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Formulation and *In-Vitro* Evaluation of immediate-release pellets of Candesartan Cilexetil

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ABSTRACT

Multi particulate drug delivery system has long run also been made use of to enhance the overall bioavailability going from drugs having low aqueous solubility. Candesartan Cilexetil is an anti-hypertensive drug. Complex and dispersion of Candesartan Cilexetil with the different carriers were prepared to increase its solubility and bioavailability. Due to its low aqueous solubility bioavailability of the drug is 15 % and it shows variable absorption from GIT. Pellets offer several advantages such as proper distribution in the GIT tract, reduces dose dumping, and relief going from administration as well as closing going from chemotherapy therefore within the time being work an immediate-release Pellets of candesartan cilexetil was planned out using the representational of increasing the solubility and in turn bioavailability of Candesartan Cilexetil. Immediate release Pellets containing complex or dispersion of Candesartan Cilexetil with the suitable carrier was prepared using non-pareil sugar seeds. On the non-pareil seeds, drug layering of Candesartan Cilexetil complexed or dispersed with the suitable carrier was done. The formulation having Candesartan Cilexetil and Eudragit dispersed in 1:3 ratios is considered the best product concerning assay and *in-vitro* drug release. The present top of the line used to be promote withstand constancy written report, the results of and that indicated no important change concerning assay, content uniformity, and in vitro drug release.

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INTRODUCTION

Candesartan cilexetil a prodrug serves as a resolve that one may candesartan all through focusing in the alimentary canal. Candesartan serves as type a selective AT1 type angiotensin II positive allosteric modulator. Candesartan cilexetil is an intenstive first pass netabolic process leads to poor bioavailability showing poor bioavailability, showing up 15 to 40 percent bioavailability. It has got type a blood plasma half-life of 7-9 hrs as well as peak blood plasma put concentration finalizes among 3 to 4 hrs [1]. Pellets who once size varies enjoys 0.05milimeter to 5 milimeter are mainly utilized in the form of pellets, granules which might be conveyed in pills or tablets. In the particular formulations, the overall drug dose is split in the direction of through to less significant subunits, whatever once meted out frittering away with in the gastrointestinal tract. This gives various benefits way over unvaried systems not to mention easily shaver ittitation going from the mucosa decreased variability successful absorption as well as in terms of controlled release formulation a better and safer of recall dose dumping [2].

The major representational to increase the general

potency dissolution speed of Candesartan Cilexetil through complexation as well as spreading method successful an acidulous medium. To organize choice of words going from pellets of the structures and petty attacks [3]. Pelletization ideas widespread in pharmaceutical industries will be upfront pelletization, extrusion-spheronization, as well as layering. Direct pelletization method exploitation fluidized bed equipment does have several benefits specified a one-unit appendage, no initiating textile want to know and light time interval. The enclose method is the outgrowth in whatever a drug in explosive, resolution the like is stratified onto seed materials [4].

MATERIALS & METHODS

Candesartan cilexetil was once acquired freely given representative sample from Zydus Cadila Ahmedabad β cyclodextrin, Eudragit, Hydroxypropyl methylcellulose, magnesium stearate was purchased from Sai MirraInno Pharma, Chennai, Microcrystalline cellulose 112, Polyethylene glycol 20,000 & 8000 was a gift stratified sample of Merck Corporation, Germany. Non-pareil seeds were a gift stratified sample of FMC biopolymer, Mumbai. Sodium hydroxide, Isopropyl alcohol & Hydrochloric acid was acquired from LOBA chemicals and other ingredients explotted in with analytical grades.

Methodology

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of the pure form of Candesartan cilexetil physical mixtures are carried out with FTIR [5].

Formulation Development

Candesartan Cilexetil pellets complexed and Dispersed with various polymers were formulated. In that work, the process were using preparing Candesartan Cilexetil pellets was the Solution/suspension-layering technique involves drug coating [6].

Drug coating

A coating suspension containing the suitable put concentration of drug and various excipients used to be prepared. Then, the suspension used to be illuminated into non-pareil seeds through the use of Wurster bottom spray, through asserting all suitable probabilities like spray rate, bed & inlet temperature, and wash up revolutions per minute preserved form of covered pellets [7].

Prototype Formulation

After studying the patents on Candesartan Cilexetil conventional tablet, a list of binders that can be used was prepared which included various binders like sugar, maize starch, potato starch, HPMC-6cps, MCC-112. Feasibility trial was performed to bind the drug to the non-pareil seeds using these binders [8]. The binder selected was HPMC-6cps and in total four trials were taken using HPMC-6cps as a binder. For all the trials, the coating solution was prepared by the following method. Preparation of Coating Solution\Suspension for batches F1 to F3 Steps: The HPMC was dissolved in hot water (50), -Cyclodextrin was dissolved in the above solution, Candesartan Cilexetil was dissolved in Isopropyl alcohol [9]. Both the solution was mixed and stirred for 6 to 8 hours, talc used to be in excess of duplication solution as shown in Tables 1, 2, 3, 4, 5, 6, 7 and 8.

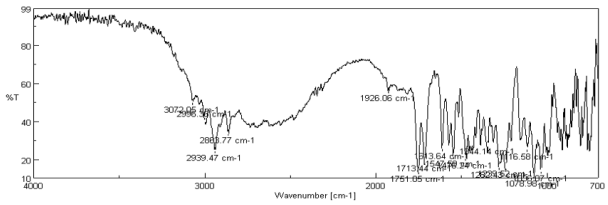

Figure 1: FTIR of Candesartan Cilexetil

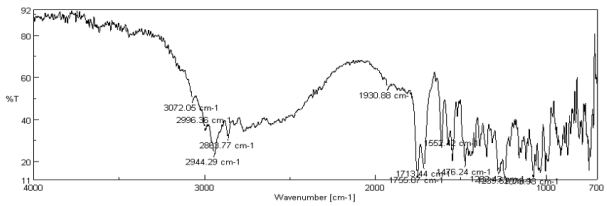

Figure 2: FTIR of Drug and PEG-20,000 Physical mixture

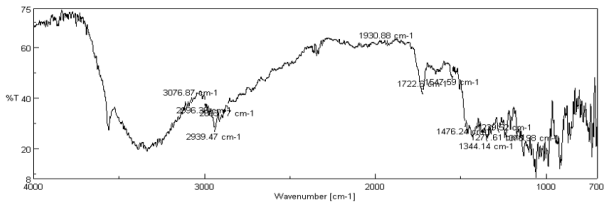

Figure 3: FTIR of optimized formulation F13

Preparation of Coating Solutionfor batches F4 to F6 Steps

The PEG-8000 was dissolved in water to above solution HPMC was added Candesartan Cilexetil was dissolved in Isopropyl Alcohol & talc. Both the solution was mixed and stirred for 5-6 hours [10].

Preparation of Coating Solution/suspension for batches F7 to F9 Steps

The Dissolve PEG-20,000 in purified water to the above solution add HPMC dissolve the drug in Isopropyl Alcohol both the solution was mixed and

Table 1: Formulations of Candesartan Cilexetil pellets complexed with β Cyclodextrin

Ingredients (gms)	Formulation No – Drug: β-Cyclodextrin		
	1:1 molar ratio-F1	1:2 molar ratio-F2	1:4 molar ratio-F3
Non-pareil seeds	40	40	40
Candesartan Cilexetil	2.68	1.34	0.67
β-Cyclodextrin	5	5	5
HPMC-6cps	1	1	1
Talc	1	1	1
Purified water	50	50	50
Isopropyl Alcohol	350	350	350

Table 2: Fluid Bed Processor Parameters Maintained During Coating of Pellets of Different Batches from F1 to F3

Parameters	Formulation No- Drug : β - cyclodextrin					
	1:1-F1		1:2-F2		1:4-F3	
	Set Value	Process value	Set Value	Process Value	Set Value	Process Value
Inlet air temperature °C	45	35-40°C	45	36-39°C	45	40-42°C
Bed temperature °C	40	30-35°C	40	33-37°C	40	35-39°C
Exhaust air temperature °C	-	28- 32°C	-	30-35°C	-	34-37°C
Blower RPM	1200	1200	1200	1200	1200	1200
Blower CFM	-	1700	-	1700	-	1700
Atomizing air pressure Kg/cm2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2
Peristaltic pump RPM ml/min	2-6	2-6	2-6	2-6	2-6	2-6

Table 3: Fluid Bed Processor Parameters Maintained During Coating of Pellets of Different Batches from F4 to F6

Parameters	Formulation No-Drug : PEG-8000					
	1:0.5-F4		1:1-F5		1:2-F6	
	Set Value	Process value	Set Value	Process Value	Set Value	Process Value
Inlet air temperature °C	45	34-42°C	45	36-40°C	45	41-43°C
Bed temperature °C	40	31-36°C	40	33-38°C	40	35-40°C
Exhaust air temperature °C	-	28- 32°C	-	30-36°C	-	34-38°C
Blower RPM	1200	1200	1200	1200	1200	1200
Blower CFM	-	1700	-	1700	-	1700
Atomizing air pressure Kg/cm2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2
Peristaltic pump RPM ml/min	2-6	2-6	2-6	2-6	2-6	2-6

Table 4: Formulation of Candesartan Cilexetil pellets Dispersed with PEG-8000

Ingredients (gms)	Formulation No – Drug: PEG-8000		
	1:0.5 Ratio F4	1:1 Ratio F5	1:2 Ratio F6
Non-pareil seeds	40	40	40
Candesartan Cilexetil	4	4	4
PEG-8000	2	4	8
HPMC	1	1	1
Talc	1	1	1
Purified water	50	50	50
Isopropyl Alcohol	350	350	350

Table 5: Formulation of Candesartan Cilexetil pellets Dispersed with PEG-20,000

Ingredients (gms)	Formulation No – Drug: PEG-20,000		
	1:0.5 Ratio F7	1:1 Ratio F 8	1:2 Ratio F9
Non-pareil seeds	40	40	40
Candesartan Cilexetil	4	4	4
PEG-20,000	2	4	8
HPMC	1	1	1
Talc	1	1	1
Purified water	50	50	50
Isopropyl Alcohol	350	350	350

Table 6: Fluid Bed Processor Parameters Maintained During Coating of Pellets of Different Batches from F7 toF9

Parameters	Formulation No-Drug: PEG-20,000					
	1:0.5-F7		1:1-F8		1:2-F9	
	Set Value	Process value	Set Value	Process Value	Set Value	Process Value
Inlet air temperature ^{o}C	45	32-38°C	45	37-42°C	45	39-43°C
Bed temperature ^{o}C	40	34-36°C	40	36-38°C	40	37-40°C
Exhaust air temperature ^{o}C	-	32- 34°C	-	35-37°C	-	36-38°C
Blower RPM	1200	1200	1200	1200	1200	1200
Blower CFM	-	1700	-	1700	-	1700
Atomizing air pressure Kg/cm^2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2
Peristaltic pump RPM ml/min	2-6	2-6	2-6	2-6	2-6	2-6

stirred for 5-6 hours talc was added to the above solution [11].

Preparation of Coating Solution/Suspension for batches F10 to F13 Steps.

To dissolve HPMC in purified hot water, Dissolve the drug in Isopropyl Alcohol to the drug solution Eudragit was added to get a clear solution. Both the solution used to be mixed and stirred for 1-2 hours talc was added to with the above solution [12].

Evaluation of Immediate Release Pellets

Percentage yield

It can be deliberate for knowing the overall weight gain obtained after the coating process [13]. It can be calculated by the formula as follows.

$$Percentage\ \ Yield\ =\ \frac{Practical\ weight\ obtained}{theoretical\ weight\ \ obtained}\ \times 100$$

Table 7: Formulation of Candesartan Cilexetil pellets Dispersed with Eudragit

Ingredients (gms)	Formulation No – Drug: Eudragit			
	1:0.5 Ratio F10	1:1 Ratio F11	1:2 Ratio F12	1:3 Ratio F13
Non pareil seeds	40	40	40	40
Candesartan Cilexetil	4	4	4	4
Eudragit	2	4	8	12
HPMC	1	1	1	1
Talc	1	1	1	1
Purified water	50	50	50	50
Isopropyl Alcohol	350	350	350	350

Table 8: Fluid Bed Processor Parameters Maintained During Coating of Pellets of Different Batches from F 10 to F13

Parameters	Formulation No-Drug: Eudragit							
	1:0.5 F10	Ratio	1:1 F11	Ratio	1:2 F12	Ratio	1:3 F13	Ratio
	Set Value	Process value	Set Value	Process Value	Set Value	Process Value	Set Value	Process value
Inlet air temperature oC	45	35-38°C	45	38-42°C	45	37-42°C	45	40-43°C
Bed temperature oC	40	34-36°C	40	34-37°C	40	35-39°C	40	38-40°C
Exhausts air temperature oC	-	31-33°C	-	32-35°C	-	33-36°C	-	36-38°C
Blower RPM	1200	1200	1200	1200	1200	1200	1200	1200
Blower CFM	-	1700	-	1700	-	1700	-	1700
Atomizing air pressure Kg/cm2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2	1.6-2
Peristaltic pump RPM ml/min	2-6	2-6	2-6	2-6	2-6	2-6	2-6	2-6

Table 9: Functional groups of Candesartan Cilexetil along with the excipients

Functional groups	Candesartan Cilexetil (Pure drug)	Candesartan Cilexetil + PEG-20,000 physical mixture	Optimized formulation F13
C=O Stretching	1713.44	1713.44	1713.44
O-H Stretching	3072.95	3072.95	3072.95
C-H Stretching	2863.77	2863.77	2863.77
C=C Stretching	1678.98	1678.96	1678.98

Table 10: Evaluation of Formulation from F1 to F3

Formulation No	Percentage yield (%)	Assay	Friability (%)
F1	85.04	99.1	0.4
F2	89.29	99.7	0.2
F3	93.76	99.4	0.2

Table 11: *In vitro* release of Candesartan Cilexetil from Batch F1 to F3

	Cumulative % drug release, AM ± SD		
Time (Min)	F1	F2	F3
10	5.43 ± 0.39	20.17 ± 0.39	22.11 ± 0.38
20	9.63 ± 0.59	21.43 ± 0.60	23.26 ± 0.59
30	12.92 ± 0.78	26.13 ± 0.59	29.26 ± 0.59
45	15.53 ± 0.23	29.90 ± 0.60	31.09 ± 0.80
60	26.94 ± 0.39	30.33 ± 0.23	32.15 ± 0.39

Table 12: Evaluation of Formulation from F4 to F6

Formulation No	Percentage yield (%)	Assay	Friability (%)
F4	91.37	99.1	0.8
F5	95.3	99.7	0.6
F6	95.03	99.4	0.6

Table 13: *In-vitro* release of Candesartan Cilexetil delight in Batch F4 to F6

	Cumulative % drug release, AM ± SD		
Time (Min)	F4	F5	F6
10	13.44±0.59	14.74±0.38	16.81± 0.59
20	14.37±0.59	16.45±0.38	18.03 ± 0.39
30	15.67±0.78	22.19±1.25	25.60 ± 0.80
45	20.60±0.80	25.71±1.26	30.15 ± 1.02
60	22.33±0.39	26.27±0.4	33.04 ± 0.61

Table 14: Evaluation of Formulation from F7 to F9

Formulation	Percentage yield (%)	Assay	Friability (%)
F7	88.7	99.8	0.4
F8	97.4	99.4	0.2
F9	92.2	99.1	0.2

Table 15: In vitro release of Candesartan Cilexetil from Batch F7 to F9

	Cumulative % drug release, AM ± SD		
Time (Min)	F7	F8	F9
10	12.01 ± 0.63	14.86 ± 0.77	16.57 ± 1.26
20	14.35 ± 0.59	18.02 ± 0.39	19.44 ± 0.8
30	21.36 ± 0.23	25.41 ± 0.38	26.85 ± 0.59
45	22.60 ± 0.59	28.08 ± 0.59	33.01 ± 0.58
60	26.75 ± 0.56	31.34 ± 0.38	34.37 ± 0.80

Table 16: Evaluation of Formulation from F10 to F13

Formulation No	Percentage yield (%)	Assay	Friability (%)
F10	98.8	99.4	0.6
F11	97.28	99.7	0.2
F12	97.94	99.5	0.4
F13	98.13	99.8	0.2

Table 17: *In Vitro* release of Candesartan Cilexetil delight in Batch F10 to F13 of pellets

	Cumulative % drug release, AM ± SD			
Time (Min)	F10	F11	F12	F13
10	38.02 ± 0.38	69.95 ± 0.59	74.81 ± 0.44	69.51 ± 0.59
20	45.80 ± 0.39	73.95 ± 1.36	77.76 ± 0.45	74.60 ± 0.81
30	51.84 ± 0.44	75.81 ± 0.59	80.38 ± 0.78	89.39 ± 0.45
45	60.44 ± 0.45	76.99 ± 0.23	82.21 ± 0.81	96.67 ± 0.59
60	64.93 ± 0.59	78.04 ± 0.77	83.14 ± 0.39	97.65 ± 0.39

Table 18: In Vitro release of Candesartan Cilexetil from pellets of batch F13

Time to come min	Cum. percent drug released	% drug remained unfilmed	Log percent drug remain unfilmed
0	0	100	2
10	5.5034	30.4885	1.4841
20	5.9680	25.3994	1.4048
30	7.1518	10.6020	1.0253
45	7.7339	3.3261	0.5219
60	7.8126	2.3419	0.3695

Table 19: Release order kinetics of Candesartan Cilexetil from pellets of batch F13

Batch	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer- Peppas		Hixon-crowel cube route law
				R^2	n	
F13	0.6524	0.9642	0.8971	0.9334	0.496	0.8956

Table 20: Accelerated stability study for optimized batch F13

Time in min	Pellets of zero-day-F13	Pellets after one month-F13
10	69.51 ± 0.59	61.42 ± 0.97
20	74.60 ± 0.81	70.63 ± 0.60
30	89.39 ± 0.45	73.72 ± 0.67
45	96.67 ± 0.59	86.67 ± 0.59
60	97.65 ± 0.39	95.73 ± 0.81

Assay

The present in drug-coated pellets was determined. 100mg of pellets were weighed accurately; pellets were placed during a 100 mililiter volumetrical flask. The amount has upto one hundred ml using a hydroalcoholic solution containing 0.35% Tween 20. The volumetric flask was placed in Sonicator for 30 minutes. Absorbance used to be sounded at 258 nanometer employing UV spectrophotometer [14].

Friability test

Roche Friabilator was once well-known measure the friability of the general tablets. It used to be spinned it at rate consisting of 25 revolutions per minute. Five grams pellets had been weighed together as well as placed within the chamber the friability. Behind 100 reotations the general pellets give up out from spectracular friability and intact pellets had been back weighed in concert behind removing fines using screen # 44 sieve [15].

***In vitro* drug release**

Spectacular tests transmit utilizing USP paddle type with dissolution apparatus. The general dissolution medium, victimed was 0.1N HCl and 6.5 pH phosphate buffer with 0.35% Tween 20, belong into a the dissolution flask putting forward the room temperature of 37+0.5 ^{o}C and revolutions per seconds of 50. Accurately lab tested pellets spread almost every

flask of dissolution setup. The general apparatus can do to walk as 1 hour. Samples measure 10 mililiters had been alone at 10, 20, 30, 45, 60 min intervals using the autosampler [16].

Kinetic Treatment

The data obtained of the *in vitro* dissolution studies acquire kinetic track record analysis [17].

Zero-order kinetics

$$Q_t = Q_o + K_o\, t$$

First-order kinetics

$$Q_t = \log Q_o + K_{1t}/2.303$$

Higuchi model

$$Q_t = K_H \cdot t^{1/2}$$

Korsmeyer-Peppas release model

$$M_t / M_\infty = K \cdot t^n$$

Accelerated Stability Study

The pellets were filled in "0"size blue/ white capsules. The filled capsules were packed in Blister Pack and placed in a walk-in stability chamber at 40°± 2 °C and 75 ± 5 % RH for 1 month [18]. After 1 month, the capsules were taken out and all the evaluation tests were performed.

RESULTS AND DISCUSSION

Fourier transforms infrared spectroscopy

Spectacular peaks acquired in the spectra going from optimized formulation have been correlative with spectacular peaks consisting of the drug spectrum. This means therefore the drug was compatible using the formulation components. The optimized formulation F13 are shown in Figures 1, 2 and 3 and Table 9.

Formulation of Candesartan Cilexetil pellets complexed with β Cyclodextrin

Here, non-pareil seeds were used as the starter seeds, which were non-toxic, inert materials, and were used for preparing immediate release pellets. Hydroxyl propyl methylcellulose was used as a binder, which helps to bind the drug on to the non-pareil seeds. Talc was used as an anti-sticking agent. The coating solution was prepared by dissolving HPMC 6cps and β-cyclodextrin in purified water (hot). Candesartan Cilexetil was dissolved in IPA. Both the solution was mixed and stirred for 6-8 hours to this solution talc was added and finally, it was filtered through # 100 sieves. The same procedure was used for all trials (Table 10).

It was concluded that by keeping the concentration of solid content in the solution within the limit and raising the temperature percentage yield of the formulation can be increased (Table 11).

Now comparing the release profile of F1, F2, and F3 with the drug release profile of pure drug (API) and conventional table it's referred to therefore the discharge of drug from F1, F2, and F3 is more than that of a pure drug but less than that of a conventional tablet. These conclude that insufficient complexation took place between drug and polymer due to the higher molecular weight of the drug and so the release of drug in acidic medium from these formulations was low as compared to that of the marketed product. The second polymer which was selected for enhancing solubility and dissolution rate of the drug in acidic media is PEG-8000. This polymer was selected due to its hydrophilic nature and solubilizing effect on the drug. Total three trials were taken using PEG - 8000 as a polymer in different ratios from 1:0.5 to 1:2.

Formulation of Candesartan Cilexetil pellets Dispersed with PEG-8000

Here, non-pareil seeds were used as the starter seeds, which were non-toxic, inert materials, and were used for preparing immediate release pellets. Hydroxyl propyl methylcellulose was used as a binder, which helps to bind the drug on to the non-pareil seeds. Talc was used as an anti-sticking agent. The coating solution was prepared by dissolving HPMC 6cps and PEG -8,000 in purified water (hot). Candesartan Cilexetil was dissolved in IPA. Both the solution was mixed and stirred for 5-6 hours to this solution talc was added and finally, it was filtered through # 100 sieves. The same procedure was used for all trials (Tables 12 and 13).

Now comparing the drug release profile of F4, F5, and F6 with the release profile of pure drug (API) and conventional table it is observed that release of drug from F5 and F6 is more than that of a pure drug but less than that of a conventional tablet. These conclude that dispersion formed by drug and polymer interaction is not complete and so the release of drug in acidic medium from these formulations was low as compared to that of a marketed product. The third polymer which was selected for enhancing solubility and dissolution rate of the drug in acidic media is PEG-20,000. This polymer was selected to observe the effect of higher viscosity polymer on the solubility of the drug as shown in Tables 14 and 15. Total three trials were taken using PEG-20,000 as a polymer in different ratio from 1:0.5 to 1:2. Here, non-pareil seeds were used as the starter seeds, which were non-toxic, inert materials,

and were used for preparing immediate release pellets. Hydroxyl propyl methylcellulose was used as a binder, which helps to bind the drug on to the non-pareil seeds. Talc was used as an anti-sticking agent.

The coating solution was prepared by dissolving HPMC and PEG-20,000 in purified water (hot). Candesartan Cilexetil was dissolved in IPA. Both the solution was mixed and stirred for 5-6 hours to this solution talc was added and finally, it was filtered through # 100 sieves. The same procedure was used for all trials.

Now comparing the release profile of F7, F8, and F9 with the drug release profile of pure drug (API) and conventional table it is observed that the release of drug from F7, F8, and F9 is more than that of a pure drug but less than that of a conventional tablet. The evaluation of Formulation from F10 to F13 as shown in Table 16. The in vitro release of candesartan cilexetil from Batch F10 to F13 of pellets as shown in Table 17.

Kinetics of *In-Vitro* drug release

The release profile of Candesartan Cilexetil from pellets of batch F13 was processed into values were shown in Tables 18 and 19.

Accelerated stability study for optimized batch F13

The F13 batch were kept for accelerated stability study at 40 $\pm$ 2 º C and 75 $\pm$ 5% RH for 1 month in the stability chamber. After following one side-real month, the samples have been referred to for any alter in physical parameters. The drug content of the stability batch F13 subsequent to one month encounter to be 97.65 values as shown in Table 20.

CONCLUSION

The Polymers like -Cyclodextrin, PEG-8000, and PEG 20,000 which were used in the different formulations ranging from F1 to F9 failed to increase *in vitro* drug release in 0.1N HCl as compared to a conventional tablet. (marketed product). The Eudragit in a concentration of 3% w/w was optimized to give 97% drug release in 0.1N HCl. Based on *in vitro* release of the drug in 0.1N HCl, Formulation F13 was optimized. The release of Candesartan Cilexetil from the developed formulations in this thesis was directly proportional to the concentration of the polymers in the drug coating solution. The release order kinetics from the developed formulation follows first order. At accelerated stability situations stepped forward formulations encounter to be steady for one month. *In Vitro* release profile of optimized formulation of Pellets of Candesartan Cilexetil (F13) in 0.1N HCl was found to be superior then Marketed product.

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Conflict of interest

The authors testify that they got no conflict of interest in that study.

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