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Preformulation study for candesartan cilexetil buccal (Effervescent) tablet

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Abstract
Candesartan cilexetil is novel, potent and highly selective non peptide angiotensin II type 1 receptor blocker. It is hydrophobic drug which belongs to BCS Class II drug. For enhancement the bioavability and quick systemic action of candesartan cilexetil a novel formulation of buccal (effervescent) tablet was designed. Preformulation is an important step in the rational formulation of an active pharmaceutical ingredient (API). Micromeritics properties: Bulk density (du), Tapped density (db), Compressibility Index (%C) and sieve analysis was performed in order to determine the best excipients to be used in the formulation development of Candesartan cilexetil (effervescent) tablets. Results show that Candesartan Cilexetil has fair flow and compressibility properties (du 0.8 g/mL, db 0.7 g/mL, %C 12.5 and sieve analysis time 4.5min. HPLC method for estimation of Candesartan cilexetil shows linearity (R^2 = 1) and specific with no interference of excipients. Solubility studies reveals that it soluble at pH 6.8 and 7.5 in phosphate buffer. The ability of material to absorb water (Hygroscopicity) was found 0.1% after 24 Hrs at 80% Relative Humidity. Melting point rage from 161-165 °C. There was no any drug excipients interaction was observed when analyzed through FTIR and DSC. There was no change in appearance after 15days at 40°C and 75% Relative humidity. These all results lead to the better development of Candesartan cilexetil buccal (effervescent) tablet.

Keywords: Candesartan cilexetil, Preformulation, Drug-excipients interaction, Effervescent

Introduction
Candesartan cilexetil is novel, potent and highly selective non peptide angiotensin II type 1 receptor blocker [1]. Its chemical name is (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl-2-ethoxy-1-[[2'-(1Htetrazol-5-yl)[1,1'biphenyl]-4-yl]methyl]-1Hbenzimidazole-7-Carboxylate as shown in Fig.1 and molecular mass is 610.66 g/mol. Its ionization constant is about 6.0 and LogP value is 4.79 [2, 3]. It is mainly used in treatment of hypertension. when it is administered orally it is completely hydrolyzed from candesartan cilexetil to candesartan, an active moiety. It is hydrophobic drug which belongs to BCS Class II drug. Its Oral bioavability is 15-40% hence it is poorly absorb from GIT. For enhancement the bioavability and quick systemic action of candesartan cilexetil a novel formulation of buccal tablet was designed [4]. Before starting formulation design we should know the properties of drug substance, its competitiveness to the formulation. Preformulation study is group of testing parameter that focus on physicochemical parameter of drug substance that could affect the drug performance and development of dosage form. The preformulation study provide information that support to develop the effective, bioavailable, safe, stable and robust formulation [5]. Preformulation study give information regarding physicochemical properties of drug substance, its compatibility with other Excipients, solubility and partition coefficient of drug substance, analytical method for evaluation of drug substance [6]. The aim of the present work was to perform preformulation studies to inform development of Candesartan cilexetil buccal (effervescent) tablet for the purpose of determining the physical-chemical characteristics of drug with possible interactions with excipients.

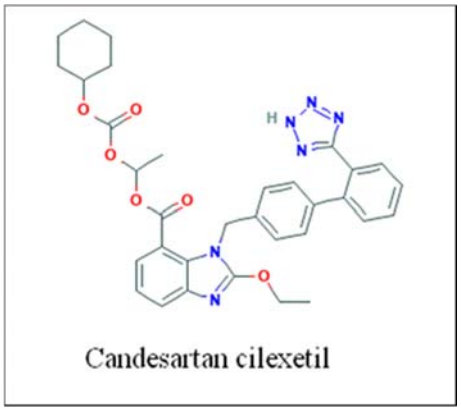


Fig. 1: Structure of Candesartan Cilexetil

Materials and Methods

Chemicals and reagents: Candesartan was received from Alembic Pharmaceutical Limited, Vadodara, Gujarat, India. Milli-Q water was used during whole study. Methanol and Acetonitrile were of HPLC grade (Make-Rankem). Potassium dihydrogen phosphate was of AR grade (Make Rankem).

Instruments and chromatographic conditions: Shimadzu LC-2010HT equipped with UV-Visible detector controlled by Labsolutions software was used with column Inertsil C8 (150mm × 4.6mm, 5µm), at 282 nm wavelength. Mobile phase having mixture of 550 mL Acetonitrile and 450 mL of Milli-Q water and 1mL Ortho Phosphoric Acid (OPA) was used with flow rate of 1.5mL/min. All weighing were done on Sartorius analytical balance. Thermo Lab made hot air oven used in study. Ultrasonic bath of Labman was used. FTIR and DSC was used of Shimadzu Make. Thermo lab made walk-in stability chamber were used for the study.

Micromeritics Properties of API: Bulk properties for the solid forms such as particle size, bulk density and surface morphology are also likely to change during process development.

Bulk Density (du): An accurately weighed sample of granulation was carefully added to the measuring cylinder with the aid of funnel. Then the volume was noted. The volume of the packing was determined in an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device. Apparent bulk density was determined by the following formula:-

du = M /Vu
Where, M = Mass of granulation in g
Vu = volume of granulation (initial untapped volume)

Tapped Bulk Density: (db): The above procedure was followed. The final volume was tapped till no further reduction in volume was noted. Packed bulk density was determined by the following formula.

db = m/Vb
Where, m = mass of granulation in gm
Vb = volume of granulation (final tapped volume)

Percent compressibility (%C): It is an important measure that can be obtained from bulk density measurements. The Following formula was used to compute the percent compressibility.

% C = ((db – du)/db) x 100
Where, db = packed bulk density, du = apparent bulk density

Quantitative Assay method: For linearity of method, standard solution were prepared in range 0.5, 1, 3, 5 and 7mg/mL. Diluent was used as blank for specificity of method.

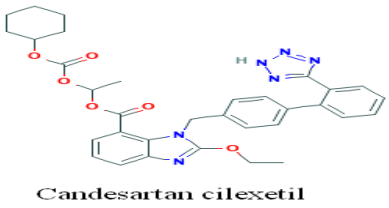
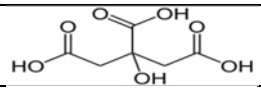
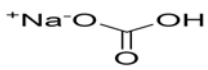
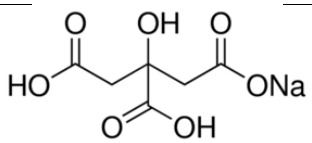
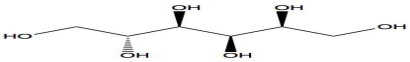
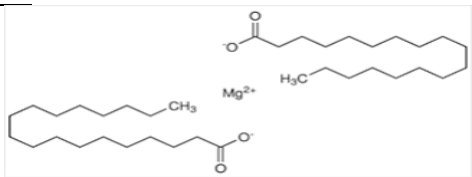
Solubility studies by shake flask method: Take 200ml flask. Add 100ml solvent (Buffers/ purified water). Shake the flake by magnetic stirrer. Maintain temperature 37°C. Add drugs untill it remain undissolved. Shake the flask for 12hr. filter the solution with 0.45µ filter. Analyses filtrate by assay analysis method. Dilute the sample if required. pH dependent solubility of candesartan cilexetil was done in various pH media at temperature 25ºC. Media for solubility test were purified water, phosphate buffer pH 1.2, 4.0, 5.0, 6.8, and 7.5

Hygroscopicity: Hygroscopicity is the measurement of a material's ability to absorb or release water as a function of humidity (ie water activity). The ideal way of measuring Hygroscopicity would be to create a Moisture sorption isotherm by looking at the change in water content vs. relative humidity at constant temperature.

Melting point determination: Fill a capillary tube with crystals about 3 mm high. Put the capillary tube (open end down) into the crystals and tap it on the bottom of the crystallization dish to get the crystals into the tube. Force the crystals to slide to the bottom of the tube using one of the following methods: tap the tube (open end up) on the lab bench; drop the capillary tube through a 2-3 foot piece of glass tubing; or rub the capillary tube along a piece of wire gauze. Place the capillary tube in the MEL-TEMP melting point apparatus. Set the MEL-TEMP at a high enough level to make a rapid determination of melting point. Observe the melting process though the magnifying lens. Once a melting point range is determined, prepare another capillary tube (tubes should only be used once and then discarded) and set the MEL-TEMP to the appropriate power level, based on the power level/temperature chart. This time, make sure that the increase in temperature is no more than 2°C per minute. Again, observe through the lens

Compatibility study: To ensure physical stability**,** all excipients and active pharmaceutical ingredient were mixed in equal proportion to make a ratio of 1:1 as shown in Table 1. The sample shall be kept in a worst condition in stability chamber. i.e. Stress testing condition (40°C /75%RH) for 15 days. The samples were evaluated for physical observation, by FTIR for change in any functional group peak and by DSC for change in meting point with respect to the initial condition.

Table 1: Proportion of all excipients for compatibility study

Sr. No.	Ingredients	Chemical structure	Specification	Quantity (gm)
1	Candesartan Cilexetil		USP	200
2	Citric acid (Anhydrous)		BP	200
3	Sodium bicarbonate (Anhydrous)		BP	200
4	Sodium citrate		BP	200
5	PVP-K 30		USP/BP	200
8	Sorbitol		BP	200
9	Magnesium Stearate		IH	200
11	Flavor Pippermenint	---	IH	200

Results and Discussion

Micromeritics properties: Result of micromeritics properties were as shown in Table 2. Bulk density and tapped density was found 0.8 and 0.7gm/mL respectively. Compressibility was found good that will minimize the step for compression trials and ultimately it will reflect in cost of the product. Compressibility helps in selection and determination of the optimal excipients and amount of excipients to be used.

Table 2: Micromeritics properties of API

Name of API	Bulk density	Tapped density	% compressibility
Candesartan cilexetil	0.8gm/ml	0.7gm/ml	12.5

Quantitative assay method: The method was found specific as shown in fig. 2 as there was no any interference at the interested retention time of candesartan cilexetil. The linearity of method shows R^2 value of 1.0 that indicates the method follows the Beer-Lamberd's law as shown in Fig. 3, 4 and area response in Table 3.

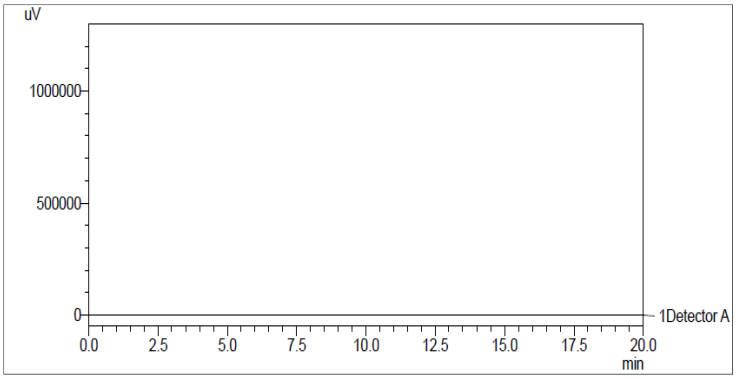


Fig. 2: Chromatogram of blank or diluent for specificity

Table 3: Linearity data for Candesartan Cilexetil

Concentration in mg/mL	Peak area
0.5	1049112
1.0	2098232
3.0	6399607
5.0	10600983
7.0	14785525

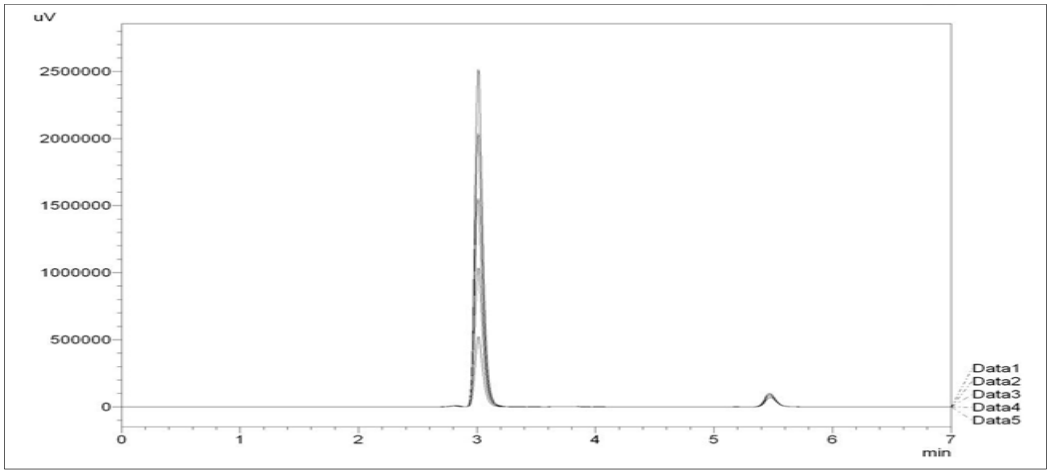


Fig. 3: Overlay chromatogram of Linearity

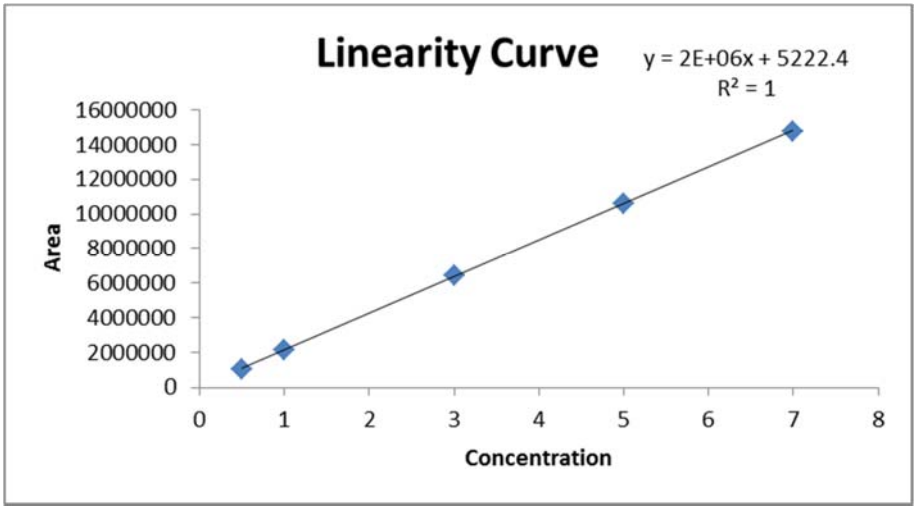


Fig. 4: Linearity curve for Candesartan cilexetil

Solubility study by shake flask method: Solubility of Candesartan cilexetil in different media was found as shown in Table 4. Solubility data helps to predict the dissolution media condition, selection of mobile phase and diluent for development of chromatographic method, possible interaction and stability of the API in particular media. From the table it can be said that at lower pH the API remain insoluble and its solubility increase as increase in pH of media. At pH 6.8 and pH 7.5 the API was found soluble.

Table 4: Solubility of API in different media

Theoretical pH	Individual concentration at saturation (Cs) values mg/mL (Theoretical)	Mean	Amount that can be dissolved mg/mL (From assay)	Mean	Results
pH 1.2	0.10	0.09	0.09	0.09	Insoluble
	0.08		0.08		
	0.11		0.10		
pH 4.0	0.95	0.98	0.92	0.97	Very slightly soluble
	0.98		0.97		
	1.0		0.98		
pH 5.0	1.9	2.2	1.85	2.1	Slightly soluble
	2.1		2.0		
	2.5		2.5		

pH 6.8	45	44.3	44.9	44.2	soluble
	46		45.8		
	42		41.8		
pH 7.5	48	49.7	47.8	49.4	soluble
	50		49.9		
	51		50.6		

Hygroscopicity: The ability of Candesartan cilexetil to absorb moisture was less than 0.1% when it was exposed to 80% Relative Humidity for 24Hrs. This indicates that the material was non-hygroscopic in nature. Non-hygroscopic nature will not degrade in higher moisture condition but it will also retard the solubility of material. So to increase the solubility and thus to made material hygroscopic, buffering system need to be develop surrounding the molecule by the concept of effervescent.

Melting Point Determination: Determining the melting point of a compound is one way to test if the substance is pure. A pure substance generally has a melting range (the difference between the temperature where the sample starts to melt and the temperature where melting is complete) of one or two degrees. Impurities tend to depress and broaden the melting range so the purified sample should have a higher and smaller melting range than the original, impure sample. The melting range for Candesartan Cilexetil was found to be 161-165

Compatibility study: The results of compatibility study are summarized in table 5. There were no any interaction found between drug and different excipients even after 15days at 40°C and 75% Relative Humidity. FTIR spectra remained same with no change in any functional group peak as shown in Fig 5-6 and Table 6. The endothermic peak in DSC indicate that there were no any impurity generated during the exposure period for drug and excipients as depicted in Fig 7-8.

Table 5: Result of Drug-Excipients Compatibility Study

Test	Acceptance criteria	Initial observation	After 15days at 40 °C +75%RH
Appearance	White, odorless, crystalline powder, having a slightly bitter taste	comply Powder was free flowing and free form lumps. No color change observed	Comply Powder was free flowing and free form lumps. No color change observed
FTIR	Functional group should remain intact	functional group picks were intake	functional group picks were remained intake
DSC	change in melting point NMT ±2%	comply	comply

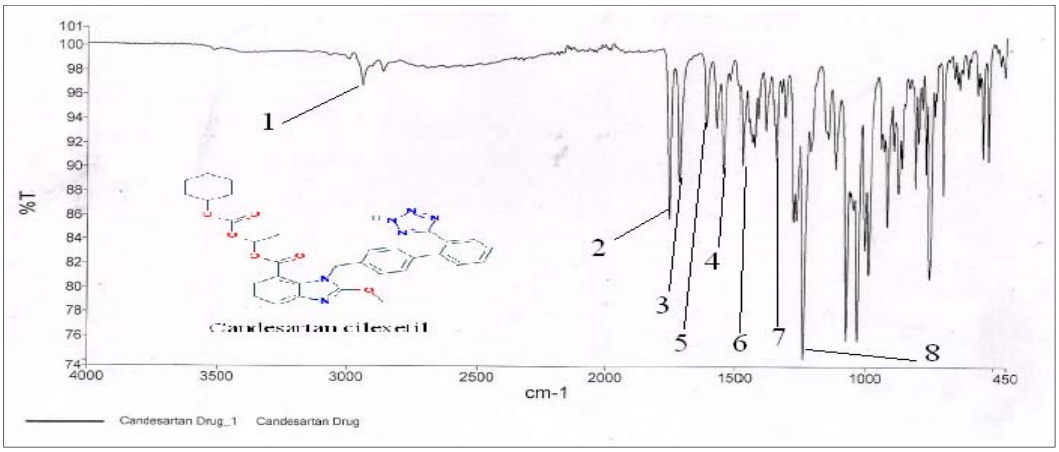


Fig. 5: FTIR spectra of Candesartan cilexetil at 0 Days

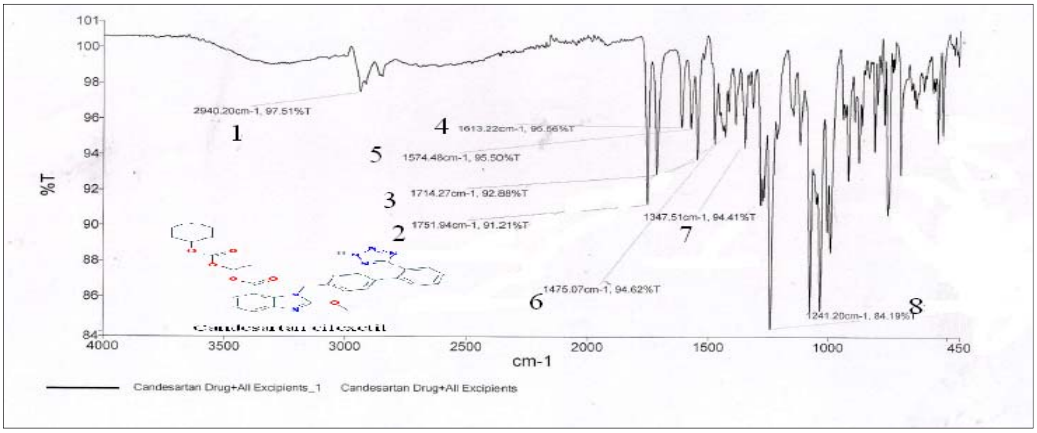


Fig. 6: FTIR spectra of Candesartan cilexetil after 15 Days at 40°C/75%RH

Table 6: Functional group Identification

peak name	Absorption cm^{-1}	functional group	observation
1	2940.58	alkyl C-H stretch	Alkyl group present
2	1751.82	Ester C=O stretch	ester group present
3	1714.22	carboxylic acid stretch	Carboxylic acid group present
4	1612.98	Amide $CONH_2$	$CONH_2$ group present
5	1574.49	N-O stretching	N-O group present
6	1475.1	C-H bending alkane group	Methyl group present
7	1387.82	C-H bending aldehyde group	
8	1240.96	R-C=O -R	ester group present

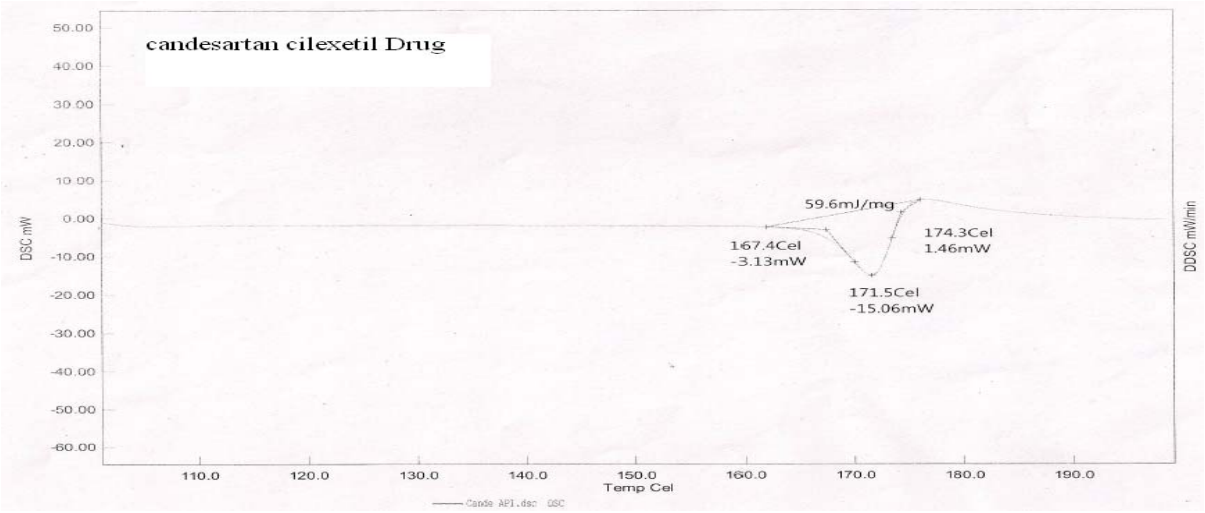


Fig. 7: DSC data of Candesartan cilexetil at 0 Days

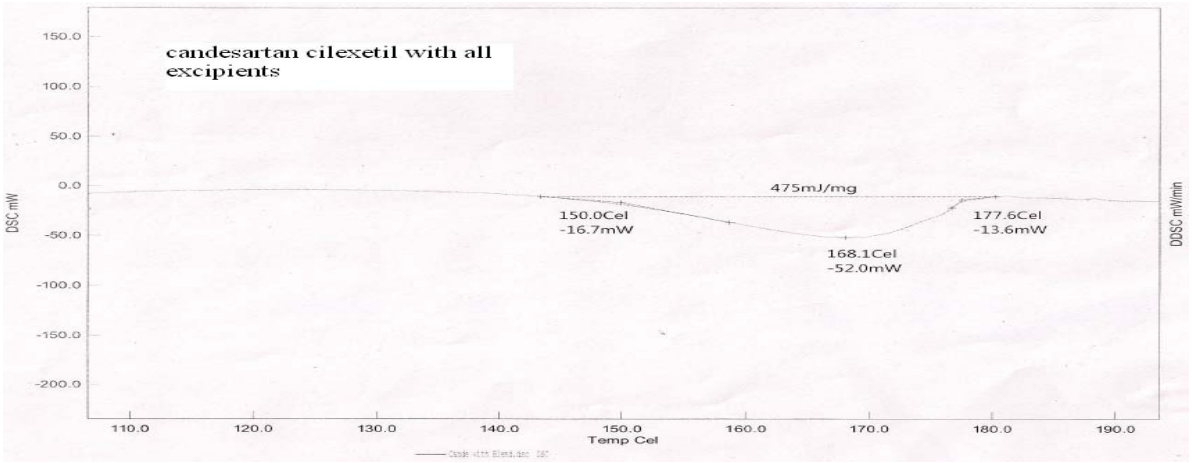


Fig. 8: DSC data of Candesartan cilexetil after 15 Days at 40°C/75%RH

Conclusion

preformulation study have significant part to play in anticipating formulation problems and identifying the logical path for development of dosage form. The physical characteristics of candesartan cilexetil comply as per USP requirement. Study of micromeritics properties revealed that the formulation can be prepared by direct compression method. Chromatographic method with the R^2=1 support the method for linearity and specificity of method tends to analyze the sample without any interference. Non-hygroscopic nature of drug will be the single hurdle for formulation development. pH dependent solubility plays important role to develop a bioavailable dosage form. The API soluble at more basic pH that can be created by the means of effervescence. Results of sold state stability candesartan cilexetil shows that it is compatible with Excipients at stressed condition too. FTIR and DSC interpretation shows that there is no any reaction between Excipients and drug.

Acknowledgement

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