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FORMULATION DEVELOPMENT AND EVALUAATION OF CANDESARTAN CILEXETIL IMMEDIATE RELEASE TABLETS

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ABSTRACT

The tablets were prepared and evaluated using wet granulation technique. In order to optimize the product, different formulations were developed. And pre compression and post compression were evaluated .To check the compatibility of drug with various polymers,. FTIR spectra of Candesartan Cilexetil were recorded, The IR spectral analysis of Candesartan Cilexetil pure drug alone showed that principal peaks were observed at wave numbers 2939.13 cm^{-1}, 1752.03 cm^{-1}, 1546.56 cm^{-1}, 1713.38 cm^{-1} and 1573.01 cmthe major peaks were observed at 2937.48 cm^{-1}, 1752.22 cm^{-1}, 1546.30 cm^{-1}, 1713.10 cm^{-1} and 1573.28 cm^{-1}.. All the formulations were evaluated for physical characteristics, Disintegration, in-vitro Dissolution and Stability studies. The Formulation F8 showed fair flow properties when compared to the reference product.From the obtained in vitro results of the above formulation Trials, We selected **F - 8** as the optimized formulation because it showed total drug release with in 30 min than all other formulations and reference product.

KEYWORDS: Candesartan, Carboxy methya cellulose, invitro studies and accelerated stability studies.

INTRODUCTION

Candesartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension and congestive heart failure. Angiotensin II receptor blockers are used primarily for the treatment of hypertension where the patient is intolerant of ACE inhibitor therapy.[1,2,3] They do not inhibit the breakdown of bradykinin or other kinins, and

are thus only rarely associated with the persistent dry cough and/or angioedema that limit ACE inhibitor therapy. More recently, they have been used for the treatment of heart failure in patients intolerant of ACE inhibitor therapy, in particular candesartan. Irbesartan and losartan have trial data showing benefit in hypertensive patients with type II diabetes.[4,5,6,7] and may delay the progression of diabetic nephropathy. A 1998 double-blind study found "that lisinoprilimproved insulin sensitivity whereas losartan did not affect it.[8] Candesartan is used experimentally in preventive treatment of migraine.[9,10,] Lisinopril has been found less often effective than candesartan at preventing migraine.[11] The angiotensin II receptor blockers have differing potencies in relation to blood pressure control, with statistically differing effects at the maximal doses.[5] When used in clinical practice, the particular agent used may vary based on the degree of response required. Some of these drugs have a uricosuric effect.[12]

MATERIALS AND METHODS

Materials

Candesartan obtained from the Aurobindo pharma ltd, Miyapur, Hyderabad, telangana India Lactose Monohydrate, PG Starch, Microcrystalline cellos (Avicel PH101), Klucel – LF, Ca. CMC, Megnesium stearate and SLS were purchased from SD fine chemical private Ltd, Mumbi, Maharastra.

Methods

The immediate release tablets containing 32mg Candesartan Cilexetil were prepared with a total tablet weight of 260mg. Based on the results of preformulation studies; to improve the flow properties tablets were prepared by Wet Granulation Technique and the composition are given in below .The required quantity of medicament and other ingredients was taken in a mortar. The binder solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No; 18 to obtain granules. The wet granules were dried at 60^0c for 2 hours. The dried granules were passed through mesh No; 12 to break the aggregates. The ingredients magnesium stearate was added to dry granules and blended in a polyethylene bag. The granules were then compressed into tablets on a rotary multi-station tablet punching machine to a hardness of 6-7 kg/sq.cm using 9 mm flat punches.

Ingredients	Formulation									
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Candesartan	32	32	32	32	32	32	32	32	32	32
Lactose Mono Hydrate	155.98	155.98	164.97	164.97	166.97	145	52	52	-	164.97
PEG 6000	12	12	6	2	-	12	12	12	-	6
Lycatab PGS/Corn starch	40	40	40	40	40	40	-	25	25	40
Ferric oxide Red	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Klucel LF	8	8	8	12	12	10	12	12	12	8
PVP – K 30	-	-	-	-	-	7.8	-	-	-	-
Avicel	-	-	-	-	-	-	125	100	150	-
Purified Water	70	70	70	70	70	70	70	70	120	70
Ca CMC	11.2	11.2	8	2	8	-	25	25	25	8
Mg.stearate	0.8	0.8	1.0	1	1	2.6	2	2	2	1.0
SLS	-	-	-	-	-	10	-	-	-	-
Total (mg)	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**

Evaluation parameters

4.1.5.1 Angle of repose (θ)

Procedure

Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$$\text{Angle of Repose } (\Theta) = \text{Tan}^{-1} (H/R)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Bulk density

Procedure

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 18 and 10 mg of pure drug was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula.

$$(Db) = M/Vo$$

Where,

M = mass of powder taken

V_o= unsettled apparent volume

Tapped density

Procedure: Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 10 mg of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated.

Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (V_o). The tapped density (Dt) was calculated in g/ml by the formula.

$$\mathbf{Dt = M/ V_o}$$

Where,

M = weight of sample powder

Vo = final tapped volume

Compressibility Index and Hausner Ratio

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such they are measures of relative importance of interparticulate interactions. In free flowing powder, such interactions are less significant and bulk & tapped density difference is close. For poorer flowing materials, this difference is greater.

Compressibility Index (% Compressibility)

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index was calculated using following equation:

$$\mathbf{CI\ (\%) = [(Dt - Db)/Dt] \times 100}$$

Where,

Dt = tapped density

Db = bulk density

b) Hausner's Ratio

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula

Hausner Ratio = Dt/Db

Compatibility Study

Procedure

API and excipient are taken in the ratios below mentioned and mixed together in a polybag for 5 min. Each mixture is allotted sample code for identification. 4 sets of sample were allocated where each sample mixture is divided in to 1g in to its corresponding glass vial (USP Type I) at different conditions.

All vials are properly sealed and loaded at respective conditions. The samples are to be checked for its Description, Related substance and water content by KF.

Drug – Excipient ratio for compatibility study details are given.

Excipient Ratio For Compatibility Studies.

S. No.	Drug – Excipient	Ratio
1	Candesartan + Corn starch	1:5
2	Candesartan + PEG 6000	1:5
3	Candesartan + Calcium CMC	1:5
4	Candesartan + Klucel EF	1:5
5	Candesartan + Klucel LF	1:5
6	Candesartan + Ferric oxide red	1:0.1
7	Candesartan+ Magnesium stearate	1:1
8	Candesartan + Avicel	1:5
9	Candesartan + Lactose	1:5

FTIR STUDIES

To check the compatability of drug with various polymers, IR spectra of drug, polymers and combination of drug and polymers were taken. FTIR spectra of Candesartan Cilexetil, MCC, CMC, Starch, Lactose and Magnesium stearate were recorded in KBr pellets and are presented. The IR spectral analysis of Candesartan Cilexetil pure drug alone showed that principal peaks were observed at wavenumbers 2939.13 cm^{-1}(C-H stretch), 1752.03 cm^{-1}(C=O stretch),1546.56 cm^{-1}(N-H Deformation),1713.38 cm^{-1}(C=O stretch) and 1573.01 cm^{-1}(C-O stretch).Further in the physical mixture of MCC, CMC, Starch, Lactose and

Magnesium stearate and Candesartan Cilexetil , the major peaks were observed at 2937.48 cm^{-1} , 1752.22 cm^{-1} , 1546.30 cm^{-1} ,1713.10 cm^{-1} and 1573.28 cm^{-1} suggesting that there is no interaction between the polymers and drug used in present study.

RESULTS AND DISCUSSION

The formulations F1, F5 and f7 shows passable flow properties, formulations F2 ,F3,F4,F8 and F9 shows fair flow properties and the formulation and the F6 and F7 shows very poor flow property. The Hardness, Friability, Thickness, Disintegration values of formulations (F1-F10) were found to be within Pharmacopeial limits. The Drug content of F8 was found to be best among all formulations. The Cumulative percent drug release of Candesartan Cilexetil tablets of F8 was found to be best among all formulations and its values is 99.8 %. The IR spectral analysis of Candesartan Cilexetil pure drug alone showed that principal peaks were observed at wavenumbers 2939.13 cm^{-1}, 1752.03 cm^{-1}, 1546.56 cm^{-1}, 1713.38 cm^{-1} and 1573.01 cm^{-1}.Further in the physical mixture of MCC, CMC, Starch, Lactose and Magnesium stearate and Candesartan Cilexetil, the major peaks were observed at 2937.48 cm^{-1}, 1752.22 cm^{-1}, 1546.30 cm^{-1}, 1713.10 cm^{-1} and 1573.28 cm^{-1} suggesting that there is no interaction between the polymers and drug used in present study.

Evaluation of Precompression Parameters.

S. No.	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
1	F-1	0.596	0.785	24.07	1.31
2	F-2	0.581	0.714	18.60	1.22
3	F-3	0.654	0.802	18.45	1.22
4	F-4	0.694	0.834	16.67	1.2
5	F-5	0.480	0.625	23.07	1.30
6	F-6	0.519	0.732	29.09	1.443
7	F-7	0.583	0.745	21.74	1.277
8	**F-8**	**0.582**	**0.714**	**18.60**	**1.22**
9	F-9	0.510	0.641	20.40	1.25
10	F-10	0.500	0.735	32	1.470

Flow properties of optimized formulation.

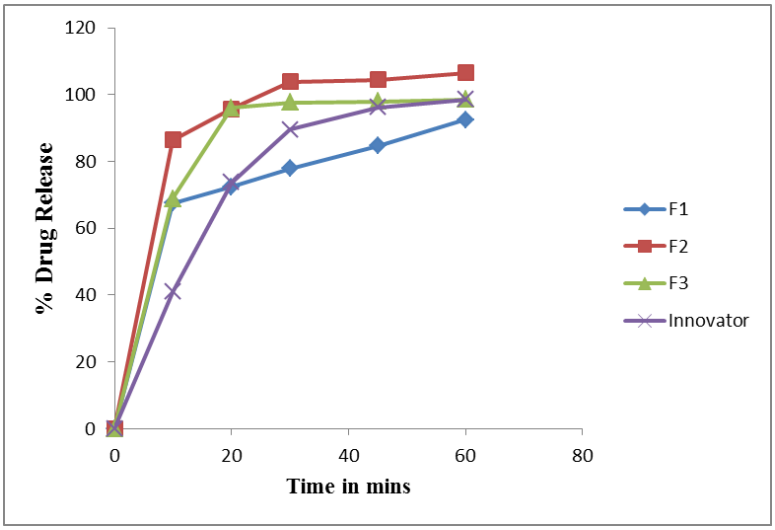
S. No.	Flow Properties	Result
1	Bulk density (g/ml)	0.581
2	Tapped density (g/ml)	0.714
3	Carr's index (%)	18.62
4	Hausner's ratio	1.22
5	Angle of repose	$22^{o}.8$

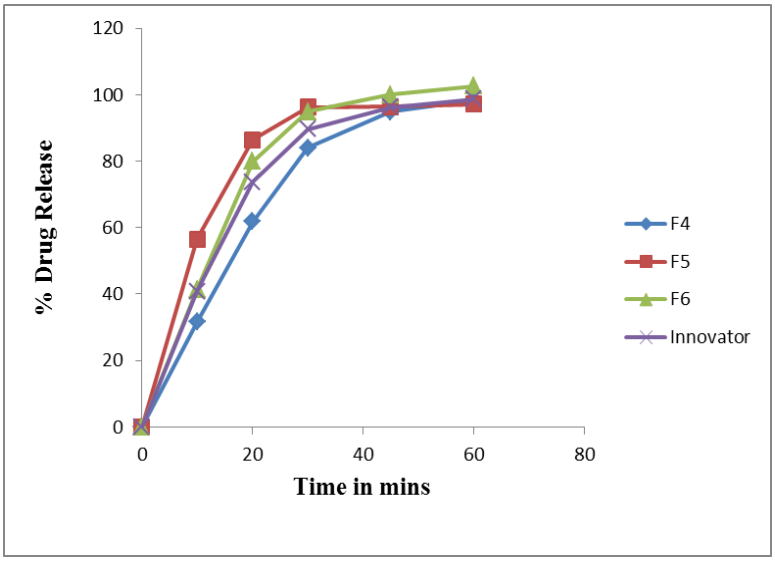
FTIR Compatibility studies results.

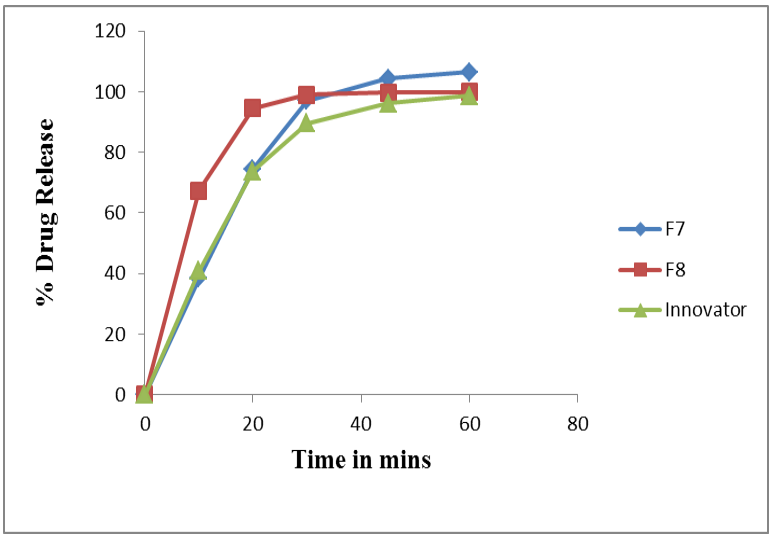
Excipients	% known impurities			%Unknown impurities			Total impurities		
	I	II	III	I	II	III	I	II	III
Lactose	0.15	0.2	0.3	0.01	0.02	0.04	0.4	0.6	0.8
PEG 6000	0.1	0.15	0.4	0.04	0.05	0.08	0.2	0.4	0.7
PG Starch	0.1	0.12	0.3	0.02	0.05	0.09	0.1	0.3	0.5
HPC	0.2	0.25	0.35	0.02	0.04	0.08	0.2	0.3	0.6
Ca CMC	0.2	0.18	0.28	0.01	0.04	0.05	0.3	0.5	0.9
Mg.Stearate	0.1	0.15	0.18	0.03	0.04	0.05	0.2	0.3	0.5

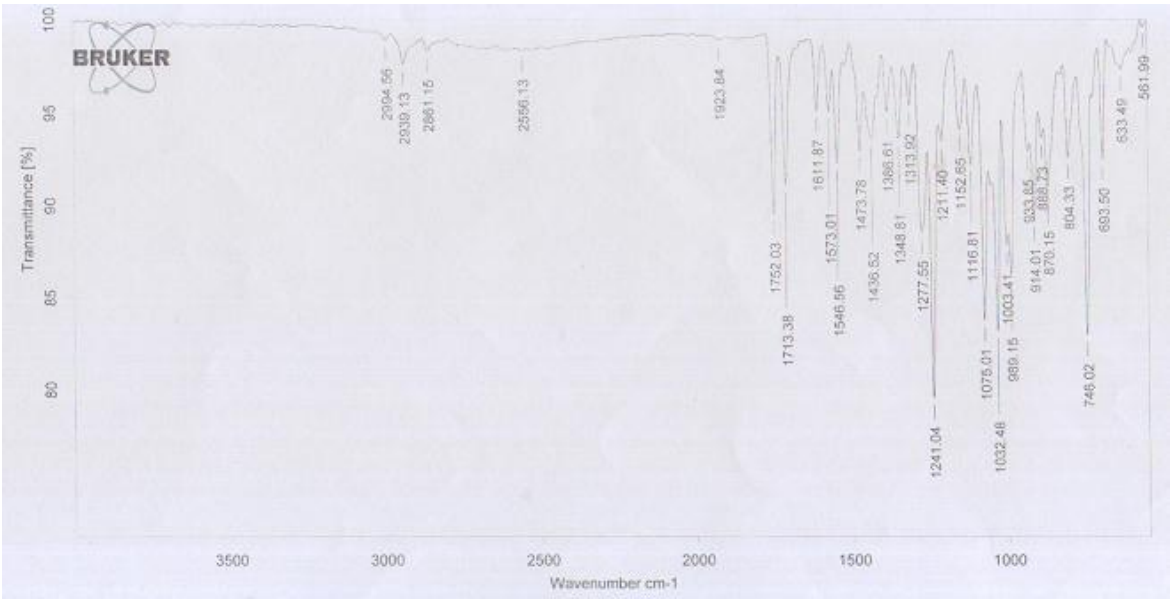
Post compression Evaluation stidies.

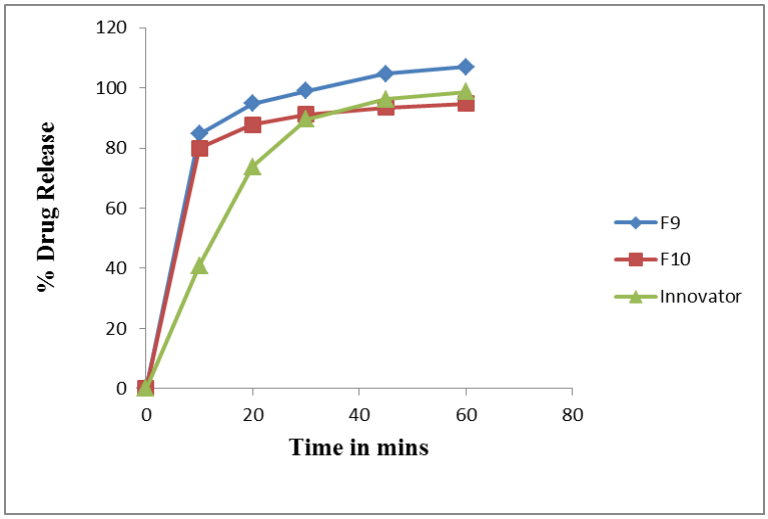
S. No.	Formula	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (%)	Assay (%)
1	F-1	3.62 ± .099	4.1 ± 0.03	3.16	0.153	96.4
2	F-2	3.62±0.016	5.1 ± 0.03	3.02	0.106	97.3
3	F-3	3.46 ± 0.035	6.19 ± 0.22	8.5	0.377	94.1
4	F-4	3.46 ± 0.024	9.75 ± 0.51	14.55	0.24	98.5
5	F-5	3.48 ± 0.029	10.44 ± 0.49	11.5	0.17	97.4
6	F-6	3.47 ± 0.053	5.46 ± 0.32	11.2	0.28	98.3
7	F-7	3.47 ± 0.052	9.45 ± 0.59	12	0.23	92.4
8	F-8	3.53 ± 0.022	8.12 ± 0.47	11	0.06	99.8
9	F-9	3.55 ± 0.019	9.6 ± 0.35	5.5	0.06	98.5
10	F-10	3.55 ± 0.016	7.1 ± 0.27	2	0.167	98.2
11	Innovator	3.50 ± 0.04	9.8 ± 0.14	11.17	0.15	98.8




% Drug Release
Time in mins
F4
F5
F6
Innovator


% Drug Release
Time in mins
F7
F8
Innovator


BRUKER
Transmittance [%]
Wavenumber cm-1



Invitro -drug release studies.

S. No.	Time	Cumulative % Drug Release										
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	Inno-vator
1	0	0	0	0	0	0	0	0	0	0	0	0
2	10	67.6	86.4	68.9	31.6	56.5	41.4	38.4	**67.4**	84.7	80	**40.9**
3	20	72.4	95.8	96	61.8	86.5	79.9	74.5	**94.5**	94.7	87.8	**73.7**
4	30	77.9	103.8	97.6	84.0	96.2	94.9	97.0	**98.9**	98.9	91.2	**89.6**
5	45	84.6	104.5	97.9	94.9	96.4	100.1	104.3	**99.7**	104.6	93.4	**96.2**
6	60	92.5	106.5	98.6	98.3	97.1	102.6	106.5	**99.9**	107.0	94.7	**98.6**

CONCLUSION

Based on Literature survey and Compatibility Test excipients like Microcrystalline Cellulose (pH 101), PEG – 6000, PGS, Hydroxypropyl cellulose, Carboxy Methyl Cellulose, Magnesium stearate were used. In this present study, the tablets were prepared by using wet granulation technique. In order to optimize the product, different formulations were developed.

To check the compatability of drug with various polymers, IR spectra of drug, polymers and combination of drug and polymers were taken. FTIR spectra of Candesartan Cilexetil, MCC, CMC, Starch, Lactose and Magnesium stearate were recorded in KBrpellets and are presented. The IR spectral analysis of Candesartan Cilexetil pure drug alone showed that principal peaks were observed at wavenumbers 2939.13 cm^{-1}, 1752.03 cm^{-1}, 1546.56 cm^{-1}, 1713.38 cm^{-1} and 1573.01 cm^{-1}.Further in the physical mixture of MCC, CMC, Starch, Lactose and Magnesium stearate and Candesartan Cilexetil , the major peaks were observed at 2937.48 cm^{-1}, 1752.22 cm^{-1}, 1546.30 cm^{-1}, 1713.10 cm^{-1} and 1573.28 cm^{-1} suggesting that there is no interaction between the polymers and drug used in present study.

All the formulations were evaluated for physical characteristics, Disintegration, *in-vitro* Dissolution and Stability studies. The Formulation F8 showed fair flow properties when compared to the reference product. From the obtained *in vitro* results of the above formulation Trials, We selected **F - 8** as the best formulation because it showed total drug release with in 30 min than all other formulations and reference product.

Based on mathematical data revealed from models, it was concluded that the release data was best fitted with first order kinetics. Higuchi equation explains the diffusion controlled release mechanism.

Stability studies were performed for this batch for 1 and 3 months under accelerated and long term testing conditions. Finally after the duration, the product was analyzed for physical appearance, Hardness, Thickness, Friability, Loss on drying, disintegration, Assay and Related substance. The results obtained were found to be within the specified limits.

The bigger scale confirmatory batch is under 6 months Accelerated stability condition, based on the result, a pilot scale will be executed.

After passing the above tests, the in-vivo studies (BA/BE Studies) will be executed to correlate the bioequivalence of best formulation (**Trial F 8)** with the reference drug.

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