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Research Article

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Formulation and evaluation of pulsatile tablet of Ramipril

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ABSTRACT

The goal of the study was to formulate pulsatile release tablets of ramipril by using a combination of core material croscarmellose sodium and coating hydrophilic polymer HPMC K100M and hydrophobic polymer ethylcellulose. Ramipril is used in the treatment of hypertension. It has a short half life (2-4 hrs). Ramipril 2.5mg pulsatile release tablets were prepared by direct compression method and evaluated for thickness, hardness, weight variation, friability, drug content and in-vitro release of drug. In-vitro drug release was carried out using USP type II apparatus at 50 rpm in 900ml of dissolution media for 7 hrs. Mean dissolution time is used to evaluate drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Various kinetics models were applied to the dissolution profile to determine the drug release kinetics. All the physical characteristics evaluated for the tablets were obtained to be within the acceptable limits. The release profile of optimized formulation of ramipril was close to korsmeyer peppas model. Irrespective of the polymer type and its concentration, the prepared optimized pulsatile tablets showed non fickian (anomalous) release. Finally it was clear that core polymer crosscarmellose sodium and coating polymer HPMC K100M and ethyl cellulose are good candidates for preparing pulsatile tablets of ramipril.

Key word: Hypertension, *In-Vitro* release, Pulsatile release, Kinetics

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INTRODUCTION

Over the last 30 years, numerous technical advancements have occurred in the formulations, biodegradable polymers and understanding of pharmacokinetics has resulted in new techniques of drug delivery. Apart from the targeted, prolonged, controlled, sustained and targeted delivery systems, a new drug delivery systems known as pulsatile delivery system has drawn attention of the scientists, which is based on the concept of chrono-therapeutics.

A pulsatile drug delivery system is one that delivers drug molecule in rapid and transient manner within a short time period immediately after a predetermined off release (lag time) period. The rationale for use of proposed system is to deliver drug at a time when disease condition is in the most morbid and mortal state during 24 hours. The particular rhythm in the onset and amount of symptoms were seen in diseases such as bronchial asthma, rheumatic disease, angina pectoris, ulcer, diabetes, hypercholesterolemia, neurological disorder and hypertension. Several pulsed release formulations have been developed, where tablets/capsules are the basis of pulsatile formulation that addresses emerging chronotherapeutic requirements. PDDS aims to release drug on programmed pattern that is at appropriate time and at appropriate site of action. The pulsatile effect, that is, the release of drug as a “pulse” after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time[1-5].

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation and in such conditions there is requirement for time or pulsatile drug delivery system. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. These systems are beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required), first pass effect and having specific site of absorption in gastro intestinal tract (GIT). Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier may erode, dissolve or rupture during/after a certain lag time after which the drug is released quickly from the inner reservoir.

The lag time prior to the rupture is mainly controlled by: (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behaviour of the swelling layer. The rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients or swelling agents. Pulsatile tablet formulations are manufactured with a rapid-release core (reservoir) encased in a barrier layer formed by rupturable press coating or liquid coating of erodible and swelling polymer. Polymers like various grades of Eudragit® or ethyl cellulose have been tested as film coating to achieve the desired lag time[6-15].

EXPERIMENTAL SECTION

Materials:
Ramipril was obtained as a gift sample from Brawn laboratories Ltd. The HPMC K100M was obtained as gift samples from ozone. Ethylcellulose and Croscarmellose sodium were obtained as gift samples from CDH distributors. All polymers and chemicals were of analytical grade and used.

Preparation of pulsatile tablet:
The core tablets of ramipril were prepared by direct compression technique. Ramipril, croscarmellose sodium, lactose, were mixed with each other. All the ingredients except talc and magnesium stearate were mixed thoroughly. Talc and mg.stearate were passed through 80 mm sieve and mixed with above powder blend. Rapid release core tablets were prepared by compressing the entire ingredient using 6 mm flat faced punch and die cavity on a rotary tablet press. The core tablets were compression coated with different weight ratios (w/w) of HPMC K100M and ethylcellulose mixtures. Half of the total quantity of coating powder blend was filled in die cavity to make a powder bed at the bottom. The previously compressed tablet using 6 mm flat faced punches placed manually in the centre on the above powder blend. The remaining equivalent powder was filled in the die, and the content was compressed using a flat faced punch, 10 mm in diameter. The different forms of tablets compressed together with the compositions are given in following table 1.

Table 1: Compositions of various pulsatile tablet formulation of ramipril

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
CCS	2%	4%	6%	8%	2%	4%	6%	8%	2%	4%	6%	8%
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
MS	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
HPMC K100M	100 mg	100 mg	100 mg	100 mg	66.6 mg	66.6 mg	66.6 mg	66.6 mg	133.3 mg	133.3 mg	133.3 mg	133.3 mg
EC	100 mg	100 mg	100 mg	100 mg	133.3 mg	133.3 mg	133.3 mg	133.3 mg	66.6 mg	66.6 mg	66.6 mg	66.6 mg

CHARACTERIZATION OF DRUG AND EXCIPIENTS:
Fourier transforms infra red spectroscopy (FTIR):
The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation. The FTIR spectra of ramipril was done and given in figure no.1 [16-18].

Differential scanning calorimetry (DSC):
DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample are measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the study. Mainly, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The DSC analysis of ramipril was given in figure no. 2[19,20].

Pre compression characterization:
Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hauser ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose[21-25].

Post compression characterization:
The thickness, weight, friability and hardness are the post compression characterisation of pulsatile tablet.

Thickness:
The diameter and thickness of the tablets of all of the formulations were determined with vernier calliper [26].

Tablet weight variation:
Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. Weight control is based on a sample of 20 tablets. Twenty matrix tablets were randomly selected and accurately weighed using an electronic balance [27].

Hardness:
The hardness of the tablets was determined using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-6 kg/cm^{2}is considered adequate for mechanical stability[28].

Friability:
The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The limit of friability is 1% w/w and weight loss not more than of this limit [29-32].

% Friability = (W0 −W)/W0 ×100

Where,
Wo is intial weight of tablet
W is final weight of tablet

Drug content:
10 tablets were weighed and powdered. Then powder equivalent to 10 mg of drug was taken and dissolved in 0.1N HCl and made the volume up to 10 mL. After that 10 ppm solution was prepared and absorbance was measured at 205.4 nm by using SHIMADZU UV-1800 spectrophotometer [33-37].

In vitro drug release characteristics:
Drug release from the matrix tablets was assessed by dissolution test using USP type II dissolution apparatus equipped with paddles at 37^{o}C ±0.5^{o}C with an rpm of 50. The test was performed using 900 ml of 0.1 N HCl (for first 2hrs) and phosphate buffered solution, pH 6.8 (up to 7 hrs) as dissolution media. After that 5 ml samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 205.4 nm.

Drug release kinetics:
The release kinetic was studied by various kinetic models as first order plot, zero order plot, korsmeyer-peppas and higuchi plot. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model.To examine the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into first order, zero order, korsemeyer-peppas, higuchi matrix. Comparing the R^2 values find out from the release equations, the best-fit model was obtained [38-47].

$C= K_o t$…… (1)

Where $K_{o=}$ zero order constant (concentration/time)
t= time (hrs)

Log C= Log Co-Kt/2.3….. (2)
Where Co= initial concentration of drug (first order constant)
t= time

$Q= kt^{1/2}$….. (3)
Where K= constant
t= time (hr)

$Mt/M_\infty = Kt^n$
Where Mt/M_∞= fractional solute release
t= release time, K= kinetic constant

RESULTS AND DISCUSSION

FTIR spectroscopy:

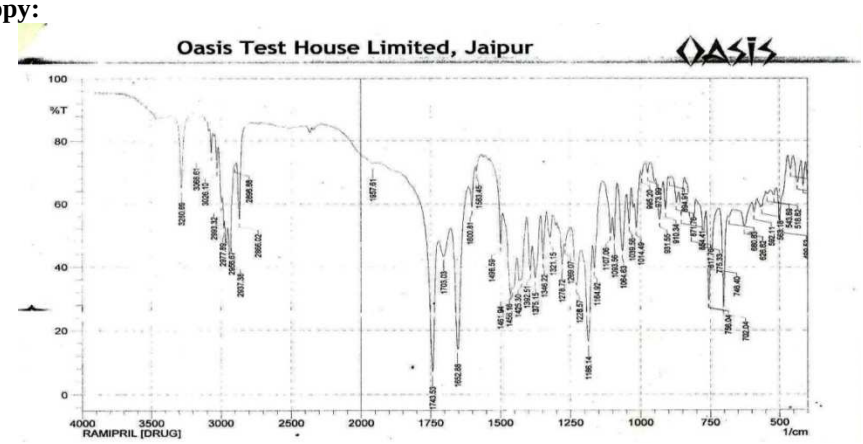

Figure 1: IR spectra of ramipril

Table 2: IR interpretation of drug (ramipril)

S.no	Functional group	Range	Observed peak
1	O- H (Streching)	3000-2500	2993.32
2	Ar-H (Aromatic)	3050-3000	3026.1
3	C=C (Aromatic)	1600	1600.81
4	C-H (Aliphatic)	2960-2850	2866.02
5	C=O (Ester)	1750-1735	1743.53
6	C-O Str (Ether)	1150-1070	1186.14

The above table shows the IR interpretation of ramipril. According to this interpretation the observed peak of drug was found in the range.

Differential Scanning Calorimetry studies:

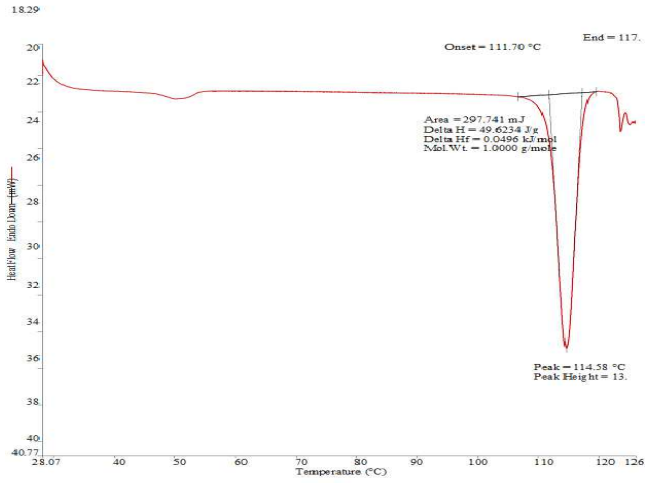

Figure 2: DSC analysis of ramipril

On the basis of DSC analysis the melting point of ramipril was found to be 114.58^0C.

Pre compression characterization: The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of pulsatile tablet are given in table no. 3.

Table 3: Pre compression characterisation

Batch	Bulk density (gm/ml)±SD	Tapped density (gm/ml)±SD	Carr's Index±SD	Hausner's ratio±SD	Angle of repose±SD
F1	0.61±0.015	0.69±0.015	11.59±1.52	1.13±0.020	23.74±1.05
F2	0.60±0.010	0.76±0.020	19.73±1.25	1.24±0.035	30.96±1.08
F3	0.62±0.015	0.75±0.010	17.33±1.20	1.20±0.025	28.81±1.30
F4	0.62±0.010	0.75±0.037	17.33±1.45	1.20±0.036	29.68±1.36
F5	0.60±0.017	0.72±0.026	16.66±1.11	1.20±0.025	27.02±1.75
F6	0.61±0.015	0.73±0.020	16.43±1.23	1.19±0.026	28.81±1.55
F7	0.62±0.010	0.75±0.015	17.33±1.33	1.20±0.015	27.92±1.10
F8	0.63±0.015	0.74±0.032	14.86±1.67	1.17±0.032	24.70±1.26
F9	0.61±0.025	0.74±0.032	17.56±1.67	1.21±0.030	27.02±1.14
F10	0.60±0.015	0.70±0.026	14.28±1.68	1.16±0.034	24.22±1.74
F11	0.61±0.010	0.75±0.036	18.66±1.23	1.22±0.26	30.96±1.54
F12	0.63±0.020	0.75±0.030	16±1.20	1.19±0.040	29.68±1.17

These parameters show that the prepared mixture of all formulation has good to excellent flow property range. The angle of repose of all formulations showed excellent to good flow.

Post compression characterization: All batches of formulation were evaluated for various physical parameters and results tabulated in table no. 4.

Table 4: Post compression characterisation

Batch	Thickness±SD (mm)	Weight±SD (mg)	Friability±SD (%)	Hardness (kg/cm^2)
F1	4.28±0.015	246.4±1.70	0.77±0.041	4.4
F2	4.28±0.010	245.5±1.00	0.85±0.030	4.8
F3	4.30±0.020	246.9±1.47	0.89±0.072	5
F4	4.31±0.010	244.5±1.51	0.94±0.100	4.2
F5	4.28±0.020	247.5±1.50	0.80±0.077	5
F6	4.31±0.010	245.5±1.16	0.93±0.089	5
F7	4.30±0.010	245.5±1.70	0.73±0.057	5.4
F8	4.30±0.020	245.0±1.15	0.85±0.101	4.8
F9	4.30±0.020	246.0±2.15	0.93±0.127	4.8
F10	4.30±0.010	245.5±2.15	0.81±0.109	5.2
F11	4.28±0.015	248.4±2.20	0.84±0.111	4.2
F12	4.28±0.015	245.5±1.90	0.77±0.097	4

All batches of formulation were evaluated for various physical parameters and tabulated in table no 3. The weight variation of each formulation was found in range. According to thickness of all formulation it was found in uniform size. The hardness of tablet was within range of 4 to 5.4 kg/cm^2 and friability found in less than 1%. These all parameters were satisfactory as specified in the pharmacopoeia.

***In-vitro* drug release study:** The % CDR and drug content are given in table no. 5 and the *in-vitro* drug release profiles of F1-F12 are shown in fig. 3, 4 and 5.

Table 5: Drug release, drug content and lag time

Formulation	%CDR (12hr)±SD	Drug content±SD	Lag time
F1	93.68±1.56	92±1.35	180
F2	93.0±1.57	92.6±1.78	190
F3	91.60±1.34	93.4±1.51	185
F4	90.83±1.92	93.8±1.45	190
F5	85.16±1.08	96.9±1.86	310
F6	93.44±1.11	96.7±1.68	300
F7	89.53±1.00	94.2±1.78	320
F8	94.24±1.52	92.4±1.55	310
F9	85.92±1.23	94.0±1.76	320
F10	91.34±1.47	95.5±1.24	315
F11	93.50±1.44	95.9±0.91	320
F12	93.74±1.62	95.3±0.69	325

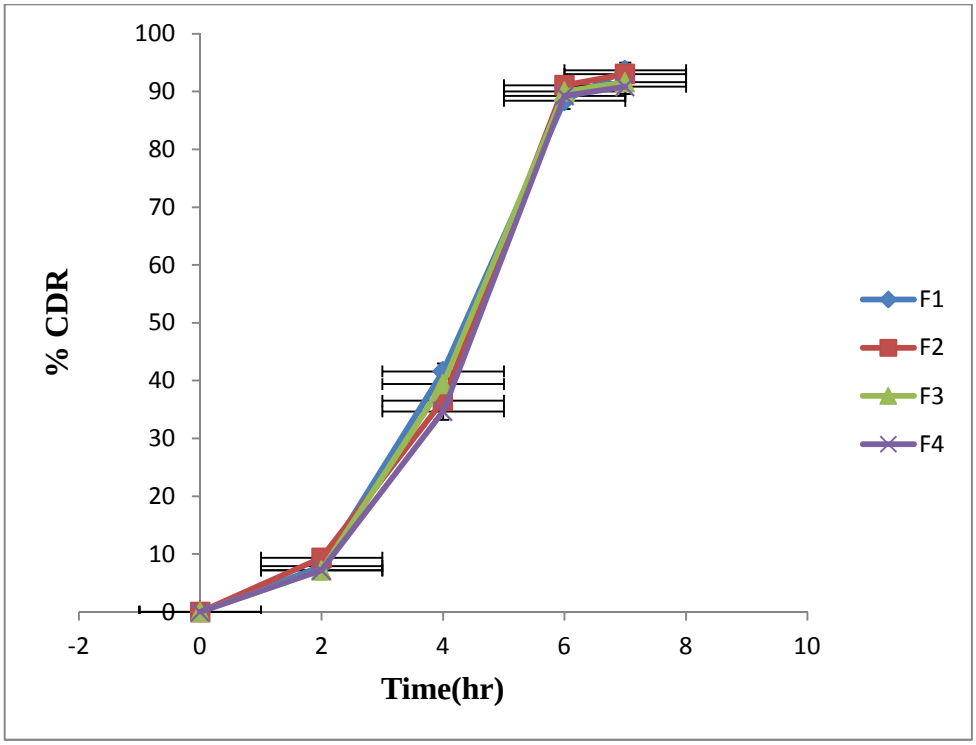

Figure 3: Drug release curve (F1-F4)

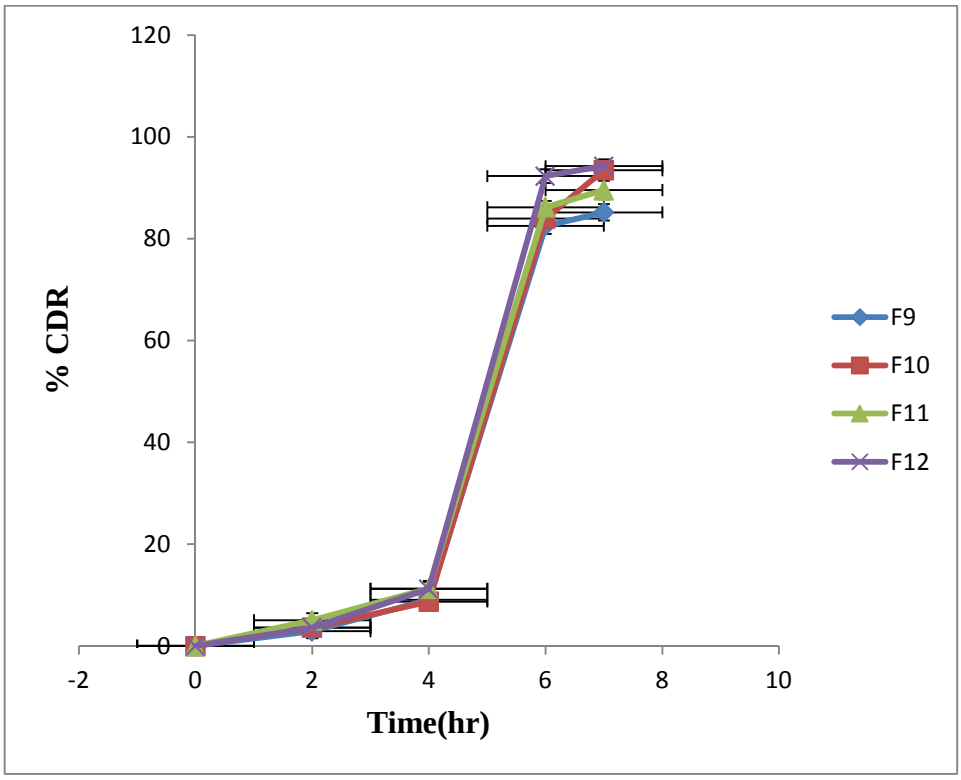

Figure 4: Drug release curve (F5-F8)

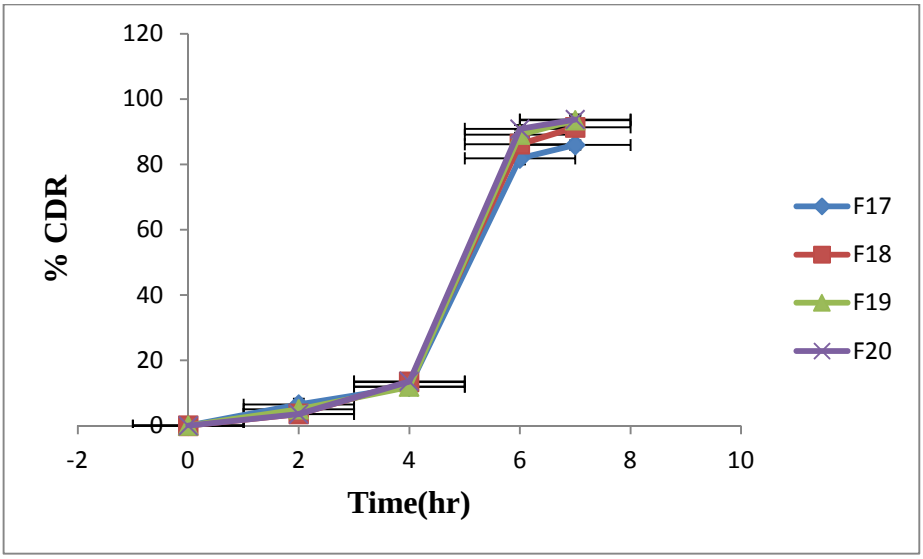

Figure 5: Drug release curve (F9-F12)

All formulation of ramipril tablet was manufactured under same condition to except the processing variables. All pulsatile tablet of ramipril were containing different % of core material Croscarmellose sodium and different ratio of coating hydrophobic polymer ethyl cellulose and hydrophilic polymer HPMC K100M were used. HPMC K100M and ethylcellulose retains drug release property due to its gelling property. Drug release for 7 hrs of all formulation from F1 to F12 were shown in figure no. 3,4 and 5.

In formulation of F1 to F4, the polymer croscarmellose sodium (2%, 4%, 6% & 8 %) was used and after that it is coated with 1:1 ratio of HPMC K100M and ethylcellulose. In this ratio the drug was released in very short lag time which was less than 5 hours. Thus the burst drug release occurred.

To overcome this problem, the ratio of HPMC K100M and ethyl cellulose was changed. In formulation of F5 to F8, the mixture of coating polymer HPMC K100M and ethyl cellulose were used having ratio 1:2 respectively. In this ratio the drug was released after a suitable lag time of 5 hours. In formulation of F9 to F12, the mixture of coating polymer HPMC K100M and ethyl cellulose were used having ratio 2:1 respectively. In this ratio also the drug was released after a suitable lag time of 5 hours.

Table 6: Data of release kinetics

Batch	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	N
F1	0.949	14.88	0.019	0.161	0.844	35.48	0.930	0.78
F2	0.926	14.66	0.032	0.112	0.864	35.22	0.926	0.77
F3	0.987	14.81	0.048	0.138	0.863	34.69	0.935	0.80
F4	0.926	14.66	0.058	0.151	0.853	34.40	0.942	0.79
F5	0.804	13.74	0.128	0.230	0.738	32.25	0.970	0.86
F6	0.806	14.60	0.046	0.142	0.746	35.39	0.971	0.81
F7	0.816	14.30	0.077	0.179	0.754	33.91	0.939	0.87
F8	0.809	15.25	0.354	0.313	0.743	35.69	0.976	0.80
F9	0.826	13.58	0.124	0.225	0.767	32.54	0.963	0.82
F10	0.830	14.57	0.061	0.161	0.764	34.59	0.983	0.82
F11	0.819	14.89	0.032	0.117	0.756	35.41	0.975	0.80
F12	0.823	15.12	0.041	0.133	0.756	35.50	0.981	0.81

The drug content in each formulation was found in a uniform range and the range was 92% to 96.9%. This range is uniform and satisfactory the specifications of pharmacopoeia. The individual drug content of each formulation was shown in above table.

According to this whole discussion, the best formulation was found to be F6. F6 is best because of its 96.7 % drug content and 83.96 % drug release for 7 hrs after a lag time of 5 hrs as it met the desired specifications of pulsatile delivery. Finally the optimised formulation is F6.

Drug release kinetics: Data of drug release kinetics is shown in table 6

The data were treated according to zero order, first order, higuchi model and korsmeyer peppas pattern for kinetics of drug release during dissolution process. The regression equation of optimized formulation F6 was found out according to zero order equation 0.806, first order equation 0.046, higuchi model 0.746 and korsmeyer peppas model 0.971. These values clearly indicate that the formulation showed to be best expressed by korsmeyer peppas model.

The dissolution data was fitted to the well known exponential equation (Koresmeyer peppas equation), which is often used to describe the drug release behavior from polymeric system. According to this model a value of $n<0.45$ indicates fickian release, $n>0.45$ but $n<0.89$ for non-fickian (anomalus) release and $n>0.89$ indicates super case II generally refers to the erosion of the polymeric chain and anomalus transport (non-fickian) refers to a combination of both diffusion and erosion controlled drug release. The n value described in table 6. On the basis of n value the best formulation F6 exhibited non fickian type drug release.

CONCLUSION

Ramipril pulsatile release tablets were successfully formulated using the mixture of core polymer disintegrant crosscarmellose sodium and coating hydrophilic swellable polymer HPMC K100M and hydrophobic rupturable polymer ethyl cellulose. The results obtained indicated that optimum amounts of HPMC K100M and ethyl cellulose more essential to produce pulsatile release tablets with desirable lag time and release characteristics. The combination of HPMC K100M and ethylcellulose showed the synergistic effect on lag time. The finding indicates that the lag time of a press coated tablet can be modulated from 4 to 6 hrs by combining ethylcellulose with HPMC K100M in different weight ratio. The system was found to be satisfactory in terms of burst release of the drug after a predetermined lag time of 5 hr which is applicable pulsatile drug delivery of ramipril for hypertension. The release of drug was rapid and complete after the lag time.

From this study, it is possible to develop oral pulsatile release compression coated tablets containing ramipril for the management of hypertension.

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