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Formulation, Development and Characterization of Chronotherapeutic Time Released Press Coated Nizatidine Tablets

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ABSTRACT

The aim of present study was to develop and characterize pulsatile release tablets of Nizatidine, H2 antagonist, for effective treatment of Peptic ulcer. The pulsatile tablets prepared by compression coating method consisted of two different parts: a core tablet, containing the active ingredient and an erodible outer coating layer of polymer. The rapid release core tablets were prepared by using superdisintegrant along with active ingredient. Compression coating of optimized core tablets was done by using HPMC K100M and Ethyl Cellulose. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. The Core tablets and press coated tablets were evaluated for weight variation test, thickness, hardness, friability, Disintegration, lag time and dissolution study. An increase in lag time was observed with the increasing concentration in each case. Formulation F4 containing HPMC K100M and Ethyl Cellulose was found to provide desired lag time, drug release profile, better integrity among all formulations and thus, compliant with the chronotherapeutic objective of Peptic Ulcer.

Key-words: Pulsatile Drug Delivery, Core Tablet, Press coated tablet, Compression, Lag time.

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Introduction :

Among all oral modified release dosage forms, much interest has been shifted to achieve time specific (pulsatile, delayed) and site-specific drug delivery systems.[1,2] It constitutes a relatively novel approach, the significance of which is specially associated with the recent advancement in the field of chronopharmacology. Chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease conditions such as asthma, ulcers, arthritis and hypertension.[4,5] Pulsatile drug delivery is characterized by initial no release followed by a rapid and complete release of the drug from the delivery system. These systems are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance, therapeutic efficacy and following programmed lag phases. Nizatidine is an H2-receptor antagonist mainly used for treatment of conditions where controlled reduction of gastric acid is required suchas acute duodenal ulcer, acute benign gastric ulcer. The elimination half-life of this drug is low i.e. 1-2 hours. As patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.[6] In order to maximize the efficacy of drug and to reduce the dose frequency regimen of the patient, this drug was selected as model drug for formulation of pulsatile tablets.

Methods:

Preparation of Core Tablets:

Accurately weighed amount of Nizatidine and (Crosspovidone in concentration 2%, 3%, 4%, and 5%) were passed through sieve no. 40 separately. Total tablet weight 150 mg adjusted with a MCC (PH-102) and directly compressed into tablets using multi-station tablet punching machine. Total four formulations were prepared with different concentration and coded them from C1 to C4. All the ingredients were mixed in proportion as shown in Table no.1.

Table no. 1 Formulation of core tablets:

Formulations	**C1**	**C2**	**C3**	**C4**
Nizatidine	75	75	75	75
Crosspovidone	4.5	6	7.5	9
MCC (PH-102)	67.5	66	64.5	63
Talc	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5
Net Weight (in mg)	150	150	150	150

Preparation of Pulsatile Release tablets:

The core tablets were used for preparation of pulsatile release tablets. Dry coating of optimized core tablets was done by using combination of polymers HPMC K100M and Ethyl cellulose in different ratios to optimize the lag time for drug release. The composition of the tablets showed in table 2. Dry coated tablet was prepared by placing 50% of pulsatile release layer in die and core tablet was placed on it, further remaining quantity of pulsatile release layer was added in cavity so as to cover the core and finally compressed by using single punch tablet machine.

Table no. 2 Formulation composition of compression coated pulsatile tablets:

Formulation composition	**F1**	**F2**	**F3**	**F4**
Core tablet formulation				
Nizatidine	75	75	75	75
Crosspovidone	9	9	9	9
MCC PH-102	63	63	63	63
Talc	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5
Coating layer Formulation				
HPMC K100M	50	75	125	150
EC	150	125	75	50
Talc	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5

Evaluation of physical properties of prepared tablets:

Weight variation:

20 tablets were randomly selected from the prepared batches and their average weight was calculated using a digital balance. Individual weight of each tablet was also determined and compared with the average weight.[5,8]

Hardness:

For each formulation, the hardness of tablets was determined using the Pfizer hardness tester. Three tablets were chosen randomly and tested for hardness.[9,11]

Thickness:

Digital screw gauge was used to determine the thickness of the prepared tablets. 3 tablets were randomly selected from each trial batch and were measured by placing the tablet between the anvils and sliding knob was rotated until the tablet was ruptured.[5,7]

Friability test:

Ten tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted, weighed & percentage friability was calculated.[6]

Drugs content:

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 75 mg of drug was dissolved in 100 ml phosphate buffer pH 6.8, filtered and diluted up to 50µg/ml, and analyzed spectrophotometrically at 314nm. The concentration of drug was determined using standard calibration curve.[4,6,8]

In vitro disintegration time:

The various tablet formulations prepared by direct compression method are subjected to disintegration studies using 900ml of phosphate buffer of pH 6.8 (as a medium) and the time taken for disintegration is noted and tabulated.[15]

Determination of lag time (t^{10}) for enteric coated tablets:

Lag time study:

The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test.

Rupture Test:

The Rupture test on coated tablets was carried out using USP paddle apparatus at 50 rpm and 37±0.5°C, pH 1.2 and pH 6.8 phosphate buffers were used as the dissolution medium. Initially tablets were subjected to dissolution in pH 1.2 buffer for 2 h and after that media is changed to phosphate buffer (pH 6.8). The time at which the outer coating layer starts to rupture was noted.[4]

IN VITRO DISSOLUTION STUDIES FOR CORE AND PRESS COATED TABLETS:

To verify how the composition of the core and press coated tablets interferes with the drug release profile, the in vitro dissolution studies were carried out using USP type I dissolution apparatus (basket method; Electrolab India Pvt. Ltd., Mumbai, India) in 900 ml medium at 37±0.5^{0}C at a rotation speed of 50 rpm. To mimic gastric pH conditions, test was carried out in 0.1N hydrochloric acid (pH 1.2) for 2 hr. followed by intestinal fluid pH 6.8. The buffer system having pH 6.8 was selected to simulate the condition in small intestine. 5ml sample was withdrawn every 1h, filtered and immediately replaced by the fresh dissolution medium. All the dissolution samples were filtered through Whatmann filter paper and analyzed immediately by UV–Visible spectrophotometer. Nizatidine released in 0.1N HCl was estimated at λ max 314 nm. In this dissolution studies the USP type I dissolution apparatus was used as it was quite suitable for carrying the samples in the next medium and dissolution is continued without disturbing and touching the surface of coated tablets.[6,11,15]

Stability Studies:

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines to assess the drug and formulation stability. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% for three months. At the end of studies, samples were analyzed for the post-compression parameters like hardness, drug content and lag time.[4,15]

Result:

Confirmation of Drug:

Confirmation or identification of drug was carried out by UV spectra, IR spectra and DSC.

UV Spectroscopy :

Estimation of Nizatidine by UV Visible spectrophotometer

Absorption Maxima of Nizatidine:

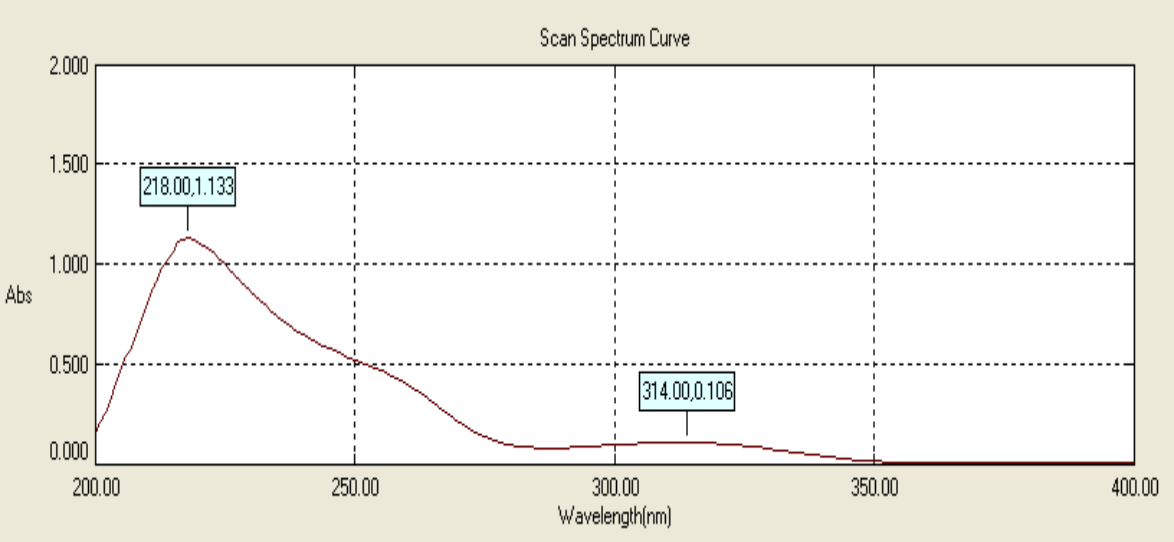

Figure: 1 UV spectrum of Nizatidine in 0.1 N HCL solution

Table no. 3 Wavelength of maximum absorption of Nizatidine in 0.1 N HCL

Sr. No.	Solevent	Wavelength
1	0.1 N HCL	314 nm

Infrared spectrum:

Fig. 2 Infrared spectrum of Nizatidine

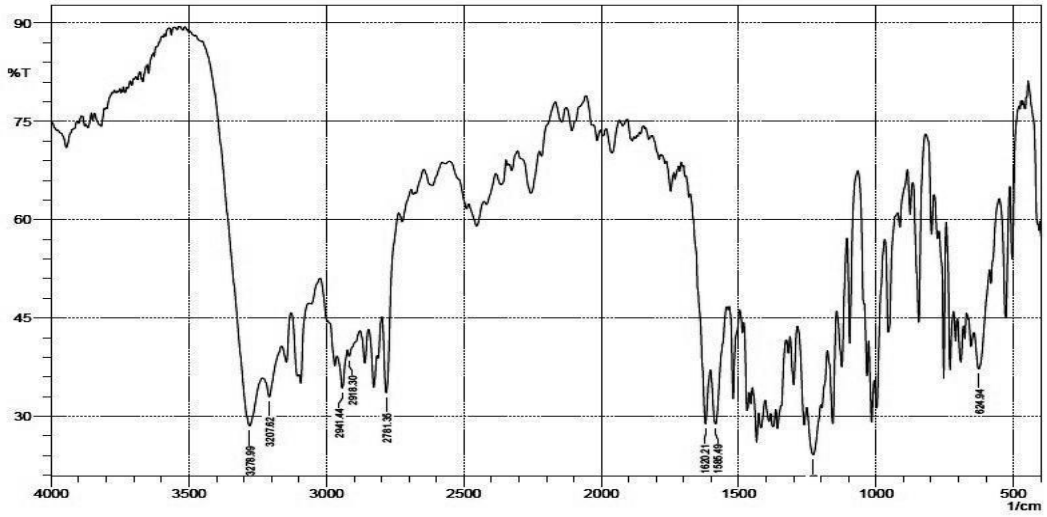

Table no. 5 Principal peak and chemical group present in IR spectrum of Nizatidine:

Nizatidine	Frequency range	Mode of vibrations
2941.44	2850-2800	CH stretching
1469.76	1454-1475	CH_2 stretching
2827.64	2850-2815	CH_3 stretching
1469.75	1475	C=O stretching
1261.45	1360-1250	C-N stretching
3278.99	3500-3180	N-H stretching
1375.25	1380-1360	NO_2 stretching

Differential Scanning Calorimetry:

DSC Thermogram of Nizatidine:

Nizatidine was confirmed by differential scanning calorimetry at scanning rate of 10^0C/min. It exhibits a sharp melting endothermic peak at temperature of 136^0C as shown in Fig. 03

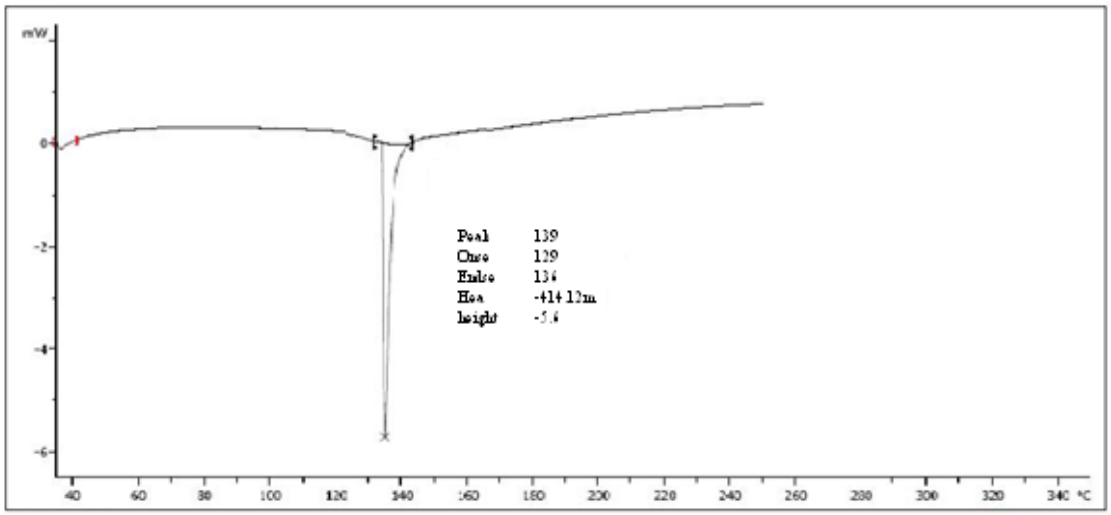

Fig. 03 DSC thermogram of Nizatidine

Drug-Polymers Interaction Study:

FTIR spectra of drug, physical mixture of Nizatidine and excipients are and its interpretation in fig. 04 from interpretation can conclude that there is no drug – polymer interaction.

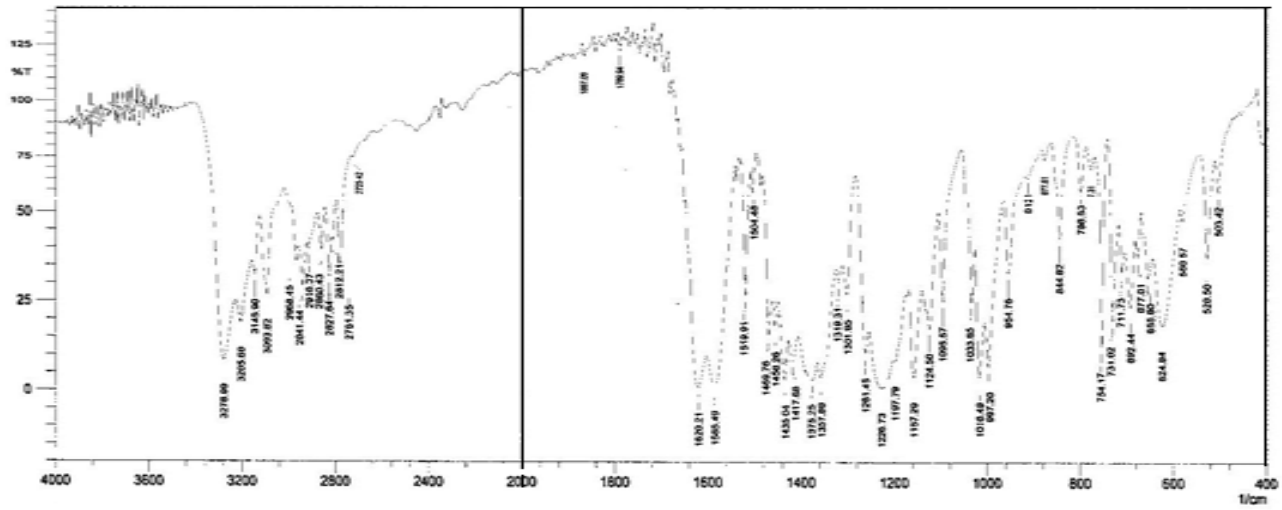

Fig. 04 Infrared spectrum of physical mixture of Nizatidine

FTIR peak positions (cm^{-1}) and assignments for Nizatidine drug and its combinations with excipients:

Nizatidine	Physical mixture of Nizatidine	Frequency range	Mode of vibrations
2941.44	2939.52	2850-2800	CH stretching
1469.76	1469.76	1454-1475	CH_2 stretching
2827.64	2827.64	2850-2815	CH_3 stretching
1469.75	1469.75	1475	C=O stretching
1261.45	1261.45	1360-1250	C-N stretching
3278.99	3278.99	3500-3180	N-H stretching
1375.25	1377.17	1380-1360	NO_2 stretching
-	3404.36	3400-3300	OH stretching
-	2351.23	2800-2340	OH stretching
-	1072.42	1260-1000	CO stretching
-	1058.92	1300-1000	C-O-C stretching

Table no. 6

Fig.05 DSC thermogram of physical mixture of Nizatidine

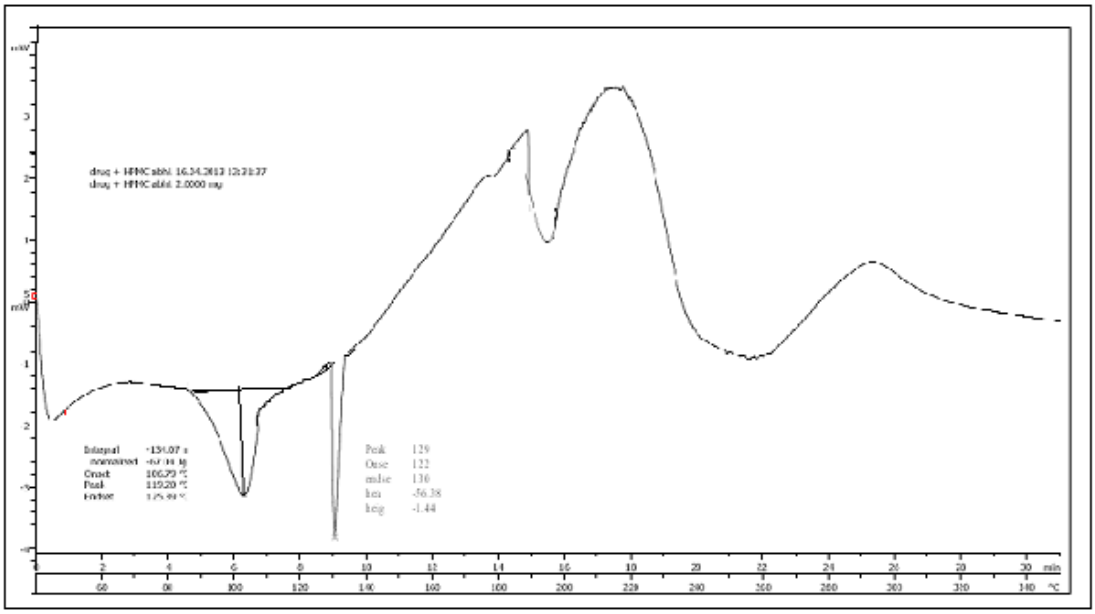

Table no. 7 Thermal characteristics of Nizatidine:

Sr. No	Thermal characteristics	Temperature (pure drug)	Temperature (F-4 formulation)
1	Onset Temperature (T_o)	129 ^{0}C	122 ^{0}C
2	Peak Temperature (T_p)	139 ^{0}C	129 ^{0}C
3	Endset Temperature (T_b)	136 ^{0}C	133 ^{0}C

Evaluation of precompression parameters of powder Blend:

Drug, Excipients and polymers were characterized for their physical properties such as angle of repose, density, compressibility, and Hausner's ratio. Results are shown in Table: 8

Batch No.	Angle of Repose (θ)	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Hausner's Ratio (%)	Carr's index (%)
C1	27.7 ± 0.14	0.35± 0.015	0.40 ± 0.012	1.14 ± 0.012	12.5 ± 0.28
C2	29.7 ± 0.28	0.33 ±0.021	0.37 ±0.020	1.13 ± 0.020	12.2 ± 0.36
C3	30.4 ± 0.16	0.37 ± 0.018	0.44 ±0.017	1.17 ± 0.022	14.77 ± 0.24
C4	30.5 ±0.18	0.36 ± 0.012	0.43 ± 0.014	1.20 ± 0.017	17.4 ± 0.21

(Mean ± SD) n=3 Table no. 8

Flow Properties of blend:

The blend prepared for core tablets was evaluated for their flow properties (Table 17). Bulk density varied between of 0.33 ± 0.021 to 0.37 ± 0.018 gm/cm^3 and tapped density lies between 0.37 ± 0.020 to 0.44 ± 0.017 gm/cm^3. Carr's index was found to be 12.2 ± 0.36 to 17.4 ± 0.21% and hausner ratio ranged from 1.13 ± 0.020 to 1.20 ± 0.017 for powders of different formulations. Angle of repose ranged between 27.7 ± 0.14 and 30.5 ± 0.18. These values indicated that the prepared powders exhibited good to fair flow properties.

Evaluation of post compression parameters of Nizatidine core tablet:

Batch No.	Hardness (Kg / cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)	Weight Variation (%)	Drug Content (%)
C1	4.6 ± 0.032	5.50 ± 0.011	0.62 ± 0.013	28 ± 3	150 ± 0.16	98.96 ± 0.16
C2	4.6 ± 0.028	5.46 ± 0.023	0.74 ± 0.012	26 ± 1.52	151 ± 0.12	99.24 ± 0.21
C3	4.5 ± 0.052	5.52 ± 0.018	0.68 ± 0.017	30 ± 3.27	149 ± 0.20	99.42 ± 0.22
C4	4.5 ± 0.057	5.56 ± 0.021	0.52 ± 0.014	22 ± 1.5	149 ± 0.24	99.82 ± 0.21

(Mean ± SD) n=3 Table no. 9 Post compression parameter of Nizatidine core tablet

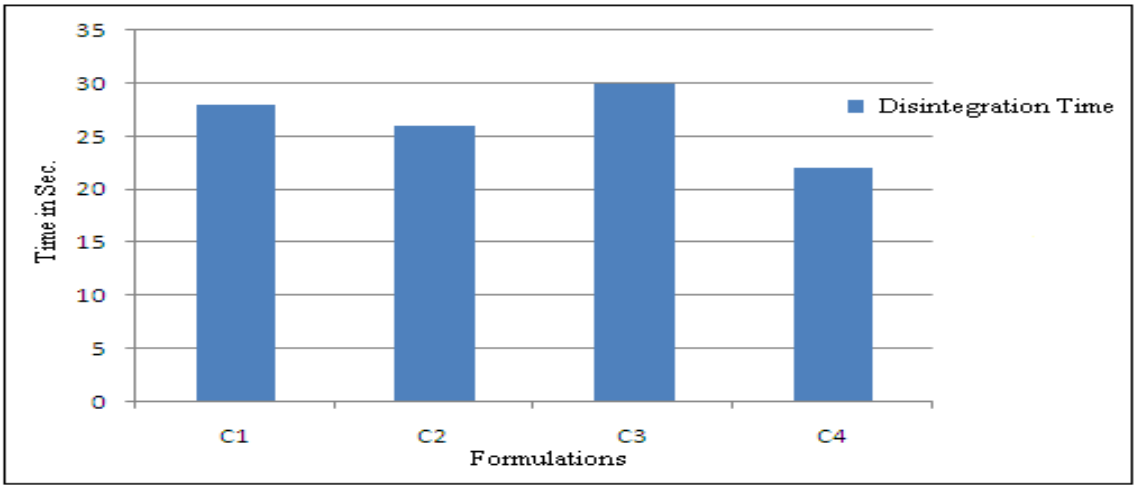

Fig.: 6 Disintegration Time

Table no. 10 Evaluation of post compression parameters of press coated Nizatidine tablets:

Batch No.	Hardness (Kg / cm^2)	Thickness (mm)	Friability (%)	Weight Variation (%)	Drug Content (%)
F1	6.52 ± 0.20	6.42 ± 0.16	0.617 ±0.01	367.15±1.4	99.38 ±0.8
F2	6.72 ± 0.24	6.67 ± 0.18	0.573 ±0.09	364.33±1.10	98.67 ±0.6
F3	6.68 ± 0.17	6.64 ± 0.21	0.603 ±0.02	365.93±1.34	98.25 ±0.5
F4	6.84 ± 0.14	6.49 ± 0.24	0.583 ±0.09	366.34±1.04	99.73 ±0.6

Lag time study:

Rupture Test:

Table no. 11 Lag time of the press coated tablet of Nizatidine formulation F1-F4. (Time in hrs)

Formulation NO.	F1	F2	F3	F4
Rupture Time (hrs)	3.30 ± 4.11	4.10 ± 3.8	4.42 ± 12.4	5.40 ± 5.4

(Mean ± SD) n=3 Table no. 11

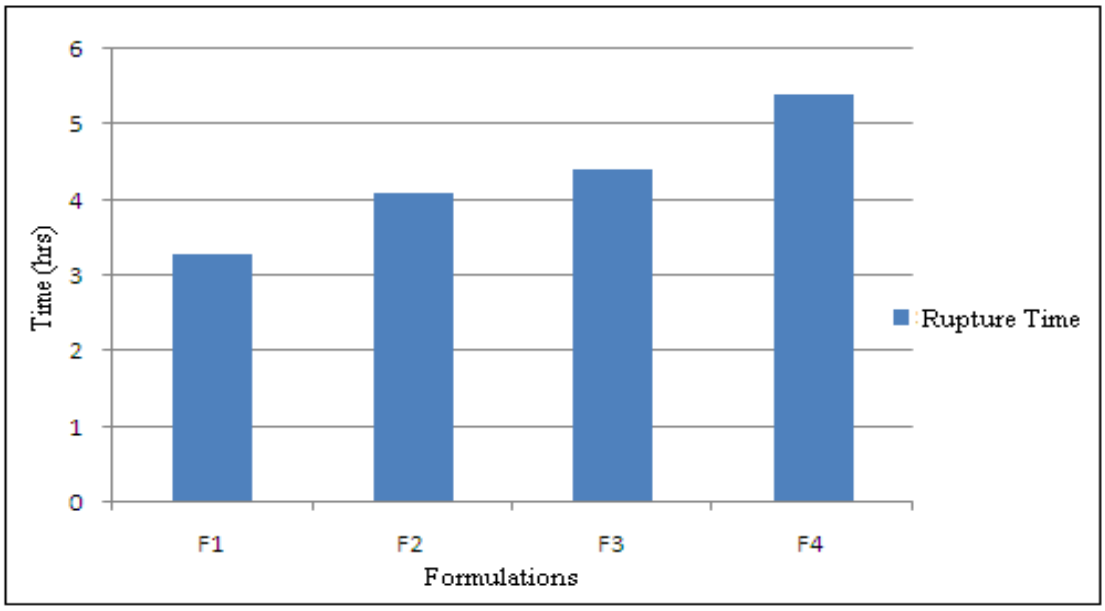

Fig.: 7 Rupture Time

In vitro drug release of core tablets and enteric coated tablets

In vitro release of Nizatidine from core and press coated tablets is shown in Fig. 8 & 9. From formulation C1, C2, C3 and C4 (core tablets), C4 showed faster drug release after 8 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. Based on the above characters formulation, C4 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the Nizatidine from enteric coated tablets. The formulations F1, F2, F3 and F4 showed maximum drug release after 11th, 11th, 8th, and 8th hr respectively. F4 showed maximum drug release after 7th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation F4 with 98.56%, drug release which meet demand of Pulsatile drug delivery. The formulation F4 containing HPMC K100M (150 mg) and EC (50 mg) for press coating was found to be optimum as enteric coating polymer.

The _In vitro_ dissolution study of Nizatidine core tablets:

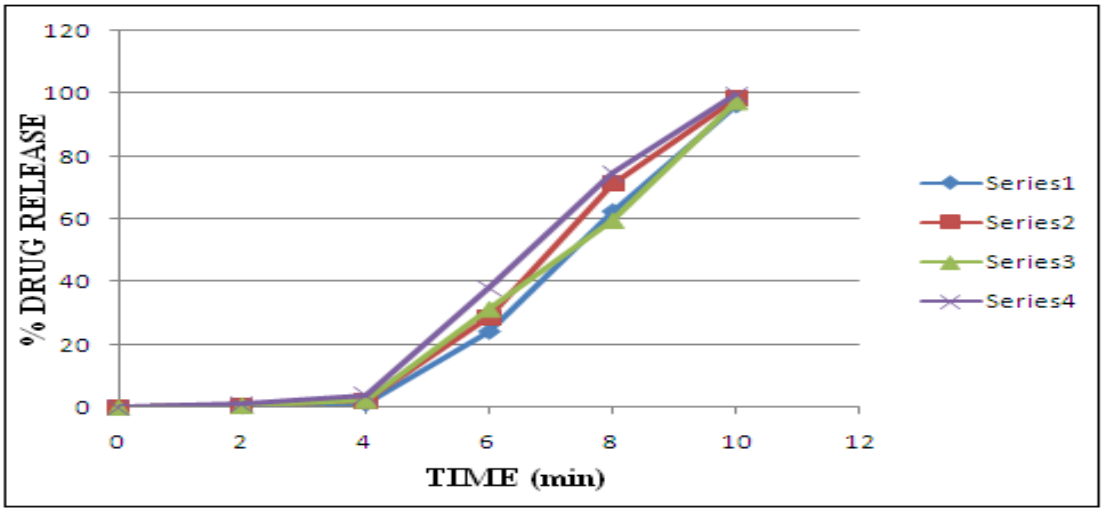

Fig. 8 Drug release profile of core tablet

The *In vitro* dissolution study of Nizatidine Press coated tablets:

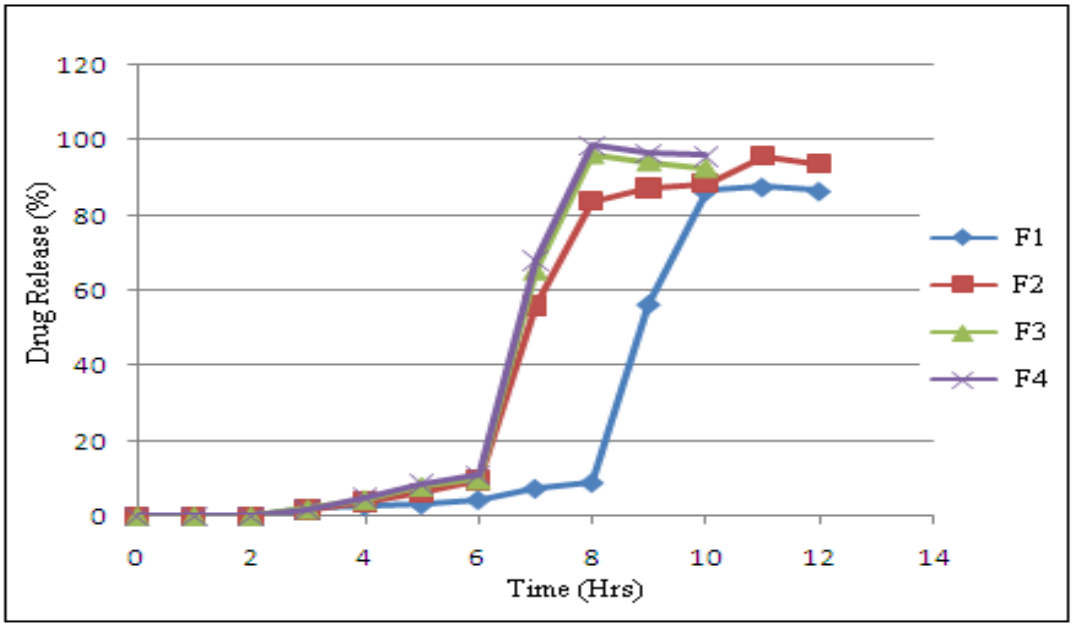

Fig. 9 Drug release profile of Press coated tablet

Stability Study:

The optimize batch F4 was kept at 40^0C/75%RH for 3 months to analyze various physical parameters, results were showed in Table 12. No major differences were found between evaluated parameters before and after ageing / storage and all are in acceptable limits.

Table no. 12 Evaluation parameters of the optimize batch F4 after stability

Parameter	Initial	1 Month	2 Month	3 Month
Hardness(kg/cm²)	6.8	6.4	6.4	6.8
Drug content (%)	99.73	99.12	99.15	99.54
Lag Time(h)	5.40	5.28	5.18	5.35
% Drug Release	98.56	98.05	97.90	97.81

(Mean ± SD) n=3

It is observed that the drug release pattern after stability study was nearly same as before stability (F4) with little difference. Thus the formulation showed the characteristics of stable dosage form with no change in the physiochemical characteristics and release pattern.

Discussion:

Pulsatile drug delivery system of Nizatidine for effective treatment of Peptic Ulcer was formulated. During midnight the rate of acid secretion is maximum due to increased activity of enzyme Helicobacter Pylori. The novel Time controlled Chronotrotherapetic pulsatile drug delivery system for oral use was successfully developed and evaluated. In present study Nizatidine could be successfully delivered to provide relief of gastric acidity in the mid night(nocturnal acid break through) by design of a pulsatile chronopharmaceutical formulation in which final optimised pulsatile formulation(C4) shown best result. The system released the drug rapidly after a certain lag time due to the rupture of the HPMC K100M and ethyl cellulose film. As it taken at bedtime the tablet would release the drug contained in its core after a desired lag time and the activity of the enzyme would be restricted to minimum providing better control of Peptic ulcer. The lag time of the system could be modified by level of swelling layer and rupturable coating.

Source(s) of support in the form of grants, equipment, drugs, or all of these
The drug Nizatidine was obtained as gift samples from Watson Pharma, Goa, India. Microcrystalline Cellulose PH-102, Hydroxy Propyl Methyl Cellulose K100M, Ethyl Cellulose were obtained as gift samples from Holden Medical Laboratories , Sinnar and Crosspovidone were obtained from Shreya Life Sci., Aurangabad, India.

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