www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 4(1): 25-32

www.thepharmajournal.com
Received: 09-01-2015
Accepted: 15-02-2015

B.Venkateswara Reddy
M.Pharm., Ph.D., MBA,
Department of Pharmaceutics,
St.Paul's College of Pharmacy,
Turkayamjal (V), Hayathnagar (M), R.R.Dist-501510, India

K. Navaneetha
M.Pharm.,
Department of Pharmaceutics,
St.Paul's College of Pharmacy,
Turkayamjal (V), Hayathnagar (M), R.R.Dist-501510, India

Correspondence:
B.Venkateswara Reddy
M.Pharm., Ph.D., MBA,
Associate professor and HOD,
Department of Pharmaceutics,
St.Paul's College of Pharmacy,
India

Formulation and evaluation of Orodispersible tablets of candesartan

B.Venkateswara Reddy*, K. Navaneetha

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. It was formulated as an orodispersible tablet as there is a need to develop a formulation for this drug which overcomes problem such as difficulty in swallowing, inconvenience in administration while traveling and better compliance. Candesartan Cilexetil orodispersible tablets were prepared by coprocessed super disintegrants like Indion 204, Tulsion 339 and Primogel. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement. A total of 12 formulations were prepared and evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, carr's index, hausner's ratio, weight variation, hardness, friability, thickness, wetting time, water absorption ratio, drug content, *in vitro* disintegration time, *in vitro* drug release. The *in vitro* disintegration time of the optimized formulation (F9) of Candesartan was found to be 10 sec. Release rate of drug was 99.3% within 8 minutes. Thus the formulation (F9) containing Indion 204 and Tulsion 339 in 1:1 ratio were found to increase patient compliance.

Keywords: Candesartan Cilexetil, Orodispersible, Antihypertension, Co-Processed super disintegrants, Indion 204, Tulsion 339, Primogel.

1. Introduction
The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water [1].
For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people [2].
An orally disintegrating tablet (ODT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed from Mouth [3].
US FDA defined ODT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".
Recently European Pharmacopoeia used the term 'Orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing [4].
Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet [5].
Candesartan Cilexetil [6-8] is an angiotensin Π type-I (ATI) receptor antagonist which is used in the treatment of hypertension and congestive heart failure [9]. It shows biological half-life of 9 hrs and bioavailability of 15%, Candesartan is having low solubility so by adding suitable super disintegrants we can improve the solubility and there by bioavailability.
Co-Processed super disintegrants technology is used to increase the water uptake with shortest wetting time and thereby decrease the disintegration time. The drug is formulated as orodispersible delivery system to improve the patient acceptance and compliance for those having difficulty in swallowing.

2. Materials and Methods

2.1. Materials

Candesartan Cilexetil was obtained as a gift sample from Hetero drugs, India. Tulsion 339, Indion 204, Primogel(SSG), Micro Crystalline cellulose, Magnesium Stearate and Talc were purchased from Merck specialities Pvt. Ltd, Mumbai, India.

2.2. Methods

Drug- Excipient Compatibility Study

The Infrared spectra of Candesartan pure drug, physical mixture of drug and excipients (Optimized formula) were recorded between 400 and 4000 cm^{-1}. The IR spectra were obtained using KBr disk method using an FTIR spectrophotometer.

Preparation of Candesartan Cilexetil Orodispersible Tablets

Different formulations of Candesartan cilexetil orodispersible tablets were designed to be prepared by direct compression technique by employing co processed super disintegrants using three super disintegrants, Indion 204, Tulsion 339 and Primogel. Before formulation, mixing of three super disintegrants in following ratios (i.e., 1:0.1, 1:0:2, 0:1:1, 0:2: 1, 1:1:0, 1:2:0) and are assigned with formulation codes shown in Table-1.

Table 1: Formulation codes

Ingredients	CP1	CP2	CP3	CP4	CP5	CP 6
Indion 204	100 mg	100 mg	-	-	100 mg	100 mg
Tulsion 339	-	-	100 mg	200 mg	100 mg	200 mg
Primogel	100 mg	200 mg	100 mg	100 mg	-	-

Procedure

CP1, CP2, CP3, CP4, CP5, CP6 were accurately weighed and passed through a 40-mesh screen to get uniform size particles and each of which is mixed in a glass mortar for 15 minutes. The drug, superdisintegrant mixture and micro crystalline cellulose PH102 were weighed accordingly as mentioned in table-2. The mixture is then mixed thoroughly in mortar. The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using 6 mm round flat faced punch of rotary tableting machine. Compression force was kept constant for all formulations. Same procedure is followed for all the 12 formulations.

Table 2: Composition of candesartan cilexetil orodispersible tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	16	16	16	16	16	16	16	16	16	16	16	16
CP1	8	16	-	-	-	-	-	-	-	-	-	-
CP2	-	-	8	16	-	-	-	-	-	-	-	-
CP3	-	-	-	-	8	16	-	-	-	-	-	-
CP4	-	-	-	-	-	-	8	16	-	-	-	-
CP5	-	-	-	-	-	-	-	-	8	16	-	-
CP6	-	-	-	-	-	-	-	-	-	-	8	16
Mg.sterate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
MCC PH 102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight of tablet(mg)	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation

Precompression Parameters [10-12]

The powder blend of the formulations is subjected to evaluation for bulk density, tapped density, hausner's ratio, carr's index and angle of repose to determine the characteristics of powder blend.

Post compression evaluation

Weight variation test [13]

20 tablets were randomly selected from each formulation and their individual weights and average weight of all 20 tablets was calculated by weighing on an electronic balance (Shimadzu, AUX 220, Shimadzu Corp, Japan). The Mean ± S.D. were noted.

Table 3: Weight Variation Limits

IP/BP	Limit	USP
80 mg or less	10%	130 mg or less
>80 mg or< 250 mg	7.5%	130 mg to 324 mg
250 mg or more	5%	More than 324 mg

Thickness [14]

Randomly 10 tablets were taken from each formulation and their thickness was measured using a digital Micrometer (Mitutoyo Corp, Kawasaki, Japan). Average thickness and standard deviation values were calculated. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness [14]

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The hardness for ODTs should be preferably 2.5 to 3 kg/cm^2.

Friability [15]

This test was performed using a laboratory friability tester known as Roche friabilator. 20 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were de - dusted and reweighed. Percentage loss of tablet weight was calculated. Friability values below 1% are generally acceptable.

$$\% \, Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 = Initial weight of 20 tablets, W_2 = Final weight of 20 tablets.

Drug Content [16]

10 tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml of 6.8 pH phosphate buffer in a conical flask. A conical flask was then placed on a rotary shaker. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22 µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible double beam spectrophotometer at a wavelength of 256 nm against 6.8 pH phosphate buffer as blank. Concentrations and amount of drug present in one tablet were calculated with the help of calibration curves.

Wetting Time [15-16]

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The wetting time was recorded using a stopwatch.

Water Absorption Ratio (R) [15-16]

The weight of the tablet before keeping in the petridish was noted (W_b) using digital balance. The wetted tablet from the petridish was taken and reweighed ($W_{a`}$) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

W_a= Weight of the tablet after absorption, W_b= Weight of the tablet before absorption.

***In-vitro* Dispersion Time** [15-16]

In-vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5 °C and the time required for complete dispersion was determined. To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

***In-vitro* Disintegration Time** [15-16]

The disintegration time was measured using disintegration apparatus. One Tablet was placed in each tube of the basket. The basket with bottom surface made of a stainless steel screen (mesh no. 10) was immersed in water bath at 37 ± 2 ^{0}C. The time required for complete disintegration of the Tablet in each tube was determined using stop watch.

***In-vitro* Dissolution Studies** [16]

Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900 ml) and was maintained at 37 ± 1 ^{0}C. Samples of 5 ml were withdrawn at predetermined intervals (2, 4, 6, 8, 10, 20, 30, 45, 60 min) filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 256 nm by using ultra violet double beam spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

3. Results and Discussion

3.1. Fourier Transform Infrared Spectroscopy (FTIR)

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients.

The wave number of mixture of drug with excipients is within the range of wave number of pure drug. This implies that the excipients are compatible with the drug since their combination did not alter the functional groups of pure drug.

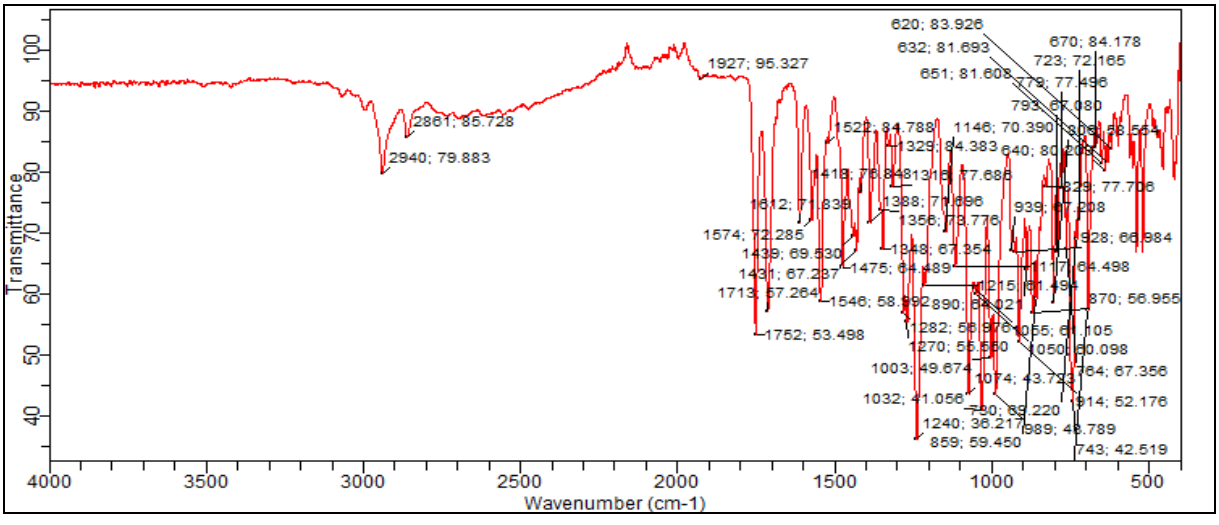

Fig 1: FTIR spectrum of drug (Candesartan Cilexetil)

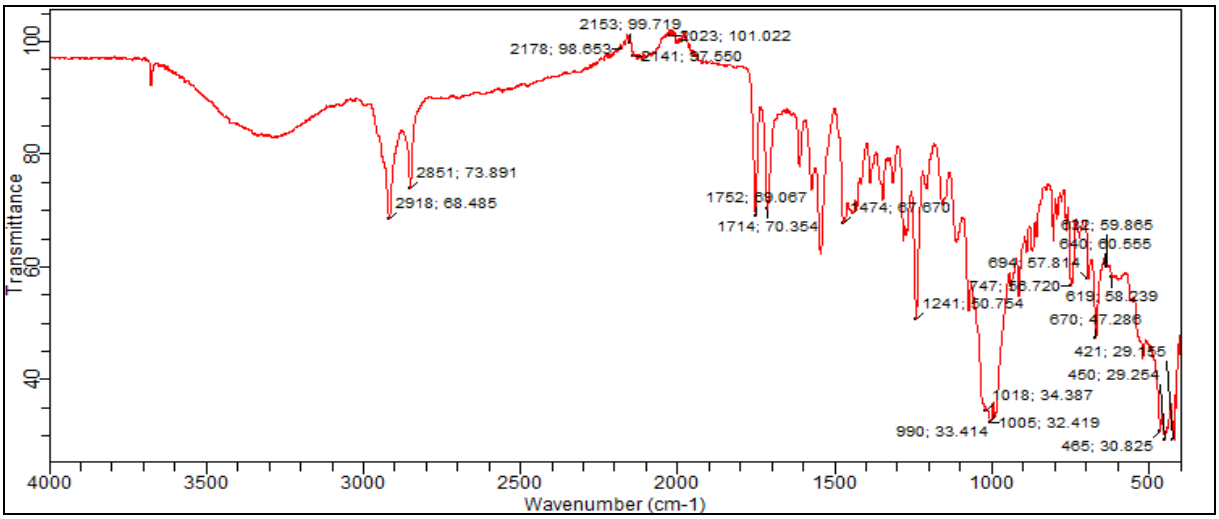

Fig 2: FTIR spectrum of optimized formulation

3.2. Evaluation of Pre - Compression Parameters of Powder Blend

The bulk density of all formulations was found in the range of (0.43±0.04 to0.61±0.02**)** and tapped density was in range of (0.49±0.04 to 0.68±0.03**)**. The carr's index and hausner's ratio was calculated from tapped density and bulk density. The powder blend of all six formulations with hausner's ratio < 1.2 and carr's index < 18 indicates good flow ability of all powder blends The flow properties for all the powder blends were good as evidentially proved by the angle of repose values obtained, which ranged between (25° – 30°) which is less than 30° as greater than 30° [has] poor flow ability which has been observed in case of pure drug. The results are given in the table 4.

Table 4: Evaluation of pre-compression parameters of powder blend

Formulation	Bulk Density* (g/ml)	Tapped density* (g/ml)	Carr's index* (%)	Angle of Repose* (θ)	Hausner's ratio*
F 1	0.43±0.04	0.49±0.04	13.95	25±0.04	1.13±0.01
F2	0.49 ±0.03	0.55±0.03	10.90	27±0.08	1.12±0.02
F3	0.48 ±0.02	0.53 ±0.04	9.43	26±0.03	1.10±0.03
F4	0.50 ±0.04	0.58±0.04	13.79	27±0.04	1.16±0.05
F5	0.46±0.05	0.53±0.01	13.20	29±0.12	1.15±0.04
F6	0.48±0.03	0.56±0.02	14.28	27±0.08	1.16±0.04
F7	0.56 ±0.01	0.63 ±0.06	11.11	29±0.11	1.12±0.02
F8	0.61±0.02	0.68±0.03	10.29	26±0.007	1.11±0.06
F9	0.56±0.05	0.63±0.02	11.11	25±0.03	1.12±0.04
F10	0.57±0.03	0.64±0.05	10.93	28±0.04	1.12±0.02
F11	0.48 ±0.03	0.55±0.04	12.72	29±0.05	1.14±0.01
F12	0.45±0.02	0.53±0.02	15.09	28±0.08	1.17±0.02

Results are the mean of 3 observations ± SD

3.3. Evaluations of Post Compression Parameters of Candesartan Odts

Weight Variation and Thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 4.3. The average tablet weight of all the formulations was found between **(**96.7-105.3**)**. The maximum allowed percentage weight variation for tablets weighing 80-250 mg by I.P is 7.5% and no formulations are exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P.

Hardness

All the ODT formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in Table 4.3. The average hardness for all the formulations was Found to be between (2.0±0.03 to 2.5 ±0.03) Kg/cm^2 which was found to be acceptable.

Friability

Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the ODT formulations were evaluated for their percentage friability using roche friabilator and the results are shown in table 4.3. The average percentage friability for all the formulations was between (0.41% and 0.65 %), which was found to be within the limit.

Drug Content

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 4.3. The assay values for all the formulations were found to be in the range of (95.13 ±0.13 to101.05 ±0.16). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the ODT formulations comply with the standards given in IP.

***In-vitro* Disintegration Time**

In vitro disintegration studies showed from10 to 15 secs. These results indicate that increasing the concentration of super disintegrates in the tablets results in the formation of more cohesive tablets that are less likely to break up or dissolve easily in water.

Wetting Time

Wetting time corresponds to the time required to wet completely when kept motionless on the tissue paper in a petridish. All the ODT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown in table 4.4. The average wetting time for all the formulations was in the range of (7 to 12) seconds. It was also observed that formula F9 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

***In-vitro* Dispersion Time**

Candesartan ODTs F9 containing CP5 dispersion time is 13secs .The dispersion time of formulations (F9) containing CP5 was lower than those containing CP1, CP2, CP3, CP4, CP6 which might be attributed due to its rapid water absorbing nature and delayed dispersion time for other super disintegrants due to their tendency to gel more than f-melt. The *in vitro* dispersion time for all formulation was found to be in a range of 13 to 18 seconds.

Water Absorption Ratio

All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown in table 6. The maximum water absorption ratio was shown by formulation F9 **(**97%). Water absorption ratio is proportional to dissolution rate profile as higher the water absorption ratio faster the dissolution.

Table 5: Evaluation of post compression parameters of Candesartan orodispersible tablets

Formulation	Weight variation*	Thickness (mm)**	Hardness Kg/cm^{2***}	%Friabilit*	Drug content***
F1	98.2	2.84± 0.07	2.0 ±0.03	0.54±0.07	95.13 ±0.13
F2	98.6	2.94 ±0.08	2.3 ±0.06	0.58±0.05	98.41 ±0.18
F3	101.3	2.81 ±0.10	2.5±0.03	0.53 ±0.08	97.34 ±0.22
F4	100.8	2.86 ±0.06	2.4 ±0.04	0.49 ±0.08	98.56± 0.15
F5	96.7	3.0 ±0.06	2.1 ±0.04	0.52 ±0.04	99.32 ±0.25
F6	102	3.12 ±0.08	2.3±0.06	0.49 ±0.04	101.05 ±0.16
F7	105.3	3.10±0.04	2.2±0.08	0.65±0.05	95.13±0.35
F8	97.8	2.86±0.03	2.3±0.05	0.63±0.03	96.23±0.42
F9	99.8	2.82±0.05	2.4±0.03	0.41±0.07	99.86±0.51
F10	97.8	2.84±0.03	2.3±0.04	0.61±0.06	97.53±0.34
F11	98.3	3.11±0.02	2.2±0.05	0.58±0.03	98.92±0.23
F12	99.3	3.18±0.04	2.3±0.02	0.64±0.08	96.77±0.41

* Results are the mean of 20 observations ± SD,

**Results are the mean of 10 observations ± SD

***Results are the mean of 3 observations ± SD

Table 6: Evaluation of post compression parameters of Candesartan orodispersible tablets

Formulation	Disintegration time(seconds)	Wetting time (seconds)	In vitro dispersion time*(sec)	%Water absorption ratio
F1	15	12	18	90
F2	14	10	17	92
F3	15	12	18	95
F4	13	10	16	94
F5	12	9	15	95
F6	11	8	14	91
F7	15	12	18	89
F8	12	9	15	96
F9	10	7	13	97
F10	11	8	15	90
F11	12	9	15	92
F12	14	10	17	94

***In-vitro* Drug Release Studies**

The % drug release for the formulations F1, F2 prepared by CP1 (Indion 204 and Primogel 1:1) at 10 min were found to be (95.55 and 96.21), formulations F3 and F4 prepared by CP2 (Indion 204 and Primogel (1:2)) at 10 min were found to be (96.8 and 97.63), formulations F5 and F6 prepared by CP3 Primogel and Tulsion 339 1:1) at 10 min were found to be (97.03 and 98.41), formulations F7 and F8 prepared by CP4 (Primogel and Tulsion 339 (1:2)) at 10 min were found to be (96.5 And 97.2), formulations F9 and F10 prepared by CP5 (Indion 204 and Tulsion 339 (1:1)) at 8 min were found to be (99.3 and 98.20), formulations F11 and F12 prepared by CP6 (Indion 204 and Tulsion 339 (1:2)) at 8 min were found to be (97.59 and 98.1).

Among all the formulations F9 formulation showed maximum drug release in 8 minutes i.e. around 100% so F9 formulation is an optimized formula.

Table 7: *In-vitro* dissolution profile for the formulations

Time (min)	Cumulative % drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
2	22.32	24.23	20.34	21.6	30.41	30.76	29.17	28.12	35.15	31.81	32.51	33.57
4	40.95	42.33	37.5	31.81	51.32	55.72	50.62	58.53	62.05	56.77	55.37	54.8
6	67.32	69.45	63.98	64.33	65.91	73.47	69.08	79.10	87.71	84.19	80.15	82.3
8	83.32	86.57	80.35	84.57	81.21	84.19	84.19	82.41	99.3	98.20	97.59	98.1
10	95.55	96.21	96.8	97.63	97.03	98.41	96.5	97.2	-	-	-	-

Comparison of Innovator Tablet (Candesar 16 mg) With Optimized Formulation

The innovator product of candesartan cilexetil, Candesar 16 mg was taken and evaluated for various parameters**.**

Physical Characterization of Marketed Product

The marketed product was physically characterized.

Average Weight (mg) 105

Thickness (mm) 2.4 ± 0.03 mm-2.8 mm±0.03 mm

Hardness (Kg/cm$^{2)}$ 2.4-2.6

Friability (%w/w) 0.8%

Disintegration time (min.) 5 min

Table 8: *In vitro* dissolution study of Optimized formulation and Innovator product

Time(min)	Cumulative % drug release	
	Optimized formulation F9	Innovator product
2	35.15	8.54
4	62.05	15.68
6	87.71	24.91
8	99.3	31.32
10	-	40.52

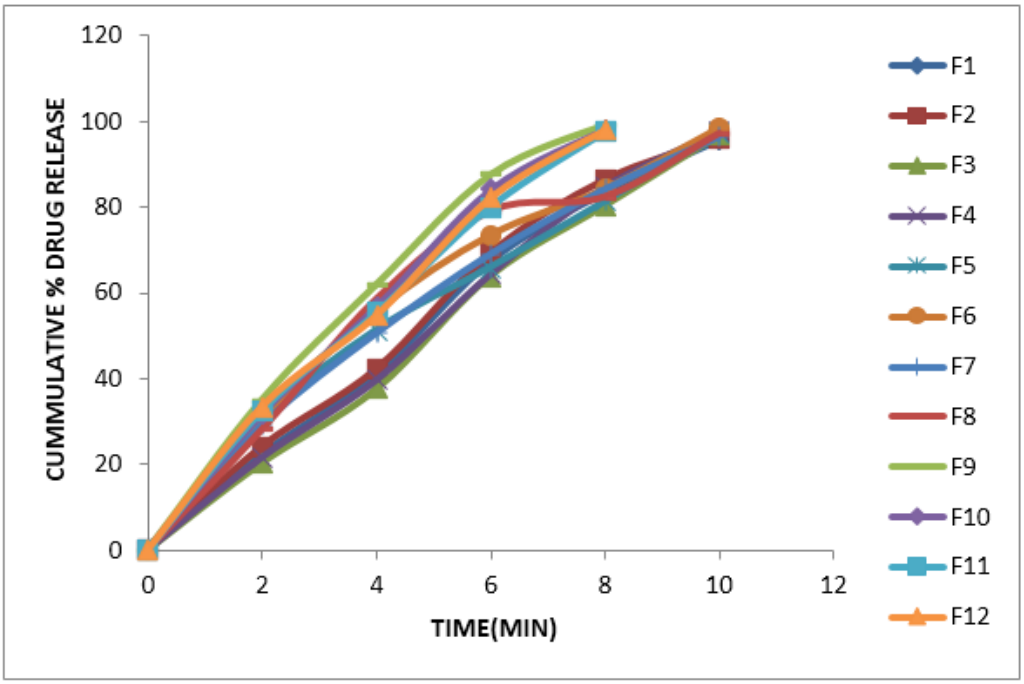

Fig 3: Comparative dissolution profile of formulations F1-F12

Comparison of optimized formulation with Innovator product is done and the optimized formulation showed better release within 8 min as compared to the innovator product.

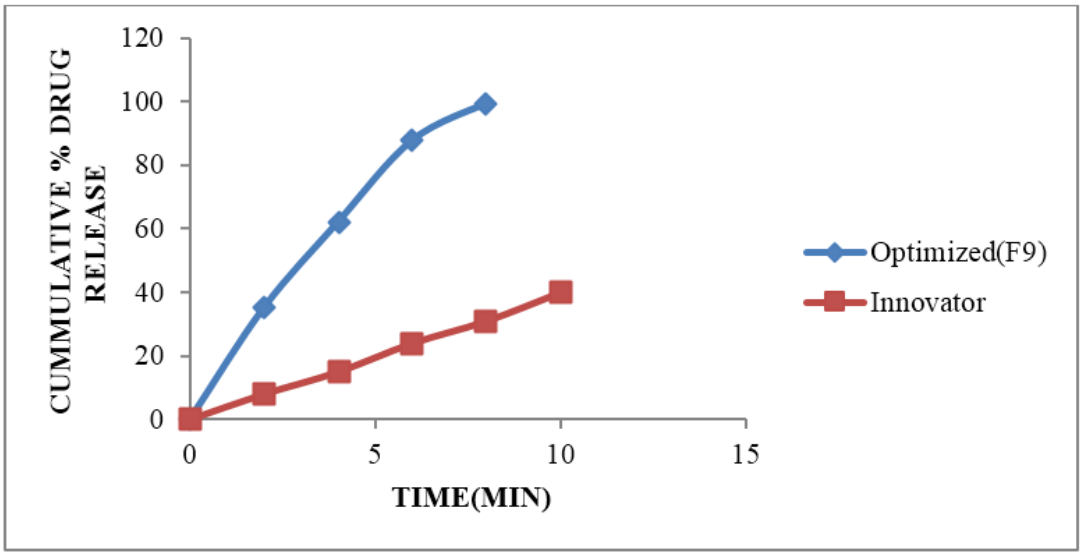

Fig 4: *In vitro* dissolution study of Optimized formulation and Innovator product

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure Drug candesartan Cilexetil showed characteristic endothermic peak at 174.9 °C indicating melting point of pure Drug. The DCS is performed to check for any interaction between excipients and Drug. It also helps to find the effect of temperature and compression forces.

From the thermogram, the endothermic peak of drug with mixture of polymers is obtained at 173.7 °C. The melting point of pure drug ranges from 160-175 °C. Thus there exists a negligible difference and is within the range. Therefore it implies good compatibility and physical stability of the drug with polymers and there is no effect of temperature and compression forces on Drug stability.

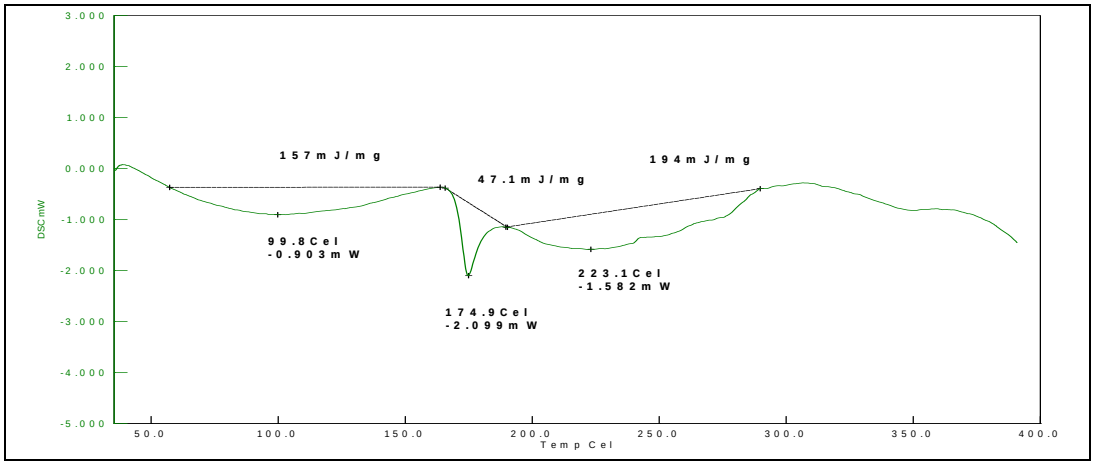

Fig 5: DSC Thermogram of drug

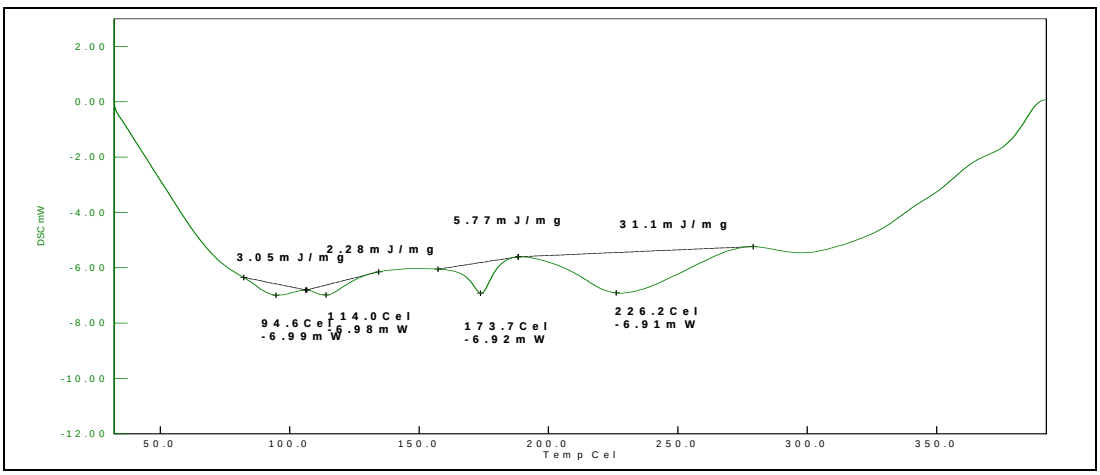

Fig 6: DSC thermogram of Optimized formulation

4. Conclusion

Candesartan Cilexetil is an angiotensin Π type-I (ATI) receptor antagonist which is used in the treatment of hypertension and congestive heart failure. It shows biological half-life of 9 hrs and bioavailability of 15%, it is having low solubility, so by super disintegrants we are improving the solubility there by drug release. The drug is formulated as orodispersible delivery system so it improves the patient acceptance and compliance for those having difficulty in swallowing. Bioavailability of drugs is enhanced due to absorption from mouth, (Pregastric absorption). The FTIR spectra revealed that, excipients used were compatible with the drug. The formulated tablets showed compliance for various physiochemical parameters viz. hardness, friability, weight variation, content uniformity and disintegration time. The drug content was within acceptable range which ensured dose uniformity in the formulation. The water absorption ratio of formulation F9 is higher and shorter wetting time than other formulations. On the basis of drug release, disintegration time and wetting studies it can be concluded that the formulation is the optimum formulation. The formulation F9 has showed the advantage of being a hybrid of both flash tab and wow tab technique with 10 seconds disintegration time and no water required. Comparison of optimized formulation with Innovator product is done and the optimized formulation showed better release within 8min as compared to the innovator product. Thus the formulation F9 may be helpful to increase the bioavailability of the drug and enhances patient compliance.

5. References

1. Velmurugan S, Sundar V. Oral Disintegrating Tablets: An Overview. International Journal of Chemical and Pharmaceutical Sciences 2010; 1 (2):1-12.
2. Kaur T, Bhawandeep G, Sandeep K, Gupta GD. Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res 2011; 3(1):1-7.
3. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth Dissolving Tablets-An Overview of Formulation Technology. Scientia Pharmaceutica 2009, 309-326.
4. Deshika R, Viness P, Yahya EC, Lisa CT. Rapidly disintegrating oramucosal drug delivery technologies. Pharm Dev Tech 2009; 14(6):588-601.
5. Suresh B, Rajender M, Ramesh G, Rao MY. Orodispersible tablets: An overview. Asian J Pharm 2008; 2(1):2-11.
6. Pfeffer M, Swedberg K, Granger C, Held P, McMurray J, Michelson E *et al*. "Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme". Lancet 2003; 362(9386):759–66.
7. Goodman and Gilman Manual of Pharmacology and Therapeutics, Second Edition by Randa Hilal-Dandan, Laurence Brunton.
8. Wilbert SA. Treatment of systemic hypertension-A review. Am J Cardiovasc Dis 2012; 2(3):160-170.
9. Howell SJ, Sear JW, Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. British Journal of Anaesthesia 2004; 92 (4):570-83.
10. James W. Pharmaceutical preformulation: The physicochemical properties of drug substances: Aulton ME. Pharmaceutics the science of dosage form design, Churchill livingstone, Spain 2006, 2,113-138.
11. Banker GS, Anderson NR. Tablets: Lachman L, Lieberman H, the theory and practice of industrial pharmacy, CBS publishers & distributors, New Delhi, Special Indian edition, 2009, 293-345.
12. Peter D. Oral solid dosage forms: Gibson M. Pharmaceutical preformulation and formulation a practical guide from candidate drug selection to commercial dosage form, Interpharm/CRC, Newyork Special Indian edition, 2008, 379-432.
13. Vinay P, Suresh S, Joshi H. Oral disintegrating drug delivery system of amoxicillin: formulation and invitro evaluation. International Journal of Pharma and Bio Sciences 2010; 1(2):1-10.
14. United State Pharmacopoeia 30- National Formulary 25, 2007, 634.
15. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Guidance for Industry, Orally Disintegrating Tablets, 2008.
16. Indian Pharmacopoeia, Fourth Edition, Vol-II, Controller of publications, Govt. of India 1996, 736.