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DEVELOPMENT AND EVALUATION OF CANDESARTAN CILEXETIL TABLETS USING CRYSTAL AGGREGATES PREPARED BY POLYMER ENRICHED BRIDGING LIQUID

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Keywords:

Candesartan cilexetil, Crystal agglomerates, Polymer enriched bridging liquid technique, PEBL, tablets, Solubility enhancement

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ABSTRACT: The main objective of the study was to formulate tablets of Candesartan cilexetil using the crystal agglomerates for the enhancement in flow properties and solubility. The crystal agglomerates were prepared by polymer enriched bridging liquid (PEBL) technique. The process requires three solvent systems, the good solvent for the drug, the bad solvent and the bridging liquid. The hydrophilic polymer PVP K30 was incorporated in the bridging liquid. The addition of hydrophilic polymer increased the hydrophilicity and wettability of Candesartan cilexetil. The saturation solubility analysis, percentage yield, drug content, micromeritic properties, FTIR, DSC, XRD, SEM were carried out for the evaluation of crystal agglomerates. The tablets were prepared by direct compression using the formulated crystal agglomerates and were subjected to various *in-vitro* evaluations. The crystal agglomerates prepared by the PEBL technique showed 25 folds enhancement in the solubility. The FTIR analysis revealed the absence of incompatibility. The DSC analysis and XRD pattern showed a reduction in crystallinity. The SEM analysis revealed the porous and sphericity of the agglomerates. The tablets showed a hardness of 7 kg/cm^2, friability (0.56%), weight variation (2.2%). The drug content found was 99.03% ± 0.33% and the disintegration time was 2 min. The tablets showed a % CDR of 99.99 ± 0.15 at the end of 30 min which was comparable with the marketed formulation. The release of pure drug observed was 28.08 ± 1.85 in 30 min. The PEBL technique provided a single step process for enhancing the flow characteristics, solubility and dissolution of Candesartan cilexetil for the development of Candesartan cilexetil tablets.

INTRODUCTION: Hypertension is the most important independent risk aspect for the development of Coronary Artery Disease (CAD, stroke and renal failure for all age/race/sex groups.

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The class of sartans is synthetic agents having their target of activity on the Renin-angiotensin system (RAS). It acts by the inhibition of Angiotensin-converting enzyme (ACE inhibitors), resulting in the inhibition of the conversion of angiotensin I to angiotensin II [1].

Candesartan cilexetil belongs to the class of Angiotensin II receptor antagonist (AT1 subtype) used in the treatment of hypertension. It is a prodrug that undergoes hydrolysis of the ester linkages and gets converted to Candesartan in the

gastrointestinal tract (GIT) during the process of absorption from the GIT [2, 3]. The major setback in the development of dosage form for the orally effective Candesartan cilexetil is due to the poor solubility of the drug. It resulted in the reduction of bioavailability [4].

Tablets have been the preferred dosage form by manufacturers over the years due to their relatively low production cost, ease of packaging, shipping, and administration, *etc*. They also have better stability and patient compliance. But the great challenge in the development of tablets is the poor solubility of the active pharmaceutical ingredient. If the powder has good fluidity and compression properties, direct compression of active pharmaceutical ingredients (API) is possible. This is a problem with most active ingredients that have low compressibility and flow characteristics [5]. The various techniques for solubility enhancement include kneading, hot-melt extrusion, solvent evaporation, nanoemulsion, liquisolid technology, cryo techniques, *etc*. Spherical crystallization is a potential technique, which comprises of crystallization, aggregation and spheronization in one step. There are several modifications in the spherical crystallization process including the crystallo-coagglomeration.

Polymer enriched bridging liquid (PEBL) technique is a novel technique for the enhancement of solubility of the class II drug of the biopharmaceutical classification system. Polymer assisted crystal agglomeration with the PEBL technique can improve the solubility of drugs with the aid of hydrophilic polymers. It also improves the micromeritic properties of drug which enables direct compression. The addition of hydrophilic polymers helps in the wetting characteristics of the hydrophobic drug and thereby improving the solubility [6]. The aim of the study was to formulate and evaluate tablets of Candesartan Cilexetil by direct compression using the crystal aggregates having enhanced solubility prepared by polymer enriched crystal agglomeration technique.

MATERIALS AND METHODS: Candesartan cilexetil was obtained from Cadila Pharma-ceuticals Ltd. Polyvinyl pyrrolidone K30 (PVP K30) was purchased from Sigma Aldrich, Germany (Merck), HPLC grade Dichloromethane and chloroform were procured from Merck Ltd. All the other chemicals used were of analytical grade. Ultra-pure grade water from Milli-Q water purification (Millipore, Germany) was used for the process.

Preparation of Spherical Aggregates of Candesartan Cilexetil by Polymer Enriched Bridging Liquid: The crystal aggregates were formulated by the PEBL method. The PVP K30 was selected as the hydrophilic polymer. The Candesartan cilexetil, PVP K30 ratio selected was 4:1. The Candesartan cilexetil was dissolved in 6 ml of chloroform and added to 50 ml of water. The stirring was carried out at 900 RPM. The PVP K30 was dissolved in 2.5 ml of dichloromethane (DCM) and added to the above dispersion. The stirring was continued for 4 h. This aids in the precipitation of crystals followed by aggregation and finally stabilization. It was filtered using a 0.45 µm membrane filter and dried under vacuum. The obtained crystal agglomerates were used for the preparation of tablets by direct compression.

Formulation of Candesartan Cilexetil Tablets by Directly Compression: The crystal agglomerates equivalent to 16 mg was taken and added the required quantity of microcrystalline cellulose to make the final tablet weight to 100 mg. About 1% each of talc and magnesium stearate was added and the mixture was very well blended and compressed into tablets using 6 mm flat-faced punches in 16 stations rotary tablet press (Cadmach industries).

Evaluation of Crystal Agglomerates:

Saturation Solubility Analysis: The saturation solubility of pure Candesartan cilexetil and crystal agglomerates were carried out in the water and 0.05 M phosphate buffer of pH 6.5 containing 0.35% of Polysorbate [20]. Excess amount of the drug as well as the crystal agglomerates was added to about 25 ml of each of the media and shaken in water bath shaker at room temperature for 24 h. It was then filtered using a 0.45 µm membrane filter and analyzed at a wavelength of 254 nm in water and 258 nm in 0.05 M phosphate buffer of pH 6.5 containing 0.35% of Polysorbate 20 [7].

Percentage Yield and Percentage Drug Content of Crystal Agglomerates: The percentage yield of the crystal agglomerates obtained was calculated by

weighing the dried crystal aggregates after preparation.

Percentage yield of crystal agglomerates = (Actual yield of crystal agglomerates) / (Theoretical yield) × 100

The drug content in percentage was determined by weighing 10 mg of crystal agglomerates and crushed and dissolved in a small volume of methanol followed by dilution to 10 ml with methanol. It was filtered and analyzed by UV spectrophotometry at 254 nm after carrying out suitable dilutions [8].

Micromeritic Property Analysis: The angle of repose of Candesartan cilexetil and the crystal agglomerates was determined by the fixed funnel method. The Hausner's ratio and Carr's compressibility index were calculated from the bulk density and tapped density, which was determined in tap densitometer (EI instruments). The experiments were carried out in triplicate [9, 10].

FT-IR Analysis: The FTIR analysis of Candesartan cilexetil and crystal agglomerates were carried out in Agilent FTIR Cary 630. About 5 mg of the samples were mixed thoroughly with potassium bromide of IR grade and compressed into discs using a hydraulic press. The discs were then placed in the sample chamber and analyzed the spectra from 4000 to 400 cm^{-1} [11].

DSC Analysis: The DSC analysis was carried out for the pure drug and crystal aggregates in DSC 8000 (Perkin Elmer). The sample was weighed (10 mg) and filled in small aluminum pans. It was sealed using a crimping machine. It was then kept in the sample chamber and analyzed by keeping empty crimped aluminum pan as reference. The nitrogen was used for purging and the heating rate was done at 10 ºC/min from 30 ºC to 250 ºC [12].

XRD Analysis: The crystallinity of the agglomerates was determined using an Xray diffractometer (Rigaku Miniflex, japan). The 2-Ɵ was measured from 30 to 80θ at optimum temperature using the filter as nickel. The current of 15 mA was used and X-Ray was generated at 40 KV. The diffraction angle was plotted against the intensity [13].

SEM Analysis: The surface characteristics and topography of the pure drug and the crystal agglomerates were determined using Scanning electron microscopy (EVO MA18 with Oxford EDS). The samples were sputter-coated with gold for analysis. The size of the crystals was also determined [14].

Evaluation of Tablets:

Hardness, Friability, Tablet Thickness, Weight Variation, Assay and Disintegration Test: The hardness and the tablet thickness were analyzed using the SOTAX instrument, Switzerland (model HT1, 500 N). The friability of the tablets was determined by Roche friabilator (EI instruments). The weight variation was carried out using 20 tablets. The average weight of the tablets was determined and the deviation of individual tablets from the average weight was expressed as percentage weight variation.

The assay of the tablet was determined by crushing 20 tablets, and weight equivalent to 16 mg of Candesartan cilexetil was weighed and dissolved in 10 ml with methanol. It was filtered and analyzed by UV spectrophotometry at 254 nm after carrying out suitable dilutions [15]. The disintegration test was performed using the disintegration test apparatus (EI instruments). It carried out using 6 tablets. The media used was ultrapure water maintained at 37 ºC ± 1 ºC. The times taken for the disintegration of the tablets were measured.

***In-vitro* Dissolution Test:** The *in-vitro* dissolution test was carried out using USP type II apparatus (Sotax, Switzerland). The dissolution media for Candesartan tablets as per United States Pharmacopoeia 41 was 0.05 M phosphate buffer of pH 6.5 incorporated 0.35% Polysorbate [20]. The dissolution was carried out in 900 ml of the above media. The experiment was carried out at 50 rpm at a temperature of 37 ± 0.5 ºC. The tablets of Candesartan cilexetil containing 16 mg of Candesartan cilexetil were taken for dissolution analysis. The pure drug, as well as the marketed Candesartan cilexetil tablets, was subjected to in vitro dissolution analysis for analyzing the efficacy of Polymer enriched bridging liquid technique. The samples were withdrawn at 15, 30, 45, and 60 min. At every time intervals, 5 ml of the samples were withdrawn and replaced with fresh buffer solution maintained at the same temperature. The samples were filtered using a 0.45 µm syringe filter and

analyzed by spectrophotometric method at 258 nm after suitable dilutions [16].

Stability Studies: The formulated Candesartan cilexetil tablets were subjected to accelerated stability studies. The samples were kept for 6 months in a stability chamber at 40 ºC ± 2 ºC and 75% ± 5% relative humidity (RH). At intervals of 0, 3 and 6 months (3 sample points), the samples were analyzed for the drug content and in vitro dissolution rate to verify the stability of the drug in the dosage form [17, 18].

RESULTS AND DISCUSSION: The crystal aggregates of Candesartan cilexetil were formulated by polymer assisted crystal agglomeration using Polymer Enriched Bridging Liquid technique (PEBL). The process requires three solvent systems, the good solvent for the drug, the bad solvent and the bridging liquid. The chloroform was used as the good solvent. The drug was dissolved in chloroform and added to the bad solvent (water) which helps in the precipitation of the drug. The bridging liquid used was dichloromethane, which helps in the formation of liquid bridges between the particles. The hydrophilic polymer PVP K30 was dissolved in the bridging liquid and added to the above dispersion. The stirring was carried out during the entire process. The speed was maintained at 900 RPM as the variation in speed leads to the formation of crystals of varying sizes. The bridging liquid has an affinity towards the good solvent. The addition of polymer in the bridging liquid helps in the better incorporation of polymer in the crystal agglomerates during the agglomeration process.

Evaluation of Crystal Agglomerates:

Saturation Solubility Analysis: The saturation solubility of Candesartan cilexetil and crystal agglomerates were carried out in the water and 0.05 M phosphate buffer of pH 6.5 containing 0.35% of Polysorbate [20]. The USP 41 specified dissolution for Candesartan cilexetil tablets in 0.35% polysorbate 20 in 0.05 M phosphate buffer pH 6.5, hence it was considered for solubility analysis. The results of the solubility analysis indicated that the pure drug Candesartan cilexetil is practically insoluble in water having a maximum solubility of 3.11 µg/ml in water and 53.93 µg/ml in the buffer. The crystal aggregates showed solubility of 80.56 µg/ml and 1248.21 µg/ml in water and buffer respectively. The crystal agglomerates have shown nearly 25 folds increase in solubility in both media in comparison with pure drugs. This suggests that the polymer enriched bridging liquid, using PVP K30 as a hydrophilic polymer can significantly enhance the solubility of Candesartan cilexetil.

Percentage Yield and Percentage Drug Content of Crystal Agglomerates: The yield of the crystal agglomerates was determined by weighing the crystal agglomerates after drying and dividing with the theoretical yield. It was expressed in percentage. The yield of the crystal agglomerates prepared by the PEBL technique was found to be 78.50%. The drug content was found to be 85.75%. The reduction in percentage drug content indicated the incorporation of PVPK30 in the crystal agglomerates, which resulted in the enhancement of solubility.

Micromeritic Property Analysis: The flow characteristics of the pure Candesartan cilexetil were found to be extremely poor in **Table 1**. The crystal agglomerates prepared by Polymer enriched bridging liquid showed excellent flow characteristics as evident from the values of Carr's compressibility index, Hausner's ratio, and angle of repose. The sphericity of particles has contributed to the enhancement of the flow characteristics of the agglomerates.

TABLE 1: RESULTS OF VARIOUS FLOW PARAMETERS

Parameters	Pure Candesartan Cilexetil	Crystal agglomerates prepared by PEBL Technique
Bulk density	0.188 ± 0.001	0.157 ± 0.001
Tapped density	0.327 ± 0.010	0.184 ± 0.001
Angle of repose	49.088 ± 0.474	19.873 ± 0.190
Carr's index	42.584 ± 2.020	14.631 ± 0.971
Hausner's ratio	1.743 ± 0.060	1.171 ± 0.013

FT-IR Analysis: The FTIR peak of the pure drug Candesartan cilexetil and the crystal agglomerates were shown in **Fig. 1**. The Candesartan cilexetil (Cand) showed characteristic peaks at 3415 (OH-stretch), 2940 (C-H -aromatic stretching), 1752 (C=O stretching of carboxylic acid), 1615 due to N-H bend and at 1240 (C-O stretch in ester). All the above significant peaks of Candesartan Cilexetil were observed in the crystal agglomerates, indicating the absence of chemical incompatibility

between Candesartan cilexetil and PVP K30 in the crystal agglomerates.

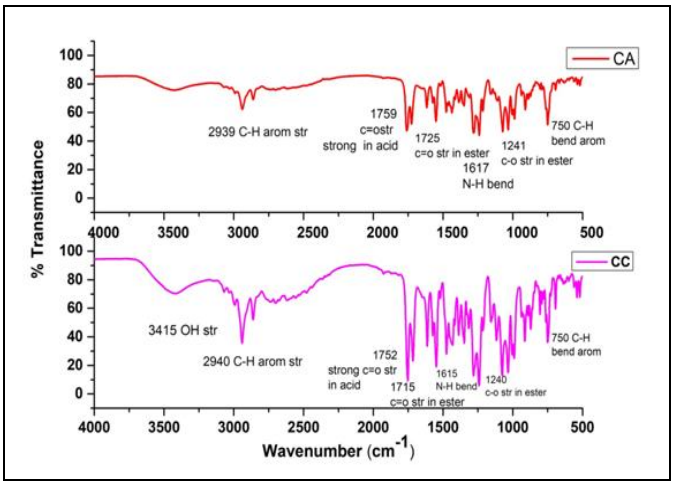

FIG. 1: FTIR SPECTRA OF CANDESARTAN CILEXETIL (CC) AND CRYSTAL AGGREGATES (CA)

DSC Analysis: The DSC analysis of Candesartan cilexetil (CC) has shown a sharp endothermic peak at a 168 ºC **Fig. 2**. The sharp endothermic peak reflected the purity and also the crystallinity of the pure drug. The broadening of the endothermic peak occurred in crystal agglomerates. The hydrophilic polymer PVPK30 showed a peak at 102.64 ºC. The crystal agglomerates (CA) showed an endothermic peak at 109.87 ºC.

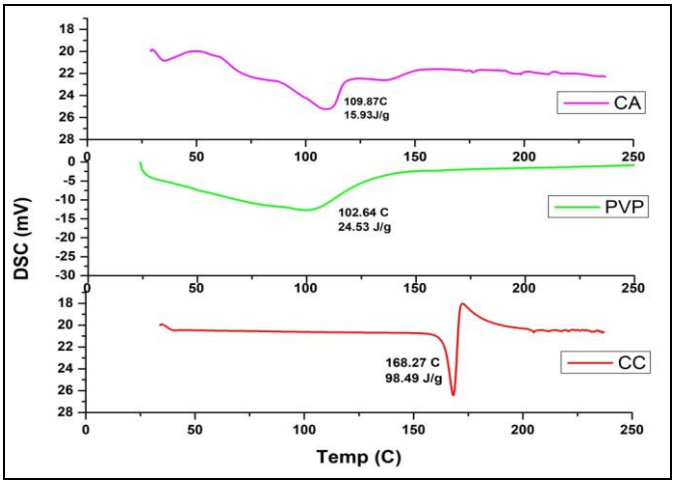

FIG. 2: DSC THERMOGRAMS OF CANDESARTAN CILEXETIL (CC), PVP K30 (PVP) AND CRYSTAL AGGLOMERATES (CA)

The reduction in the melting endotherm was observed for crystal agglomerate formulation. The addition of PVP K30 has contributed to the reduction in the melting point. The enthalpy of the pure drug also has reduced significantly in the crystal agglomerates. The reduction in melting point, widening of the melting endothermic peak, and also the lowering of enthalpy in the formulation suggested the reduction in crystallinity of crystal agglomerates formulated with PVP K30 using Polymer enriched bridging liquid technique.

XRD Analysis: The pure drug Candesartan cilexetil (CC) exhibited intense diffraction peaks which indicated the crystallinity **Fig. 3**. The crystal agglomerates of CC displayed a reduction in the intensities of the characteristic crystalline peaks of Candesartan cilexetil and showed an increase in the halo areas.

This suggested the enhancement of amorphization and reduction in crystallinity. The preparation of crystal agglomerates using polymer enriched bridging liquid significantly reduced the crystallinity, which has contributed to the increase in the solubility.

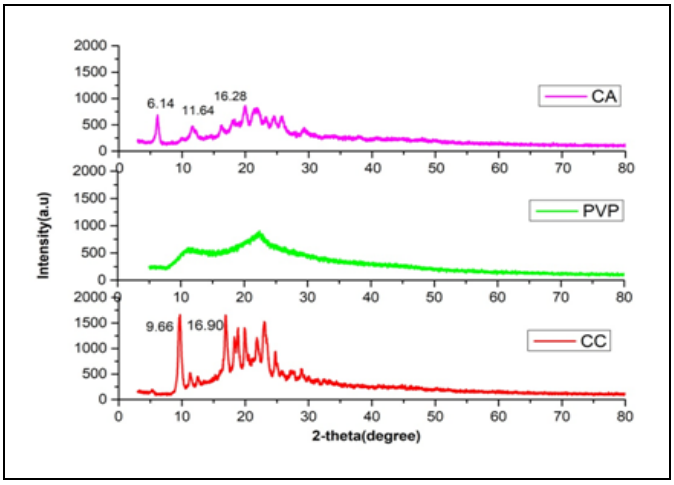

FIG. 3: XRD OF CANDESARTAN CILEXETIL (CC), PVP K30 AND CRYSTAL AGGLOMERATES (CA)

SEM Analysis: The SEM analysis indicated that the pure Candesartan cilexetil was rod-shaped flakes like morphology and highly crystalline **Fig. 4A**. The average particle size was found to be 5.48 µm ± 1.34 µm. The crystal agglomerates prepared by polymer enriched bridging liquid showed nearly spherical, which improved the flow characteristics of **Fig. 4B**.

The particle size of the formulation was found to be 168.28 µm ± 14.03 µm. The increase in particle size suggested the aggregation of small crystals. The surface morphology indicated that the crystals were highly porous in nature. This contributed to the enhancement in the wetting and solubility of the crystal aggregates.

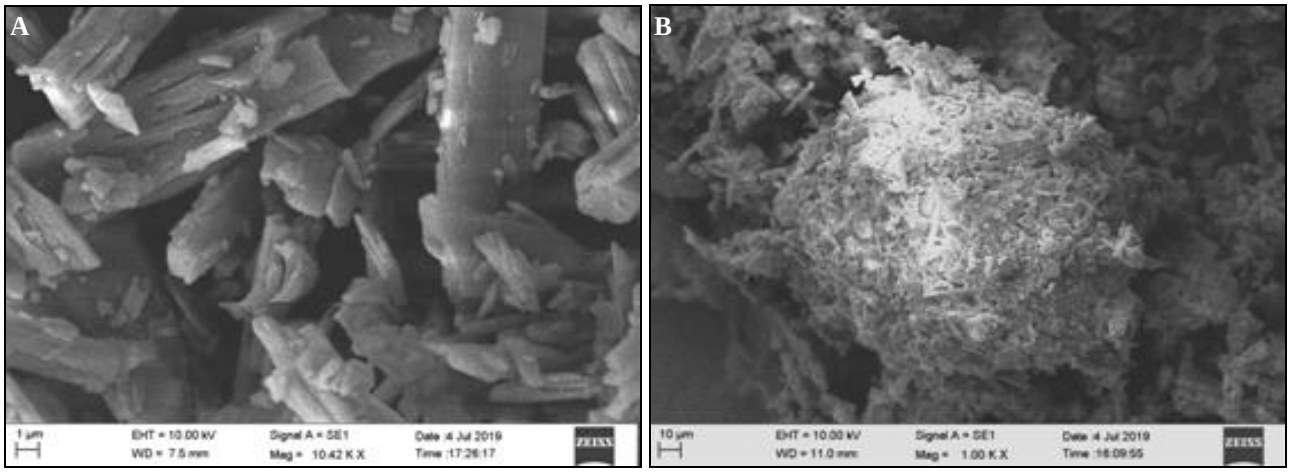

FIG. 4: SEM IMAGES OF A) CANDESARTAN CILEXETIL B) CRYSTAL AGGLOMERATES

Evaluation of Tablets:

Hardness, Friability, Tablet Thickness, Weight Variation, Assay and Disintegration Test: The hardness of the tablets was found to be 7 kg/cm^2, which was sufficient for ensuring strength during handling. The friability of the tablets was found to be 0.56% and has a thickness of 0.35 ± 0.12 cm, in the acceptable range. The average weight of one tablet was found to be 99.24 mg. The weight variation was found to be within 2.2%. The drug content was found to be 99.03% ± 0.33%, which indicated that the loss of drugs was insignificant during formulation. The disintegration time observed was 2 min and was found to be in the acceptable range for uncoated tablets.

***In-vitro* Dissolution Test:** The in vitro dissolution profile of the pure Candesartan Cilexetil, Candesartan Cilexetil tablets prepared from crystal agglomerates, and the marketed formulation were given in **Fig. 5**. It was determined in 900 ml, pH 6.5 phosphate buffer of 0.05 M containing 0.35% polysorbate [20]. The pure drug showed a percentage cumulative drug release of 20.52 ± 1.03, 28.08 ± 1.85, 36.25 ± 2.30, 42.92 ± 2.28 at the end of 15, 30, 45, and 60 min. The Candesartan cilexetil tablets showed a % CDR of 99.98 ± 0.21 at the end of 15 min and 99.99 ± 0.15 at the end of 30 min. The marketed formulation showed 97.25 ± 0.83% CDR in 15 min and 99.99 ± 1.02 in 30 min.

This clearly indicated that the Candesartan cilexetil tablets prepared from the crystal aggregates greatly enhanced the dissolution rate. Polymer enriched bridging liquid can be considered as an efficient technique for dissolution enhancement of poorly water-soluble drug Candesartan cilexetil.

The comparable results of tablets prepared from the crystal agglomerates and the marketed formulation also confirm that this process can be used as an alternative for various techniques for solubility enhancement without any difficulty in processing [16].

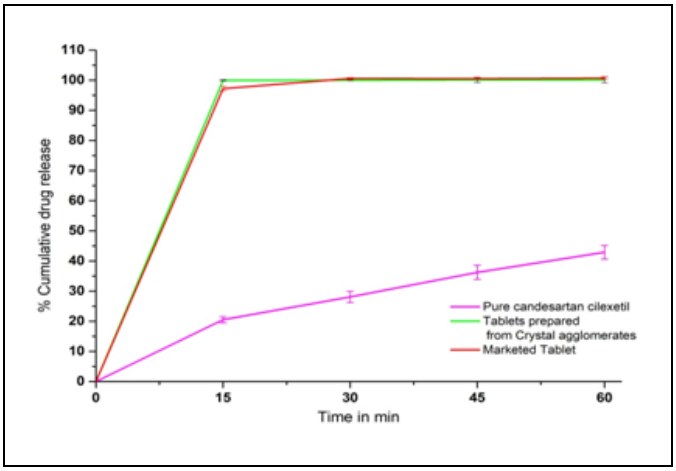

FIG. 5: *IN-VITRO* DISSOLUTION PROFILE OF PURE CANDESARTAN CILEXETIL, TABLETS PREPARED FROM CRYSTAL AGGLOMERATES AND THE MARKETED FORMULATION

Stability Studies: The formulated Candesartan cilexetil tablets were subjected to accelerated stability studies. The samples were kept for 6 months in a stability chamber at 40 °C ± 2 °C and 75% ± 5% relative humidity (RH). At intervals of 0, 3, and 6 months (3 sample points), the samples were analyzed for drug content and in vitro dissolution rate to verify the stability. The drug content and the percentage cumulative drug release of the crystal agglomerates were determined at various time points of 0, 3 and 6 months. The results were shown in **Table 2**.

The formulation has retained the percentage drug content at the end of 6 months. It also showed a percentage CDR of 96.66 ± 0.56 in 30 min at the end of 6 months. This confirmed the stability of the tablets prepared from the crystal agglomerates prepared by Polymer enriched bridging liquid.

TABLE 2: RESULTS OF STABILITY ANALYSIS OF CANDESARTAN CILEXETIL TABLETS PREPARED FROM CRYSTAL AGGLOMERATES

Test time (months)	% Drug Content	% CDR (30 min)
0	99.03 ± 0.33%	99.99 ± 0.15
3	98.75 ± 1.62%	98.88 ± 0.28
6	97.35 ± 1.38%	96.66 ± 0.56

CONCLUSION: The Polymer enriched bridging liquid technique with the aid of hydrophilic polymer PVP K30 was used for the enhancement of the solubility of poorly water-soluble drug Candesartan cilexetil.

The prepared crystal agglomerates have shown good flow characteristics and solubility. The tablets of Candesartan cilexetil were prepared by direct compression using the crystal agglomerates and subjected to various evaluations.

The results revealed that the polymer enriched bridging liquid can be used as an efficient technique for the solubility enhancement of poorly water-soluble Candesartan cilexetil. The PEBL technique provided a single step process for enhancing the flow characteristics, solubility, and dissolution.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest regarding this publication.

REFERENCES:

1. Vidal-Petiot E, Greenlaw N, Ford I, Ferrari R, Fox KM and Tardif JC: Relationships between components of blood pressure and cardiovascular events in patients with stable coronary artery disease and hypertension. Hypertension 2018; 71(1): 168-76.
2. AboulFotouh K, Allam AA, El-Badry M and El-Sayed AM: Development and *in-vitro* / *in-vivo* performance of self-nanoemulsifying drug delivery systems loaded with candesartan cilexetil. European Journal of Pharmaceutical Sciences 2017; 109: 503-13.
3. Islas MS, Rojo T, Lezama L, Merino MG, Cortes MA and Puyol MR: Improvement of the antihypertensive capacity of candesartan and trityl candesartan by their SOD mimetic copper (II) complexes. Journal of Inorganic Biochemistry 2013; 123: 23-33.
4. Dudhipala N and Veerabrahma K: Candesartan cilexetil loaded nanodelivery systems for improved oral bioavailability. Therapeutic Delivery 2017; 8(2): 79-88.
5. Patel R, Palmer JL, Joshi S, Di Cio Gimena A and Esquivel F: pharmacokinetic and bioequivalence studies of a newly developed branded generic of candesartan cilexetil tablets in healthy volunteers. Clin Pharmacol Drug Dev 2017; 6(5): 492-98.
6. Manoj K, Seenivasan P, Arul K and Kumar SM: Study of the effect of PVP K30 in the enhancement of solubility of Telmisartan by polymer assisted crystal agglomeration using polymer enriched bridging liquid technique. Int J of Research in Pharma Sciences 2019; 10(3): 2290-99.
7. Muller RH, Jacobs C and Kayser O: Nanosuspensions as particulate drug formulations in therapy. Advanced Drug Delivery Reviews 2001; 47(1): 3-19.
8. Manoj K, Seenivasan P, Arul K and Kumar SM: Development, characterization and solubility enhancement of poorly water soluble drug telmisartan by polymer enriched bridging liquid technique using peg 4000 as hydrophilic polymer. International Journal of Research in Pharmaceutical Sciences 2019; 10(3): 2234-41.
9. Schiermeier S and Schmidt PC: Fast dispersible ibuprofen tablets: Euro J of Pharma Sciences 2002; 15(3): 295-305.
10. Ibrahim MA and Abou El Ela AESF: Optimized furosemide taste masked orally disintegrating tablets. Saudi Pharm J 2017; 25(7): 1055-62.
11. Amer AM, Allam AN and Abdallah OY: Preparation, characterization and *ex-vivo* – *in-vivo* assessment of candesartan cilexetil nanocrystals *via* solid dispersion technique using an alkaline esterase activator carrier. Drug Dev and Industrial Pharmacy 2019; 45(7): 1140-8.
12. Detroja C: Enhanced anti-hypertensive activity of candesartan cilexetil nanosuspension: formulation, characterization and pharmacodynamic study. Scientia Pharmaceutica 2011; 79(3): 635-51.
13. Bhalekar M, Upadhaya P and Madgulkar A: Formulation and characterization of solid lipid nanoparticles for an anti-retroviral drug darunavir. Appl Nanosci 2017; 7(1-2): 47-57.
14. Gecer A, Yildiz N, Calimli A and Turan B: Trimethyl chitosan nanoparticles enhances dissolution of the poorly water soluble drug Candesartan-Cilexetil. Macromolecular Research 2010; 18(10): 986-91.
15. Kamalakkannan V, Puratchikody A and Ramanathan L: formulation and *in-vitro* evaluation of solid lipid microparticles of candesartan cilexetil floating tablets. Drug Deliv Lett 2012; 2(3): 202-12.
16. Yuksel N, Bayindir ZS, Aksakal E and Ozcelikay AT: In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: *in-vitro* and *in-vivo* evaluations. Int Journal of Biological Macromolecules 2016; 82: 453-63.
17. Sravya M, Deveswaran R, Bharath S, Basavaraj BV and Madhavan V: Development of orodispersible tablets of candesartan cilexetil-β-cyclodextrin complex. Journal of Pharmaceutical Sciences 2013; 2013: 1–13.

18. Wu T, Wang G, Shi C, Li J, Zhao N and Dong Z: Development and evaluation of orally disintegrating tablets containing the mosapride resin complex. Acta Pharmaceutica 2018; 68(2): 159-70.

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