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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CANDESARTAN USING SOLID DISPERSION TECHNIQUE

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Abstract

Recent developments in fast dissolving/disintegrating tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The objective of the present study was to prepare the mouth disintegrating tablet of Candesartan. Solid dispersion of drug was prepared. The drug Candesartan is fused with carriers i.e; PEG, urea, cyclodextrin, PVP, mannitol. The carrier which gives the best release of Candesartan is selected to prepare the fast dissolving tablet. Different super disintegrants such as CCS, SSG, CP were used. The tablets were prepared by direct compression technique. Candesartan, Being a class II drug, it exhibits low solubility and high permeability.

Present work involves attempts to improve bioavailability of Candesartan through solid dispersion technique and induce fast dissolving property using super disintegrants. In the formulation of Candesartan fast dissolving tablets, Candesartan fused with mannitol (optimised carrier), is used as API and super disintegrant CP (5%) were added to the formulation, results showed that 88% was released in 30min in formulation (CSF1) and 81% was released in 30min from the formulation(CSF2) containing super disintegrant CCS. In the formulation 3,(CSF3) the super disintegrant SSG (5%) was added and 93% was released in 30min. In formulation 4,(CSF4) the super disintegrant CP (7.5%) was added and 90% was released in 30min.In formulation 5,(CSF5) the super disintegrant CCS (7.5%) was added and 89% was released in 30min. In formulation 6, (CSF6) the super disintegrant SSG (7.5%) was added and 96% was released in 30min, which is the highest amongst all and hence this is finalised. All these tablets showed required hardness, limited friability and good disintegration time (with in IP limits). All the formulations were evaluated for drug content and results are obtained. Amongst all formulations, formulation CSF6 and SSG as super disintegrant showed the least disintegration time and faster dissolution.

Key words: Candesartan, Solid Dispersion, Bioavailability, Super Disintegrants

1. Introduction

1.1. Solid Dispersions Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation[1]

The rate process include

- Dissolution of the drug in an aqueous environments.
- Absorption across cell membranes into systemic circulation.

For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step[2].

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. They have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole & chloramphenicol come immediately to mind. With the recent advent of high through put screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes – Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$dc/dt = \frac{AD\,(C_s - C)}{h}$$

Where dc/dt = rate of dissolution

A = Surface area available for dissolution.

D = Diffusion coefficient of the compound

C_s = Solubility of the compound in the dissolution medium.

C = Concentration of drug in the medium at time t

h = Thickness of the diffusion boundary layer adjacent to surface of the dissolving compound.

1.1.1. Definition of solid dispersions

Chiou and Riegelman defined the term solid dispersion as a "dispersion of one or more active ingredients in an inert carrier or matrix at a solid state prepared by the melting (fusion), solvent or melting solvent method.

1.1.2. Materials used as Carrier for Solid Dispersions:[4,5,6]

Sugars: Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose.

Acids: Citric acid, succinic acid.

Polymeric Materials: Povidone, polyethylene glycol, hydroxypropyl methyl cellulose, cyclodextrins, hydroxypropyl cellulose, pectin.

Insoluble or Enteric Polymers: Hydroxy propyl methyl cellulose phthalate, Eudragit L-100, Eudragit-S 100, Eudragit RL and Eudragit RS.polyoxyethylene stearate[4,5,6].

Surfactants: Polyooxyethylene stearate.

Miscellaneous: Urea and Urethane

2. Materials and Method

Part 1:- Materials

Part 2:- Methods

2.1. Part 1 – Materials

The following materials are used in the present study

- Ingredients
- Equipments

Ingredients: [(7)] The Materials used in the present work are as follows.

S.NO	INGREDIENTS	SUPPLIERS
1	Candesartan	Chandra lab, hyd
2	Crospovidone[(7)]	S.D Fine chem. LTD Mumbai.
3	CrossCarmellose Sodium[(7)]	S.D Fine chem. LTD Mumbai.
4	Sodium Starch Glycolate[(7)]	S.D Fine chem. LTD Mumbai.

5	Microcrystalline Cellulose[7]	S.D Fine chem. LTD Mumbai.
6	Talc[7]	S.D Fine chem. LTD Mumbai.
7	Magnesium Stearate[7]	S.D Fine chem. LTD Mumbai.

Table no. 2.1.a

II. Equipments

S.NO	Equipments	Manufacturer	MODEL
1	Digital balance	Wensar weighing scales Ltd.	PGB-600
2	Bulk Density Apparatus	Thermo lab	ETD- 1020
3	Tablet hardness tester	Lab Hosp Corporation	
4	Friability test apparatus	Lab Hosp	
5	Vernier calliper	Aerospace	
6	FTIR spectrophotometer	Agilent technologies	Cary 630 FTIR
7	Compression machine	Rimek	RSB4 - 1
8	Tablet dissolution apparatus	LAB INDIA	DS 8000/S
9	UV/Visible Spectrophotometer	Elico, PG instruments	T60 UV

Table no. 2.1.b

2.2. Part 2:- Method

Methods of Preparation of Solid Dispersion

Solid dispersions were prepared by different methods like solvent evaporation and fusion method.

Fusion method:

Each of water soluble carrier Urea, PEG6000, mannitol were weighed accurately in various ratios (1:1, 1:2, 1:3) and melted in a porcelain dish at 80-85ºC and to this calculated amount of candesartan was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies.

Solvent evaporation method:

Candesartan and each of water soluble carrier UREA, PEG 6000 and mannitol were weighed accurately in various ratios (1:1, 1:2, 1:3) and transferred to beaker containing sufficient quantity of methanol to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion were passed through sieve no.85 and stored in desiccator till further use.

Preparation of fast dissolving tablets of Candesartan solid dispersion by direct compression method[8)]

Solid dispersion of optimized formulation equivalent to 32mg of drug were taken and mixed with directly compressible disintegrant, filler and glident , in a plastic container. Powder blend were directly compressed using tablet compression machine

2.3. Analytical method development by U.V. Spectroscopy

Scanning of λ_{max} of candesartan

Preparation of Stock Solution - 100 mg of candesartan was taken in a 100 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 6.8 PH phosphate buffer solutions.

Stock solution was subsequently diluted with phosphate buffer to get 4µg/ml, 8µg/ml, 12µg/ml, 16µg/ml, 20µg/ml, 24µg/ml 28µg/ml, 32µg/ml. The results are tabulated and the linearity curve was constructed. The solution was than scanned in UV range between 200- 400nm UV-VIS Spectrophotometer, to determine the absorption maxima of the drug against blank as methanol.

2.4. Formulation Development

2.4.1. Selection of carriers for optimizing the best carrier to be used in the formulation.

***IN VITRO* dissolution studies**

TIME	SDUC 1	SDUC 2	SDUC 3	SDPEG 1	SDPEG 2	SDPEG 3	SDCYC 1	SDCYC 2
MIN	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2
5	7.2	8.0	7.9	8.4	10.2	10.1	16.4	18.8
10	19.3	20.3	22.1	20.3	19.0	26.4	22.8	21.3
15	36.6	32.2	34.4	30.0	35.2	37.8	35.4	28.4
20	45.3	46.5	49.9	48.6	46.4	48.8	48.7	41.3
30	59.4	59.9	56.6	60.2	60.3	56.4	56.1	58.9
45	64.3	66.2	69.5	65.1	63.6	64.5	60.4	64.5
60	70.2	78.5	78.9	74.2	76.4	78.6	66.1	72.3

TIME	SDCYC 3	SDPVP 1	SDPVP 2	SDPVP 3	SDMAN 1	SDMAN 2	SDMAN 3
MIN	1:3	1:1	1:2	1:3	1:1	1:2	1:3

5	**15.5**	**8.2**	**9.1**	**9.9**	**15.4**	**18.7**	**15.4**
10	**22.5**	**10.1**	**10.4**	**12.0**	**25.3**	**25.6**	**21.2**
15	**26.7**	**26.5**	**22.3**	**24.3**	**38.4**	**39.6**	**36.3**
20	**43.4**	**35.3**	**36.4**	**39.8**	**48.1**	**50.9**	**49.4**
30	**57.5**	**49.7**	**49.9**	**46.7**	**54.2**	**79.5**	**56.5**
45	**63.9**	**54.1**	**56.2**	**59.5**	**65.1**	**88.3**	**74.6**
60	**74.2**	**60.2**	**68.6**	**68.9**	**79.7**	**93.7**	**94.9**

Table no. – 2.4.a

Discussion: mannitol is optimised as the carrier for the tablet preparation as mannitol showed the highest percentage drug release.

2.4.2. Calculation

Drug : Carrier = 1:3 ratio

1part of drug = 32 mg (dose)

3 parts of carrier = 96mg

total 4parts of drug=128mg or 0.128g

Mannitol : Drug = 1200mg:400mg (approximately taken to prepare API)

1.2g:0.4g

Mixing both to get the drug and carrier mixture.

This mixture is used in the 6 formulations as drug and excipient mixture

Preparation of 6 formulations of Candesartan using various super disintegrating agents.

	CSF1	**CSF2**	**CSF3**	**CSF4**	**CSF5**	**CSF6**
API	**128mg**	**128mg**	**128mg**	**128mg**	**128mg**	**128mg**
CP	**5%**	**--**	**--**	**7.5%**	**--**	**--**
CCS	**--**	**5%**	**--**	**--**	**7.5%**	**--**
SSG	**--**	**--**	**5%**	**--**	**--**	**7.5%**
MCC	**qs**	**qs**	**qs**	**qs**	**qs**	**qs**
Talc	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**
Mag ste.	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**
Total	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**

Table no. 2.4.b

Formulation of 6 candesartan formulations changing ratios of super disintegrating agents.

	CSF1	**CSF2**	**CSF3**	**CSF4**	**CSF5**	**CSF6**
	(mg)	**(mg)**	**(mg)**	**(mg)**	**(mg)**	**(mg)**

API	**128**	**128**	**128**	**128**	**128**	**128**
CP	**12.5**	**-**	**-**	**18.75**	**-**	**-**
CCS	**-**	**12.5**	**-**	**-**	**18.75**	**-**
SSG	**-**	**-**	**12.5**	**-**	**-**	**18.75**
MCC	**97**	**97**	**97**	**90.75**	**90.75**	**90.75**
Talc	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**
Mg. Stearate	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**
Total	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**

Table no. 2.4.c.

API- ACTIVE PHARMACEUTICAL INGREDIENT

MCC- MICRO CRYSTALLINE CELLULOSE

SSG-SODIUM STARCH GLYCOLATE

CCS- CROSCARMELLOSE SODIUM

CP- CROSPOVIDONE

Direct compression technique is used

2.5. Evaluation of Tablets [9]

***In-vitro* dissolution:**

The prepared tablets were subjected to *in vitro* dissolution. Dissolution test was carried out using USP 2 paddle method [apparatus 2]. The stirring rate was 50 rpm, PH-6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±1°C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for **Candesartan** at **277 nm** by using UV-visible spectrophotometer.

Phosphate Buffer PH-6.8: Dissolve 28.80g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in sufficient water to produce 1000ml **(I.P)**

2.6. Kinetics [3]

Over the past few decades, significant medical advances have been made in the area of drug delivery with the development of controlled release dosage forms. There are large variety of formulations devoted to oral controlled drug release, and also the varied physical properties that influence drug release from these formulations. The release patterns can be divided into those that release drug at a slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component. The purpose of the controlled release

systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration . For this purpose, generally, controlled release system initially release part of the dose contained in order to attain rapidly the effective therapeutic concentration of the drug. Then, drug release kinetics follows a well defined behavior in order to supply the maintenance dose enabling the attainment of the desired drug concentration. In the light of wide versatility of application of controlled release formulations, in the field of med- ical sciences, they are unavoidable tools for the exploitation of the modern concept of therapeutic treatment whose aim is to increase drug effectiveness and patient compliance, to reduce the administration frequency and side effects connected to dosing. As a matter of fact, controlled release formulations bring engineers and pharmacists to work together with the common aim of realizing more and more effective products. For this purpose, the use of mathematical modeling turns out to be very useful as this approach enables, in the best case, the prediction of release kinetics before the release systems are realized. More often, it allows the measurement of some important physical parameters, such as the drug diffusion coefficient and resorting to model fitting on experimental release data. Thus, mathematical modeling, whose development requires the comprehension of all the phenomena affecting drug release kinetics, has a very important value in the process optimization of such formulation. The model can be simply thought as a mathematical metaphor of some aspects of reality that, in this case, identifies with the ensemble of phenomena ruling release kinetics. For this generality, mathematical modeling is widely employed in different disciplines such as genetics, medicine, psychology, biology, economy and obviously engineering and technology.

3. Results and Discussion

3.1. Candesartan λ - MAX Determination

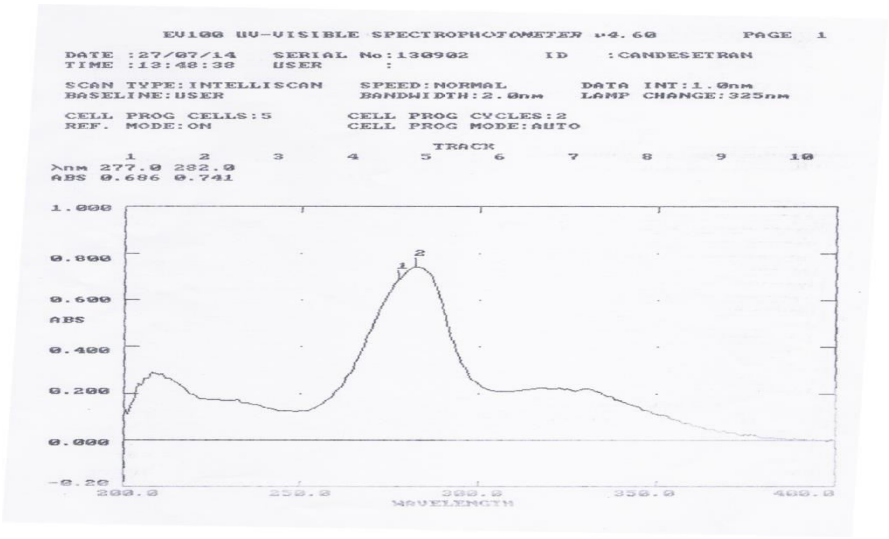


Fig no. 3.1.a

Discussion: From the above graph, the maximum absorbance (λ_{max}) peak was observed at 277nm.

3.2. Standard Graph of Candesartan

Result:

As shown in Fig the maximum absorbance of candesartan in24 µg/ml is found to be 277 nm. Hence all further UV estimations were done at λ_{max}277 nm.

S.NO.	CONCENTRATION(µcg/ml)	ABSORBANCE (nm)
1	0	0
2	4	0.112
3	8	0.223
4	12	0.339
5	16	0.451
6	20	0.569
7	24	0.686
8	28	0.741
9	32	0.858

Table no. 3.2.a.

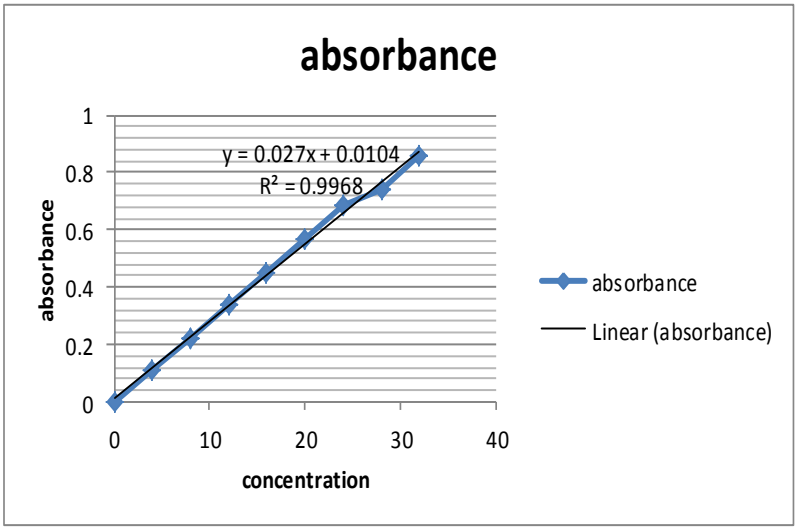


Fig No. 3.2.a.

Title	Value
Correlation coefficient	0.9968
Regression equation	Y =0.028 X +0.0104
Slope (m)	0.028
Intercept ©	0.0104

Table no. 3.2.b.

3.3. Drug Excipient Compatibility Studies By FTIR.

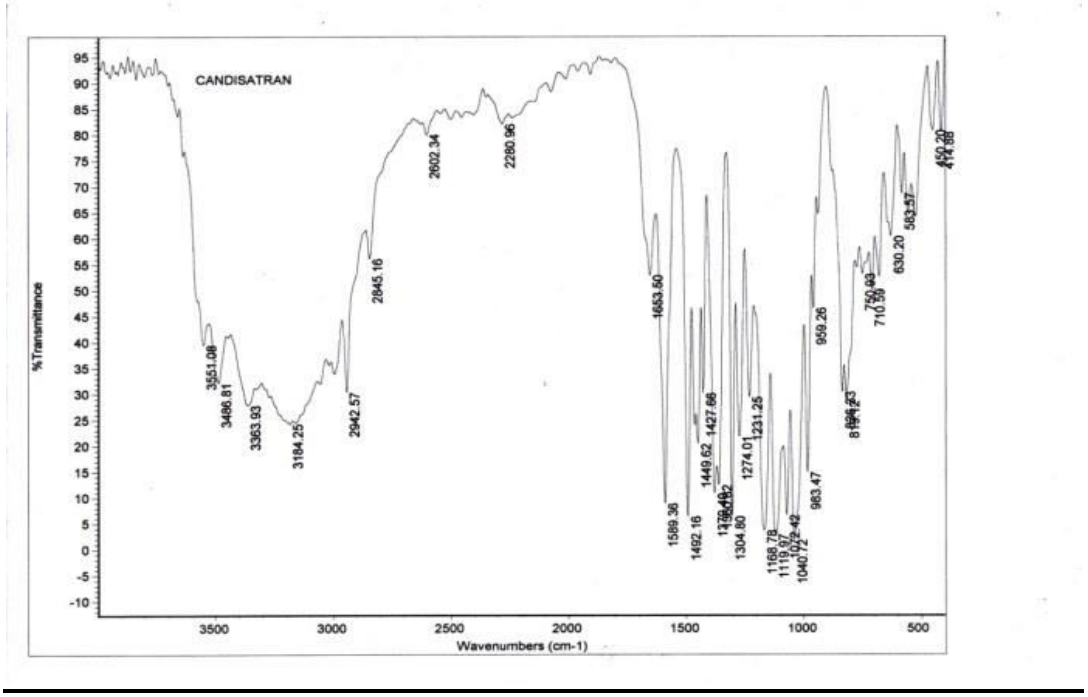
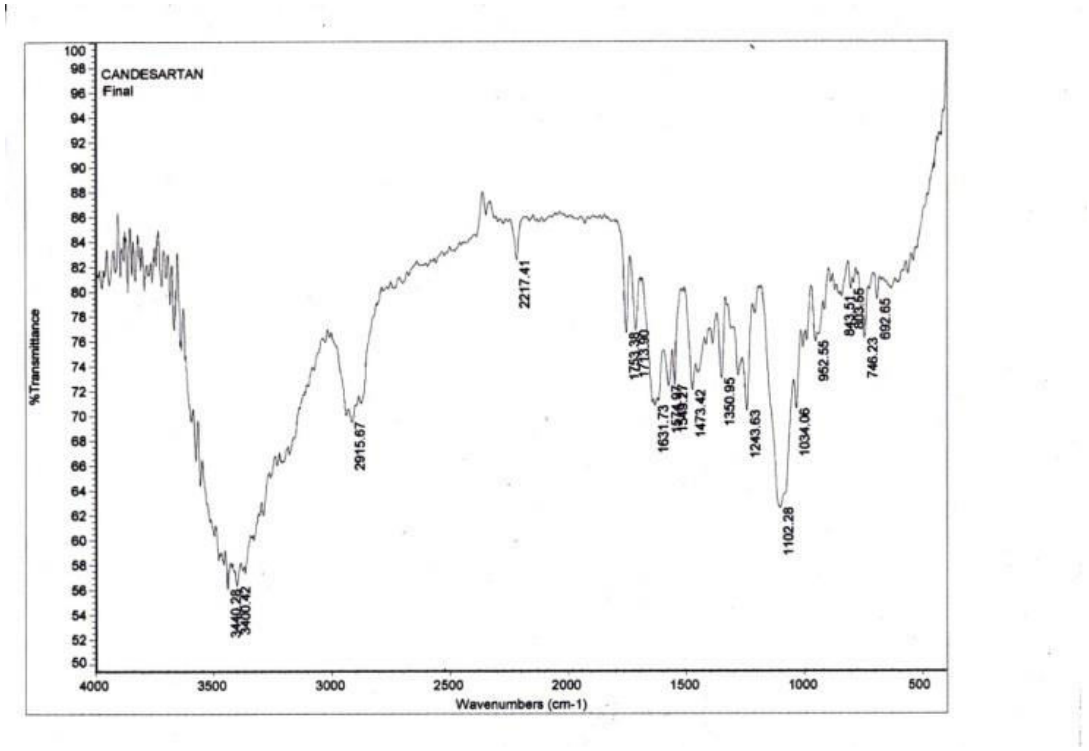


Fig. 3.3.a FTIR spectra of pure drug Candesartan.



3.3.b. FTIR spectra of final drug candesartan (candesartan+excipients).

S.NO.	STRECHING	RANGE (cm^{-1})
1	AROMATIC C-H	2850-2950
2	C=0 STRECH	1700-1750
3	C-O STRECH	1200-1250
4	O- SUBSTITUTION	700-750
5	C-N STRECHING	1600-1650

Table no. 3.3.a.

Discussion: FTIR studies revealed that there was no physico-chemical interaction between Candesartan and other excipients.

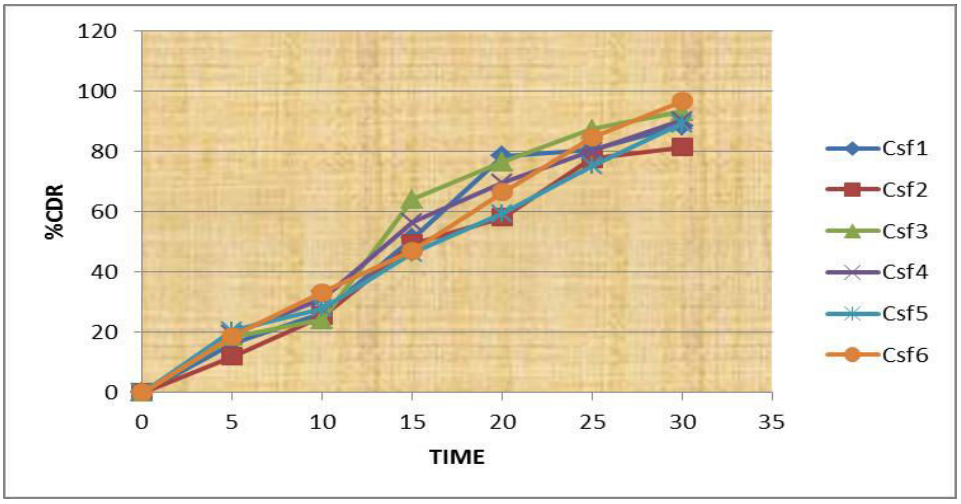
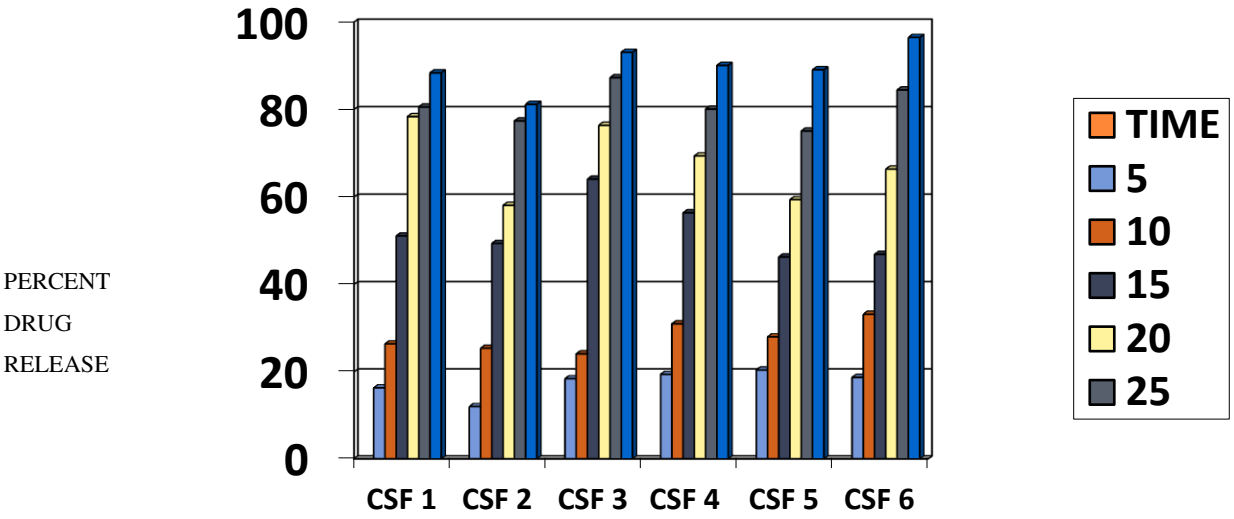


Fig. No. 3.3.c Graph Indicating the Drug Release Profiles of Different Fast Dissolving Formulations of Candesartan.



3.3.d. Percentage drug release of all Candesartan six formulations.

3.4. Kinetics of candesartan formulation.

For formulation CSF6 the following values of kinetics are obtained.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	3.245	-0.043612505	17.86168574	1.313656947
Intercept	0.782142857	2.18571623	-12.34605177	0.133558448
Correlation	0.998651519	-0.918628594	0.95648767	0.985442132
R 2	0.997304856	0.843878494	0.914868662	0.971096195

Table no. 3.4.

Formulation 6 (CSF6), optimized formulation was determined for the kinetics and graphs are obtained.

For Formulation CSF6 the Zero Order Graph Of Kinetics Obtained Is As Follows

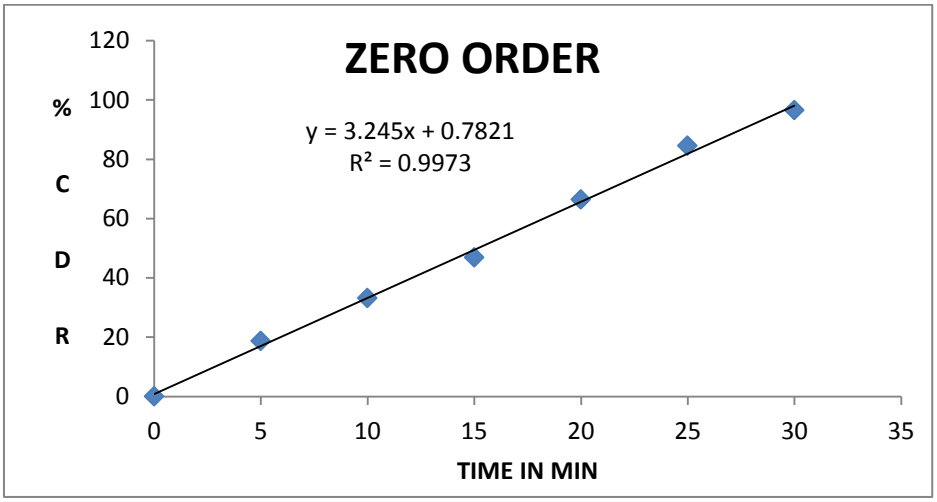


Fig no. 3.4.a

For Formulation CSF6 the First Order Graph of Kinetics Obtained Is As Follows

Fig no. 3.4.b.

For formulation CSF6 higuchi plot obtained is as follows.

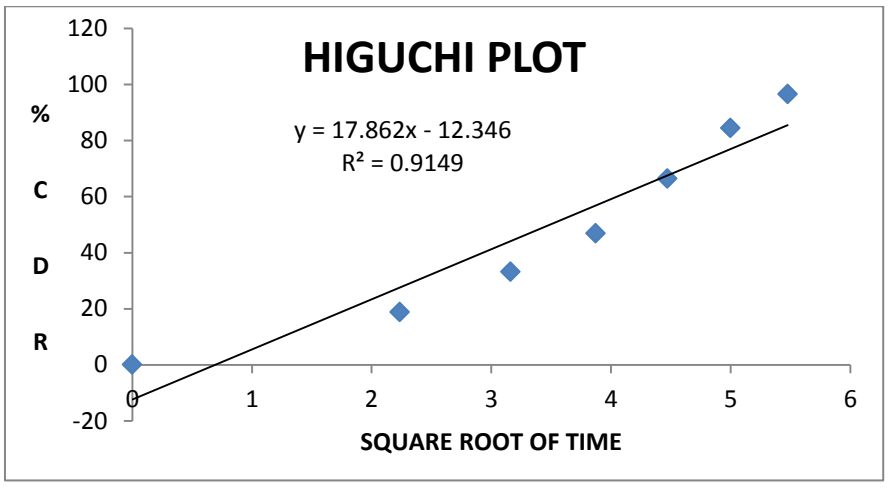


Fig no. 3.4.c.

For Formulation CSF6 Peppas Plot Obtained is as Follows.

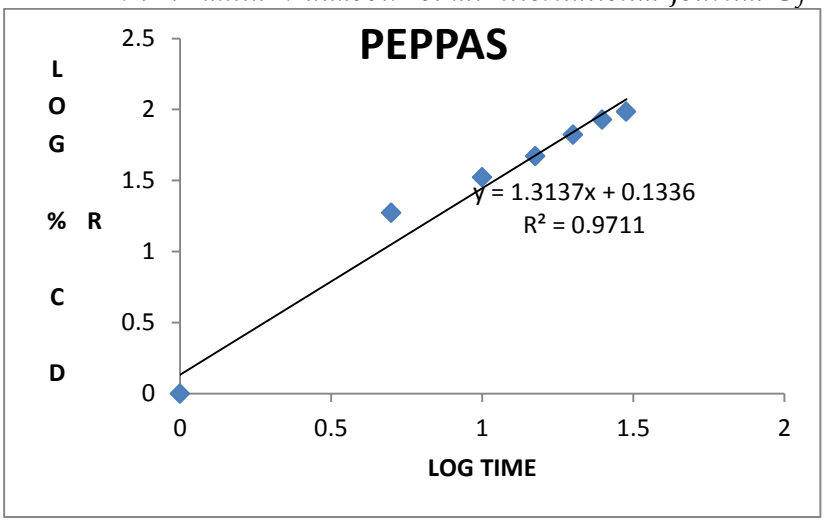


Fig no. 3.4.d.

Discussion: From the above graphs of kinetics it is observed that it follows zero order

3.5. Precompression Results of the six Candesartan Formulations.

Formulation	Blend Property				Angle of Repose
	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	
CSF1	0.380	0.501	23.91	1.310	26.1^0
CSF2	0.710	0.873	19.714	1.251	25.4^0
CSF3	0.371	0.483	23.188	1.299	25.1^0
CSF4	0.483	0.681	29.03	1.409	24.4^0
CSF5	0.461	0.608	24.177	1.32	26.7^0
CSF6	0.710	0.873	19.714	1.251	24.5^0

Table no 3.5.a.

Discussion: The flow properties of the formulations were found to be in limit and the optimised formula was in limit and has a fair flowing property. This had no effect during compression of tablet.

3.6: Post Compression Results of Tablets.

S. No	Physical parameter	CSF1	CSF2	CSF3	CSF4	CSF5	CSF6
1	AvgWeight (mg)	248	249	251	252	250	248
2	Hardness (kg/cm^2)	4.82	4.66	4.31	3.53	3.12	3.25
3	Thickness (mm)	2.1	2.11	2.15	2.2	2.13	2.16
4	Friability %	0.45	0.52	0.21	0.18	0.38	0.57

5	**Disintegration time**	1min 36sec	1min 52sec	2min 32sec	1min 22sec	1min 44sec	1min 18sec
6.	**Wetting time**	89.65 sec	73.24 sec	68.46 sec	46.29 sec	35.38 sec	18.42 sec

Table no. 3.6.a

Discussion: The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table. All the tablets complied with the official requirements of uniformity of weight. All the physical attributes of the prepared tablets were found to be practically within control.

3.7. (Percentage Drug Release of 6 Formulations of Candesartan).

Time (mins)	**CSF1**	**CSF2**	**CSF3**	**CSF4**	**CSF5**	**CSF6**
5	16.3	12.0	18.4	19.4	20.4	**18.7**
10	26.4	25.4	24.1	31.0	28.0	**33.2**
15	51.1	49.4	64.1	56.4	46.3	**46.9**
20	78.4	58.1	76.4	69.4	59.4	**66.4**
25	80.6	77.4	87.3	80.1	75.1	**84.5**
30	88.4	81.2	93.1	90.1	89.1	**96.5**

Table no. 3.7.a

Discussion: candesartan formulation 6 (csf6) was optimised because the percentage drug release was found to be highest when compared to all the formulations.

3.8. Stability Studies

Candesartan tablets of **CSF6** formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 40^0C &75% RH.

Physical evaluation of Tablets for stability studies of optimized formulation

Parameter	**Initial**	**40^0C / 75%RH**
Disintegration (min)	1min 22sec	1min 30sec
Drug release after 20 min(%)	98.1	97.0

Table no. 3.8.a

Observation: The Candesartan tablets were subjected to stability studies at 40^oC and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be with in the limits according to ICH guidelines.

4. Conclusion:

- FTIR studies revealed that the fundamental peaks of candesartan showed no chemical interaction between the drug and polymer. Hence the further study can be carried out.
- The powdered blend showed Good flow properties and was suitable for direct compression.
- All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity was found to be within limits.
- Results of dissolution profiles of various formulations showed that formulation csf6 showed 96.5% drug release at the end of 30 minutes which is much more than the other formulation. Thus due to fast release of drug within stipulated time CSF6 was chosen as best formulation.
- The Dissolution data were fitted into kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) indicate that the drug release was following Zero order release kinetics.
- The Candesartan tablets were subjected to stability studies at 40^{o}C and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be with in the limits according to ICH guidelines. There was no significant changes in % release of drug after 3 months indicating that the formulation is stable.

From the above points, it is clear that, candesartan is suitable drug to formulate into fast disintegrating tablet and may provide a better therapeutic profile than that of conventional dosage form.

Introduction of fast disintegrating dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world`s population. Hence, patient demand and availability of various technologies have increased the acceptance of fast disintegrating tablets, which in prolongs the patient life of a drug. Keeping in view of the advantages of the delivery system, fast disintegrating dosage forms have been successfully commercialized and these dosage forms very well accepted at doctors as well as patient level.

5. References

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