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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF CANDESARTAN BY DIRECT COMPRESSION METHOD USING SUBLIMATING AGENTS

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ABSTRACT

This research was to formulate and evaluate oral dispersible tablets (ODT) of Candesartan by direct compression technique using sublimation agents like Menthol and superdisintegrants Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium and taste masking agent mannitol. Nine different formulations of Candesartan were prepared by using different ratios of these ingredients by direct compression method. These tablets were characterized by hardness, thickness, weight variation, wetting time, disintegration time, water Absorption ratio, in vitro drug release. All batches of oral dispersible tablets were satisfactory in terms of dissolution profile. The hardness, wetting time, disintegration time were also shows the satisfactory results. The batches of all formulations, F2 batch of oral dispersible tablets was found to be 99.02% of drug release in 10 minutes. The F2 was the best of all nine formulations of oral dispersible tablets of candesartan. Bioavailability of candesartan can be increased by formulating it as oral dispersible tablet.

Key words: Oral dispersible tablets, Candesartan, Menthol, Crospovidone, Croscarmellose, sodium starch Glycolate, Mannitol.

INTRODUCTION

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market.

The U.S food and drug administration center for drug evaluation and research (CDER) defines an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue.

The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules[3]. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmaco kinetic and pharmacodynamic characteristics of drugs.

These dosage forms disintegrate within 30sec with very less quantity of water. This can be achieved by addition of various superdisintegrants like Croscarmellose sodium, Crospovidone, sodium starch glycolate [1,2].

These tablets are also called as Orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts [3]. However, of all the above terms, United States of pharmacopoeia (USP) approved these dosage forms as ODTs (orally disintegrating tablets). Recently, European Pharmacopoeia has used the term Orodispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing [1]. United States of Food and Drug Administration (FDA) defined ODT as " A solid dosage

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form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute [2,4].

Criteria for mouth dissolving Drug Delivery System:

The tablets should

- not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- be compatible with taste masking.
- be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.

Salient Feature of mouth Dissolving Drug

Delivery System:

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- the risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic

Drugs, due to rapid disintegration and dissolution of these tablets.

- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability [5-7].

Limitations of Mouth Dissolving Tablets

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly [8].

Candesartan

Candesartan selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Candesartan is greater than 10,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion. Following administration of the candesartan the absolute bioavailability of candesartan was estimated to be 15%.

MATERIALS AND METHODS

Materials

Candesartan was obtained as a gift sample from Ranbaxy Labs Ltd. All ingredients were obtained as a gift sample from Chandra labs. All solvents were pure analytical grade purchased, Double distilled water was used throughout the experiment.

Formulation of Candesartan oro dispersible tablets by direct compression method

Tablets of Candesartan were prepared by direct compression method employing menthol as sublimating agent. The concentrations of the above ingredients were optimized as shown in below table on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate enhancing disintegrants and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication). About 150mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8mm flat- surface punches. Tablets were allowed for drying about 24 hours air drying or 45^0C in hot air oven for 1hr.

EVALUATION OF TABLETS

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters [9,10].

Physical appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

Tablet size and Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

%Friability = $(W_1-W_2)/W_1$ X 100

Where, W_1= weight o f tablets before test

W_2 = weight of tablets after test

Weight variation of Tablets

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:

Twenty tablets were taken randomly and weighed accurately. The average weight was calculated by,

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time in-vitro and in-vivo, several methods were proposed, developed and followed at their convenience. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2°c and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients .the time required for water to reach upper surface of tablet is noted as a wetting time .a piece if tissues paper folded double was placed in a petri dish (internal diameter is 6.5cm) containing 6ml of water the tablet was placed on the paper and the time for complete wetting of the tablet was measured .the method was slightly modified by maintaining water at 37^0c. a tablet was placed on the tissue paper and small amount of amaranth power was placed on upper surface of tablets . the time required for development of red colour on the upper surface of the tablets was recorded as wetting time

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

Where, W_a is weight of tablets before water absorption; W_b is the weight of tablet after water absorption; R is the water absorption ration [11].

Dissolution test

Dissolution: It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure.

Method: dissolution media was taken as6.8pH, 900ml was placed in the vessel and the USP apparatus –II (paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 ± 0.5°C. Tablet was placed in the basket and placed in the vessel; the apparatus was operated for 15min at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed using UV [12,13].

STABILITY STUDIES

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life. The ICH tripartite guidelines have established accelerated stability testing should be done at 40^0 C/75%RH for 6 months [14].

Table 1. Composition of Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
candesartan	16mg	16mg	16mg	16mg	16mg	16mg	16mg	16mg	16mg
C.P	1.5mgg	3mg	4.5mg	-	-	-	-	-	-
S.S.G	-	-	-	1.5mg	3mg	4.5mg	-	-	-
C.C.S	-	-	-	-	-	-	1.5mg	3mg	4.5mg
Mannitol	45mg	45mg	45mg	45mg	45mg	45mg	45mg	45mg	45mg
Menthol	22.5mg	22.5mg	22.5mg	22.5mg	22.5mg	22.5mg	22.5mg	22.5mg	22.5mg
M.C.C	59.5mgg	55.9mg	55.9mg	55.9mg	55.9mg	55.9mg	55.9mg	55.9mg	55.9mg
Mg stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
vanilline	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total weight	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg

C.P-Crospovidone, S.S.G-Sodium Starch Glycolate, C.C.S-Croscarmellose Sodium, M.C.C-Microcrystalline Cellulose,

Table 2. Acceptance criteria for tablet weight variation

Average weight of tablet(mg)	Maximum % difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 3. ICH Guidelines for stability study

Study	Storage Condition	Duration
Accelerated temperature	40±2°C, RH 75±5%	6 months

POST COMPRESSION PROPERTIES

Table 4. Evaluation formulations of tablets before drying(A)

Formulation code	Thickness ± S.D. (mm) n = 3	Hardness ± S.D. (Kg/cm^2)n = 3	Friability (%)	Average weight variation (mg) n = 3	Drug content candesartan (%) n = 3	Disintegration Time ± S.D. (mins) n = 3
F1	2.58±0.05	6.00±1.5	0.54	151±5.60	99.13±0.53	3.2±0.35
F2	2.59±0.07	6.100±1.3	0.45	152±5.45	96.27±0.64	2.2±0.30
F3	2.57±0.06	6.400±1.2	0.35	145±8.10	97.63±0.55	2.0±0.45
F4	2.57±0.10	6.400±1.1	0.41	155±6.00	98.36±0.58	3.4±0.56
F5	2.58±0.09	6.300±1.3	0.42	149±7.89	98.33±0.62	3.3±0.35
F6	2.57±0.04	6.400±1.1	0.31	150±5.98	98.64±0.84	2.9±0.23
F7	2.54±0.07	6.500±1.0	0.29	152±2.45	98.76±0.81	3.2±0.31
F8	2.56±0.10	6.400±1.3	0.25	149±3.67	97.36±0.94	3.4±0.28
F9	2.52±0.08	6.500±1.2	0.31	150±4.87	98.44±0.84	3.4±0.15

Table 5. Evaluation parameters for formulations of tablets after drying (B)

Formulation code	Thickness ± S.D. (mm)n = 3	Hardness ± S.D. (Kg/cm^2) n = 3	Friability (%)	Average weight variation (mg) n = 3	Drug content candesartan (%) n = 3	Disintegration Time ± S.D. (mins) n = 3
F1	2.58±0.05	3.8±1.0	0.64	128.5±1.19	99.26±0.45	1.2±0.02
F2	2.59±0.07	3.7±1.2	0.55	129.5±1.93	96.38±0.56	0.12±0.05
F3	2.57±0.06	4.1±1.7	0.45	122.5±1.82	97.03±0.61	0.16±0.06
F4	2.57±0.10	4.1±2.0	0.51	132.5±1.27	98.26±0.55	1.13±0.10
F5	2.58±0.09	4.2±1.5	0.52	126±1.67	98.29±0.42	1.5±0.13
F6	2.57±0.04	3.9±1.0	0.41	127±1.92	98.60±0.68	1.15±0.23
F7	2.54±0.07	4.1±1.3	0.31	129.5±1.60	98.71±0.78	1.23±0.31
F8	2.56±0.10	3.8±1.0	0.30	126.5±1.89	97.40±0.84	1.24±0.28
F9	2.52±0.08	3.9±1.2	0.41	127.5±1.24	98.25±0.79	3.4±0.15

Table 6. Post Compression Properties

Formulation	Water absorption Ratio n=3	Wetting time (sec) n=3
F1	55.5 ± 0.47	15 ± 0.12
F2	86± 0.25	6 ± 0.32
F3	69.5 ± 0.14	8 ± 0.54
F4	64 ± 0.14	36± 0.24
F5	55.9 ± 0.41	32± 0.14
F6	45.4 ± 0.58	22 ± 0.17
F7	60.7± 0.25	37± 0.36
F8	62.5 ± 0.54	41± 0.65
F9	70.8 ± 0.14	42± 0.14

RESULTS OF IN-VITRO RELEASE PROFILE

Table 7. Comparative Cumulative drug release of Candesartan from formulations (F1-F9)

Time (min)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	31.00 ±1.02	**40.03 ±1.56**	39.02 ±1.13	27.05 ±1.28	29.00 ±1.48	32.06 ±1.18	18.09 ±1.33	23.08 ±1.34	27.02 ±1.31
4	49.00 ±0.98	**58.02 ±1.64**	56.04 ±1.03	43.05 ±1.05	47.00 ±1.22	52.08 ±1.28	33.06 ±1.42	39.00 ±1.17	40.04 ±1.28

6	62.00 ±1.06	**70.06 ±1.26**	72.08 ±1.35	60.04 ±1.33	63.00 ±1.34	71.03 ±1.45	54.02 ±1.28	58.03 ±1.28	61.03 ±1.37
8	78.00 ±1.25	**85.08 ±1.14**	86.00 ±1.28	76.05 ±1.24	80.00 ±1.37	83.08 ±1.24	69.08 ±1.34	68.06 ±1.21	76.00 ±1.47
10	89.00 ±1.04	**99.06 ±1.29**	90.06 ±1.28	86.09 ±1.34	83.06 ±1.27	86.07 ±1.32	75.06 ±1.26	79.04 ±1.18	84.05 ±1.28
12	91.02 ±1.12	**99.06 ±1.18**	96.01 ±1.34	90.06 ±1.28	87.04 ±1.21	94.01 ±1.14	82.02 ±1.24	84.03 ±1.27	92.03 ±1.31

Table 8. Comparative Cumulative drug release of F2, F3, and F6 with marketed conventional tablet formulation

Time	F2	F3	F6	MARKETED
2	**40.03±1.56**	39.02±1.13	32.06±1.18	**18.09±1.18**
4	**58.02±1.64**	56.04±1.03	52.08±1.28	**24.06±1.28**
6	**70.06±1.26**	72.08±1.35	71.03±1.45	**30.03±1.45**
8	**85.08±1.14**	86.00±1.28	83.08±1.24	**39.07±1.24**
10	**90.06±1.29**	90.06±1.28	86.07±1.32	**50.08±1.32**
12	**99.06±1.18**	96.01±1.34	94.0±1.14	**56.00±1.14**

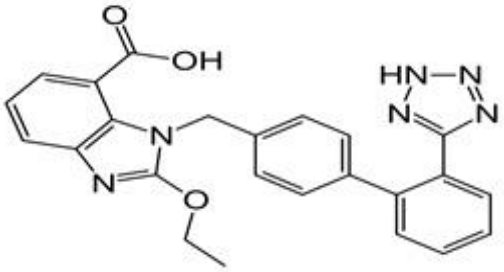
Table 9. Release kinetics of formulation F2

Formulation	Zero order R^2 value	First order R^2 value	Higuchi R^2 value	Korsmeyer peppas R^2 value
F-2	0.8938	0.9549	0.9865	0.9873

Table 10. Physical evaluation of Tablets for stability studies of Optimized formulation:

Parameter	Initial	40^0C / 75%RH
Colour	white	White
Surface	Smooth	Smooth
Disintegration(min)	12sec	12sec
Thickness(mm)	2.59±0.07mm	2.59±0.07mm
Hardness(Kp)	6.1±1.3	6.1± 1.3
Weight(mg)	152±5.45	151±5.45
Assay	98.51 ± 0.33	97.70 ± 0.28

Figure no-1



FTIR COMPATABILITY

Fig.2 FTIR of Candesartan Pure Drug

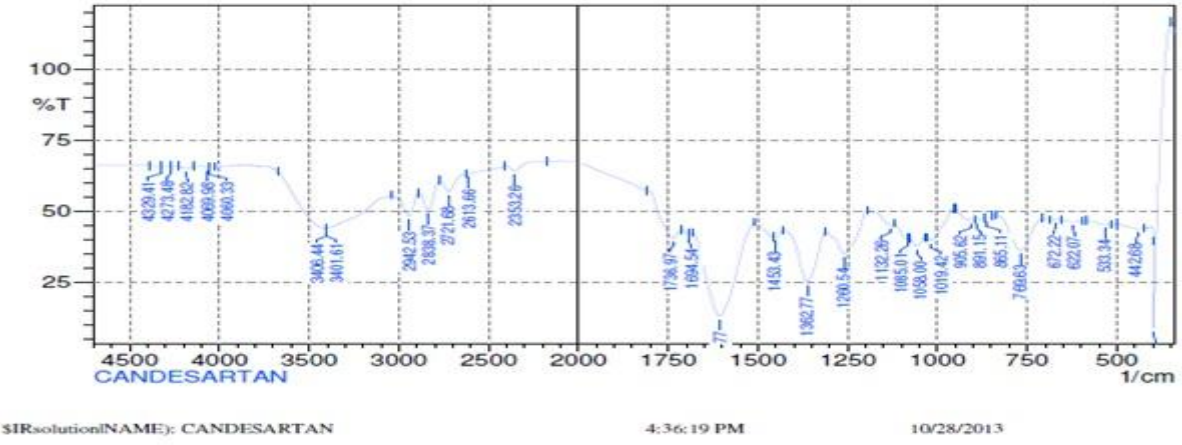


Fig. 3. FTIR of Candesartan of Final Formulation

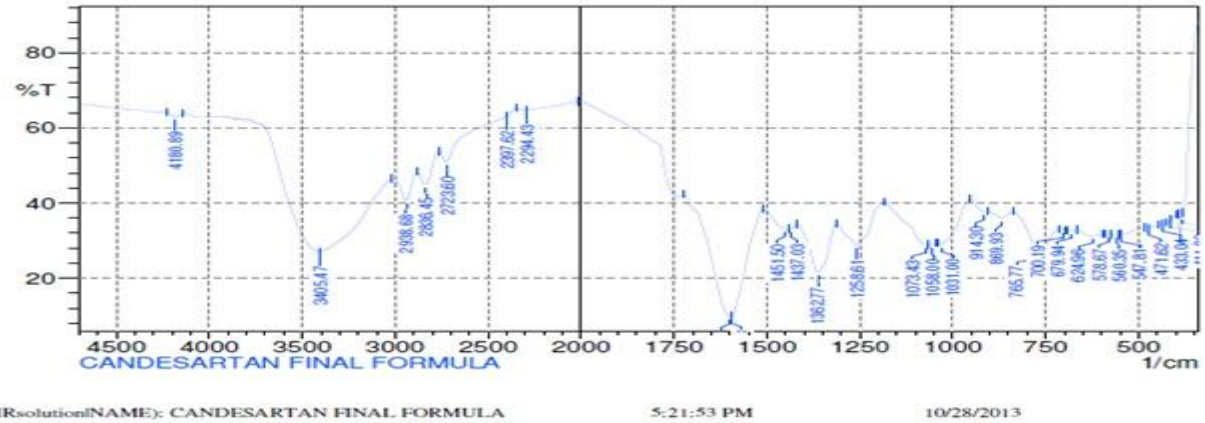


Fig. 4. Comparative Dissolution profiles of Candesartan in Formulations (F1-F9) in 6.8ph phosphate buffer

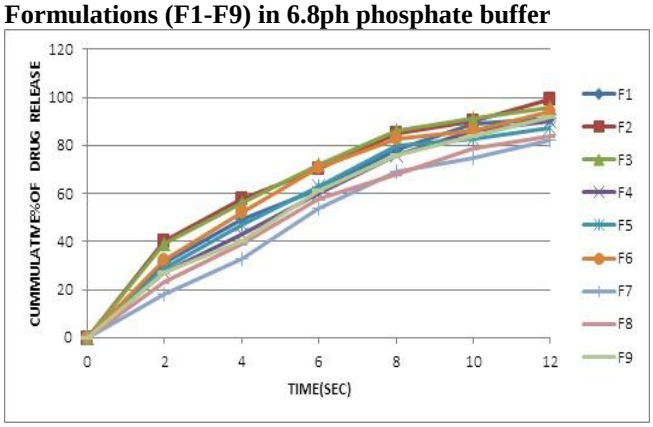
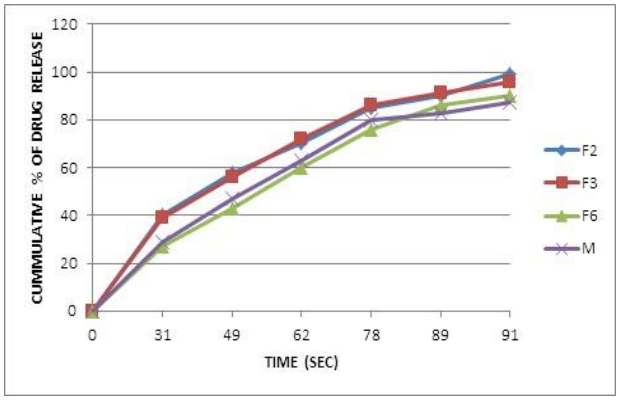
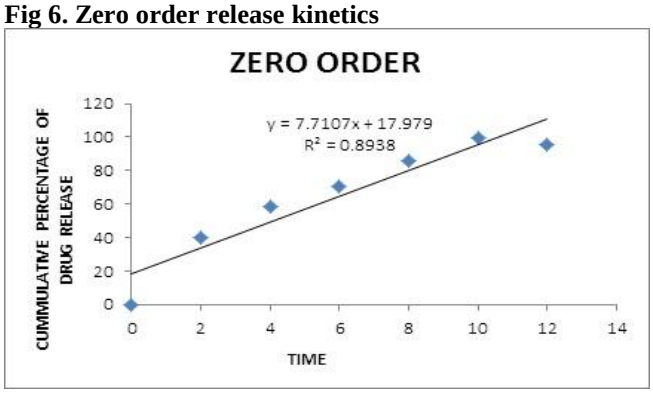


Fig. 5 Comparative Cumulative drug release of F2, F3, F6 with marketed



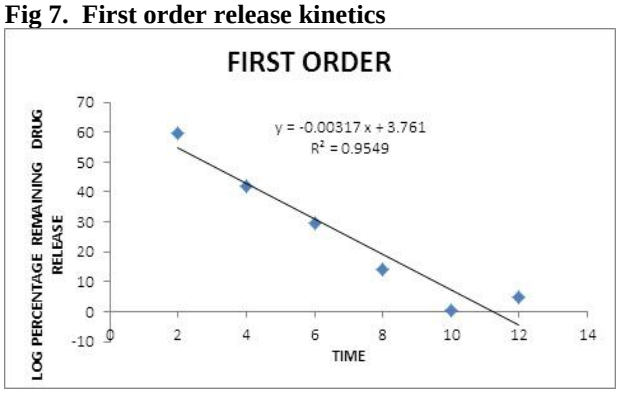
ZERO ORDER MODELL FITTING -F2:

Fig 6. Zero order release kinetics



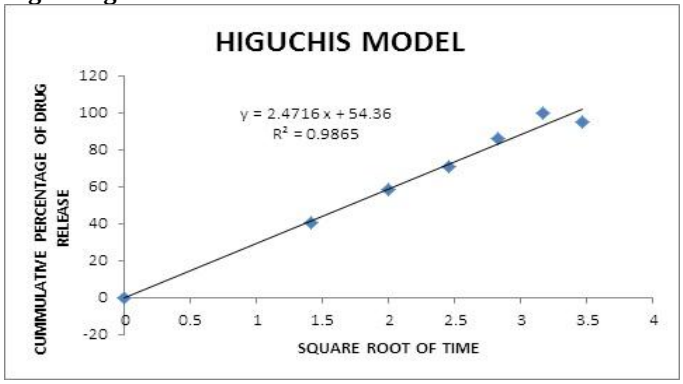
FIRST ORDER MODDEL FITTING-F2:

Fig 7. First order release kinetics



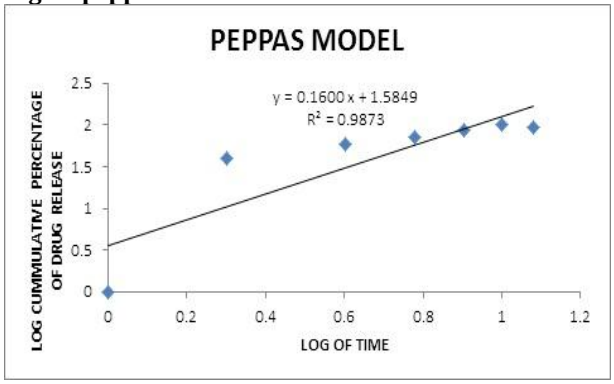
HIGUCHI MODELL FITTING-F2:

Fig 8. Higuchi model release kinetics



PEPPAS MODELL FITTING-F2:

Fig 9. peppas model release kinetics



DISCUSSION

FTIR

All the characteristic peaks of Candesartan were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the carrier.

PRE COMPRESSION PARAMETERS

The flow property for angle of repose ranges from 270-380; carr's index ranges from 12-19; and hausner's ratio ranges from 1.11-1.25 and it was concluded that the flow property was found to be good whers as the hausners's ratio for crospovidone has values 1.17-1.20 indicating excellent flow property.

POST COMPRESSION PARAMETERS

All the formulated (F1 to F9) tablets were passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight.

The maximum thickness of the formulation was found to be 2.59mm. The minimum thickness of the formulation was found to be 2.52mm.

The hardness of the tablet was found to be 3.7 to 4.2 Kg/cm^2.

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

The drug content for the all formulation was found to be in the range of 96.38%-99.26%. The results were within the limit specified by the IP.

In vitro Disintegration time was found to be in the range 12 to 84 sec. From all formulations, F2 (2 % CP) has minimum disintegration time. Formulations containing CCS (3%) has taken more time for disintegration.

Wetting Time was found to be in the range 6 to 42 sec. From all formulations, F2 (2% CP) has minimum wetting time.

All the 9 formulations were subjected to in vitro dissolution studies by using 6.8pH phosphate buffers. Dissolution data shows that formulation F2 shows improved dissolution as compared to other formulations.

The data obtained for *in-vitro* release were fitted into equations for the zero order and first order, Higuchi, Korsmeyer peppas models; the interpretation of the data was based on the values (Table 9) of the resulting regression co-efficient.

In case of best formulation, the first order and peppas model were found to be fairly linear and the 'r' coefficient value for pure drug Candesartan and its formulations with polymers. So the regression data of first order and peppas plots indicates that the drug was released by peppas model kinetics.

Comparison of formulated tablet with marketed tablet [Table 8]

In vitro dissolution study was carried out for conventional marketed Candesartan tablet and compared with best formulation F2.

Stability Study[Table 10]

The Candesartan tablets were subjected to stability studies at 40^oC and 75% RH for 3 month and from the above results, it was found that there is no significant effect on the tablets.

CONCLUSION

The conclusion drawn from the present investigation is given below;

- ❖ Pre-formulation studies of candesartan were performed. From the FT-IR, the interference was verified and found that candesartan did not interfere with the polymers used.
- ❖ Nine batches of oral disintegrating tablets of candesartan were successfully prepared using sodium starch glycolate, Crosscarmellose and Crospovidone by sublimation method.
- ❖ The tablets were evaluated for parameters like thickness, hardness, friability, *in vitro* dispersion time, wetting time, water absorption ratio, % drug content and *in*- vitro drug release studies.
- ❖ Based on the results, formulation containing Crospovidone (F-2) was identified as ideal and better formulation among all formulations developed for candesartan tablets.
- ❖ The results suggests that oral disintegrating tablets containing 3mg of CP (F2) show the best results in terms of percent drug release(99.06%) in 12 sec.
- ❖ The final optimized formulation (F2) was compared with marketed product of candesartan tablets which shows 99.06% drug release within 30 mins. From this observation it was concluded that the formulated tablets of candesartan (F2) were superior and effective in achieving patient compliance.

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