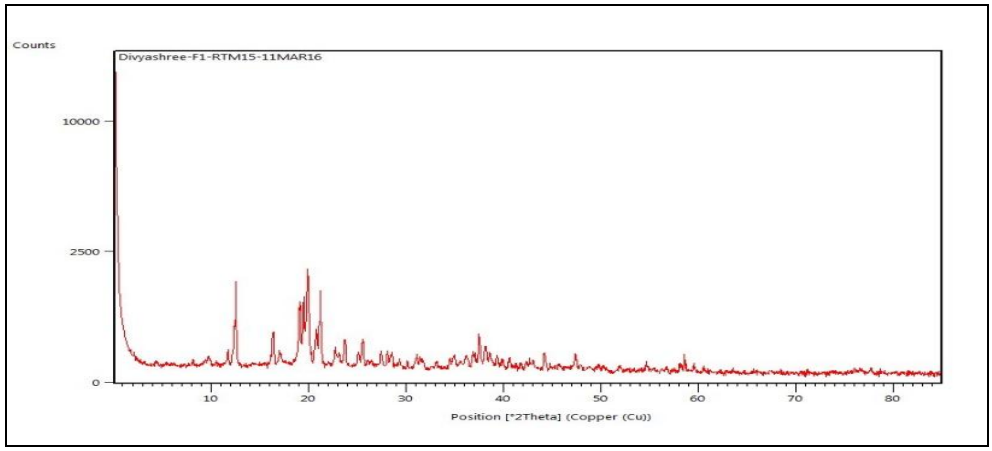

FIG. 18: X-RAY POWDER DIFFRACTION OF HYDROXY PROPYL BETA CYCLODEXTRIN

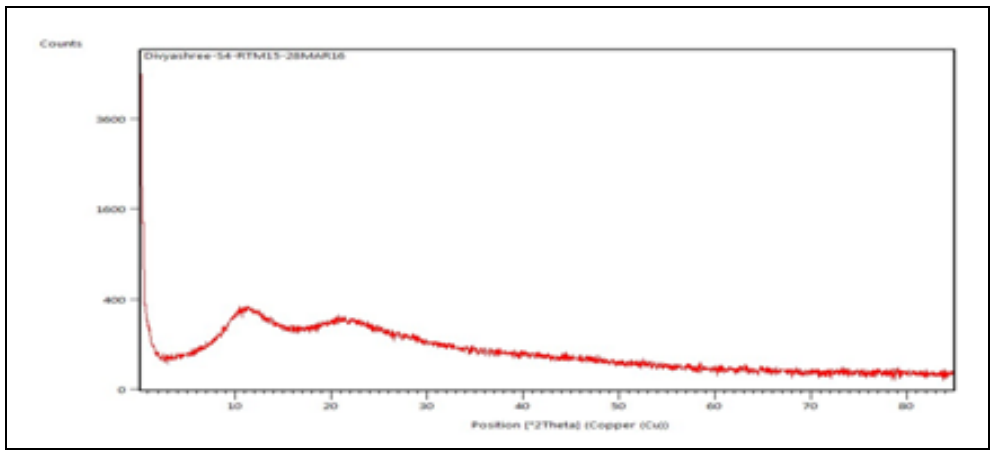

FIG. 19: X-RAY POWDER DIFFRTION OF OPTIMIZED FORMULATION SD3

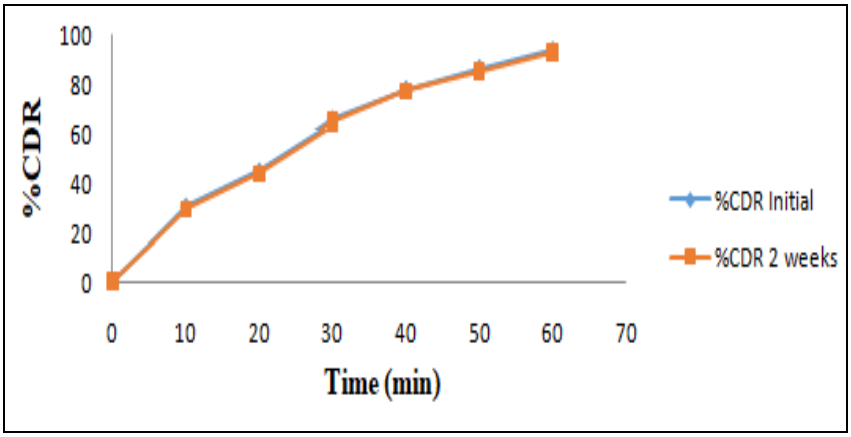

FIG. 20: COMPARATIVE *IN-VITRO* DISSOLUTIONS DATA OF STABILITY SAMPLE SD3 AT 250 C CONDITIONS FOR 2 WEEKS

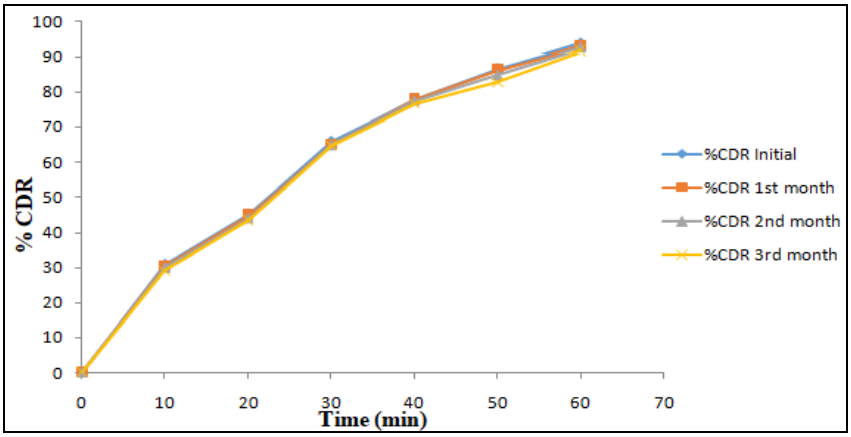

FIG. 21: COMPARATIVE *IN-VITRO* DISSOLUTION DATA OF STABILITY SAMPLE SD3 AT ACCELERATED CONDITIONS FOR 3 MONTHS

DISCUSSION: The objective of the present study was to enhance the dissolution rate of a poorly soluble anti-hypertensive drug Candesartan cilexetil by SD method. In this study, SD of Candesartan cilexetil was formulated using carriers HPβCD & PVP K 30 with polymers lactose, starch, talc, aerosil and evaluated for various *in-vitro* parameters. Candesartan cilexetil capsules were prepared using different excipients like HPβCD / PVP K 30, starch, lactose, aerosol & talc. Solubility of Candesartan cilexetil is enhanced by the use of water soluble carriers HPβCD & PVP K 30. They were prepared by direct mixing, and the powder was filled into an empty hard gelatin capsule using the manual capsule filling method. The method of direct mixing and manual filling utilizes minimum machinery and manpower. From the economic point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies to prepare SD products. The formulated SD were evaluated for various *in-vitro* parameters. Candesartan cilexetil was analyzed for IR, UV, X-Ray studies. The obtained results of Candesartan cilexetil were concordant with reference specifications. The results showed no interaction between the drug Candesartan cilexetil and the polymers employed in the formulation. FT-IR studies indicated no interaction between the drug, polymers, and other excipients as the principal peaks of the drug in the spectra obtained for drug and carrier SD mixture was not altered. X-RD studies revealed the absence of characteristic peaks of Candesartan cilexetil and reduced in the intensity of peaks in the solid dispersion formulation SD3 as it is converted into an amorphous or solubilized form or reduction of their crystalline nature. The absence of crystallinity in the solid dispersion system is perhaps the result of solubilization in the carrier HPβCD, and the amorphization or solubilization of Candesartan cilexetil may result in an increased dissolution rate. The evaluation and the dissolution characteristics were performed for all the SD batches SD1- SD18.

Among all the formulations, SD3 formulation showed a better drug release over 1 hour of time. SD of Candesartan cilexetil capsules prepared by kneading method using HPβCD as the carrier in the ratio of 1:1.5 was proved to be the most promising dosage form for SD of Candesartan cilexetil. It also found to be that there was no interaction between the drug and polymer in all the formulations. Stability studies were conducted according to ICH guidelines, carried out for optimized formulations for a period of 2 weeks, 3 months, and the obtained results were within the specification at short term accelerated conditions. From the above, it can be concluded that HPβCD mixture prepared by kneading method is a simple and better strategy to enhance the dissolution rate.

CONCLUSION: The objective of the present study was to enhance the dissolution rate of a poorly soluble anti-hypertensive drug Candesartan cilexetil by SD method. In this study, SD of Candesartan cilexetil was formulated using carriers HPβCD & PVP K 30 with polymers lactose, starch, talc, aerosil and evaluated for various *in-vitro* parameters.

Candesartan cilexetil capsules were prepared using different excipients like HPβCD / PVP K 30, starch, lactose, aerosol & talc. Solubility of Candesartan cilexetil is enhanced by the use of water-soluble carriers HPβCD & PVP K 30. They were prepared by direct mixing, and the powder was filled into an empty hard gelatin capsule using the manual capsule filling method. The method of direct mixing and manual filling utilizes minimum machinery and manpower. From the economic point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of SD products. The formulated SD were evaluated for various *in-vitro* parameters. Candesartan cilexetil was analyzed for IR, UV, X-Ray studies. The obtained results of Candesartan cilexetil were concordant with reference specifications. The results showed that there was no interaction between the drug Candesartan cilexetil and the polymers employed in the formulation. FT-IR studies indicated no interaction between the drug, polymers, and other excipients as the principal peaks of the drug in the spectra obtained for drug and carrier SD mixture was not altered. X-RD studies revealed the absence of characteristic peaks of Candesartan cilexetil and reduced the intensity of peaks in the solid dispersion formulation SD3 as it is converted into an amorphous or solubilized form or reduction of their crystalline nature. The absence of crystallinity in the solid dispersion system is perhaps the result of solubilization in the carrier HPβCD and the amorphization or solubilization of Candesartan cilexetil may result in an increased dissolution rate. The evaluation and the dissolution characteristics were performed for all the SD batches SD1- SD18. Among all the formulations, SD3 formulation showed a better drug release over 1 hour of time. SD of Candesartan cilexetil capsules prepared by kneading method using HPβCD as a carrier in the ratio of 1:1.5 was proved to be the most promising dosage form for SD of Candesartan cilexetil. It also found that there was no interaction between the drug and polymer in all the formulations. Stability studies were conducted according to ICH guidelines, carried out for optimized formulations for 2 weeks, 3 months, and the obtained results were within the specification at short-term accelerated conditions. From the above, it can be concluded that the HPβCD mixture prepared by the kneading method is a simple and better strategy to enhance the dissolution rate.

ACKNOWLEDGEMENT: We take this privilege and pleasure to acknowledge the contribution of many individuals who have been inspirational and supportive throughout our work, and we would be thankful to the management of St. John's Pharmacy College, Bangalore, and extend our thanks to Dr. G. Kulkarni and Mr. Subhash P. G. and Mr. Rajshekar Valluru for their support during the work.

CONFLICTS OF INTEREST: The authors declared no conflicts of interest in this study.

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How to cite this article:
Shree AJD and Ravichandra VD: Design and evaluation of Candesartan cilexetil solid dispersion incorporated in hard gelatin capsule. Int J Pharm Sci & Res 2022; 13(7): 2856-69. doi: 10.13040/IJPSR.0975-8232.13(7). 2856-69.