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Research Article

FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL FLOATING TABLETS BY MELT GRANULATION TECHNIQUE

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ABSTRACT

The purpose of this study was to formulate Candesartan cilexetil floating matrix drug delivery system by melt granulation technique. These tablets were developed to prolong gastric residence time and increase its bioavailability. The Candesartan cilexetil tablets were prepared by melt granulation technique, using polymers such as Hydroxy Propyl Methyl Cellulose (HPMC K100M), ethyl cellulose, Gelucire 54/02, 43/01 alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The prepared granules were subjected to pre & post compression studies. The optimized studies with monolithic tablets with optimum post compression parameters. The results of dissolution studies floating lag time indicate that formulation F10 exhibited good and desired drug release with in 12 hrs.

Keywords: Candesartan, Gastro-retentive floating tablet, Gelucire 54/02, 43/01, HPMC K100M.

INTRODUCTION

Candesartan cilexetil (CDS) a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist[1].

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5ylphenyl) benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester)[2]. Its extensive first pass metabolism results in poor bioavailability, showing 15 to 40 % bioavailability. It has a plasma half life of 7- 9 hrs and peak plasma concentration reaches within 3 to 4 hrs[3-4].

The ODDS triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time[5]. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices have been discovered till now. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values[6-7].

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Now a day by using melt granulation process in the pharmaceutical industry variety of dosage forms and formulations such as immediate release and sustained release pellets, granules, tablets are formulated. The process is less time consuming and uses less energy than wet granulation. Melt granulation is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drug[8-10].

The main purpose of this study was to design sustained release floating tablet of Candesartan Cilexetil by melt granulation technique to improve bioavailability, therapeutic efficiency, reduce dosing

frequency due to It produces toxicity like renal and hepatic impairment if given in higher doses(30mg) resulting inconvenience to the patient and the possibility of reduced compliance with prescribed therapy.

MATERIALS AND METHODS

MATERIALS

Candesartan cilexetil was received as a gift sample from Spectrum pharma research solution Pvt Ltd, Hyderabad, India. Hydroxy Propyl Methyl Cellulose K100M (HPMC K100M) was obtained from Yarrow Chem. Products, Mumbai, India. Gelucire 43/01 was obtained from Gattefosse india pvt ltd, Mumbai. Sodium bicarbonate, Aerosil and talc were obtained from Sd fine Chemicals, Mumbai, India. Microcrystalline cellulose was obtained from Chemdyes Corporation, Ahmedabad, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

METHODS

Preparation of Candesartan cilexetil floating tablets by melt granulation

Gelucire (43/01&54/02) was melted in a large china dish at 70°C and the required quantity of Candesartan cilexetil was added to melted mass. Previously prepared geometric mixture of HPMC K100M and sodium bicarbonate was added to Candesartan - Gelucire (43/01&54/02) mixture and stirred well to mix. This mass was removed from a hot plate and subjected to scrapping until it attained room temperature. The coherent mass was passed through 22 mesh and the resulting granules were resifted using 44 meshes to separate fines. The granules were collected and mixed with talc (2%) and Aerosil (1%)as shown in table 1. The lubricated blend was compressed using round tooling on Rimek-I rotary tablet machine (Karnavati Engineering, Kadi, India). Compression pressure was adjusted to obtain tablets with hardness in a range of 2–4 kg/cm^2.

In vitro buoyancy studies

The *in vitro* buoyancy of the tablets was studied at 37 ± 0.5°C in 100 ml of simulated gastric fluid (SGF) at pH 1.2 without pepsin (USP). The duration of tablet floatation was observed visually.

In vitro dissolution study

The *in vitro* dissolution study of Candesartan tablets was performed using USP apparatus (model TDT-08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37 ± 0.5°C using 0.1NHcl (pH 1.2; 900 mL) as a dissolution medium. At predetermined time intervals, 5-mL samples were withdrawn, filtered through a 0.45μm membrane filter, diluted and assayed at 256 nm using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from calibration curve[11-12].

Drug content

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 16 mg of Candesartan cilexetil was transferred to a 100 ml volumetric flask containing 100 ml of buffer of pH 1.2 it was shaken by mechanical means for 1 hr. Then it was filtered through a whatman filter paper. From this resulted solution 1ml was taken, diluted to 100 ml with buffer of pH 1.2 and absorbance was measured against blank at 256 nm.

Drug Release kinetics

To determine the values of correlation coefficient (R2) and the mechanism of drug release from the formulations, the data were treated according to zero-order (cumulative percentage drug released *vs.* time, Eq 1), first order (Log cumulative percentage drug retained *vs.* Time, Eq 2), the Highuchi equation [21] (Cumulative percentage drug released *vs.* square root of time, Eq 3) models.

M t = M 0 + k 0 t …… (1)
InM t = InM 0 + k 1 t …… (2)
M t = M 0 + k H t1/2 ……..… (3)

Where Mt/ Mα is the cumulative amount of drug released at any time, t and M0 is the dose of the drug incorporated in the delivery system. k0, k1 and kH are rate constants for zero-order, first order and Higuchi models, respectively. The dissolution data were also fitted according to the well-known exponential equation of Peppas (Log of fraction of drug released *vs.* Log time, Eq (4) which is often used to describe drug release behaviour from polymeric systems.

$$\frac{M_t}{M_\alpha} = kt^n \quad \text{..... (4)}$$

Where, is the fraction of drug released at time, t, k is the kinetic constant, and n is the diffusional exponent for drug release. The

diffusional exponent, n, is dependent on the geometry of the device as well as the physical mechanism for release. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release rate is time dependent process. The values of n indicating drug release mechanism, if 0.1 < n < 0.5 indicating fickian diffusion mechanism and 0.5 < n < 1 indicating non-fickian diffusion mechanism[13-16].

RESULTS AND DISCUSSION

Pre-compression Evaluation

The granules of various formulations containing drug and meltable binders were evaluated for the angle of repose, loose bulk density(LBD), tapped bulk density(TBD), void volume, bulkiness, total porosity and Compressibility(carr's) index (Table 2). The angles of repose for all formulations were found to be in the range of 28 to 36^0 indicating passable (good) flow properties. The values for LBD and TBD were found to be in the range of 0.499 to 0.533 g/cm3 and 0.615 to 0.671 g/cm3 indicating good packing capacity. The Carr's indexes for all formulations were found to be in the range of 18.09 to 24.09% indicating passable flow properties, cohesiveness.

Post-compression Evaluation

The each formulation type (CF1 –CF12) were evaluated for parameters such as weight variation, drug content, hardness, friability, Total floating time and (BLT) Buoyancy Lag time (Table 3). The weight of all formulation tablets were within the range according to IP. The hardness were in range of 2.0 ± 0.1 to 3.5±0.07kg/cm2,which indicating that the increase in polymer content increase the interparticulate bonding during compaction which results in increase in crushing strength of tablets. The Friability was found to be 0.020±0.052 to 0.92±0.036%. As friability was below 1% tablets in each formulation can withstand the mechanical shocks. Percentage drug content in formulations CF1 to CF12 were found to be in the range of 96.87±0.3 to 100.7±0.78%. It showed uniform distribution of drug in matrix. All the parameters were run 3 times (n=3).

In Vitro Drug Release Study

The formulations CF1, CF2 were prepared using drug to lipid polymers ratio of 1:2 which were not giving desired buoyancy, total floating time and rapid drug released was observed (Fig1). The formulation CF3, CF4 prepared using 7.5% of Ethyl Cellulose (EC) which is floating enhancer and also act as release retardant. These formulations maintained required floating time of 12hr and drug release was found to be 96%,98% at the end of 8hrs respectively (Fig1).

Effect of lipid polymer on Invitro drug release

The formulations CF5, CF6 and CF7 were prepared using 1:1, 0.5:1.5 and 1.5:0.5 ratios of Gelucire54/02 and Gelucire43/02 respectively. Dissolution studies reviled that CF6 was giving sustained release of 89 % drug release for 10hrs when compared to 94% and 92% for CF5 and CF7respectively. From study, it was found that as concentration of Gelucire43/01 wax increases compared to ratio with Gelucire54/02, release of drug from matrices decreases (Fig 2). It may be due to slower penetration of dissolution medium in the matrices due to increase lipophilicity of waxy substances.

Effect of sodium bicarbonate on Buoyancy, FLT and Invitro drug release

Sodium bicarbonate generates CO2 gas in a presence of hydrochloric acid present in dissolution medium. Generated gas is trapped and protected within a gel formed by hydration of HPMC K100, thereby decreasing the density of tablet. As a density of tablet fall below 1 (density of water), the tablet becomes buoyant. The formulations CF6, CF8 and CF9 were prepared using same amount of polymer (Gelucire 54/02: Gelucire 43/01) and HPMC K100 while different amount of sodium bicarbonate (7.5%, 10%, and 12.5%). It was observed that as the amount of sodium bicarbonate increased from 7.5% to 12.5%, BLT was decreased. At higher amount of sodium bicarbonate, a tablet remained intact only for 10h and lost the matrix integrity. CF8 shown increased buoyancy of 56sec when compared to CF6 (4min).The formulation CF9 shown further increase in buoyancy of 48sec but the formulation lost its integrity and showed burst effect of drug released(Fig 3). Formulation CF8 containing 10% sodium bicarbonate remained buoyant and intact for 12h.

Effect of hydrophilic polymer concentration on drug release

The formulations CF8, CF10, CF11and CF12 were prepared using same amount of lipid polymers ratio (Gelucire 54/02: Gelucire 43/01), sodium bicarbonate (10%) and different concentration of HPMC K100 (10%, 15%, 20% and 25%) respectively. It was observed that as the concentration of polymer

increased the drug release decreased. Formulations CF8, CF10, CF11and CF12 were subjected to in vitro dissolution study. All formulations exhibited buoyancy lag time of less than 110sec. Tablets of batch CF10 retained integrity throughout a study and released the drug in controlled manner (98 CPR in 12h as shown in Fig 4). Tablets of formulation CF11 and CF12 released only 85% and 61% drug in 12 h, which may be due to higher amount of polymer. Among the all formulations CF10 showed desired time for total drug release of 98% for 12hrs (Fig 5).

Kinetic modeling of dissolution data

Kinetics of dissolution data were well fitted to zero order, Higuchi model, and Korsemeyer-Peppas model as evident from regression coefficients [Table 4]. In a case of –controlled or sustained release formulation, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers shows swelling as well as diffusion mechanism because a kinetic of swelling includes relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from glassy to rubbery state. Diffusion exponent n is an indicative of mechanism of drug release from the formulation. For a swellable cylindrical (tablet) drug delivery system, the n value of 0.45 is indicative of Fickian diffusion controlled drug release. Value of n between 0.5 and 0.85 signifies anomalous (non-Fickian) transport, n value of 0.85 indicates case II transport, and n value greater than 0.85 indicates super case II transport[15-16].

CONCLUSION

From present investigation it was concluded that a combined matrix system containing hydrophobic (Gelucire54/02: Gelucire43/01) and hydrophilic polymer (HPMC k 100) minimized bust release of drug from tablet. The study showed that ratio of hydrophobic polymer is appropriate waxy material, which can be used as matrix forming agent to sustain the release of drug such as Candesartan cilexetil. As concentration of polymer was increased, the drug release rate was decreased. Among these all formulations, CF10 was found to be best formulation. The formulations followed zero order, Higuchi kinetics and Peppas Equation while the drug release was found to be non fickian diffusion mechanism.

Table 1: Formulation composition of Candesartan cilexetil

S.No	Ingredients	Formulation code											
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10	CF11	CF12
1.	Candesartan	16	16	16	16	16	16	16	16	16	16	16	16
2.	Gelucire 54/02	32		32		16	8	24	8	8	8	8	8
3.	Gelucire 43/01		32		32	16	24	8	24	24	24	24	24
4.	HPMC K100	20	20	20	20	20	20	20	20	20	30	40	50
5.	Sodium bi carbonate	15	15	15	15	15	15	15	20	25	20	20	20
6.	Ethyl cellulose			15	15	15	15	15	15	15	15	15	15
7.	Micro crystalline cellulose	111	111	96	96	96	96	96	91	86	81	71	61
8.	Aerosil	2	2	2	2	2	2	2	2	2	2	2	2
9.	Talc	4	4	4	4	4	4	4	4	4	4	4	4
10.	**Total weight (mg)**	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Pre-compression evaluation matrix tablets of Candesartan cilexetil

S.No	Formulation code	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Index (%)		Angle of Repose (°)
1.	CF1	0.500	0.615	18.69	1.23	35±0.62
2.	CF2	0.533	0.653	19.9	1.24	33 ±0.25
3.	CF3	0.523	0.689	24.09	1.31	29±0.32
4.	CF4	0.512	0.625	18.08	1.22	31±0.15
5.	CF5	0.515	0.662	22.20	1.28	32±0.26
6.	CF6	0.521	0.671	22.35	1.28	34±0.32
7.	CF7	0.501	0.625	20	1.25	31±0.16
8.	CF8	0.519	0.659	21.24	1.26	33±0.24
9.	CF9	0.511	0.625	18.24	1.22	35±0.35
10.	CF10	0.524	0.630	19.84	1.23	28±0.29
11.	CF11	0.533	0.645	17.36	1.21	36±0.23
12.	CF12	0.499	0.630	17.07	1.20	34±0.15

Table 3: Post-compression evaluation matrix tablets of Candesartan cilexetil

S.No	Formulation code	Hardness (kg/cm2) ±SD	Friability (%)±SD	Tablet Weight (mg) ±SD	Drug Content (%)±SD	Buoyancy Lag Time	Floating time (hrs)
1.	CF1	2.0±0.1	0.71±0.030	197.5±0.61	96.87±0.3	200sec	4
2.	CF2	2.75±0.05	0.92±0.036	202.0±0.71	97.13±0.81	220 sec	4.5
3.	CF3	2.2±0.25	0.87±0.061	201.0±0.74	99.87±0.63	135 sec	6
4.	CF4	2.8±0.05	0.020±0.052	200.0±0.62	100.7±0.78	130 sec	5.5
5.	CF5	2.5±0.30	0.28±0.042	201.0±0.58	98.7±0.53	120 sec	6
6.	CF6	2.0±0.10	0.84±0.064	200.0±0.18	99.84±0.36	125 sec	9
7.	CF7	2.8±0.07	0.58±0.012	202.0±0.67	98.87±0.83	74 sec	8
8.	CF8	2.2±0.12	0.47±0.034	204.0±0.57	99.48±0.39	56 sec	9
9.	CF9	2.8±0.77	0.38±0.054	203.0±0.48	97.89±0.73	48 sec	8
10.	**CF10**	**3.1±0.31**	**0.15±0.065**	**200.5±0.75**	**99.98±0.33**	**55 sec**	**12**
11.	CF11	3.2±0.10	0.68±0.084	199.5±0.25	99.99±0.43	71 sec	11
12.	CF12	3.5±0.07	0.48±0.054	200.0±0.56	96.98±0.83	66 sec	12

Table 4: Regression coefficients and n values of (CF10) optimized formulation

	R^2value				n value
Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas	Korsmeyer peppas
CF10	0.9040	0.7990	0.9640	0.6250	0.8150

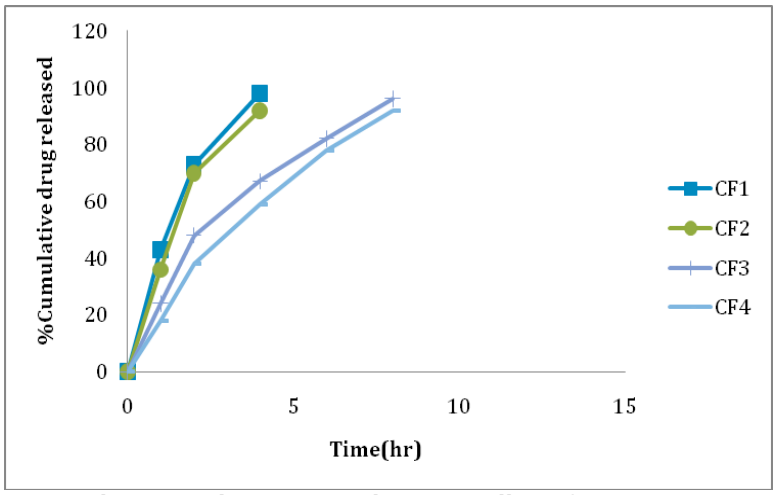

Fig. 1: In Vitro Drug Release Studies of CF1-CF4

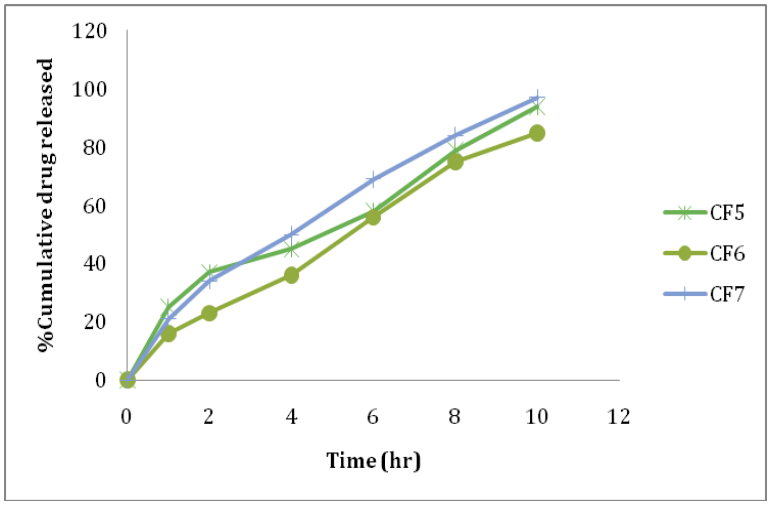

Fig. 2: Effect of lipid polymer on Invitro drug release

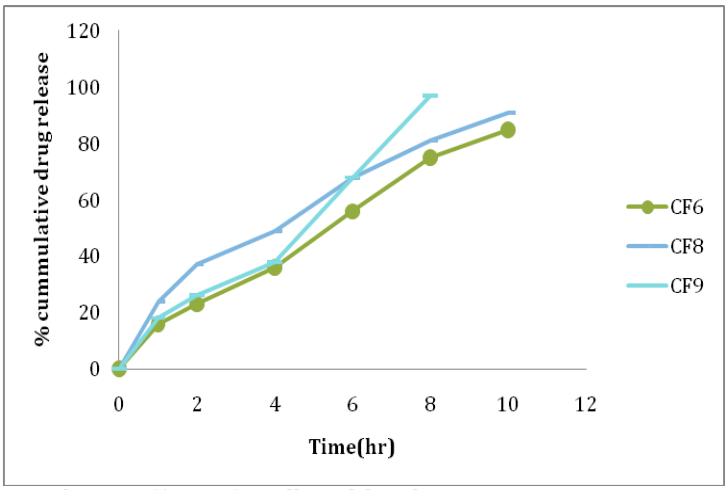

Fig. 3: Effect of sodium bicarbonate on Buoyancy, FLT and Invitro drug release

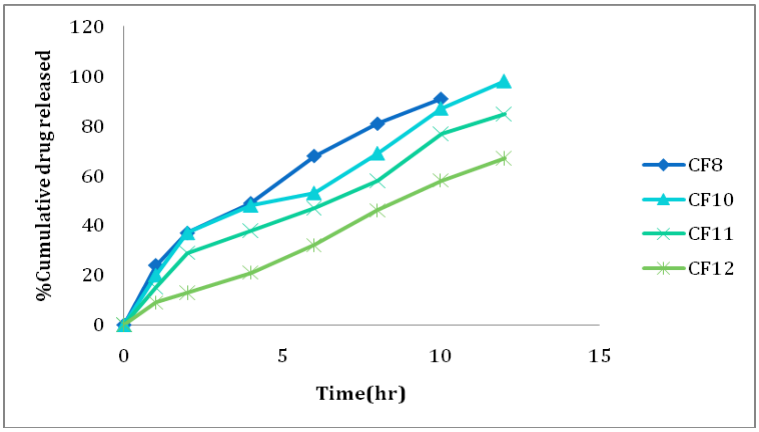

Fig. 4: Effect of hydrophilic polymer concentration on drug release

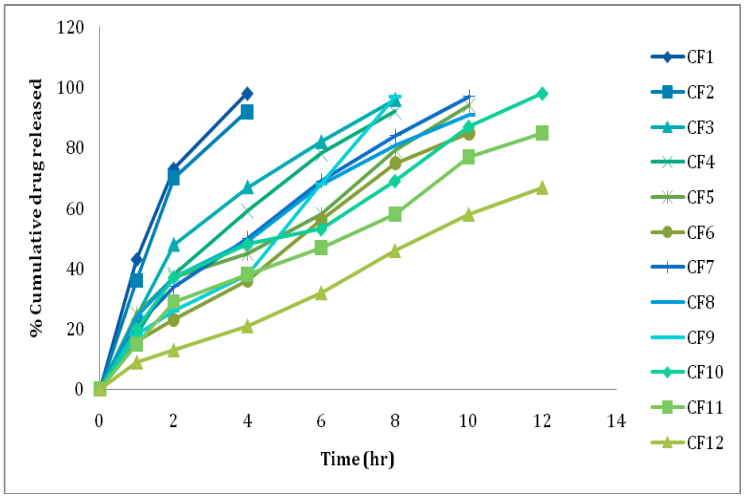

Fig. 5: Invitro drug release of Candesartan Formulations CF1-CF12

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