eISSN: 2231-0541 CAS CODEN: PHARN8 An ELSEVIER Covered Journal

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 4 | Issue 6 | November-December 2013 | Pages 1625-1638

Original Research Article

FORMULATION AND EVALUATION OF BILAYERED TABLETS OF CANDESARTAN CILEXITIL

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Received: 27-08-2013 Revised: 12-09-2013

Accepted: 29-10-2013 Available online: 01-11-2013

ABSTRACT

Candesartan cilexitil is an angiotensin II receptor antagonist used mainly for treatment of hypertension. Results from the CHARM (Candesartan in Heart failure - Assessment of moRtality and Morbidity) study in the early 2000s demonstrated the morbidity and mortality reduction benefits of Candesartan therapy in congestive heart failure. Candesartan cilexetil is sold under the brand name "Atacand" in the United States by ASTRAZENECA. So, the aim of the present study is to develop and evaluate Candesartan cilexetil bilayered tablets.Candesartan cilexitil immediate release formulation were prepared by direct compression technique using Cross povidone as super disintegrant in order to enhance its solubility and bioavailability and S.R formulation were prepared by direct compression technique using carbopol as polymer In total 21(9 I.R and12S.R)formulations have been prepared. Precompression and post compression parameters have been evaluated. The dissolution studies were carried out using USP Type 2 apparatus. Among the formulations F-12 showing a maximum drug release of 99.9% in 16 hrs was selected as the best one.

Key words: Candesartan cilexitil, bilayered tablets, direct compression technique Cross povidone, carbopol.

INTRODUCTION

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow [1-3]. Bilayered tablets offer definite advantages over conventional release formulation of the same drug. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing, to reduce capital investment etc. Zinc compatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose, reducing the dose frequency or providing uniform drug delivery, promoting patient convenience and compliance [4-8]. Candesartan cilexitil is an angiotensin II receptor antagonist used mainly for treatment of hypertension. Results from the CHARM (Candesartan in Heart failure - Assessment of moRtality and Morbidity) study in the early 2000s demonstrated the morbidity and mortality reduction benefits of Candesartan therapy in congestive heart failure. Thus, while ACE inhibitors are still considered first-line therapy in heart failure, Candesartan can be used in combination with an ACE to achieve improved mortality and morbidity vs. an ACE alone and additionally is an alternative in patients intolerant of ACE inhibitor therapy.[9]

MATERIALS AND METHOD:

Materials:

Candesartan cilexitil was obtained as gift sample from Dr. Reddy's laboratories (Hyderabad,India).Crosspovidone, AC-DI-SOL,SSG,Sodiumalginate, HPMCK100M, Carbopol 934, Xanthum gum were supplied by Aurabindo Pharmaceutical (Hyderabad, India). All other chemicals used were of analytical grade.

Pre compression parameters:

1. Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The flow characteristics are measured by angle of repose.

$$\theta = \tan^{-1} h/r$$

Where h = height of pile, r = radius of the base of the pile = angle of repose.

Angle of repose below 25^0 indicates an excellent powder flow.

2. Bulk density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the part of the inter particulate void volume. It is expressed as gm/ml and calculated using the equation.

$$P = W/V_b$$

Where P = bulk density. W = mass of the powder blend. V_b = bulk volume of powder blend.

3. Tapped density: Tapped density is the ratio of mass of powder to the tapped volume. It is calculated using the following equation and expressed as gm/ml.

$$P_{b,\,max} = W/V_{50}$$

Where $P_{b,\,max}$ = tapped density, W = mass of the powder blend.,V_{50} = volume of powder blend at 50 taps.

4. Carr's consolidation index:

It is defined as:

$$\text{Consolidation Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. Hausner's ratio: It is defined as

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

METHOD

The immediate release tablets containing 4mg Candesartan Cilexetil were prepared with a total tablet weight of 75mg. Based on the results of preformulation studies tablets were prepared by direct compression Technique and the composition Based on Literature survey and Compatibility Tests excipients like Crosspovidone, AC-DI-SOL, sodium starch glycolate, aerosil, di-calcium phosphate and magnesium stearate were used. Whereas for sustained release formulation polymers like carbopol 934p, sodium alginate, HPMCK100m, and natural polymer xanthum gum was used. The powder blend was mixed for ten minutes after which magnesium stearate was added to the blend and the mixing was continued for another 5 minutes. After obtaining a uniform blend, it was passed through sieve no: 60 and was prepared for compression. The compression of the powder blend was carried out using multi station punching machine (CADMACH MULTI STATION) by employing concave punches of 8mm diameter for and adjusting thickness and hardness accordingly.

EVALUATION OF TABLETS

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed and their average weight is calculated, such that each tablet weight should within the range of ± 5%.

Results are expressed as mean values ± SD.

Tablet hardness:

The Hardness of tablets was tested using Pfizer hardness tester.

Tablet thickness

A vernier caliper was used to determine thickness of 10 randomly selected tablets. Results are Expressed as mean values

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (250 mg) was extracted in 100 mL of 6.8 p^H buffer + Tween 80. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analyzed at 264 nm using a UV/ visible spectroscopy after suitable dilution with 6.8 p^H buffer +Tween 80.

Tablet friability

According to the BP specifications , 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus and rotated 100 times in 4 min at 25rpm. The percent weight loss was calculated for all formulation and was reported.

In- vitro Drug release studies:

Dissolution test was carried out using USP XXIV rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 6.8 p^H buffer + Tween 80 were used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Candesartan Cilexetil at 264nm nm by using a double beam UV spectrophotometer.

RESULTS

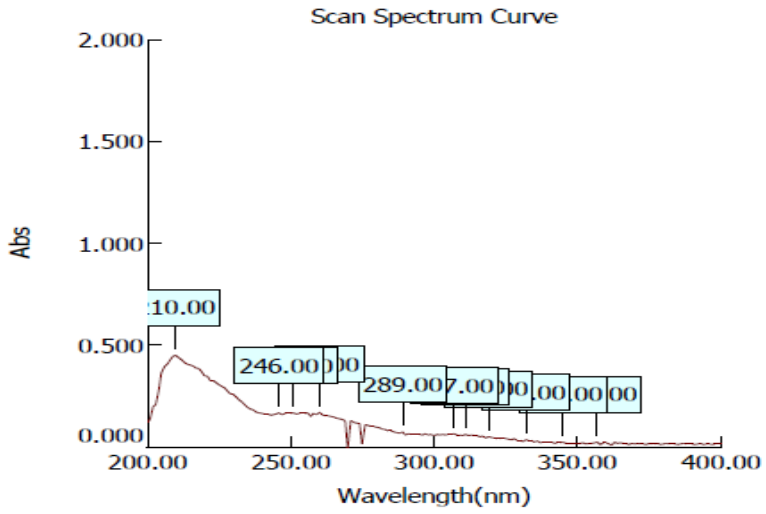

Fig.1.λmax in 6.8 pH buffer at 260 nm

Measured absorbance in 6.8 pH buffer

Concentration(µg) Vs Absorbance(nm)Values
2µg-0.059
4 µg-0.110
6 µg-0.171
8 µg-0.228
10 µg-0.284

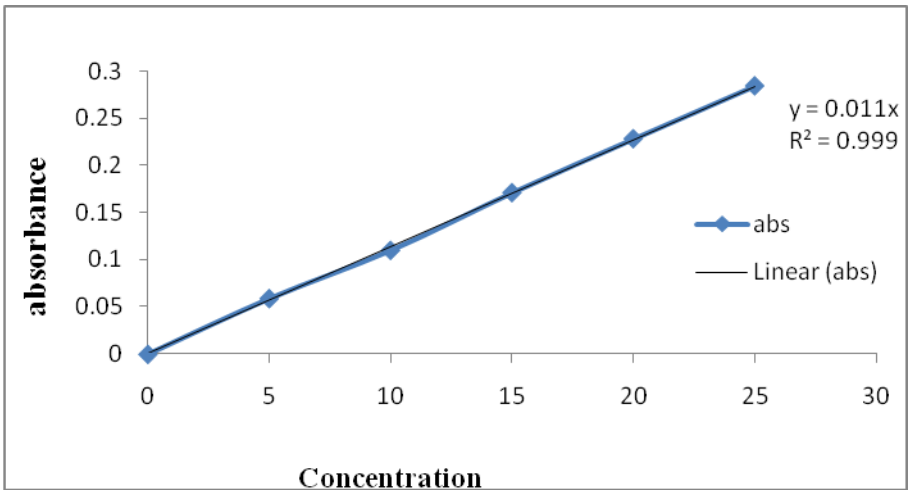

Fig.2.Calibration curve in 6.8 pH buffer

Table.1.Formulation chart for IR formulations

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan	4	4	4	4	4	4	4	4	4
Cross Povidone	3	-	-	4.5	-	-	6	-	-
AC-DI-SOL	-	3	-	-	4.5	-	-	6	-
SSG	-	-	3	-	-	4.5	-	-	6
DCP	65	65	65	63.5	63.5	63.5	62	62	62
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mag.stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	75	75	75	75	75	75	75	75	75

Table.2.Formulation chart for SR formulation

Ingredients (in mgs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Candesartan	8	8	8	8	8	8	8	8	8	8	8	8
Sodium alginate	17.5	-	-	-	26.25	-	-	-	35	-	-	-
HPMC K 100M	-	17.5	-	-	-	26.25				35		
Xanthum Gum	-	-	17.5	-	-	-	26.25				35	
carbopol	-	-	-	17.5	-	-		26.25				35
M.C.C	144	144	144	144	135.2	135.2	135.2	135.2	126.5	126.5	126.5	126.5
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mag.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	175	175	175	175	175	175	175	175	175	175	175	175

Precompression parameters:

Table.3.Flow properties of IR formulation

Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hauser's Ratio	Angle of Repose
F-1	0.383±0.01	0.498±0.01	23.09±0.03	1.300±0.02	28.32±0.31
F-2	0.451±0.01	0.581±0.00	22.37±0.04	1.288±0.01	26.23±0.07
F-3	0.482±0.02	0.621±0.05	22.38±0.03	1.288±0.01	28.92±0.07
F-4	0.383±0.01	0.498±0.01	23.09±0.03	1.300±0.02	28.32±0.31
F-5	0.380±0.01	0.485±0.01	21.64±0.02	1.276±0.01	24.59±0.17
F-6	0.429±0.01	0.555±0.00	22.70±0.04	1.293±0.01	25.63±0.06
F-7	0.441±0.01	0562±0.02	21.53±0.04	1.274±0.01	27.23±0.07
F-8	0.393±0.01	0.501±0.01	21.55±0.04	1.274±0.01	25.34±0.14
F-9	0.400±0.02	0.517±0.01	22.63±0.01	1.292±0.01	23.63±0.06

Table.4.Flow properties for SR formulation

Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (˚)
F1	0.451±0.01	0.581±0.00	22.37±0.04	1.288±0.01	26.23±0.07
F2	0.482±0.02	0.621±0.05	22.38±0.03	1.288±0.01	28.92±0.07
F3	0.383±0.01	0.498±0.01	23.09±0.03	1.300±0.02	28.32±0.31
F4	0.380±0.01	0.485±0.01	21.64±0.02	1.276±0.01	24.59±0.17
F5	0.393±0.01	0.501±0.01	21.55±0.04	1.274±0.01	25.34±0.14
F6	0.400±0.02	0.517±0.01	22.63±0.01	1.292±0.01	23.63±0.06
F7	0.376±0.01	0.489±0.01	21.99±0.03	1.300±0.02	25.31±0.24
F8	0.378±0.02	0.490±0.02	22.85±0.03	1.296±0.00	24.61±0.28
F9	0.429±0.01	0.555±0.00	22.70±0.04	1.293±0.01	25.63±0.06
F10	0.441±0.01	0562±0.02	21.53±0.04	1.274±0.01	27.23±0.07
F11	0.459±0.01	0.590±0.01	22.71±0.03	1.257±0.01	28.26±0.15
F12	0.446±0.03	0.573±0.01	22.16±0.05	1.284±0.02	26.34±0.14

Table.5.Evaluated parameters of IR formulations

Formulations	Thickness (mm)	Hardness (kg/cm²)	Weight variation	Friability (%)	Assay (%)
F-1	2.8±0.099	5.5±0.03	0.16±0.04	0.11	97.01±0.94
F-2	2.6±0.016	5.4±0.03	0.22±0.017	0.06	98.35±0.14
F-3	2.5±0.035	5.6±0.22	0.18±0.02	0.14	99.50±0.47
F-4	2.8±0.024	6±0.49	0.17±0.03	0.04	97.40±0.29
F-5	2.7±0.029	5.1±0.51	0.20±0.05	0.14	99.40±0.2
F-6	2.6±0.053	5.4±0.59	0.16±0.06	0.06	98.01±0.14
F-7	2.6±0.052	5.5±0.27	0.20±0.04	0.16	99.91±0.15
F-8	2.6±0.022	5.5±0.17	0.19±0.04	0.41	98.5±o.57
F-9	2.65±0.016	5.4±0.57	0.18±0.06	0.02	99.21±0.92

Table.6.Evaluated parameters of bi layered formulations

Formulations	Thickness	Hardness	Friability	Weight Variation	Drug Content
F1	4.9±0.01	10.2±0.15	0.11	0.20±0.04	99.2±0.2
F2	4.56±0.01	9.4±0.14	0.06	0.14±0.09	99.4±0.1
F3	4.8±0.02	10.1±0.22	0.14	0.21±0.05	98.2±0.4
F4	4.56±0.02	7.1±0.16	0.04	0.17±0.03	99.1±0.5
F5	4.77±0.01	9.7±0.17	0.14	0.20±0.23	100 ±0.2
F6	4.45±0.02	5.23±0.06	0.06	0.16±0.06	98.9±0.5
F7	4.62±0.03	5.51±0.03	0.16	0.20±0.04	99.2±0.2
F8	4.16±0.04	4.76±0.12	0.41	0.19±0.04	101.1±0.2
F9	4.01±0.02	5.25±0.15	0.02	0.18±0.06	99.2±0.2
F10	4.21±0.04	4.96±0.12	0.19	0.16±0.04	101.1±0.2
F11	4.23±0.03	5.73±0.12	0.16	0.22±0.017	101.7±0.4
F12	4.45±0.05	5.51±0.15	0.14	0.18±0.02	99.8±0.3

***invitro* Drug Release Studies:**

Table.7.Invitro drug release of IR tablets

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	18.28	14.52	16.82	23.25	20.01	21.45	36.25	22.5	25.45
10	29.45	21.54	25.25	37.25	29.54	32.45	54.46	39.55	48.45
15	39.45	34.25	36.59	45.45	49.99	40.25	78.49	57.45	65.56
20	59.52	47.42	49.25	62.15	56.95	58.69	87.99	78.45	80.45
30	72.58	67.85	68.53	79.23	71.25	72.52	100.45	89.66	93.45
40	89.99	78.32	80.52	86.79	84.25	84.52	-	98.45	99.66
50	94.95	84.52	88.45	98.25	89.95	92.56	-	-	-
60	99.89	90.25	92.45	-	97.45	101.25	-	-	-

Table.8.Invitro Drug Release for Bilayered tablet

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
10	18.33	16.45	17.55	18.23	16.99	17.13	16.52	17.23	15.25	18.99	17.43	16.25
20	29.16	28.45	27.33	29.43	26.85	27.99	26.95	28.99	27.54	28.12	26.52	27.89
30	33.40	31.42	30.23	31.99	33.49	32.29	31.45	32.23	30.93	31.43	33.12	32.48
1	40.45	44.45	40.99	39.52	37.85	43.45	40.23	36.45	35.45	38.45	39.42	34.59
2	53.45	59.65	54.65	49.23	49.45	55.95	51.56	46.32	39.93	59.43	47.45	38.59
3	64.55	74.95	72.92	68.56	62.99	70.45	69.45	54.65	44.95	65.35	63.54	42.15
4	74.23	89.45	80.53	73.45	72.55	85.95	78.66	61.45	49.94	73.84	78.59	47.25
5	84.34	96.85	89.53	82.45	80.45	92.15	82.22	69.45	54.89	82.15	77.77	52.86
6	98.45	-	98.32	89.95	92.92	99.45	89.45	74.50	60.23	88.64	81.13	59.84
7	-	-	-	99.52	100.2	-	94.95	80.19	64.75	91.35	86.45	65.55
8	-	-	-	-	-	-	98.98	86.29	68.99	96.95	92.95	69.99
9	-	-	-	-	-	-	-	91.45	73.45	101.23	96.55	71.97
10	-	-	-	-	-	-	-	96.65	78.88	-	101.35	76.23
12	-	-	-	-	-	-	-	100.25	90.45	-	-	89.25
14									98.45	-	-	95.24
16	-	-	-	-	-	-	-	-	-	-	-	99.9

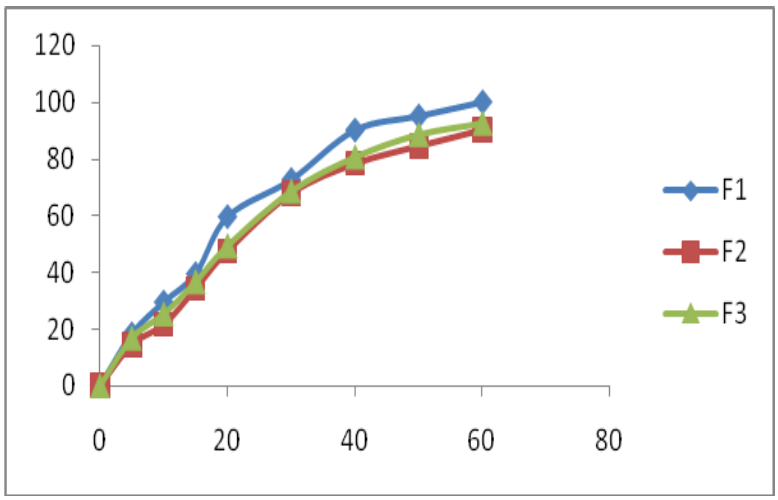

Fig.3.comparative In vitro Drug Release Profiles of IR formulations F1-F3

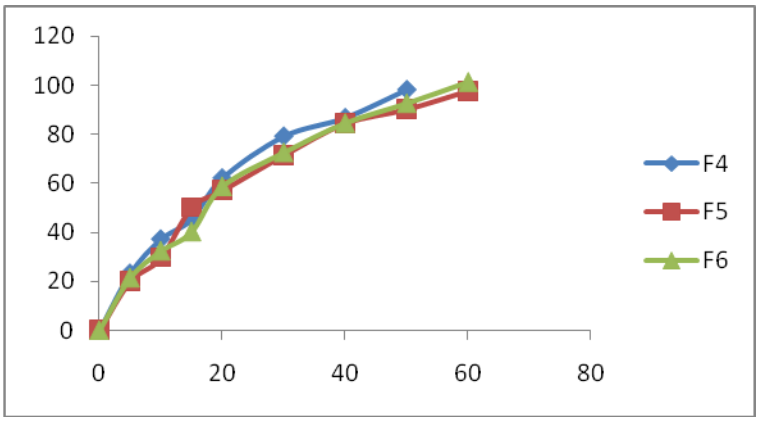

Fig.4.Comparative In Vitro Drug Release Profiles of IR formulations F4-F6

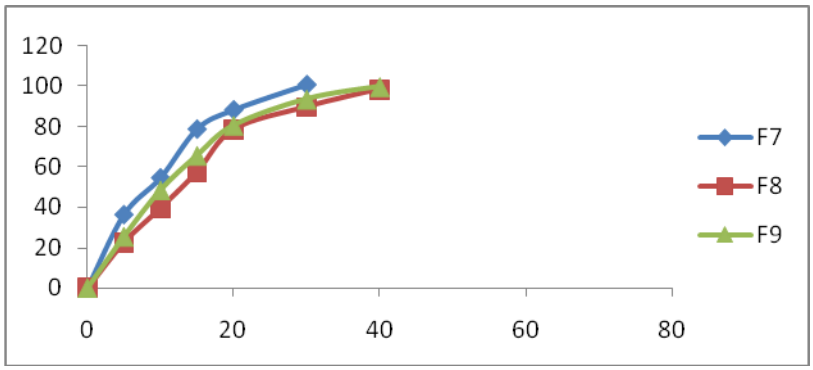

Fig.5.Comparative In Vitro Drug Release Profiles of IR formulations F7-F9

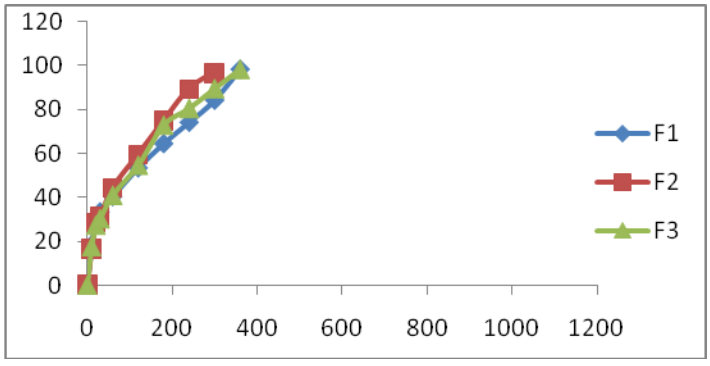

Fig.6.Comparative In Vitro Drug Release Profiles of Bilayered Formulations F1-F3

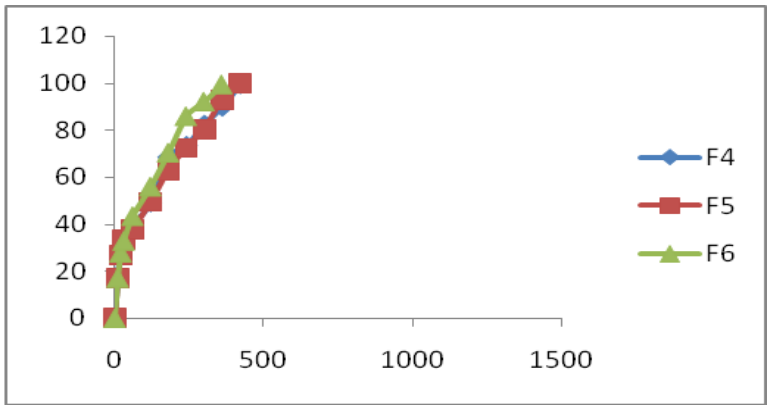

Fig.7.Comparative In Vitro Drug Release Profiles of Bilayered Formulations F4-F6

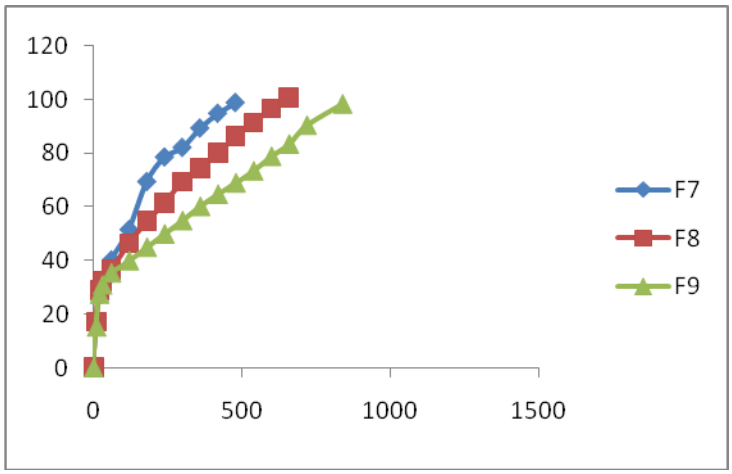

Fig.8.Comparative In Vitro Drug Release Profiles of Bilayered Formulations F7-F9

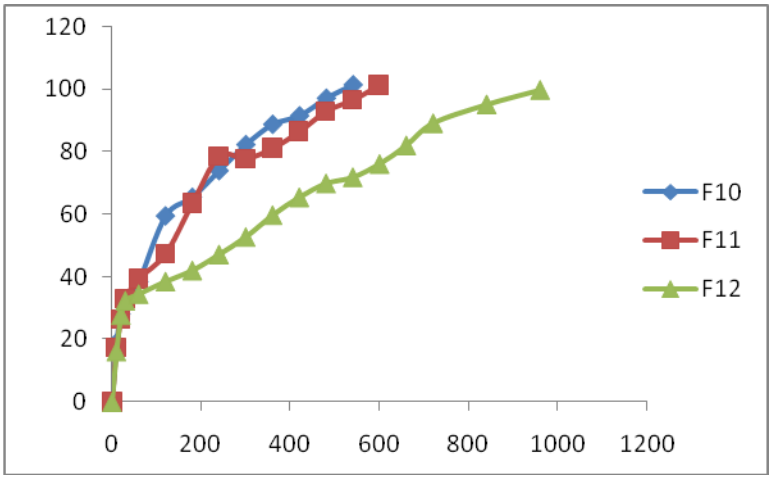

Fig.9.Comparative In Vitro Drug Release Profiles of Bilayered Formulations F10-F12

DISCUSSION

The wavelength maxima (λmax) of candesran cilexitil were found to be 260nm in 6.8pHbuffer as shown in Fig.1. The calibration curve was plotted between absorbance and concentration. The linearity was found to be in the range of 5-25µg/ml in pH 6.8buffer. The regression value was as shown in Fig.2. Drug and excipient compatibility was confirmed by comparing spectra of FTIR analysis of pure drug with that of various excipients used in the formulation. The bilayered tablets were formulated by using super disintegrates such as SSG, AC-DI-SOL, Cross Povidone and polymers like Sodium alginate, Xanthum gum, HPMCK100m, Carbopol. The flow properties of different immediate release formulation are shown in the Table. 3. The results for angle of repose (θ) obtained was found to vary from 23.10^0 - 28.19^0 which indicates the coating material has good flow property and can be used for direct compression. The Bulk and Tapped density of immediate release powder blend were from 0.382-0.482 gm/ml and 0.489-0.629 gm/ml respectively. Carr's index calculated showed to vary from 21.4-23.7% indicating that the blend has a good flow property. Whereas Hauser's ratio analyzed is in 1.16-1.22 range representing a good flow. The flow properties of bi layered formulation are shown in the Table. 4. The results for angle of repose (θ) obtained was found to vary from 23.10^0 - 28.19^0 which indicates the coating material has good flow property and can be used for direct compression The Bulk and Tapped density of various bi layered material blend were from 0.372-0.489gm/ml and 0.483-0.629gm/ml respectively. Carr's index calculated showed to vary from 21.4-23.7% indicating that the blend has a good flow property. Whereas Hauser's ratio analyzed is in 1.16-1.22 range representing a good flow. All the evaluated parameters result obtained from different formulations of tablet is shown in Table 5. Hardness of various immediate release tablets were in range of 5.2-6.0kg/cm^2 enabling good mechanical strength. The thickness observed was 2.6-2.8mm. The tablets selected from different formulation passed the uniformity of weight test prescribed in IP. The individual tablet weights when compared with average weight were within the official limit (±5%) of % deviation. The friability of immediate release tablets formulations were within the acceptable limits and ranged from 0.36-0.42%. All the evaluated parameters result obtained from different formulations of tablet is shown in Table .5. Hardness of various bi layered tablet were in range of 10.2-6.5kg/cm^2 enabling good mechanical strength. The thickness observed was 4.1-4.8mm. The tablets selected from different formulation passed the uniformity of weight test prescribed in IP. The individual tablet weights when compared with average weight were within the official limit (±5%) of % deviation. The friability of press coated tablet formulations were within the acceptable limits and ranged from 0.36-0.42.The results acquired from the

dissolution study of tablets are shown in Table 7. Tablets were subjected to dissolution in 6.8pH buffer with tween 80.Nine formulations were formulated using crosspovidone, ac-di-sol, SSG, F1-F3 were formulated using 4% concentration , F4-F6 were formulated using 6% concentration, F7-F9 were formulated using 8% concentration. The drug release was increased with increase in concentration. And from the above %CDR Values F7 formulation was selected as best formulation. IR layer of all the formulation showed the burst release (4mg) of candesartan cilexitil within 30 min. Presence of super disintegrant (cross povidone) 8% w/w in immediate release layer showed faster disintegration of the layer. Formulations F1,F2,F3,F4 were formulated using the polymers sodium alginate, HPMCk100M, Xanthum gum, carbopol 934 in the ratio 10% showed a sustained release for a period of 5hr to 7hr. Formulations F5, F6, F7, F8 were formulated using the polymers sodium alginate, HPMCk100M, Xanthum gum, carbopol 934 in the ratio 15% showed a sustained release for a period of 7hr to 12hr. Formulations F9, F10, F11, F12 were formulated using the polymers sodium alginate, HPMCk100M, Xanthum gum, carbopol 934 in the ratio 20% showed a sustained release for a period of 14hr to 16hr. A drug release of 99.9% at 16th hour was provided by F12 which was considered as best formulation based upon the results obtained from dissolution study performed.

The drug release pattern of formulation F12 which is formulted using carbopol934p was fitted in different kinetic models which showed highest regression for zero order kinetics with Higuchi's type of drug release mechanism.

ACKNOWLEDGEMENT

The Authors would like to thank Spectrum Pharma Ltd for providing facilities for pursuing the project.

CONCLUSION

The floating tablets of Candesartan Cilexetil were successfully formulated the bi layered tablets containing cross povidone, carbopol 934p (F12) showed satisfactory sustained drug release properties. The optimized formulation F12 followed zero order kinetic and the mechanism of drug release was found to be Higuchi mechanism.

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