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Formulation Development and Evaluation of Immediate Release Tablet of Poorly Soluble Candesartan Cilexetil

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ABSTRACT:

Candesartan cilexetil is prodrug of candesartan. It is a non-peptide angiotensin Π type-I (ATI) receptor antagonist which is used in the treatment of hypertension and congestive heart failure. The aim of this research was to formulate a stable as well as robust dosage form. Candesartan cilexetil show extensive first pass metabolism and less bioavailability. Candesartan cilexetil having low solubility and has half-life of 9 hrs suggest its suitability for a immediate release formulation. The basic objective was to develop a generic version of anti-hypertensive tablet in line with the innovator. A generic version of tablet was developed that is safe, efficacious and bioequivalent to the reference product. The compatibility study of drug with excipients was studied by FTIR spectroscopy. It shows that there was no chemical interaction between the drug and excipients. Immediate release tablets were prepared by top spray granulation method by using carmellose calcium as superdisintegrant and PEG as stabilizer and HPC as binder. Prepared tablets showed acceptable IPQC parameters and were evaluated for *in vitro* drug release. Optimized batch (Batch F10) gave desired results in terms of % drug release after 15-30 min in pH=6.8 and in pH=1.2, it gives <50% release. Similarity factor were calculated for all formulations and it shows that the values of similarity factor (f_2) for the batch F010 showed maximum value (89.83 and 73.66 respectively). Stability study of optimized batch was carried out at 45 ± 2 ^{0}C and 75 ± 5 % RH for one month in a PVDC-PVC aclar blisterpackaing and it was found that there was no statistically significant difference found in *invitro* drug release before and after stability study.

Keywords: Angiotensin Π type-I (ATI) receptor antagonist, Top spray granulation, Candesartan Cilexetil, Immediate release tablet,carmellose calcium as superdisintegrant.

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INTRODUCTION:

Introduction to Immediate Release Dosage Form [1]:

Immediate release formulation is more advanced than other formulation because tablets disintegrate and dissolve rapidly in GI tract. The faster the drug disintegrates in to GI tract, the quicker the absorption was occured and gives onset of clinical effect. Candesartan had high affinity towards the angiotensin type 1 ATI receptors belongs to the drug class known as Angiotensin Receptor Blocker (ARB). Candesartan is highly bound to plasma protein (more than 99%).

Compare to other ARBs Candesartan shows, has a long duration of action. It has half-life of 9 hrswhere asTmax is 3-4 hr so rapidly achieve desired plasma concentration and stands for long time ,so once daily dose is enough for onset of clinical effect , which is also convenient to the patient.Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption.Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency

resulting in decreased use levels when compared to traditional disintegrants.Traditionally, starch has been the disintegrate of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants.

Mechanism ofDisintegrants:

1) High swellability
2) Capillary action and high swellability
3) Chemical reaction

In this work; an attempt is made to formulate immediate release tablets of Candesartan to increase patient compliance by reducing dosing frequency and to achieve even plasma concentration profile.

MATERIALS AND METHODS

Candesartan cilexetil was obtained from Cadila healthcare ltd. Ahmedabad,India. Hydrochloric acid and Potassium dihydrogen phosphate were purchased from B.K.Chemicals,pune,India. Lactose monohydrate (Pharmatose 200) was purchased from Fonterra excipients,Netherland. Polyethylene glycol was used from Imperial industrial chemicals, Thialand. Hydroxyl propyle cellulose- Lf (HPC-Lf) was purchased from lucidcolloids, Mumbai. Corn starch and Magnesium stearate used in the research from Roquette,france andDr. Paul Lohman,Germeny. Ferric oxide red was used from Signet, worli, Mumbai.All other chemicals and solvents used are of analytical reagent grade.

Equipments

Weighing balance, pH meter, Mechanical stirrer, Bulk density Tester (USP), Fluid bed processor, Hot air oven, Tablet compression machine, Hardness tester, Friability tester, Verniercaliper scale, Cone blender,Halquadrocomillen moisture balance, Sieve shaker, UV spectrophotometer.

Experimental work

Determination of absorption maxima of candesartan cilexetil[2]:

Candesartan cilexetil (100mg) was accurately weighed, transferred to 100ml volumetric flask and dissolved in small quantity of ethanol. The volume was made up with ethanol to get a concentration of 1000µg/ml. From this 10 ml was withdrawn and diluted to 100ml in HCl pH1.2/pH 6.8 phosphate buffers to get concentration of 100µg/ml. From this solution, 1 ml was withdrawn and added to the 10 ml volumetric flask. Finally, the standard solution (1µg/ml) of Candesartan cilexetil was scanned between 200-400 nm on UV-visible spectrophotometer to record the wavelength of maximum absorption (λ max). The $\lambda_{max}$was found to be 224nm from UV spectrum of candesartan in ethanol; Absorbance was measured at 224nm against ethanol as blank spectrophotometrically.

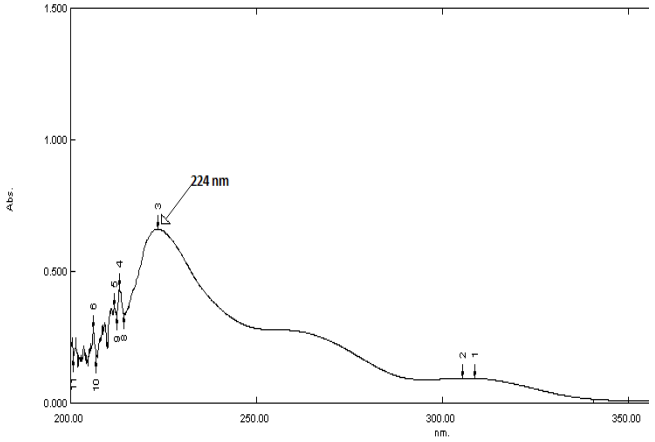

Figure1: Absorption maxima of candesartan cilexetil in Hydricloric acid buffer pH= 1.2

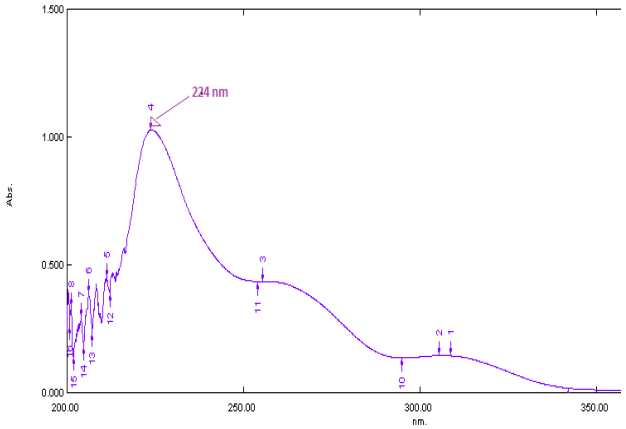

Figure 2: Absorption maxima of candesartan cilexetil in phosphatebuffer pH= 6.8

Calibration curve of Candesartan celexetil[2]:

Preparation of standard solution:

Candesartan cilexetil (100mg) was accurately weighed into 100ml volumetric flask and dissolved in small quantity of ethanol. The volume was made up with ethanol to get a concentration of 1000µg/ml. From this 10 ml was withdrawn and diluted to 100ml in HCl pH1.2/pH 6.8 phosphate buffers to get concentration of 100µg/ml.

Preparation of working solutions:

From the standard stock solution aliquots 2ml, 4ml, 6ml, 8ml and 10ml were pipetted out into 100ml volumetric flask .The volume was made up with phosphate buffer pH6.8 andHCl pH1.2 to get final concentration of 2 µg/ml, 4 µg/ml,6 µg/ml,8 µg/ml and 10µg/ml respectively .The absorbance of each concentration was measured at 224nm.Absorbance was measured at 224nm against ethanol as blank spectrophotometrically.

Preformulation study

Organoleptic properties of API:

The organoleptic property was determined by visually observation, Candesartan cilexetil is odourless, tasteless, andwhite to off white crystalline powder.

Physicochemical property of drug[3] [4]:

1. Loose Bulk Density (BD)

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula

Bulk density = Weight of powder / Bulk volume……..(1)

2. Tapped bulk density (TD):

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and tapped volume (V_1) was measured to the nearest graduated units. Tapping was repeated an additional 750 times and the tapped volume (V_2) was measured to the nearest graduated units.The tapped bulk density was measured in gm/ml by the following formula

Tapped Density = Weight of powder / Tapped volume……..(2)

3. Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD)x100]/TD…….(3)

4. Hausner's Ratio

The hausner's ratio was determined by the following equation

. **Hausner's Ratio = TD / BD……..(4)**

5. Melting point of drug:

Melting point of the drug was determined as per USP method by DBK prog. Melting point apparatus.Melting point of Candesartan cilexetil was found to be **162°C**, which is in the range as given in literature (158-166°C).Hence the drug can be stated as pure.

6. Particle size and particle size distribution [5]:

The particle size analyzed by **Hot Stage Microscopy (HSM)** is based on the principle of light scattering. In present study, the particles size was determined using **dry method.**Slides were prepared by mixing the powdered sample with low viscosity silicon oil, and the resulting dispersion placed between a clean glass slide and cover slip. Each prepared slide was examined using bright field and slightly uncrossed polarized light using a LEICA HC Plan 10X 20 eye piece and 10X objective. Images were obtained using a LEICA DMLM Polarizing Light Microscope (PLM) with JVC digital color video camera having METTLER TOLEDO FP 82 hot stage movable attachment.

7. Solubility profile:

Solubility studies were conducted by placing an excess amount of Candesartan (approximately 200 mg) in a 2 ml microtube containing 1 ml of each buffer. Then, the mixture was vortexed and kept for 3 days at 37°C in a shaking water bath to facilitate the solubilization. The samples were centrifuged at 10,000 rpm for 10 min to remove the undissolved candesartan. The supernatant was taken, diluted with ethanol upto 10 times and filtered through Whatman filter paper for quantification of drug by UV spectroscopy at 224 nm.

Drug excipient compatibility studies by FTIR Study:

Fourier transform infrared (FTIR) spectra of candesartan cilexetil and physical mixture of drug and excipients were recorded using potassium bromide KBr mixing method on FTIR instrument as depicted in Figure 1 to 8.

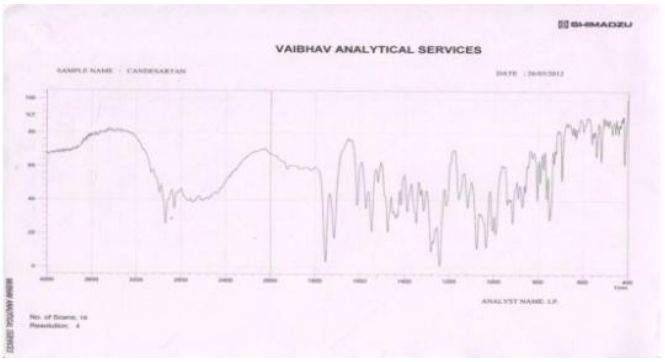

Figure 1 FT-IR spectra of API

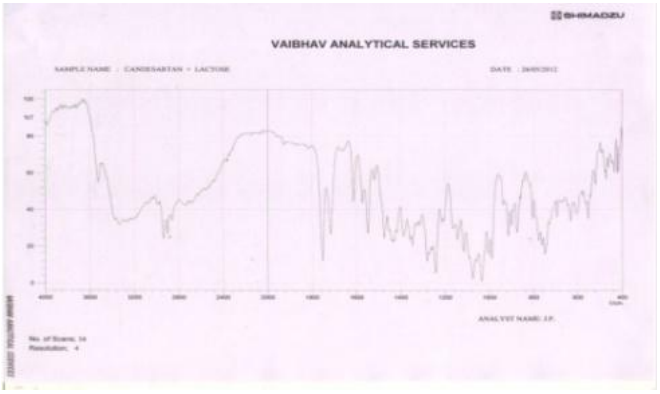

Figure 2 FT-IR+Lactose

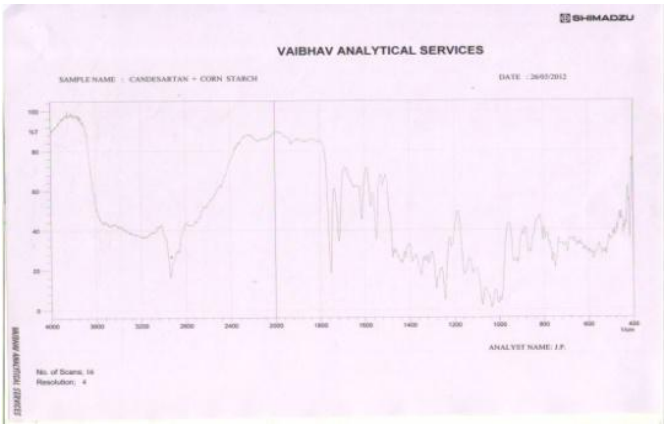

Figure 3 FT-IR spectra of API+Corn starch

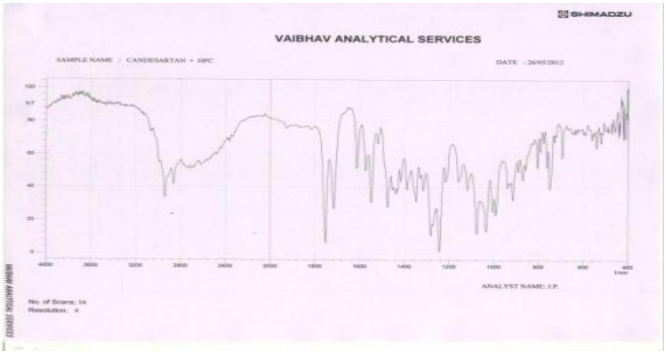

Figure 4 FT-IR spectra of API+HPC-Lf

Drug excipients compatibility by physical observation:

Procedure:

(a) Drug: Excipients Ratio
(b) Drug and excipients were taken in the ratios as mentioned in table no.15

(b) Pack details

USP type I Clear transparent glass vials with bromobutyl rubber stopper and aluminum seal.

(c) Storage condition

1. 25ºCº±2°C / 60%RH± 5 % RH
2. 40ºC±2°C / 75%RH± 5 % RH

API and excipients were been thoroughly mixed in predetermined ratio given in above table and passed through the 40# sieve. The blend was to be filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminum seal and charged in to stress condition at above condition. Similarly API should also be kept at all condition as for the samples. Samples were withdrawn for analysis within two day of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and FTIR studies were carried out to determine the compatibility of excipients with the drug.

Formulation study:

Formulation of Candesartan Immediate Release (IR) tablet by top spray granulation method:

1 Preparation of granulation liquid or spray-solution[6] [7]:

Measured quantity of purified water was taken into a suitable stainless steel vessel. In sequence, measured quantity of PEG 6000and HPC Lf were dissolved in the purified water under intensive stirring until a virtually clear solution was obtained.

2 Sifting:

Candesartan cilexetil, Lactose and Croscarmellose are passed through 30# sieve and mixed properly in polybag.Colour and corn starch were passed through 100# sieve and mixed with the above blend.

3 Granulation:

Measured quantity of API and excipients were placed into a fluid-bed granulator and sprayed with granulation liquid (containing dry mass) under diffetent sets of conditions by varying the various process parameters. (Table 2) The granulation mass was then sprayed with binder, followed by a drying step and a screening step.

TableNo.2: Process Data of Granulation

Parameter/Process Variable	Specification
GRANULATION	
Inlet air temperature	50-60 °C
Product temperature	30-35 °C
Exhaust temperature	35-36 °C
Blower drive speed	15-23 %
Spray pump RPM	5-15 rpm
Spraying rate	5-10 gm/min
Air flow	20-25 cfm
Inlet RH	4-8%
Exhaust RH	70-89%
Atomization air pressure	1.2 bar

4 Drying

The drying of the material was done in the same processor.The product temperature was maintained 32°C,The inlet temperature was adjusted 50-60 °C. The Loss on drying(LOD) was observed during the drying process which was not more than 2.5%.

5 Screening:

The prepared granules were screened before the lubrication. The granules were screened through the 24# sieve.

6 Lubrication with Extra-granular excipients:

Screened granules were lubricated by cone blender with a revolution of 18 rpm.

Weighed quantity of carmelloseCa was screened through the 40# sieve and mixed for 5 min. Weighed quantity of magnessiumstearate was screened through the 60# sieve and mixed for 3 min.

7 Tablet compressions:

The granules prepared were subjected to compression using "B" Tooling rotary tablet machine. The final blend for tablet compression was compressed into tablets. The target weight was 130 mg.

Process parameters for tablet were recorded in table no; 3.

TableNo.3: Process Data of Compression

Parameter/Process Variable	Specification
Compression	
Tablet press	CMD-4 "B" Tooling
Compression force	4-5 KP
Die	7 mm
Upper punch	Embossed with ZJ 94
Lower punch	Embossed with 12 mg

Development trials by top spray granulation with GlattPlam Coater and Granulator (GPCG).

Table no. 4 Formulation Trial F01 to F07 of candesartan cilexetil

Batch No.	F01	F02	F03	F04	F05	F06	F07
Quantity	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
Intragranular							
Candesartan cilexetil	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Lactose monohydrate	72.44	70.75	71.77	**50.53**	83.83	101.04	70.13
Corn starch	29.90	30.00	29.27	**50.53**	**17.22**	--	**29.62**
HPC-Lf	5.2	5.2	5.2	5.2	5.2	5.2	5.2
PEG 6000	**1.30**	**2.89**	**2.60**	2.60	2.60	2.60	2.60
Croscarmellose Ca	-	-	-	-	-	--	**3.9**
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extragranular							
Croscarmellose Ca	7.8	7.8	7.8	7.8	7.8	7.8	**5.2**
Ferric oxide red	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Mg. Stearate	1.3	1.3	1.3	1.3	1.30	1.3	1.3
Total	**130**	**130**	**130**	**130**	**130**	**130**	**130**

Trial batches with codes F08 to F17 with different compositions were formulated. Detailed composition of each trial was recorded in Table 5.

Evaluation of Candesartan Cilexetil Tablet

Evaluation of Innovator / Reference Product Characterization:

1 Description of reference product: The reference product wasorange to pink colored, round shaped, uncoated tablets, debossed with "ZJ" and "94" on upper side and "12" on lower side.

2 Physical characterization of reference product: The reference product blopresswas physically characterized .

Table No.6: Physical characterization of reference product

Average Weight (mg)	130 ± 3%
Thickness (mm)	2.4 ± 0.03mm-2.8 mm ± 0.03mm
Hardness (Kp)	4-5±0.5kp
Friability (%w/w)	Nil
disintegration time (min.)	12-13 min

3 Acceptance Criteria for Final Product:

Table No.7: Acceptance criteria for final product

Test Parameter	Acceptance Criteria
Appearance	Orange to pink colour, round shaped, uncoated tablets, debossed with "ZJ" and "94" on upper side and "12"on lower side.
Average weight	130±3% mg
Uniformity of weight	Average weight ± 5 %
Hardness	4±0.5-5±0.5 kp
Disintegration time	10-12 min
Thickness	2.4± 0.03mm-2.8 mm ± 0.03mm.
Friability	NMT 1%
Dissolution	NLT 85.0 % is dissolved in 15-30 min.
Assay	NLT 99%.& NMT 101% of label claim

4: Evaluation of Candesartan cilexetil immediate release tablet:

General Appearance:Any variation in tablet thickness within the particular lot of tablets or between manufacturer's lots should not be apparent to unaided eyes for consumer acceptance of the product. In addition thickness and diameter must be controlled to facilitate packaging. Thus thickness and diameter of tablets were important for uniformity of tablet size. Ten tablets were taken and their thickness and diameter were recorded using vernier caliper.

Average weight and weight variation [3]**:** For weight variation test JP procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively using electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation

TableNo.5: Formulation Trial F08 to F16 of candesartan cilexetil

Batch No.	F08	F09	F10	F11	F12	F13	F14	F15	F16	F17
	Binder Optimization			Disintegrant optimization			Lubricant optimization			
Intragranular										
Candesartan cilexetil	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Lactose monohydrate	72.42	71.11	71.93	69.33	68.73	73.23	70.63	73.23	73.84	73.23
Corn starch	28.62	26.03	28.52	29.82	28.82	29.82	29.81	29.82	30.01	29.82
HPC-Lf	**3.9**	**7.8**	**4.49**	4.49	4.49	4.49	4.49	4.49	4.49	4.49
PEG 6000	2.60	2.60	2.60	2.60	2.60	2.60	2.60	2.60	2.60	2.60
Croscarmello-se Ca	3.9	3.9	3.9	**6.5**	**8.1**	**3.25**	3.25	3.25	3.25	3.25
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extragranular										
Croscarmello-se Ca	5.2	5.2	5.2	**3.9**	**3.9**	**3.25**	3.9	3.25	3.25	3.25
Ferric oxide red	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Mg. Stearate	1.3	1.3	1.3	1.3	1.3	1.3	**3.9**	**1.3**	**0.50**	**1.3**
Total	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**

was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.

In vitro disintegration time: In the present study disintegration test was carried out on six tablets using the apparatus specified in USP (Electroquip, disintegration apparatus USP). The distilled water at $37^0C \pm 2^0C$ was used as a disintegration media.

In vitro dissolution study: In vitro dissolution of the tablets was determined using USP- Type-II dissolution test apparatus rotating at 50 rpm in 900 ml pH=6.8 phosphate buffer and pH=1.2 hydrocloric acid buffer as medium at 37.0 ºC $\pm$ 0.5 ºC. Aliquots (5ml) were withdrawn at intervals of 5,10,15,20,30,45,60 minutes. Set the dissolution parameter of the instruments as mention above place one tablet in each six vessels and operate the instruments for the specified time. Withdraw 5 ml of solution from zone midway between the surface of dissolution medium and top of paddle not less than 1 cm from the vessel wall. Filter the solution collect the filtrate by discarding the excess of filtrate. 2 ml of this solution was added with 100 ml of dissolution media in 100ml volumetric flask. Measure the absorbance in 1 cm cell on UV spectrophotometer at 224 nm, using dissolution medium as blank. The amount of Candesartan cilexetil in solution was determined spectrophotometrically at 224 nm.

In-vitro release study in phosphate buffer pH=6.8 The average dissolution from reference products reaches 85% between 15 and 30 min ,the average dissolved amount of the test product does not deviate by more than 15% from that of the reference product at two time points when the average dissolved amount of the reference product was around 60 and 85%. The f2 value should be not less than 42 for this condition.

In-vitro release study in phosphate buffer pH=1.2

The average dissolution of reference product doesnot reach 50% within the testing time specified. There is no sample of test products that shows the deviation of more than 9% in Dissolution from the average dissolution of the test product at the testing time specified as well as at a time point when the average dissolved amount of the reference product reaches half of the average dissolved amount at the testing time specified. When f2 is used, the f2 valueshould be not less than 53.

Stability studies[8]**:**Stability of a drug has been defined as the ability of a particular formulation, in aspecific container, to remain within its physical, chemical, therapeutic and toxicological specifications. In any rational design and evaluation of dosage forms for drugs, stability of the active component must be a major criterion indetermining their acceptance or rejection.

The International Conference on Harmonization (ICH) Guidelines titled 'stability testing of New Drug substance and products" describes the stability test requirements for drug registration applications in the European Union, Japan and the USA.ICH specifies the length of the study and storage conditions,which were as following table no.8

Procedure:

The selected formulations were packed in the PVC-PVDC aclar blister packaging, which were packed in the card board box

and labeled. They were then stored at 40°C/ 75% RH and room temp. They were kept for one month and evaluated for their physical appearance, Inprocess tablet parameters and drug release at specific intervals of time as per ICH Guide lines.In the present work stability study was carried out for the optimized formulation F10 for following condition and time period: 40° C / 75% RH for 1 months.

Table: 8 ICH guide lines for stability study

Study	Storage condition	Time period
Long term	25°C±2°C/60%RH±5%RH or 30°c±2°C/65%RH±5%RH	12 months
Intermediate	30°c±2°c/65%RH±5%RH	6 months
Accelerated	40°c±2°c/75%RH±5% RH	6 months

RESULTS AND DISCUSSIONS:

1.Calibration curve:Table. 9Linearity data of candesartan cilexetil in HCl buffer pH=1.2

Concentration (µg/ml)	Average absorbance
0	0.000 ± 0.000
2	0.070± 0.001
4	0.111± 0.003
6	0.160± 0.002
8	0.212± 0.003
10	0.280± 0.002
Absorbance = Slope × Concentration + Intercept	
Absorbance = 0.026 × Conc. + (0.004)	

Note: All values represent mean ± SD (n=3)

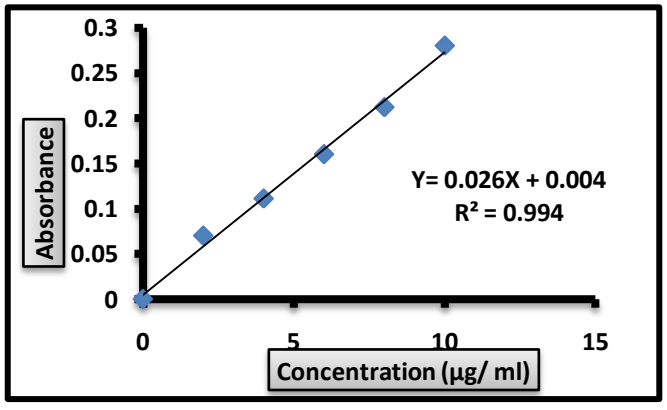

Figure 9: Calibration curve of candesartan cilexetil in HCl buffer pH=1.2

Table 10: Linearity data of candesartan cilexetil in phosphate buffer pH= 6.8

Concentration (µg/ml)	Average Absorbance
0	0.000 ± 0.000
2	0.150 ± 0.003
4	0.348 ± 0.001
6	0.520 ± 0.002
8	0.730 ± 0.002
10	0.900 ± 0.001
Absorbance = Slope × Concentration + Intercept	
Absorbance = 0.091× Conc. + (-0.016)	

Note: All values represent mean ± SD (n=3)

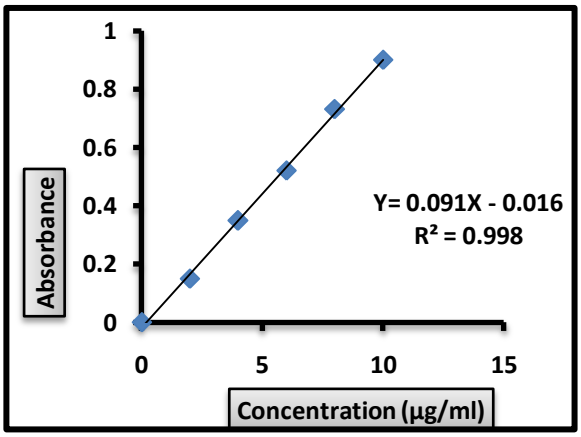

Figure 10: Calibration curve of candesartan cilexetil in phosphate buffer pH= 6.8

Discussion:

UV based Spectrophotometric estimation of Candesatan Cilexetil was conducted at 224 nm in buffer pH= 1.2 and phosphate buffer pH= 6.8. Linearity was observed in concentration range of 2-10 µg/ml. It was found that regression coefficient was closer to 1.Estimation of *invitro* drug release studies are based on this standard curve.

2. Preformulation:

Table no.11 physicochemical property of drug

Parameters	Results
Bulk density	0.508 gm/ml
Tapped density	0.680 gm/ml
Carr's index	25.29 %
Hausner's ratio	1.33
Angle of repose	39.19^0

From the physicochemical evaluation of pure drug as depicted in Table 11ss it was concluded that Candesartan cilexetil has angle of repose 39.19^0, Carr's index 25.29 % and Hausner's ratio 1.33 which indicate that Candesartan cilexetil has **very poor flow** property.

Particle size analysis of candesartan cilexetil :

Table No.12: Particle size analysis of candesartan cilexetil

Particle size distribution	Particle size (µm)	Particle size (µm)	Particle size (µm)	AVG
D (0.9)	10.46	10.44	10.45	10.45
D (0.5)	3.56	3.54	3.55	3.55
D (0.1)	1.05	1.06	1.05	1.05

Discussion: In order to assure consistent product quality, the particle size of the API has been characterized. From the above table it is observed that D (v, 0.9) means 90 % of the drug particles were smaller than 10.45 µm and D (v, 0.5) means 50 % of the given drug particles were smaller than 3.55 µm and D (v, 0.1) means 10 % of the given drug particles were smaller than 1.05 µm.

Solubility Profile: Table No.13

Media	Solubility (mg/ml)	Solubility (mg/900ml)
pH 1.2 Buffer	**0.0050**	**4.50**
pH 3.0 Buffer	0.0000	0.00
pH 4.0 Buffer	0.0010	0.90
pH 5.0 Buffer	0.0000	0.00
pH 6.8 Buffer	**0.0360**	**32.40**
Water	0.0000	0.00

Practically insoluble (soluble in ethanol).

2-butanone > acetone> 1-propanol > methanol > 2-propanol > acetonitrile.

Results of compatibility study:

Table No.14: Interpretation of FTIR spectra of physical mixture and Drug

Functional group	Characteristicic peaks of drug observed in IR region (Cm-1)	Characteristicic peaks of physical mixture observed in IR region (Cm-1)
-O-H Stretching	2800-2850	2800-2850
-C=O Stretching	1700-1750	1700-1750
-C-O Stretching	1200-1250	1200-1250
O-Substitution	700-750	700-750
Aromatic C-H Stretching	2850-2950	2850-2950

Candesartan cilexetil exhibits peak due to hydroxyl (2800-2850 cm^{-1}), ketone (1700-1750 cm^{-1}), carbonyl (1200-1250 cm^{-1}), O-substitution (700-750 cm^{-1}) and aromatic C-H (2850-2950 cm^{-1}) group. From Figure 4.8 it was observed that there were no changes in their main peaks in the FTIR spectra of physical mixture of drug and excipients. Hence, it was concluded that no physical or chemical interactions of Candesartan cilexetil with Carmellose and lactose.

Table No.15: Drug excipients compatibility study

Drug + Excipient	Ratio	25ºCº±2°C / 60%RH± 5 % RH	40ºC±2°C / 75%RH± 5 % RH
Drug (Candesartan)	1	4 Weeks	4 Weeks
Drug: Lactose (pharm-200)	1:10	4 Weeks	4 Weeks
Drug : PEG 6000	1:1	4 Weeks	4 Weeks
Drug : HPC Lf	1:1	4 Weeks	4 Weeks
Drug : Corn starch	1:1	4 Weeks	4 Weeks
Drug: CarmelloseCa	1:1	4 Weeks	4 Weeks
Drug : Mg Stearate	1:0.1	4 Weeks	4 Weeks
Drug+ physical mixture	Proportional Mixture	4 Weeks	4 Weeks

Table No.16 Result of Drug excipients compatibility study After 1 month at 40ºC±2°C / 75%RH± 5 % RH

Drug + Excipient	Initial Observation	After 1 month at
Drug (Candesartan)	A white to	Compatible
Drug: Lactose	A white to	Compatible
Drug : PEG	A white to	Compatible
Drug : HPC	A white to	Compatible
Drug : Corn starch	A white to	Compatible
Drug: CarmelloseCa	A white to	Compatible
Drug : Mg Stearate	A white to	Compatible
Drug+ All Excipients	A white to	Compatible

Preformulation Discussion:

Candesartan cilexetil has angle of repose 39.19^0, Carr's index 25.29 % and Hausner's ratio 1.33 which indicate that Candesartan cilexetil has very poor flow property.The particle size was matched with recommended particle size which was 5-15 µm.As observed from the results of FTIR studies,the drug and excipients were compatible and there was absence of any significant chemical interaction between drug and excipients.Candesartan cilexetil exhibits peak due to hydroxyl (2800-2850 cm^{-1}), ketone (1700-1750 cm^{-1}), carbonyl (1200-1250 cm^{-1}), O-substitution (700-750 cm^{-1}) and aromatic C-H (2850-2950 cm^{-1}) group.Characteristicic peaks of drug and physical mixture was observed in IR region. and determined that there was no any chemical interactions between the drug and excipients.

Formulation:

Results of physicochemical property and In-process quality control(IPQC) test:

The physicochemical properties of all the formulation were observed and recorded in the table no.5.7 and the evaluation of In-process parameters were determined and recorded in table no.5.8.

Table No.17: Physicochemical property of prepared granules:

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio -	Angle of repose (º)
F01	0.551±0.004	0.680±0.002	18.97±0.02	1.23±0.2	29.07±1.23
F02	0.562±0.003	0.690±0.002	18.55±0.02	1.22±0.3	27.32±1.36
F03	0.545±0.002	0.671±0.002	18.77±0.02	1.23±0.2	28.23±1.24
F04	0.517±0.004	0.679±0.002	23.85±0.02	1.31±0.3	31.12±1.72
F05	0.508±0.003	0.693±0.003	26.69±0.02	1.36±0.1	32.26±1.14
F06	0.513±0.003	0.695±0.002	26.18±0.01	1.35±0.2	26.96±1.15
F07	0.564±0.004	0.675±0.002	16.44±0.02	1.19±0.2	24.36±1.45
F08	0.583±0.002	0.686±0.001	15.01±0.02	1.17±0.2	26.32±1.83
F09	0.517±0.001	0.679±0.001	23.85±0.02	1.31±0.2	30.12±1.47
F10	0.581±0.003	0.689±0.003	15.67±0.02	1.18±0.3	28.12±1.57
F11	0.570±0.002	0.681±0.001	16.22±0.02	1.19±0.2	24.26±1.67
F12	0.586±0.001	0.697±0.002	15.92±0.02	1.18±0.3	23.96±1.35
F13	0.581±0.004	0.689±0.002	15.67±0.02	1.18±0.2	24.14±1.27
F14	0.579±0.003	0.675±0.003	14.22±0.02	1.16±0.2	22.36±1.33
F15	0.613±0.002	0.685±0.001	10.51±0.02	1.11±0.2	21.13±1.36
F16	0.583±0.003	0.686±0.002	15.01±0.02	1.17±0.2	24.45±1.47
F17	0.615±0.001	0.679±0.002	9.42±0.01	1.10±0.2	21.46±1.38

Table No.18: Evaluation parameters of Candesartan IR tablets

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)	D.T. (min)
F01	130 ± 3%	2.4 -2.8 ± 0.03mm	5-6 ±0.05	0.11	16-17
F02	130 ± 3%	2.4 -2.8 ± 0.03mm.	5-6 ±0.05	0.13	16-17
F03	130 ± 3%	2.4 -2.8 ± 0.03mm.	5-6 ±0.05	nil	16-17
F04	130 ± 3%	2.4 -2.8 ± 0.03mm.	5-6 ±0.05	nil	15-18
F05	130 ± 3%	2.4 -2.8 ± 0.03mm.	5-6 ±0.05	0.12	7-8
F06	130 ± 3%	2.4 -2.8 ± 0.03mm.	5-6 ±0.05	0.23	5-6
F07	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	nil	14-15
F08	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	0.11	13-14
F09	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	0.13	16-17
F10	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	nil	13-14
F11	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	nil	10-12
F12	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	0.07	8-9
F13	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	nil	11-12
F14	130 ± 3%	2.4 -2.8 ± 0.03mm.	4-5 ±0.05	0.05	10-11
F15	130 ± 3%	2.4-2.8 ± 0.03mm.	4-5 ±0.05	nil	12-13
F16	130 ± 3%	2.4-2.8 ± 0.03mm.	4-5 ±0.05	0.11	11-12
F17	130 ± 3%	2.4-2.8 ± 0.03mm.	4-5 ±0.05	nil	12-13

Preformulation Discussion:

Trial F01-03 batches were taken with different concentrations of PEG 6000. The batches were prepared by uniformly spraying the PEG 6000 (Concentration: 2% w/w) throughout the bed. The disintegration time(D.T.) of F01-F03 (16-17 min)was not in accordance with that observed in case of innovator (12-13 min).Trial FO4 was taken with 1:1 ratio of lactose and starch (Concentration : 38.87%w/w) to determine the effect of starch and lactose on compression parameters. This batch exhibited poor flow property and D.T. was observed to be 15-18 min. This may be probably due to incorporation of relatively higher amount of binder which resuts in formation of a strongly cohesive mass leading to formation of tablets that exhibit slow disintegration.[6] Hence, to increase the rate of disintegration i.e. in order to reduce the disintegration time,.Trial F05 was taken by decreasing the proportion of corn starch (Concentration :13.26%w/w) to control the disintegration time. Disintegration time was observed to be 7-8 min. in case of F05. Trial F06 was taken with omitting the starch from the intragranular part to control the D.T., Disintegration time was observed to be 5-6 min. in case of F06, and the granules had poor flow property because starch was not added in the intragranular part.

Trial F07 was taken with the starch to improve the flow property, however, the disintegration profile of the tablet was not found to be satisfactory (14-15 min). As compared to that of an innovator (12-13 min). Hence, it was decided to incorporate super disintegrant so as to obtain the desired disintegration time for the immediate release tablet. CarmelloseCa was added intragranularly to control the D.T. and bring it close to the standard D.T. values observed in case of innovator.

Trial F08 to F10 batches were formulated for optimization of the binder quantity. 3-6% w/w concentrations of HPC-Lf were taken.From these, tablets prepared using HPC (Concentration: 6%) did not exhibit acceptable disintegration profile and had poor flow property because of high binder concentration in case of trial F09. It was observed that tablets incorporated with HPC-Lf at concentration of 3.45%w/w exhibited better D.T (13-14 min) and good flow property (Carr's index 15.67, hausner's ratio 1.18 and angle of repose 28) in case of trial F10.

Trial **F11 to F13** batches were taken for optimization of the disintegrant quantity.2.5-6.23%w/w concentrations in intragranular part and 2.5-3%w/w concentrations in exragranular part of carmellose Ca were taken. From these tablets prepared using Carmellose (Concentration: 6.23%) exhibited fast disintegration (8-9 min) in case of trial F12. It was observed that tablets incorporated with Carmelloseca at concentration of 2.5%w/w in both the parts exhibited better D.T (11-12 min)in case of F13. The disintegrant quantity was optimized 2.5%w/w in both the parts.

Studies had shown that magnesium Stearate may affect the release time of the active ingrediants.Hence, to study the rate of disintegration ,**Trial F14 to F16** was taken with proportion of magnesium stearate (Concentration :0.3-3%w/w) to determine the effect on release time and disintegration time.[11]Trial code F14 was taken with higher lubricant quantity(Concentration:3%) exhibited disintegration(10 min) not in accordance with that observed in case of innovator (12-13 min). Trial code F15 was taken with lubricant quantity(Concentration:1%) exhibited disintegration(12-13 min) in accordance with that observed in case of innovator (12-13 min),So furthure to determine the reproducibility of the batch we had taken the trial code F17.That was the optimized formula.

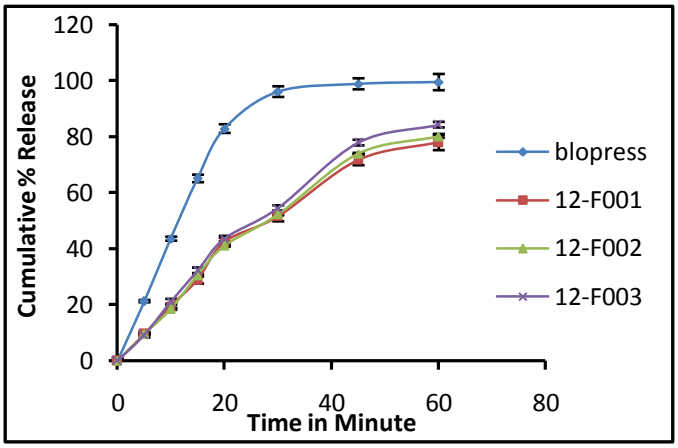

Figure 11: *In-Vitro* drug release of trial batches F01-03 in pH= 6.8

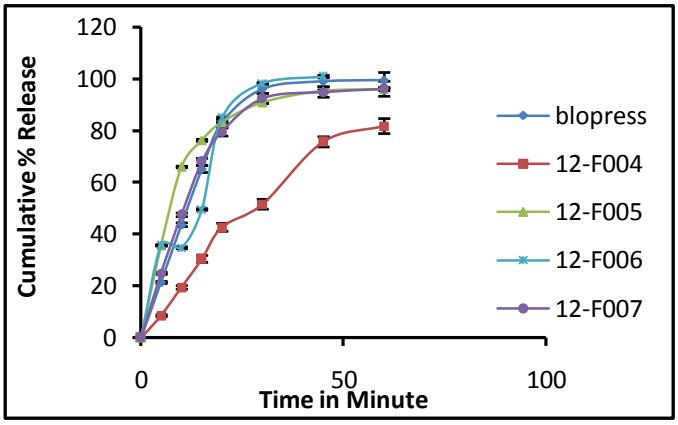

Figure12: *In-Vitro* drug release of trial batches F04-07in pH= 6.8

Table 19 Result of *In-Vitro* drug release of trial batches F01-F07 in pH=6.8 buffer

Time (Min)	Innovator	F01	F02	F03	F04	F05	F06	F07
5	21.3±0.3	9.6±0.4	9.6±0.3	9.3±0.5	8.45±0.11	35.6±0.17	35.6±0.5	24.8±0.18
10	43.6±0.71	19.6±0.71	18.5±0.70	21.1±0.69	19.4±0.31	65.9±0.38	34.7±0.70	47.4±0.60
15	**65.1±1.33**	**28.9±1.34**	**30.5±1.31**	**32.3±1.30**	**30.4±0.42**	**76.2±0.41**	**49.5±1.22**	**67.9±0.95**
20	82.9±1.51	42.4±1.54	41.2±1.52	43.6±1.51	42.6±0.32	83.1±0.37	84.8±1.56	79.4±1.53
30	**96.1±1.8**	**51.7±1.9**	**52.4±1.8**	**54.5±1.6**	**51.5±0.45**	**90.8±0.55**	**98.2±1.80**	**92.4±0.87**
45	**98.9±0.64**	**71.8±1.97**	**73.9±1.87**	**77.9±1.91**	**75.6±0.34**	**95.2±0.56**	**100.8±1.9**	**94.8±0.64**
60	**99.5±0.54**	**78.1±2.9**	**80.1±2.1**	**84.3±2.1**	**81.7±0.51**	**95.9±0.52**		**96.1±0.59**
F2		***20.65***	***21.57***	***23.38***	***21.72***	***38.97***	***51.79***	***71.51***

Table 20: Result of *In-Vitro* drug release of trial batches F08-F13 in pH=6.8 buffer

Time (Min)	Innovator	F08	F09	F10	F11	F12	F13
5	21.3±0.3	18.5±0.11	17.1±0.71	25.1±0.55	25.1±0.10	35.6±0.4	19.5±0.11
10	43.6±0.71	38.2±0.31	35.7±1.34	45±0.42	45±0.34	34.7±0.71	48.4±0.31
15	**65.1±1.33**	**52.4±0.42**	**49.8±1.54**	**60.3±1.32**	**61.3±0.46**	**49.5±1.34**	**63.7±0.42**
20	82.9±1.51	65.7±0.32	64.4±1.90	74.1±1.54	74.1±0.54	84.8±1.54	74.4±0.34
30	**96.1±1.8**	**83.5±0.45**	**81.5±1.76**	**88.6±1.9**	**86.6±0.78**	**98.2±1.9**	**89.4±0.43**
45	**98.9±0.64**	**90.3±0.34**	**89.9±1.25**	**93.7±1.97**	**92.7±0.65**	**100.8±0.9**	**99.4±0.53**
60	**99.5±0.54**	93.4±0.55	91±0.45	95.8±2.90	95.8±0.32		100.5±0.5
F2		***46.95***	***42.41***	***60.95***	***57.8***	***51.79***	***69.43***

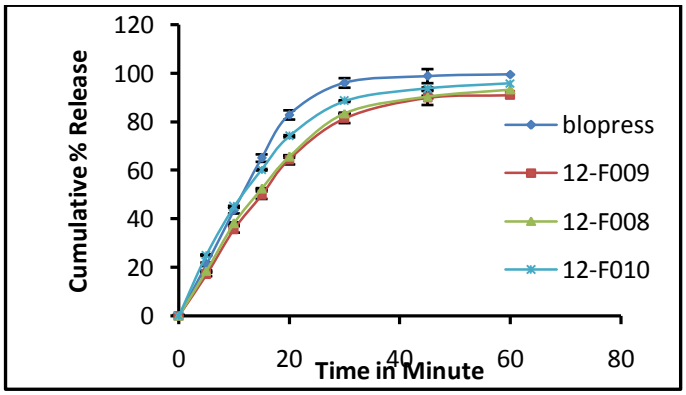

Figure 13: In-*Vitro* drug release of trial batches F08-10 in pH= 6.8

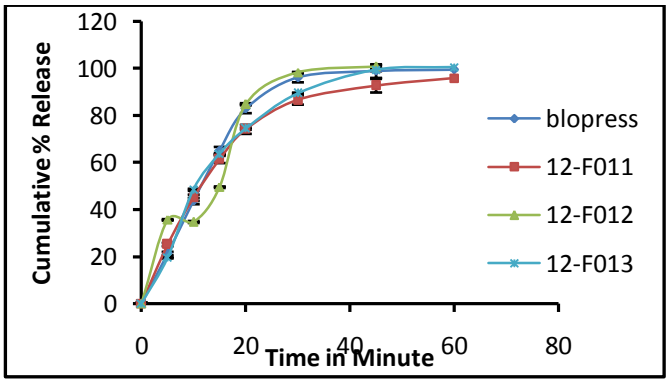

Figure 14: *In-Vitro* drug release of trial batches F11-13in pH=6.8

Table 21: Result of *In-Vitro* drug release of trial batches F14-F17 in pH=6.8 buffer

Time (Min)	Innovator	F14	F15	F16	F17
5	21.3±0.3	19.6±0.4	21.8±0.11	18.7±0.6	21.8±0.11
10	43.6±0.71	46.4±1.1	43.4±0.31	40.4±1.3	43.4±0.31
15	**65.1±1.33**	**63.7±0.71**	**64.9±0.41**	**63.7±1.41**	**64.9±0.42**
20	82.9±1.51	79.6±1.54	80.4±0.32	79.4±1.63	80.4±0.32
30	**96.1±1.8**	**97.1±1.8**	**95.4±0.43**	**94.9±1.34**	**95.4±0.45**
45	**98.9±0.64**	**97.6±1.78**	**98.2±0.31**	**96.4±1.67**	**98.2±0.34**
60	**99.5±0.54**	99.9±2.1	99.9±0.52	98.3±1.97	99.9±0.51
F2		***89.83***	***96.82***	***84.37***	***98.86***

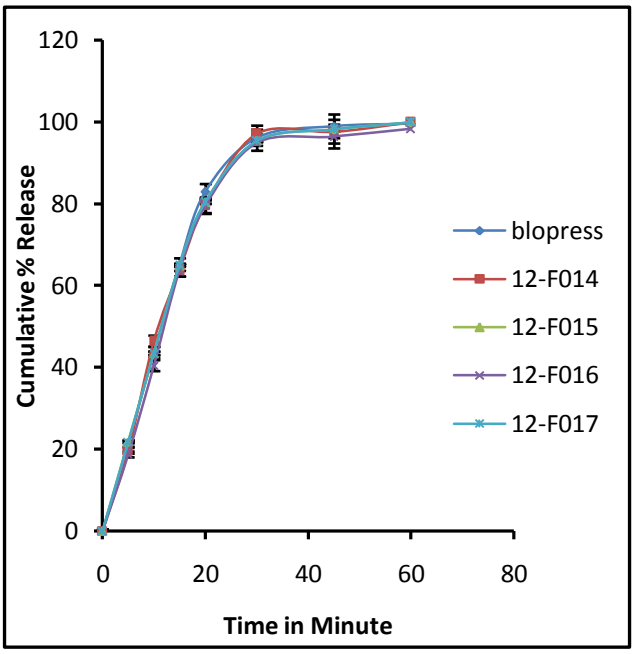

Figure 15: *In-Vitro* drug release of trial batches F14-17in pH= 6.8

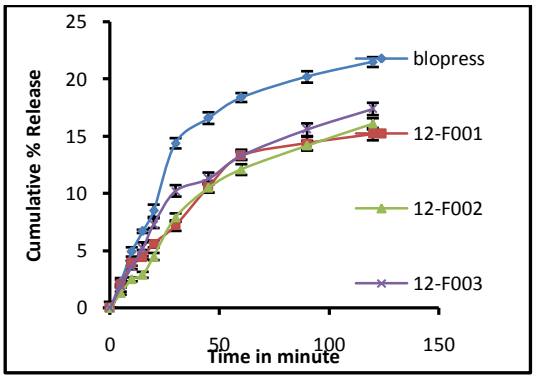

Figure 16: *In-Vitro* drug release of trial batches F01-03 InpH= 1.2

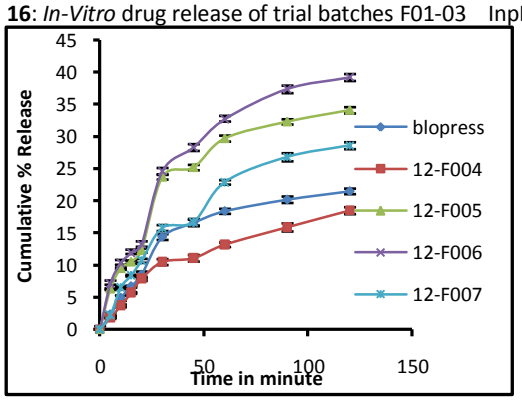

Figure 17: *In-Vitro* drug release of trial batches F04-07in pH= 1.2

Table 22: Result of *In-Vitro* drug release of trial batches F01-F07 in pH=1.2 buffer

Time (Min)	Innovator	F01	F02	F03	F04	F05	F06	F07
5	2.3±0.11	2±0.32	1.3±0.13	1.9±0.15	1.8±0.17	6.3±0.11	7.1±0.13	2.2±0.32
10	4.9±0.21	3.9±0.41	2.5±0.17	3.6±0.16	3.7±0.42	9.5±0.27	10.3±0.17	6.5±0.41
15	**6.7±0.13**	**4.4±0.14**	**2.9±0.26**	**5.2±0.28**	**5.7±0.65**	**10.5±0.38**	**11.9±0.26**	**8.4±0.14**
20	8.5±0.31	5.6±0.54	4.5±0.31	7.3±0.35	7.9±0.76	12.3±0.42	13.2±0.34	10.7±0.54
30	**14.4±0.46**	**7.2±0.45**	**7.9±0.37**	**10.2±0.41**	**10.5±0.46**	**23.7±0.58**	**24.6±0.45**	**15.8±0.45**
45	**16.6±0.51**	**10.6±0.51**	**10.5±0.42**	**11.3±0.51**	**11.1±0.65**	**25.2±0.68**	**28.3±0.41**	**16.7±0.51**
60	**18.4±0.35**	**13.3±0.39**	**12.1±0.47**	**13.3±0.45**	**13.2±0.36**	**29.7±0.78**	**32.7±0.45**	**22.9±0.39**
90	20.2±0.63	14.4±0.5	14.2±0.41	15.6±0.67	15.9±0.66	32.3±0.54	37.4±0.49	26.8±0.50
120	21.5±0.49	15.2±0.54	16.1±0.54	17.4±0.47	18.5±0.38	34.1±0.51	39.2±0.41	28.6±0.43
F2		***59.75***	***58.54***	***64.76***	***64.83***	***49.79***	***45.0***	***75.70***

Table 23: Result of *In-Vitro* drug release of trial batches F08-F13 in pH= 1.2Buffer

Time (Min)	Innovator	F08	F09	F10	F11	F12	F13
5	2.3±0.11	6±0.13	8.5±0.11	3.6±0.32	6.9±0.12	7.1±0.13	2.4±0.29
10	4.9±0.21	9.2±0.17	12.5±0.21	7.5±0.41	9.9±0.18	10.3±0.22	6.8±0.45
15	**6.7±0.13**	**11±0.26**	**15.4±0.13**	**9.6±0.14**	**11.7±0.24**	**11.9±0.15**	**8.9±0.16**
20	8.5±0.31	12.3±0.31	17.3±0.31	11.2±0.54	12.8±0.35	13.2±0.34	10.5±0.53
30	**14.4±0.46**	**13.6±0.37**	**19.3±0.46**	**13±0.45**	**13.6±0.41**	**14.6±0.46**	**11.3±0.46**
45	**16.6±0.51**	**14.5±0.42**	**19.5±0.51**	**14.2±0.51**	**17.2±0.45**	**17.3±0.53**	**14.4±0.51**
60	**18.4±0.35**	**15±0.47**	**19.8±0.35**	**15±0.39**	**18.4±0.49**	**20.3±0.38**	**14.6±0.39**
90	20.2±0.63	15.9±0.41	21.4±0.63	16.4±0.5	20.5±0.43	22.6±0.68	16.2±0.5
120	21.5±0.49	17.1±0.49	22.9±0.54	18.8±0.43	22.6±0.47	24.4±0.52	17.3±0.42
F2		***72.4***	***60.59***	***74.75***	***75.36***	***73.58***	***72.8***

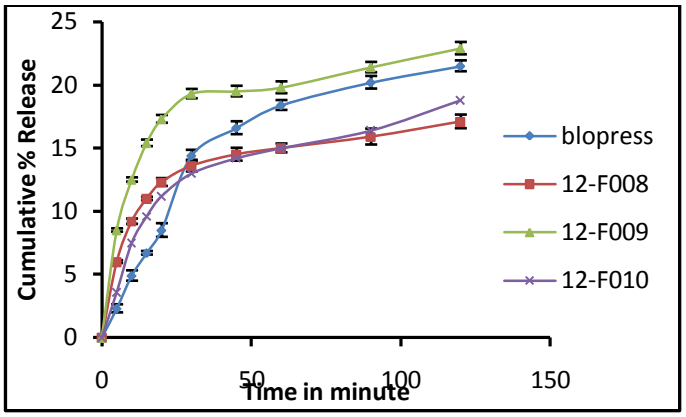

Figure 18: *In-Vitro* drug release of trial batches F08-10 inpH= 1.2

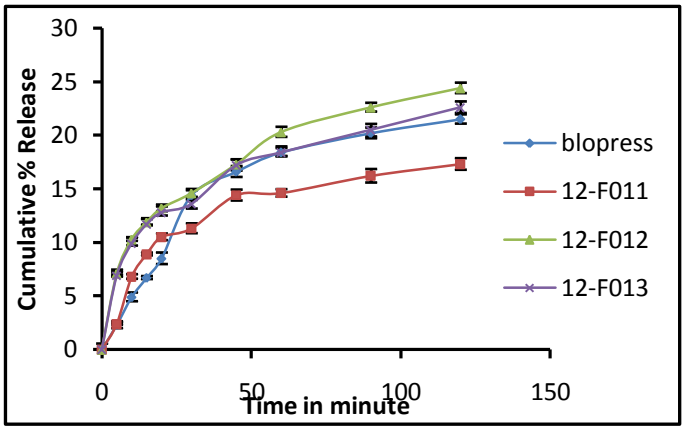

Figure 19*: In-Vitro* drug release of trial batches F11-13in pH=1.2

Table 24: Result of *In-Vitro* drug release of trial batches F14-F17 in pH= 1.2 buffer

Time (Min)	Innovator	F14	F15	F16	F17
5	2.3±0.11	6.2±0.32	2.2±0.11	6±0.13	2.2±0.11
10	4.9±0.21	9.8±0.41	4.8±0.23	9.2±0.16	4.8±0.21
15	**6.7±0.13**	**11.5±0.14**	**6.5±0.12**	**11.2±0.25**	**6.5±0.13**
20	8.5±0.31	12.9±0.54	8.4±0.34	12.3±0.32	8.4±0.31
30	**14.4±0.46**	**14.2±0.45**	**14.2±0.44**	**13.5±0.45**	**14.2±0.46**
45	**16.6±0.51**	**17.2±0.51**	**16.4±0.53**	**14.7±0.53**	**16.4±0.51**
60	**18.4±0.35**	**19.9±0.39**	**18.3±0.37**	**15.9±0.38**	**18.3±0.35**
90	20.2±0.63	22.2±0.5	20±0.64	15.9±0.41	20±0.63
120	21.5±0.49	23.4±0.43	21.3±0.49	17.1±0.49	21.3±0.43
F2		***75.48***	***99.53***	***73.66***	***99.53***

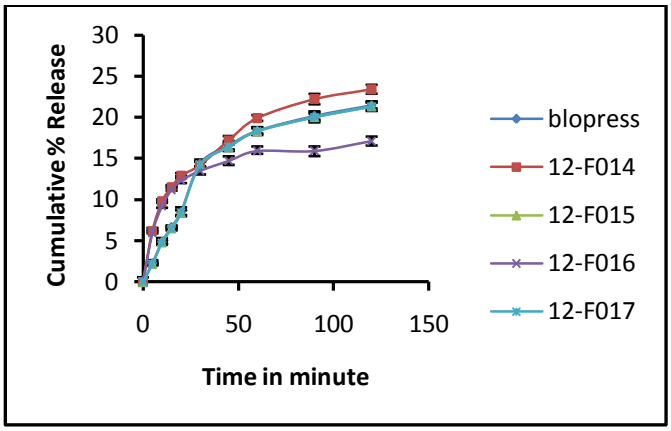

Figure 20: *In-Vitro* drug release of trial batches F11-13in pH= 1.2

Discussion:

From the dissolution study, we had determined that F17 was optimized formula and it was complies with the blopress innovator profile. In pH=1.2 buffer we could not obtain 85% release in 15-30 min. As per the guideline (1) if <50% drug release was obtained in 30-120 min the requirement of F2 is >51 and the time points 15, 30, 45 and 60 min was seen. In pH= 6.8 we obtained 85% release in 15-30 min. So as per the guideline (1) we had compared time points 15, 30 and 45 min. As mentioned in guideline, the value of similarity factor F2 is >42 for phosphate buffer pH=6.8, which was matched with optimized batch F17. Above all the requirements was complies with the F17 batch, so that was the optimized formulation.

Stability Study:

From the given stability data at 40°C/75%RH, it reveals that the product is stable at 40°C /75 % RH for 4 weeks (1 month).

In present investigation, F1-F17 were prepared using HPC and PEG as binder and carmellose as disintegrant. From result it was found that the granule prepared had angle of repose (23.55±0.50 to 28.45±0.64), Hausner's ratio (1.07±0.03 to 1.15±0.03) and Carr's index (7.04±0.04 to 14.4±0.02), which shows good flow property and compressibility of granules. Tablets of all batches show good hardness (4±0.09 to 5±0.06), friability (0.11±0.09 to 0.23±0.05) and All the formulations were evaluated for *in vitro* drug release in pH= 6.8 buffer and pH=1.2 buffer, over a period of 1-2 hours using USP type II dissolution apparatus at 50 rpm. The dissolution profiles of the batches were compared with that of innovator product. Among the entire formulations F010 batch showed matching *in vitro* drug release to that of innovator. Batch F010 was charged for stability. After 1 months of stability study, samples were withdrawn and tablet showed nochange physical appearances, drug release which indicate that the formulation was stable. Hence anti-hypertensive Drug can be successfully formulated as immediate release tablet.

Table 25: One month stability data

Test	Specifications	Initial	Period in Months 1
Description	Orange colored, round shaped uncoated tablets.	Complies	Complies
Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies
Hardness (kp)	Between 4± 0.05 -5± 0.05	4-5	4-5.5
Thickness (mm)	2.4± 0.03mm -2.8 mm ± 0.03mm.	2.4-2.8 mm ± 0.03mm.	2.4-2.8 mm ± 0.03mm.
Dissolution			
5 Min	As per the JP Specification	21.3%	21.8%
10 Min.		43.6%	43.4%
15 Min.		65.1%	64.9%
20 Min.		82.9%	82.4%
30 Min.		96.1%	95.4%
45 Min.		98.9%	98.2%
60 Min.		99.5%	99.9%

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