IJPSR (2021), Volume 12, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 January 2021; received in revised form, 03 May 2021; accepted, 29 May 2021; published 01 December 2021

ENHANCEMENT OF SOLUBILITY OF POORLY SOLUBLE DRUG BY INCLUSION COMPLEXATION WITH γ-CYCLODEXTRIN

B. Radha Madhavi [*1], B. Divya [2], K. Anusha [2], G. Tejaswi [2], G. Yamini Divya Teja [2] and K. Kiran Kumar Reddy [2]

Department of Pharmaceutics [1], Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram, West Godavari - 534202, Andhra Pradesh, India.
Department of Pharmaceutics [2], Vignan Pharmacy College, Vadlamudi, Guntur - 522213, Andhra Pradesh, India.

Keywords:

Candesartan cilexetil, γ-cyclodextrin, Phase solubility studies, Solubility, Dissolution

Correspondence to Author:
Dr. Radha Madhavi Baluguri

Associate Professor,
Department of Pharmaceutics,
Shri Vishnu College of Pharmacy,
Vishnupur, Bhimavaram, West Godavari - 534202, Andhra Pradesh, India.

E-mail: drbrmadhavi@gmail.com

ABSTRACT: Candesartan is an angiotensin receptor blocker, used as an anti-hypertensive drug. It is available in the salt form of cilexetil *i.e.*; Candesartan cilexetil belongs to class II of the Biopharmaceutical classification system. It is a poorly soluble drug, and the bioavailability is 15%. The intention of the study is to improve the solubility of the poorly soluble drug, Candesartan cilexetil using the inclusion complexation technique with γ-CD as a complexing agent. Complexation is the association between two or more molecules to form a non-covalent-based complex that has a higher solubility than the drug itself. Binary mixtures of Candesartan cilexetil were prepared with three different techniques (Physical Mixture, Kneading method, Solvent evaporation method)in three different ratios (1:1, 1:2, 1:3). The prepared complexes were analyzed using Fourier transform infrared spectroscopy. *In-vitro* dissolution studies were performed for all the prepared complexes by different methods in different ratios in order to define the most appropriate ratio and preparation method.

INTRODUCTION: Candesartan cilexetil is the most widely used drug for the treatment of hypertension. It comes under BCS class-II, which has low solubility and high permeability. So, to enhance the solubility of candesartan there are many strategies one such method is complexation. Complexation is a process of combination of atom groups, ions or molecules to form a complex. Inclusion complexation is formed by using a complexing agent like cyclodextrin. The cyclodextrin molecules possess a hydrophobic cavity and hydrophilic surface,

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(12).6593-99

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

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(12).6593-99

which can form an inclusion complex with a wide variety of guests. Cyclodextrins and their derivatives are used for the encapsulation of bioactive compounds that protects the compounds from environmental conditions as well as improve the aqueous solubility to increase their capacity to functionalised the products. Cyclodextrins are classified as natural and derived cyclodextrins. There are three well-known cyclic oligosaccharides that are industrially produced natural cyclodextrins.

The most common natural cyclodextrins are α, β, γ consisting of 6,7 & 8 glucopyranose unit's respectively [1-2]. Cyclodextrins are formed by the action of cyclodextrin glucosyl transferase enzyme on the medium containing starch. Cyclodextrins are macrocyclic oligosaccharides consisting of minimum 6 D-(+)-glucopyranose units that are linked by α (1-4) bond and one of the unique

features of cyclodextrins is their ability to form inclusion complexes with a variety of compounds and this is due to entrapment of molecules inside the cyclodextrin cavity, which act as host.

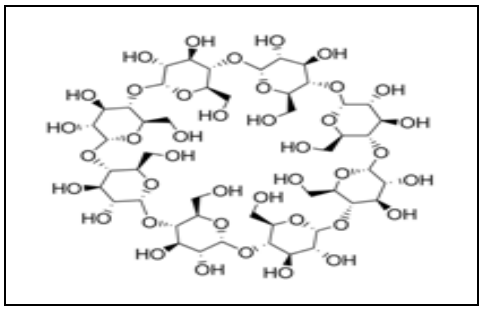

FIG. 1: STRUCTURE OF γ –CYCLODEXTRIN

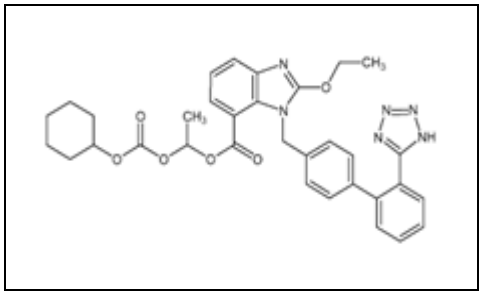

FIG. 2: STRUCTURE OF CANDESARTAN CILEXITIL

MATERIALS AND METHODS:

Materials: Candesartan cilexetil was obtained as a gift sample from Aurabindo Pharmaceutical Co. Ltd, Hyderabad, γ –Cyclodextrin, methanol, acetone was supplied by Merck Specialities Pvt. Ltd. Mumbai and all other chemicals used were of pharmaceutical grade.

Phase Solubility Studies: Phase Solubility studies were performed based on Higuchi and Connors method. Approximately 5 mg of the drug were added to each 25 ml of solvent in test tube. Increasing amounts of cyclodextrin (3, 6, 9, 12, 15µm) is added to determine the change in the solubility of the Candesartan cilexetil [3-4]. To form complexes in solutions, these test tubes were placed in orbital shaker for 72 hrs to attain the equilibrium between the drug and the cyclodextrins. The samples were then filtered using Whatman filter, the filtered samples were analyzed by UV spectrophotometer at λ_{max} of 256nm, 270nm, 257nm in Millipore water, 0.1N HCL, Phosphate buffer solution pH 7.4 respectively. A graph is plotted with the x-axis as the concentration of γ-CD and the y-axis concentration of Candesartan cilexetil. From graph, slope and intercept (S_0) is used to calculate the apparent stability constant (K).

Preparation of Inclusion Complex of Candesartan Cilexetil with γ –CD: It has been reported that complexation with cyclodextrins can improve the solubility and dissolution rate of poorly soluble drugs. To improve solubility and dissolution rate of Candesartan *via* complexation with γ- cyclodextrin of different molar ratio (1:1, 1:2, 1:3) were prepared. Candesartan inclusion complexes were prepared by using various methods such as Physical mixtures, Solvent evaporation, and the Kneading method.

Physical Mixtures: Accurately weighed quantities of drug and γ-CD were taken in a glass mortar and were mixed thoroughly with light trituration. The resultant mixture was passed through sieve number 100 and was stored in a desiccator for complete removal of moisture and was tested for content uniformity.

Kneading Method: In this method, an accurately weighed quantity of γ-CD was taken in a mortar, and a small volume of methanol: water (1:1) solvent blend was added to it and triturated. The obtained thick slurry was kneaded for 45 min, and the solvent was added from time to time to maintain the consistency of the paste. The dispersion obtained was dried at room temperature for 1h, and then dried at 70 °C for 6h in hot air oven [5-6]. The prepared complex was ground using mortar and pestle, sieved through #100 sieve and stored in a desiccator.

Solvent Evaporation Method: In this method, accurately weighed quantities of γ-CD was transferred into a boiling test tube and dissolved in acetone. The drug inaccurately weighed quantity was added to the solution and allowed to dissolve. The solution was transferred to a petri dish, the solvent was allowed to evaporate at room temperature and the dispersions were dried at room temperature for 1 h [6-7], and then dried at 70 °C for 6h in a hot air oven. The prepared complex was ground using mortar and pestle, sieved through #100 sieve and stored in a desiccator.

Drug and Excipient Compatibility Studies: Drug and excipient compatibility studies were performed using Fourier Transform Infrared Spectrophotometer. A baseline correction was made using the KBr and the spectrum of drug and excipients were obtained.

TABLE 1: VARIOUS INCLUSION COMPLEXES OF CANDESARTAN WITH γ- CYCLODEXTRIN

S. no.	Method	Ratio	Drug	γ -Cyclodextrin	Code
1	Physical Mixing	1:1	1	1	PM1
2	Physical Mixing	1:2	1	2	PM2
3	Physical Mixing	1:3	1	3	PM3
4	Kneading Method	1:1	1	1	KM1
5	Kneading Method	1:2	1	2	KM2
6	Kneading Method	1:3	1	3	KM3
7	Solvent Evaporation	1:1	1	1	SE1
8	Solvent Evaporation	1:2	1	2	SE2
9	Solvent Evaporation	1:3	1	3	SE3

Drug Content Analysis: An accurately weighed quantity of solid dispersion equivalent to 100 mg of Candesartan was taken into a 100ml volumetric flask and dissolved in methanol. The stock solutions were filtered, suitably diluted and assayed for drug content using a double beam UV/VIS spectrophotometer at 224 nm [8-9].

***In-vitro* Dissolution Studies:** *In-vitro* release rate of Candesartan solid dispersion of different samples was determined using USP-II dissolution apparatus using an eight-stage dissolution rate testing apparatus with paddle. The dissolution medium consisted of the buffer. Inclusion complex equivalent to 100 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium *i.e.*, buffer at 37 °C ± 0.5 °C. Aliquots of 5 ml were withdrawn at regular intervals of time, *i.e.*, (5, 10, 15, 20, 25 & 30 min) and the sample is replaced with the fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper and the absorbance was measured at 224 nm [10-11].

Dissolution Parameters:
Apparatus: USP29, Apparatus-II
Dissolution Medium: 6.8 pH Phosphate buffer
RPM: 50rpm
Sampling intervals (min): 5, 10, 15, 20, 25, 30
Temperature: 37 °C ± 0.5 °C

RESULTS AND DISCUSSION:

Phase Solubility Studies: The phase solubility diagram for the complex formation between Candesartan and γ-CD was shown in **Fig. 2**. The aqueous solubility of the drug increased linearly as a function of γ-cyclodextrin concentration. At all, the concentrations of γ-CD used for the preparation of the inclusion complexes showed a significant increase in the solubility of Candesartan. As the concentration of the γ-CD increased, the solubility of the drug was found to be increased due to molecular interactions with γ- cyclodextrin.

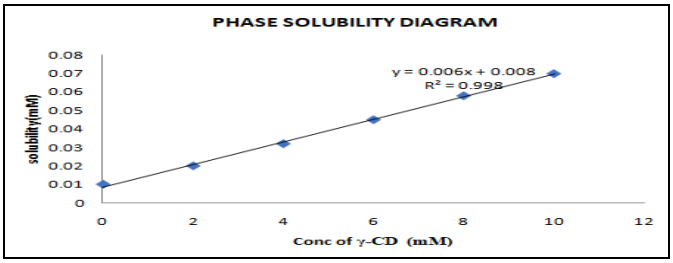

FIG. 3: PHASE SOLUBILITY DIAGRAM OF CANDESARTAN CILEXETIL IN AQUEOUS SOLUTION OF γ-CD

FTIR Studies: The IR spectrum of Candesartan, γ-CD, and Candesartan: γ-CD (1:3) kneading complex was shown in **Fig. 3, 4, 5, 6** and **7**, respectively. The IR spectrum of the drug exhibited peak at 2938.54 cm^{-1} due to aromatic C-H stretching, while the peak at 1751.14 cm^{-1} indicates C=O stretching and peak at 1611. 01 indicates C-N stretching. The above characteristic peaks appear in the spectra of all inclusion complexes at the same wavenumber, indicating no incompatibility between the drug and γ-CD.

Drug Content: The Candesartan inclusion complexes were tested for drug content, and it was found that the drug was within the compendial limits 98-102% w/w. All the inclusion complexes were uniform in drug content. The results were shown in below table

TABLE 5: DRUG CONTENT OF PREPARED COMPLEXES

S. no.	Complex Code	% Drug Content
1	PM1	98.1± 1.09
2	PM2	96.2 ± 0.08
3	PM3	98.9 ± 0.03
4	KM1	98.2 ± 0.05
5	KM2	97.3 ± 0.02
6	KM3	99.5 ± 0.07
7	SE1	99.8 ± 0.01
8	SE2	100.4 ± 0.06
9	SE3	101.8 ± 0.09

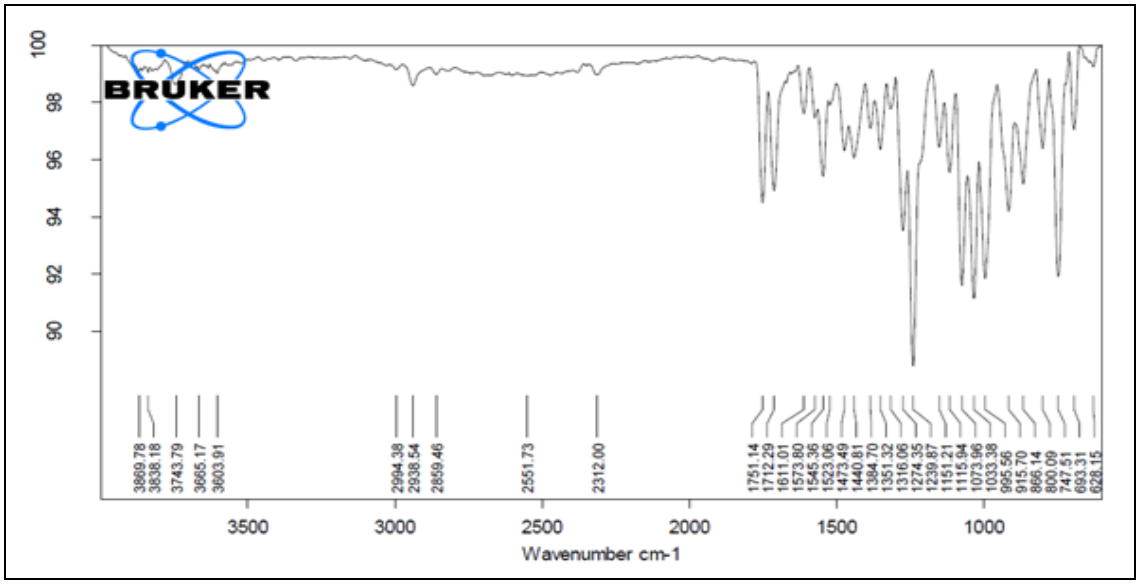

FIG. 4: FTIR SPECTRA OF CANDESARTAN CILEXITIL

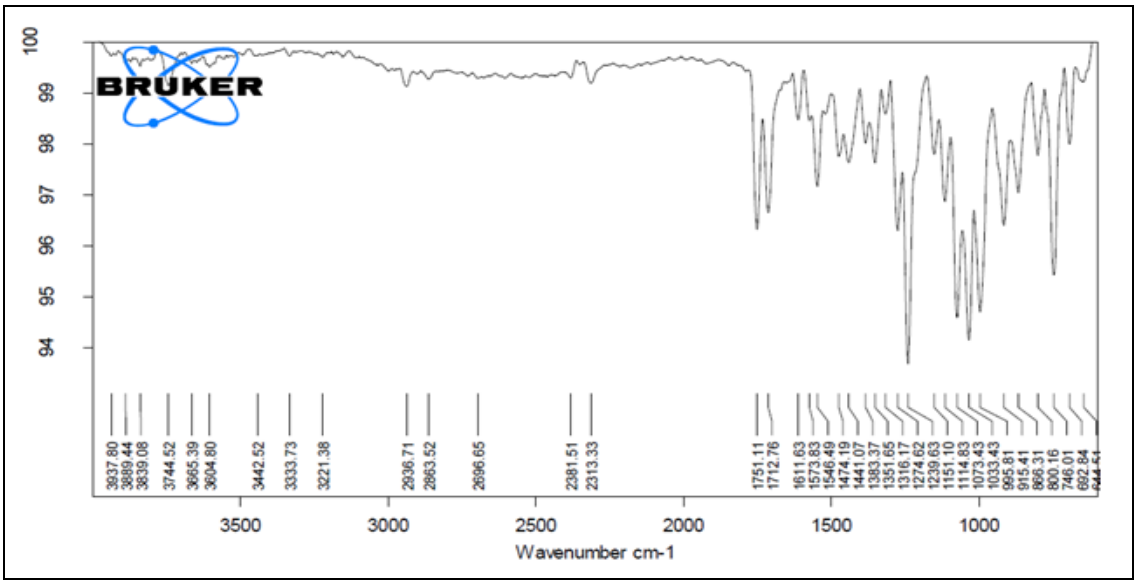

FIG 5: FTIR SPECTRA OF γ –CD

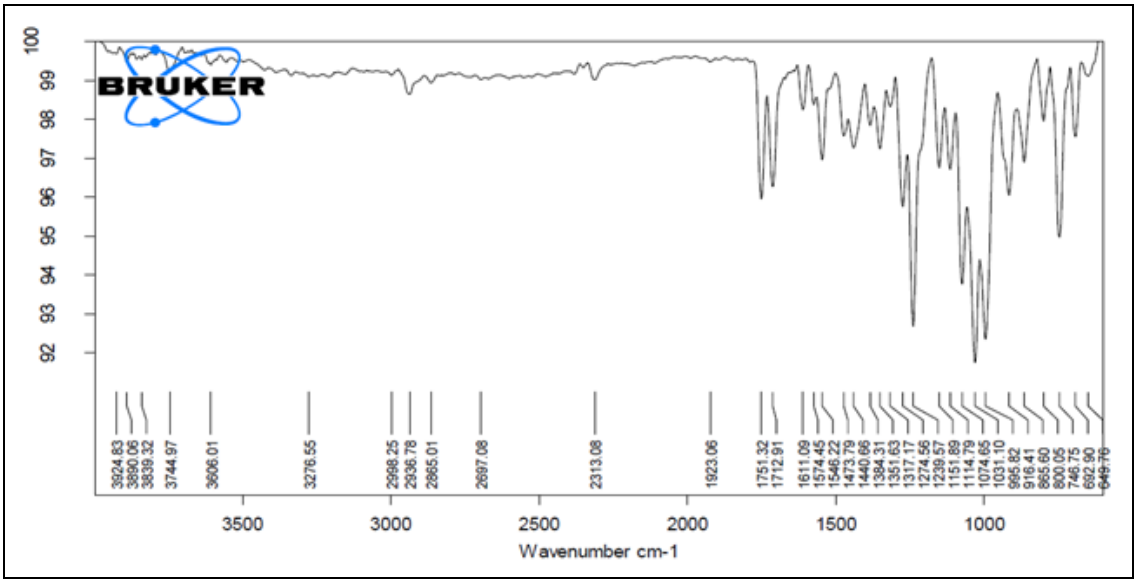

FIG. 6: FTIR SPECTRA OF 1:3 PM METHOD

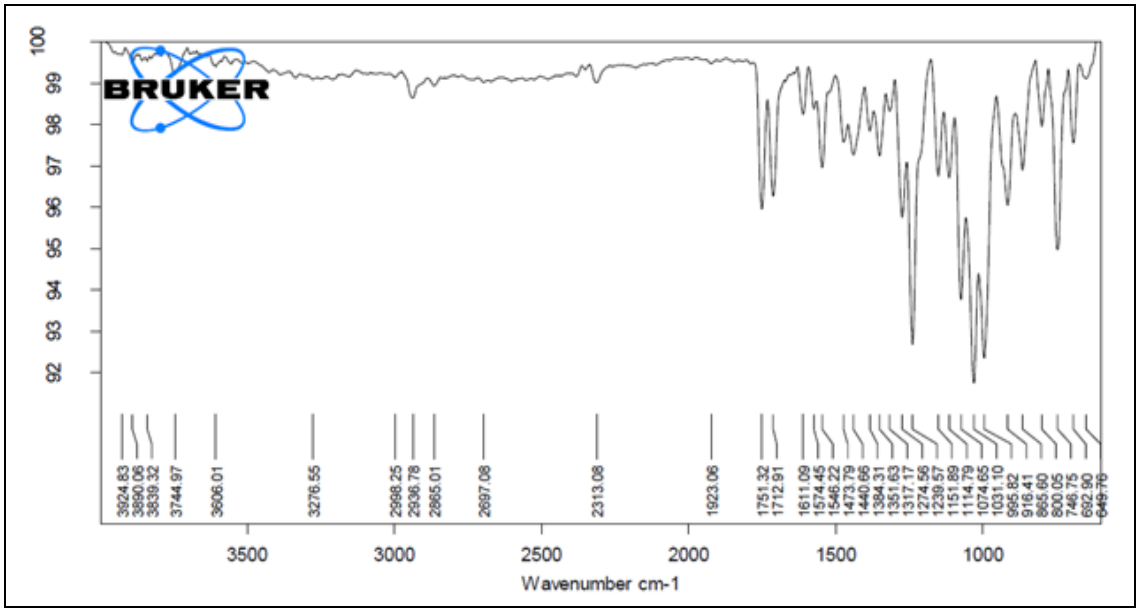

FIG. 7: FTIR SPECTRA OF 1:3 SE METHOD

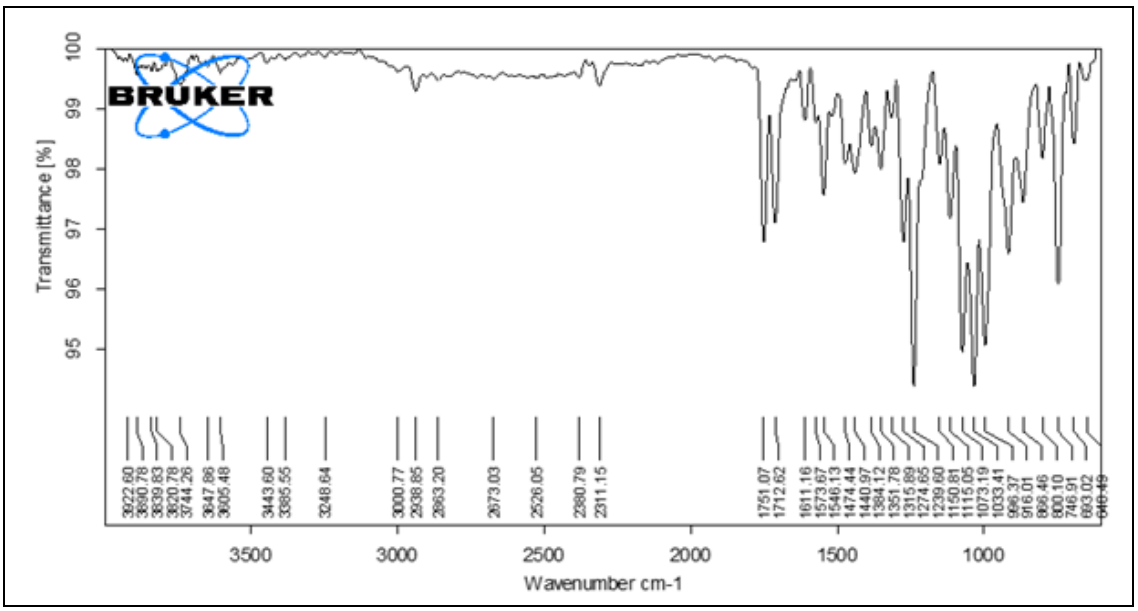

FIG. 8: FTIR SPECTRA OF 1:3 KE METHOD

***In-vitro* Dissolution Studies:** Candesartan release from the solid dispersion and the drug alone was studied upto 30 minutes. The average percentage release of the pure drug was found to be 38.1% in 30 minutes. In the solid dispersions formulation, γ-cyclodextrin was used as a carrier, and the dissolution rate increased with an increased amount of γ-CD. The best results among solid dispersions with γ-CD were obtained for the complex B-9 (Figure-8). Dissolution parameters of Candesartan and its cyclodextrin complexes prepared by three methods in different ratios were given. The increased dissolution rate may be due to the higher solubility of γ-CD in the dissolution medium and better wettability of the drug in the complex.

Dissolution Parameters of Prepared Inclusion Complexes: The dissolution studies of Candesartan inclusion complexes prepared were performed in 6.8 pH Phosphate buffer by using the paddle method. The dissolution study of inclusion complexes was found to be rapid than its pure drug. The dissolution parameters like T50 (min) which indicates that the time taken to release 50% of the drug, DE 15%, DE 30% values which indicates the dissolution efficiency of complexes at 15 min and 30 minutes respectively and percentage dissolved in 10 minutes of prepared complexes indicated the rapid drug dissolution than the pure drug of Candesartan. It was observed that as the concentration of γ-cyclodextrin increases in

inclusion complexes prepared by the kneading method, the rate of dissolution of the drug was also increased. Inclusion complexes prepared by the Kneading method using γ-cyclodextrin in ratio of 1:3 was found to undergo rapid dissolution rates than the other inclusion complexes. The dissolution studies of Candesartan marketed tablet and all the tablet formulations were performed by using 6.8 pH Phosphate buffer using the paddle method.

TABLE 7: DISSOLUTION PARAMETERS OF PREPARED INCLUSION COMPLEXES

S. no.	Complex Code	T50(min)	DE 15%	DE 30%	%Dissolved in 10 minutes
1	PM 1:1	15	13.82	30.50	12.98
2	PM 1:2	7.5	24.14	44.34	19.98
3	PM 1:3	5	33.80	56.48	26.73
4	KM 1:1	10	15.95	32.66	13.06
5	KM 1:2	6	27.43	50.79	21.82
6	KM 1:3	2.5	48.89	75.30	37.86
7	SM 1:1	7	19.23	38.22	18.11
8	SM 1:2	3	27.50	52.05	23.90
9	SM 1:3	1.5	49.02	81.19	43.72

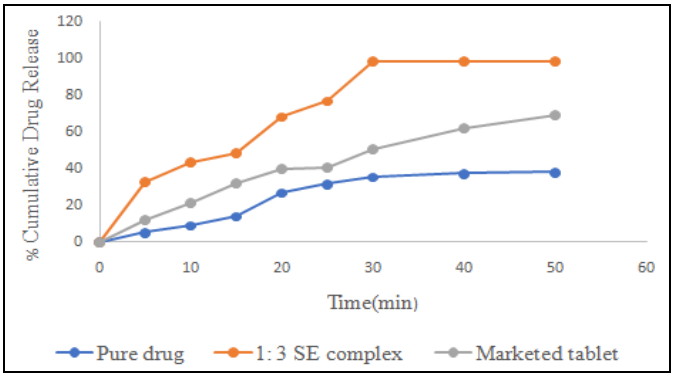

FIG. 9: COMPARISON OF DISSOLUTION PROFILES OF PURE DRUG, MARKETED TABLET AND 1:3 KNEADING COMPLEXES

CONCLUSION: The drug Candesartan cilexetil is practically insoluble in water and aqueous fluids. As such, dissolution is the rate-limiting step in the process of drug absorption, to improve the dissolution of Candesartan, inclusion complexes of Candesartan with γ-CD were prepared, and evaluation studies were performed. It was evident from the evaluation study that the dissolution rate of Candesartan drug may be enhanced to a large extent by solid dispersions with γ-CD using kneading method. This is due to the reason that the cyclodextrins increased the aqueous solubility of poorly soluble drugs by forming inclusion complexes with their polar molecules and functional groups. The increase in the solubility of Candesartan solid dispersions is also due to the lack of crystallinity, *i.e.*, amorphization, increased wettability, dispersibility, and particle size reduction.

ACKNOWLEDGEMENT: The authors wish to thank Aurobindo Pharmaceutical Co. Ltd; Hyderabad, for providing Candesartan gift sample, Management of Vignan Pharmacy College, Vadlamudi, Guntur, for their unvarying support and encouragement.

CONFLICTS OF INTEREST: No conflict of interest.

REFERENCES:

1. Carneiro SN, Duarte FIC, Quintans LHJDS, Quintans-Júnior LJ, da Veiga Júnior VF and de Lima AAN: Cyclodextrin–drug inclusion complexes: *in vivo* and *in vitro* approaches Int J Mol Sci 2019; 20.
2. Saokham P, Do TT, den Mooter dv and Loftsson T: Inclusion complexes of p-hydroxybenzoic acid esters and γ-cyclodextrin. Journal of Inclusion Phenomena and Macrocyclic Chemistry 2018; 90: 111-22.
3. Heck SL, Gulati G, Hoffmann P, von Knobelsdorff-Brenkenhoff F, Storås TH, Ree AH, Gravdehaug B, Røsjø H, Steine K and Geisler J: Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial European Heart Journal - Cardiovascular Imaging, Volum 2018; 19(5): 544-52.
4. Cho KI, Kim BH, Park YH, Ah JC, Kim SH, Chung WJ, Kim W, Sohn IS, Shin JH, Kim YJ, Chang K, Yu CW, Ahn SH, Kim SY, Ryu JK, Lee JY, Hong BK, Hong TJ and Park CG: Efficacy and Safety of a Fixed-Dose Combination of Candesartan and Rosuvastatin on Blood Pressure and Cholesterol in Patients With Hypertension and Hypercholesterolemia: A Multicenter, Randomized, Double-Blind, Parallel Phase III Clinical Study, Clinical Therapeutics 2019; 41(8): 1508-21.
5. Zhao X and Wang X: Candesartan targeting of angiotensin II type 1 receptor demonstrates benefits for hypertension in pregnancy *via* the NF κB signalling pathway 2018; 18(1): 705-14.
6. Loe MWC, Lee RCH and Chu JJH: Antiviral activity of the FDA-approved drug candesartan cilexetil against Zika virus infection, 2019; 172: 104637.
7. Pradhan A, Tiwari A and Sethi R: Azilsartan: Current Evidence and Perspectives in Management of Hypertension. International Journal of Hypertension, vol. 2019; 1-8.

8. Pinto JMO, Leão AF, Riekes MK, França MT and Stulzer HK: HPMCAS as an effective precipitation inhibitor in amorphous solid dispersions of the poorly soluble drug candesartan cilexetil. Carbohydra Poly 2018; 184: 199-06.
9. Jusufovic M, Berge TE, Guo R, You S, Delcourt C, Anderson C, Bath PM, Karlson BW, Berge E and Sandset EC: Effects of candesartan in the acute phase of intracerebral hemorrhage. Journal of Stroke and Cerebrovascular Diseases 2019; 28(8): 2262-67.
10. Miura S, Okabe A, Matsuo Y, Karnik SS and Saku K: Unique binding behavior of the recently approved angiotensin II receptor blocker azilsartan compared with that of candesartan. Hypertension Research 2013; 36: 134-39.

How to cite this article:
Madhavi BR, Divya B, Anusha K, Tejaswi G, Teja GYD and Reddy KKK: Enhancement of solubility of poorly soluble drug by inclusion complexationwith γ-cyclodextrin. Int J Pharm Sci & Res 2021; 12(12): 6593-99. doi: 10.13040/IJPSR.0975-8232.12(12).6593-99.