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Research Article

Chronotherapeutic Drug Delivery of Ezetimibe Using Press Coating Technology

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ABSTRACT

In the present research work pulsatile drug delivery system of Ezetimibe tablets were formulated by employing compression coating technology. Initially the core tablets were prepared by using various concentrations of super disintegrants, the formulated core tablets were coated with the polymers by using compression coating technology. All the core and press coated tablet formulations were subjected to various evaluation tests. The inner core formulated with ethyl cellulose and outer core with Eudragit L- 100. Invitro release of Ezetimibe of core tablet formulations F4 was optimized and showed less amount of drug release during lag time. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation F4 which meets demand of chronotherapeutic for drug delivery.

Keywords: Ezetimibe, Super disintegrants, Ethyl cellulose, Eudragit L-100, Pulsatile tablets.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R&D sector. Such systems offer temporal or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration[1]. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems, the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms[2]. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern of pharmaceutical drugs is known as pulsatile drug delivery/release system[3].

MATERIALS AND METHODS

Ezetimibe was obtained as a gift sample from pharmaceuticals Hyderabad. Micro crystalline cellulose (MCC, Avicel PH-102), Sodium starch glycolate, Talc, Ethylcellulose, magnesium stearate, eudragit L-100, were procured from Merck chemicals Pvt Ltd, Mumbai, India.

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. As shown in table powder mixtures of Ezetimibe, microcrystalline cellulose (MCC, Avicel PH-102), SSG, crosspovidone, Talc ingredients were dry blended for 20 min, followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min.; the resultant powder blend was manually compressed using lab press limited, India with a 5mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer

The various formulation containing Ezetimibe, Eudragit L-100.With Different compositions were weighed dried blended about 10 min and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Formulation of press coated tablets

The core tablets were press-coated with 50 mg of mixed blend as given in Table. 50mg of barrier layer material was weighed and transferred into a 6mm die then the core tablet was placed manually at the centre. The remaining barrier layer material was added into the die and compressed using Lab press limited India.*In-vitro Dissolution methods for Core tablets*

In vitro dissolution studies for pulsatile delivery dosage form examined with the conventional paddle method of core tablets were performed at 37 ± 0.5 °C using 6.8 phosphate buffers in USP II paddle method at 50 rpm for 60 minutes. 5 ml of filtered aliquot was manually withdrawn at predetermined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature[4]. The samples were analysed at 232nm using a UV spectrophotometer and percentage release was determined each formulation

In-vitro Dissolution methods for press-coated tablets

In –vitro dissolution studies of pulsatile delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5 °C using 0.1N HCL for 2hrs and then replaced with 6.8 phosphate buffer in USP II paddle method at 50 rpm 0.5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature. The samples were analysed at 232nm using a UV spectrophotometer. The lag time and

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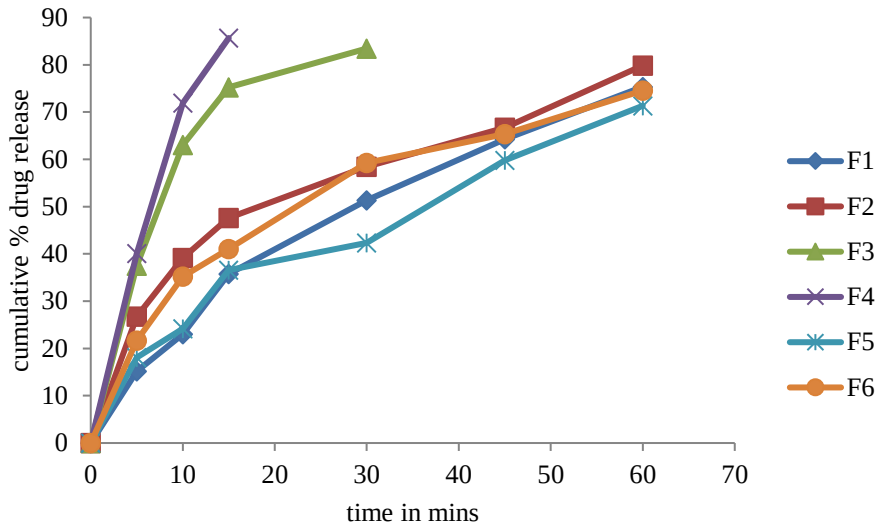

Figure 1: Dissolution graph for core tablets.

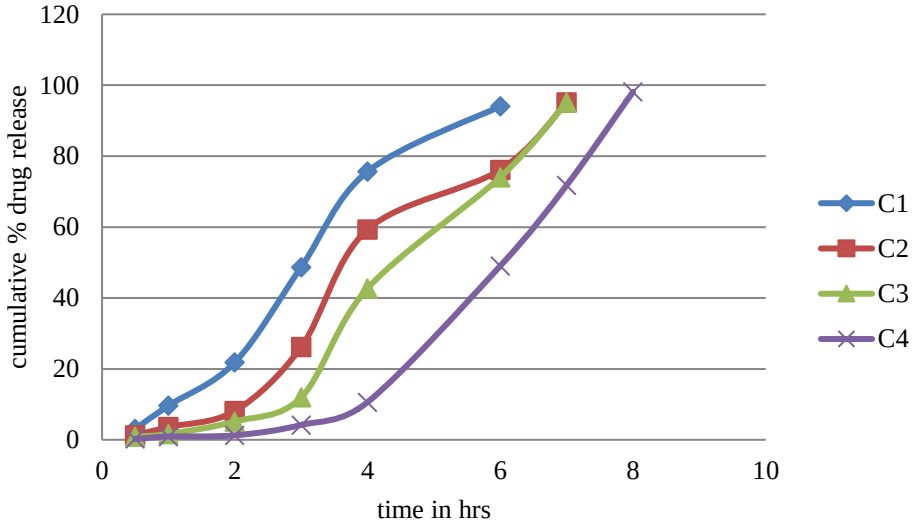

Figure 2: Dissolution graph for press coated tablets.

Table 1: Composition of core tablets.

S. No.	Ingredients(mg)	C1	C2	C3	C4	C5	C6
1.	Ezetimibe	10	10	10	10	10	10
2.	SSG	2.5	5	7.5	---	---	---
3.	CP	---	---	---	2.5	5	7.5
4.	Mg Stearate	2	2	2	2	2	2
5.	Talc	2	2	2	2	2	2
6.	MCC PH 102	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
7.	TOTAL WT	50	50	50	50	50	50

percentage release was determined for each formulation[5].

Evaluation of Parameters for Pre Compression Blend[6]

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved blend into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of blend}}{\text{Bulk volume of blend}}$$

Bulk density was expressed in g/cc.

Tapped density

Tapped density is determined by placing a graduated

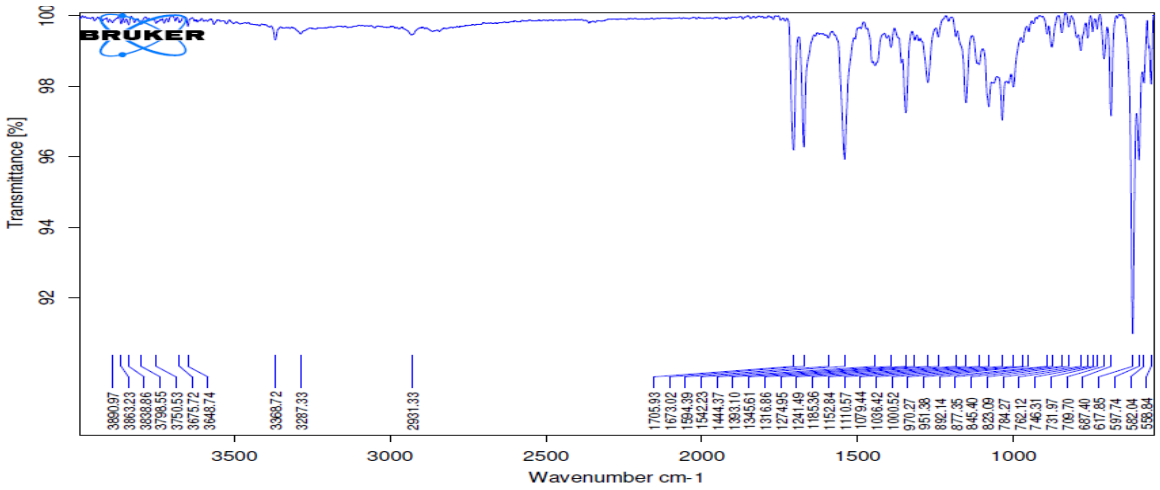

Figure 3: FT-IR Spectrum of Ezetimibe pure drug.

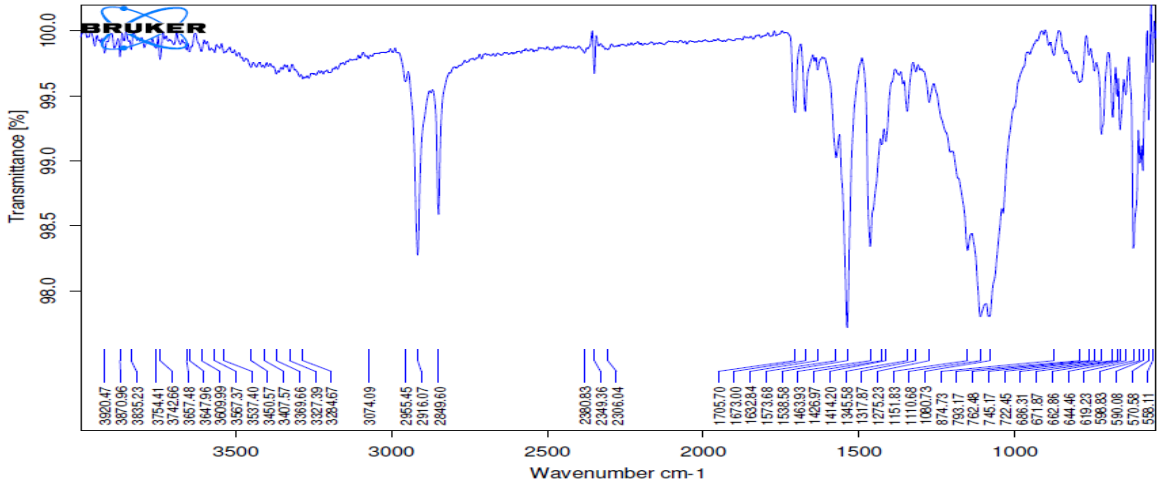

Figure 4: FT-IR Spectrum of Optimized formulation.

Table 2: Composition of press coated tablets.

S. No.	Ingredients	PF1	PF2	PF3	PF4
1.	Ethylcellulose	-	-	50	100
2.	Eudragit L 100	50	100	-	-
4.	Talc	2	2	2	2
5.	Mg. Stearate	2	2	2	2
6.	Core tablet	50	50	50	50
7.	Total wt.	100	150	100	150

cylinder containing a known mass of blend and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of blend}}{\text{Tapped volume of blend}}$$

Carr's Index (CI)

It is used to find the Carr's index.

$$CI = \frac{(TD\text{-}BD) \times 100}{TD}$$

Where TD = Tapped density, BD = Bulk density

Hausner's ratio

It indicates the flow properties of the powder and ratio of tapped density to bulk density of the powder.

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

Angle of repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder on a conical heat on a level, flat surface and measure the included angle with the horizontal.

$\text{Tan}\theta = h/r$

Where h= height of the heap, r= Radius of the heap

Post Compression Parameters for Tablets

Weight variation

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the

Table 3: Carr's index value.

Carr's Index	Properties
Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

Table 4: Hausner's ratio value.

Hausner's ratio	Properties
Excellent	1.00 – 1.11
Good	1.1 – 1.18
Fair	1.19 – 1.25
Possible	1.26 -1.34

Table 5: Angle of repose values.

Angle of Repose	Powder Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre-weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = \frac{(W1\text{-}W2)}{W} \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation

Drug content

Tablets were tested for their drug content. Ten tablets were

Table 6: Drug release profiles of various formulations.

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	15.8	26.77	37.51	36.2	18.07	21.68
10	23.02	39.18	63.05	62.5	24.18	35.25
15	35.78	47.59	71.95	71.25	36.58	41.06
30	51.37	58.45	75.24	74.23	42.32	59.27
45	64.25	66.71	83.45	82.45	59.79	65.36
60	75.34	79.86	--	---	71.34	74.56

Table 7: Dissolution data for press coated tablets.

Time (hr)	PF1	PF2	PF3	PF4
0	0	0	0	0
0.5	3.09	1.29	0.89	0.24
1	9.64	3.60	1.65	0.91
2	21.82	8.14	5.16	1.26
3	48.71	26.18	12.3	4.19
4	75.66	59.32	42.71	10.61
6	94.08	76.14	74.08	49.06
7	--	94.08	95.06	71.81
8	--	--	--	98.16

finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV Visible spectrophotometer. The drug concentration was calculated from the calibration curve

RESULTS AND DISCUSSION

Dissolution Studies

The Present study was aimed to develop pulsatile release tablets of Ezetimibe using press coated method. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies. Based on the drug release within the required time period F4 was optimized and further formulated for press coating. From the above core formulations PF4 was selected for press coat by using eudragit L-100, ethyl cellulose was optimized based on the lag time and percent of drug release and also further evaluated.

Pre compression formulation of powder blend

Tablet powder blend was subjected to various pre-formulation parameters like bulk density, tapped density, Carr's compressibility index, hausner's ratio and angle of repose.

Post compression Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the

Table 8: Pre compression formulation of powder blend.

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose
F1	0.42±0.045	0.47 ± 0.07	11.90±0.6	1.11±0.04	23.58±0.15
F2	0.44±0.044	0.49 ± 0.09	11.36±0.8	1.13±0.08	25.44±0.11
F3	0.45±0.045	0.51 ± 0.04	13.33±0.1	1.15±0.06	26.36±0.13
F4	0.47±0.044	0.54± 0.01	14.89±0.6	1.18±0.08	29.52±0.19
F5	0.41±0.045	0.46 ± 0.04	12.19±0.8	1.13±0.09	27.32±0.19
F6	0.43±0.045	0.48 ± 0.04	13.59±0.8	1.15±0.09	25.69±0.19

Table 9: Invitro drug release studies.

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	95.54±0.23	5.4±0.36	0.22%	2.2±0.037	96.47%
F2	97.52±0.36	5.2±0.53	0.39%	2.6±0.058	95.55%
F3	95.23±0.16	5.5±0.23	0.52%	3.0±0.023	97.66%
F4	99.37±0.29	5.6±0.28	0.63%	2.3±0.047	98.49%
F5	95.33±0.12	5.3±0.79	0.84%	2.9±0.012	95.28%
F6	99.45±0.33	5.5±0.68	0.49%	2.1±0.05	96.86%
F7	96.55±0.20	5.2±0.74	0.74%	2.4±0.041	98.37%
F8	96.20±0.13	5.2±0.52	0.13%	3.1±0.043	96.57%
F9	99.23±0.65	5.5±0.19	0.44%	2.5±0.082	97.61%
F10	99.75±0.39	5.7±0.89	0.77%	2.3±0.079	99.05%

Table 10: Accelerated stability studies for optimised formulation F4.

Property	Initial	After 1month	After 2 month	After 3 month
Drug content	97.39%	97.23%	97.07%	96.86%
Physical Appearance	White color	No Change	No change	No change

parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limit.

Drug-Excipient Compatibility Studies

Fourier Transform-Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the ATR (attenuated total reflectance) technique. For this technique ZnSe crystal was used to know the wavelength of those drug and carriers. The spectra were scanned over a frequency range 4000-550 cm-1. FTIR spectrum of pure drug ezetimibe is shown in figure number 3 whereas ft IR spectrum its drug formulation is shown in figure number 4 overlapping of drug and its formulation clearly indicates presence of Intact drug in the formulation, important peaks of drug, such a such as OH and carbonyl functional groups appeared in the formulation FTIR spectrum.

Accelerated stability studies

The formulation packed in aluminium foil was subjected to accelerated stability testing for 3 months as per ICH norms at a temperature 40 ± 2°C and relative humidity 75 ± 5%. Samples were taken at regular time intervals of 1 month for over a period of 3months and analysed for the change in physical appearance and drug content by procedure stated earlier. Any changes in evaluation parameters, if observed were noted. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation. The optimized formulation was taken for accelerated stability studies. That formulation was shown for drug content for every month up to 3 months. These studies were given good results which mean optimized formulation had good stability up to 3months period.

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