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Development and Evaluation of Rabeprazole Sodium Core In Cup Tablets for Pulsatile Drug Delivery

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ABSTRACT

Pulsatile Drug Delivery systems (PDDS) are basically time-controlled drug delivery systems in which the system controls the lag time and drug is released in an immediate or extended fashion. The present study was conducted to develop and evaluate pulsatile release tablets of Rabeprazole sodium for the treatment of peptic ulcers. The compression coated tablets consisted of a core tablet containing drug with superdisintegrant, which was further coated by erodible outer layer consisted of HPMC K15M, ethyl cellulose and Karaya gum. After carrying out preformulation studies, the developed tablets were evaluated for post-compression parameters like weight variation, thickness, hardness, friability, drug content and *in-vitro* drug release study. The best formulation was selected on the basis of post-compression parameters and was subjected to accelerated stability studies for 1 month. Amongst 6 formulations prepared, C5 produced convincing results with a maximum cumulative drug release of 99.97% in 150 minutes. Also the formulation didn't show any significant changes during 1 month period of stress testing. By virtue of its release pattern and delivering the drug at the right time, right place and in right amounts, the developed delivery system holds good promises of benefiting the patients suffering from peptic ulcers. The release profile of optimized formulation C5 was close to korsmeyer peppas model. Irrespective of the polymer type and its concentration, the prepared optimized pulsatile tablets showed non fickian (anomalous) release.

Keywords: Pulsatile, Chronotherapeutic, Circadian rhythms, Proton pump inhibitor, Superdisintegrant

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INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates as per the need. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance, however, there are certain conditions for which such a release pattern is not desirable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released during the initial phase of dosage form administration. Such a release pattern is known as time controlled or pulsatile release.[1, 2]

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e. lag time. This delivery system aims to release the drug on programmed pattern i.e. at appropriate time and at appropriate site of action.[3] A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and then pulse of drug release. The pulsatile effect, i.e. 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. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.[4]

In recent years, there is a continuous interest in the development of controlled drug release systems to achieve the optimal therapeutic effect of drugs. This is based on the increasing awareness of the importance of circadian rhythms with respect to physiology, disease state and drug action which has given rise to the related fields of chronotherapeutics and chronopharmacology. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired.[5]

The pulsatile/delayed release process may be started in response to external signals or alternatively, be regulated by inherent mechanisms, as in the case of time-controlled devices that are expected to perform consistently irrespective of major physiological variables. Coatings with differing compositions are applied to solid cores that contain the active ingredient in order to defer the onset of its release as they help in the development of desired results.[6] Indeed, the assessment of temporal rhythms in an increasing number of disease states, the consolidation of chronotherapeutic approaches and a growing awareness of the impact of patient compliance are

likely to strengthen the research efforts towards the design, preparation and evaluation of such devices[7,8].

Normal gastric acid secretion follows a circadian rhythm. Immediately after meals, intragastric pH is elevated by the buffering effect of food but since meals also stimulate acid secretion, which results in decrease in intra-gastric pH later on. Gastric acid secretion is most pronounced in the evening and early night that results in a surge of gastric acidity at around 2 am, which starts decreasing later on.[9]

In patients suffering from gastroesophageal reflux disease (GERD), prolonged nocturnal esophageal acid exposure has been shown to contribute to the development of erosive esophagitis.[10] During night, reflux episodes are of longer duration owing to loss of gravity mediated drainage and decrease in swallows that result in reduction of primary peristalsis and thus delivery of saliva to the distal esophagus during sleep. As a result of this, the reported night-time reflux symptoms include heartburn, a bitter or sour taste in mouth, burning sensation in throat, coughing and morning phlegm. These symptoms adversely affect the sleep as well as impair functional abilities during day-time.[11]

The model drug selected for the present work is Rabeprazole sodium (Anti-ulcer agent; Proton Pump Inhibitors). Its chemical name is 2-{[4-(3-methoxypropoxy)-3-methylpyridine-2-yl]methanesulfinyl}-1H-1, 3-benzodiazole with a molecular formula $C_{18}H_{21}N_3O_3S$ and molecular weight 359.444 g/mol. Rabeprazole sodium (RS) is white to off-white crystalline powder which is freely soluble in water, soluble in chloroform, methanol and ethyl acetate (I.P., 2007). The drug acts by suppressing the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect. PPIs are indicated in the management of acid-related disorders such as GERD and peptic ulcer disease, in association with *Helicobacter pylori* eradication therapy when needed.[12]

The proposed formulation comprises of a core tablet, containing Rabeprazole sodium and superdisintegrant with an erodible outer coating layer of polymer so that an immediate pulse of drug release can be achieved. Further, the compression coating of core tablet was done by using cellulosic polymers so as to have a lag time where there is no drug release. Thus, the proposed delivery system by achieving a rapid drug release (sigmoidal drug release curve) immediately after lag time, attempts to overcome the challenge of prompt drug release[13]. Moreover, the formulation attempts to alleviate the challenge associated with delivery of acid-labile nature of Rabeprazole sodium.[14]

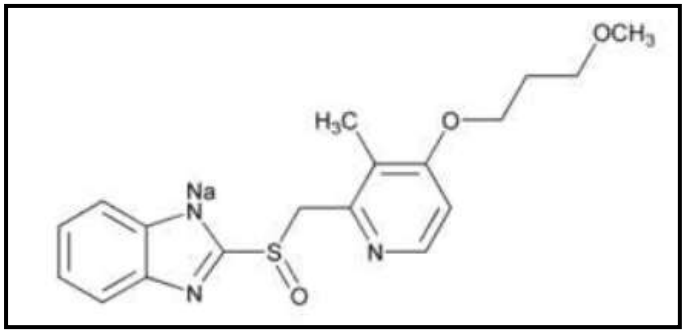

Figure 1:Structure of Rabeprazole sodium

MATERIALS AND METHOD

Materials

Rabeprazole was obtained as an *ex-gratis* sample from Magbro Healthcare Ltd., H.P., India. Ethyl cellulose (5Cps), HPMC K15M, Microcrystalline cellulose & Croscarmellose sodium (CCS) from Yarrow Chem. Ltd., Mumbai, were purchased. Karaya gum was obtained as an *ex-gratis* sample from Girijan Cooperative Corporation, Vishakhapatnam. All other reagents used in the study were of analytical grade and were used as received.

Preformulation Studies

Melting Point

Melting point of the drugs was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in Theil's melting point apparatus and the temperature at which the drug melted was noted down.[15]

Assay

Assay of the drug was performed by UV spectrophotometric method. Rabeprazole sodium (10 mg) was dissolved in few ml of phosphate buffer (pH 6.8) and volume was made up to 100 ml in volumetric flask using phosphate buffer (pH 6.8). From this stock solution 1 ml solution was withdrawn and diluted up to 10 ml in volumetric flask (10µg/ml). The absorbance of the solution was measured at 284 nm using UV spectrophotometer.

Partition Coefficient

The partition coefficient of the drug was determined by taking equal volumes of n-octanol and aqueous phases in a separating funnel. A drug solution was prepared and 1ml of the solution was added to n-octanol: water (50:50) taken in a separating funnel, shaken for 10 minutes and allowed to stand for 1 h, it was continued for 24 hrs. Then aqueous phase and octanol phase were separated, centrifuged for 10 min at 2000 rpm. The aqueous phase and octanol phase were assayed before and

after partitioning using UV Spectrophotometer at their respective λ_{max} (i.e. 284 & 280 nm) to get partition coefficient.[15]

Calibration curve for Rabeprazole sodium in 0.1 N HCl

10 mg of accurately weighed drug was dissolved in 0.1 N HCl in a 100 ml volumetric flask and volume was made up with 0.1 N HCl to get a concentration of 100 µg/ml.

From the above stock solution, various dilutions were prepared to get the concentrations in a range of 5µg-30µg/ml. The working standard was scanned for λ_{max} using UV visible spectrophotometer.

Calibration curve for Rabeprazole sodium in pH 6.8 Phosphate Buffer

Following the above procedure, 10 mg of accurately weighed drug was dissolved in pH 6.8 phosphate buffer in a 100 ml volumetric flask and volume was made up using the same buffer to get a concentration of 100 µg/ml.

From the above stock solution, various dilutions were prepared to get the concentrations in a range of 5µg-30µg/ml. The working standard was scanned for λ_{max} using UV visible spectrophotometer.

FTIR Analysis

FTIR analysis was carried out to find out the compatibility between the drug and excipients such as hydroxyl propyl methyl cellulose (HPMC K15M), Karaya gum, Magnesium stearate, Ethyl cellulose (EC), Microcrystalline cellulose (MCC). Samples were prepared for drug, polymer and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group bands.

Formulation of Rabeprazole Sodium Pulsatile Release Tablets

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 as shown in table 1. 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 K15M and EC along with Karaya gum as a binder for strengthening of coating layer. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. The compression coated tablets were evaluated for weight variation test, thickness, hardness, friability, lag time and dissolution study. Each tablet contained 20 mg of Rabeprazole Sodium.[16, 17]

Table 1: Formulation ingredients

Formulations Ingredients (mg)	C1	C2	C3	C4	C5	C6
Core tablet formulation						
Rabeprazole Sodium	20	20	20	20	20	20
Cross Carmellose Sodium	3	3	3	3	3	3
MCC (PH-102)	44	44	44	44	44	44
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Coating layer formulation						
HPMC K15M	55	65	75	85	100	105
EC (5Cps)	70	60	50	40	25	20
Talc	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Karaya Gum	4	4	4	4	4	4

Evaluation

Pre-compression characterization

It included recording of colour and odour of the drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specifications for later production.[18,19]

Density

Powder density may influence compressibility, sphericity, pellet porosity, dissolution and other properties.

Bulk density (BD)

Bulk density is ratio of mass of powder to bulk volume of powder. The parameter was measured following standard procedure. The equation for determining bulk density is

$\rho_b = m/ v_b$ ---------- (1)

Where,

ρ_b = Bulk density

m = Mass of powder

v_b = Bulk Volume

Tapped density (TD)

The pre-weighed powder was filled in measuring cylinder. Then it was tapped in bulk density test apparatus. After 50 taps the volume was measured. It is a measure used to describe void space of powder. The equation for determining tapped density is-

$$\rho_t = m/ v_t \text{ ---------- (2)}$$

Where,

ρ_t = Tapped density

m = Mass of powder

v_t = Tapped volume

Carr's (Compressibility) Index (CI)

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Tapped density (ρ_t) and bulk density (ρ_b) of powder material was used to measure compressibility of a powder material. The equation for determining Carr's index is:

$$\text{Carr's index (\%)} = (\rho_t-\rho_b)/\rho_t*100 \text{ --------- (3)}$$

Where,

ρ_b = Bulk density

ρ_t = Tapped density

Hausner's Ratio (HR)

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. It is a measure used to describe compressibility of powder. Tapped density (ρ_t) and bulk density (ρ_b) of powder material was used to measure Hausner's Ratio.

Angle of Repose

Angle of repose is the maximum angle possible between pile of powder and horizontal plane. The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel and tip of funnel was blocked by thumb at initially. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend (fixed at approximately 2 cm from plane to tip of funnel).

The powder blend was allowed to flow through the funnel freely on to the surface. It is a measure used to describe flow ability of the powder material.

The equation for determining Angle of Repose is

$$\theta = \tan^{-1} h/r \text{ ---------- (5)}$$

Where,

θ = Max. angle between pile of powder and horizontal plane

h = Height of pile of powder

r = Radius of the base of conical pile

Post-compression parameters

Hardness

The prepared tablets were subjected to hardness test. It was carried out by using Monsanto hardness tester and is expressed in kg/cm^2. [20]

Friability (F)

The friability was determined using Roche friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability was calculated for each batch by using the following formula-

$F = (W_{initial} - W_{final}) / W_{initial} X 100$ ---------- (6)

Weight variation test

The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provided an average weight of a tablet. The average weight and standard deviation of the tablets were calculated.

Uniformity of drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 10 mg was added in 100 ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45 µm membrane filter, diluted suitably and the absorbance of resultant solution was measured by using Shimadzu Pharmaspec UV-visible spectrophotometer using pH 6.8 Phosphate buffer.[21]

Dissolution testing

In-vitro release of Rabeprazole sodium from compression coated tablets was determined using USP Dissolution Testing Apparatus type II (paddle type). The dissolution test was performed using 900 ml HCl buffer (pH 1.2) which was replaced with phosphate buffer (pH 6.8) after two hours. The temperature of the dissolution medium was maintained at 37±0.5ºC. The speed of rotation of paddle was set at 50 rpm. At a predetermined time interval of 15 minutes, 5 ml samples were withdrawn, filtered through Whatmann filter paper and replaced with equivalent amount of fresh buffer to maintain the *in-vitro* sink conditions.[22, 23].

Stability studies of optimized formulation

Stability of pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/package, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life.[24]

Method

Short-term stability study of final formulation was carried out for 1 month at accelerated stability conditions (40°C and 75% RH). The optimized formulation C5 was packed in aluminium pouch pack and then exposed to accelerated conditions of temperature and humidity for 1 month. Tablets were evaluated for their physical appearance, drug content and drug-excipient compatibility at specified intervals of time.

Release Kinetics

The different mathematical models may be applied for describing the kinetics of the drug release process from tablets; the most suited being the one which best fits to the experimental results. These models best describe drug release from pharmaceutical systems resulting from a simple phenomenon, or when this phenomenon, by being the rate-limiting step, conditions all the process occurring in the system.

The kinetics of Rabeprazole Sodium release from tablets formulations were determined by finding the best fit of the release data to zero order, first order, matrix, Hixson-Crowell, Higuchi, and Korsmeyer- Peppas plots.[25]

Higuchi developed several theoretical models to study release of high and low water soluble drugs incorporated in the semi-solid and/or solid matrices. According to this model, drug release was described as a square root of time-dependent diffusion process based on Fick's law. This relation can be used to describe drug dissolution from several types of modified release pharmaceutical dosage forms.

$$Q_t = K_H \sqrt{t}$$

Where K_H is Higuchi's rate constant, and Q_t is the amount of drug released at time t. If a plot of square root of time vs cumulative amount of drug released yields a straight line, and the slope is 1 or more than 1, then the particular dosage form is considered to follow Higuchi kinetics of drug release. Under some experimental situations the release mechanism deviates from the Fick's equation, following an anomalous behavior (Non-Fickian release). In these cases a more generic equation can be used. Korsmeyer et al. developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time.

$$Q_t/Q_\alpha = Kt^n$$

Where Q_t/Q_α is the fraction of drug released at time t; K is the constant comprising a structural and geometric characteristics of the tablets; and n, the release exponent, is a parameter that depends on the release mechanism and is thus used to characterize it. Peppas[26] used this n value in order to characterize different release mechanisms. If the n value is 0.5 or less, the release mechanism follows Fickian diffusion, and higher values ($0.5 < n < 1$) for mass transfer follow a non-Fickian model (anomalous transport). Hixson-Crowell recognized that particle regular area is proportional to the cubic root of its volume, derived an equation that can be describe in the following manner.

$$W_0^{1/3} - W_t^{1/3} = K_S\, t$$

Where W_0 is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t, and K_S is a constant incorporating the surface volume relation (Table 2).

Table 2: Interpretation of diffusional release mechanisms

Release exponent (n)	Drug Transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{0.5}$
0.5-1.0	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
>1.0	Super Case II transport	t^{n-1}

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties

Drug was observed to be a white to slightly yellowish-white powder with a slightly bitter taste.

Melting Point

The value of observed melting point range is given in the table 3, along with the reported melting point range.

Table 3: Observed Melting Point of Drug

Parameter	Reference value	Experimental value
Melting point	140-141 °C	140±0.6°C

***Mean ± S.D.**

Assay

The assay showed the drug content as 97 ± 0.5% which was found within the official limits (I.P., 2007).

Partition Coefficient

The aqueous phase and octanol phase were assayed before and after partitioning using UV Spectrophotometer at their respective λ_{max} to get partition coefficient. The log p value of RS was found to be 0.549 which is in accordance with the reported value i.e. 0.60.[27]

Calibration plot of Rabeprazole sodium in 0.1 N HCl

Concentrations of 5-30 µg/ml were analyzed at scanned wavelength of 280 nm and straight line obtained is shown in the figure below.

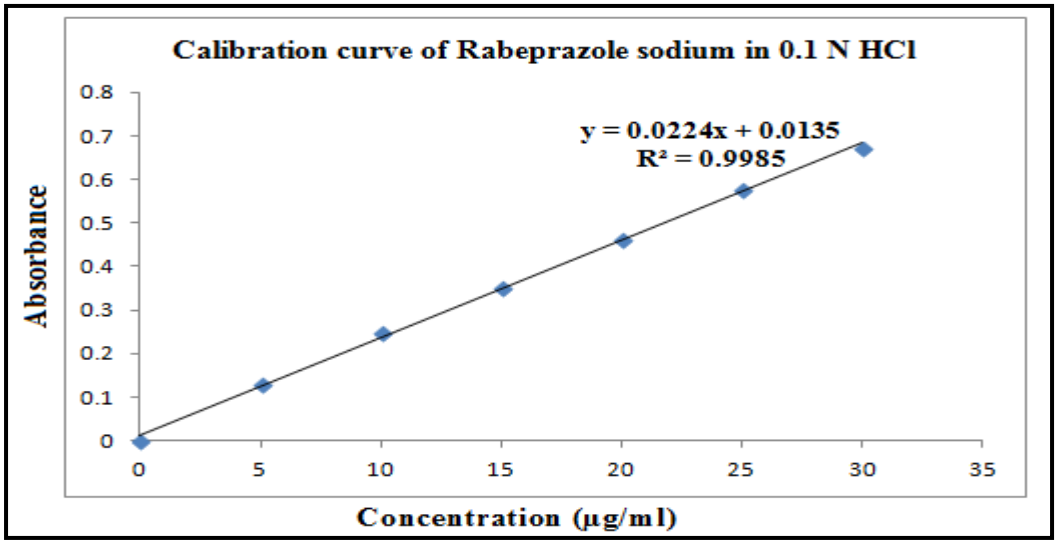

Figure 2: Calibration plot of RS in 0.1N HCl

Calibration plot of Rabeprazole sodium in 6.8 phosphate buffer

The drug in pH 6.8 Phosphate buffer solution showed a λ_{max} of 284 nm. Different concentrations were analyzed at scanned wavelength (i.e. 284 nm) and the straight line equation so obtained is shown in the figure below.

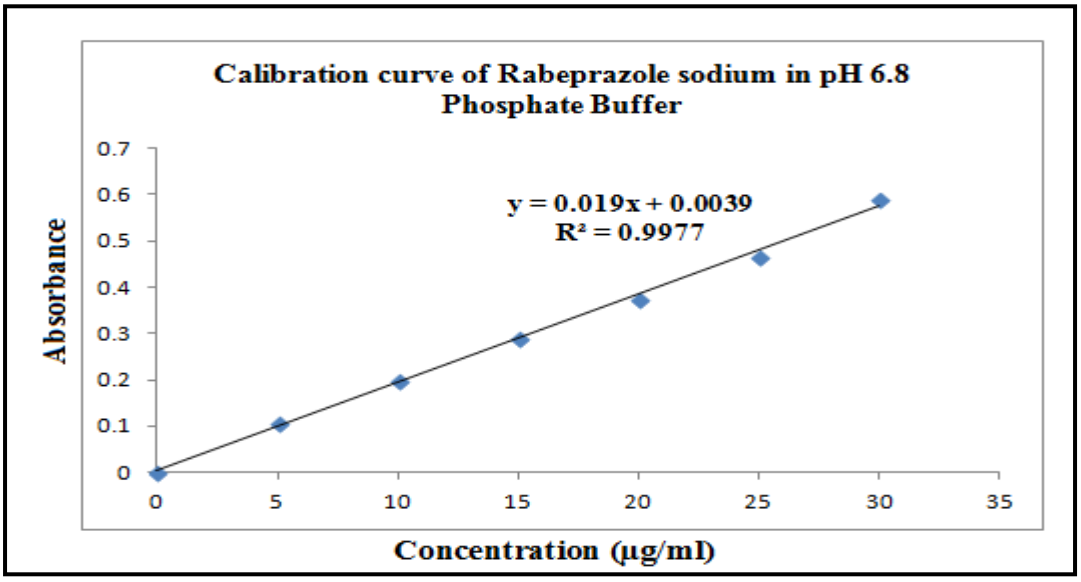

Figure 3: Calibration plot of RS in pH 6.8

FTIR Analysis

Drug-excipient interactions play a vital role with respect to release of drug from the formulation amongst others. In the FTIR studies, it was observed that there was no chemical interaction between the drug and excipients used as shown in different FTIR spectra (as shown in Figure 4, 5, 6,7and 8) and table 4. From the obtained spectra, it was evident that there were no significant

changes in the main functional groups of drug in final formulation, which confirmed the absence of any interactions whatsoever.

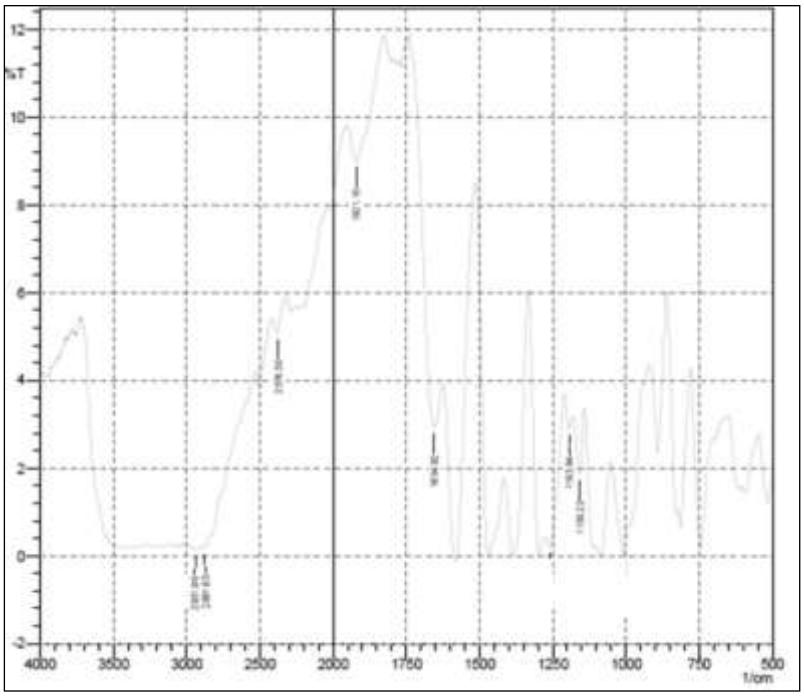

Figure 4: IR spectrum of Rabeprazole sodium (RS)

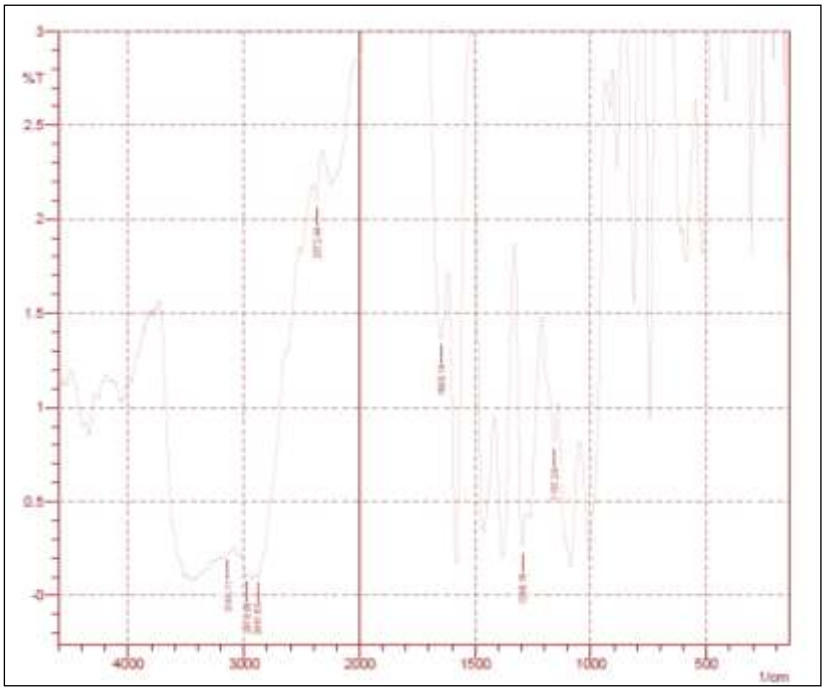

Figure 5: IR spectrum of RS + HPMC K50 M

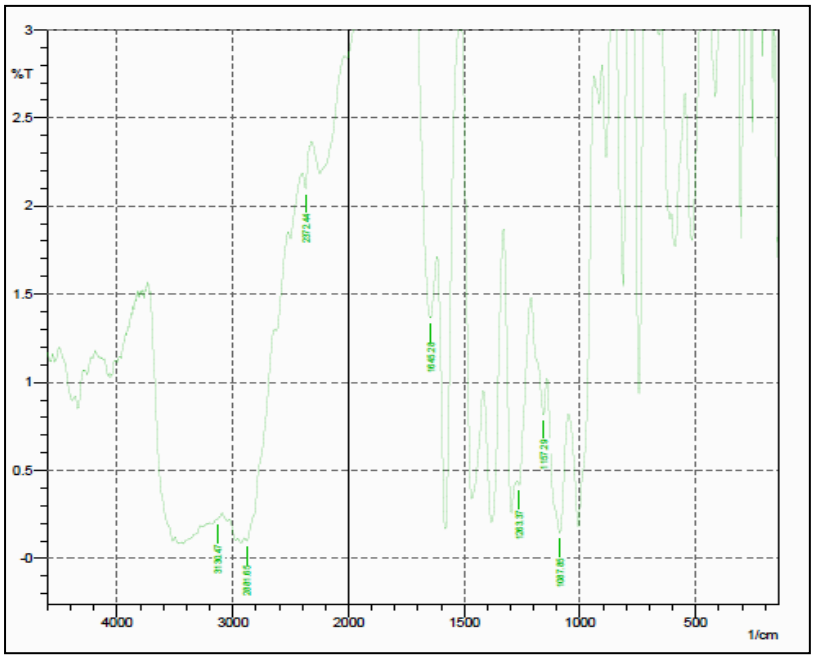

Figure 6: IR spectrum of RS + EC

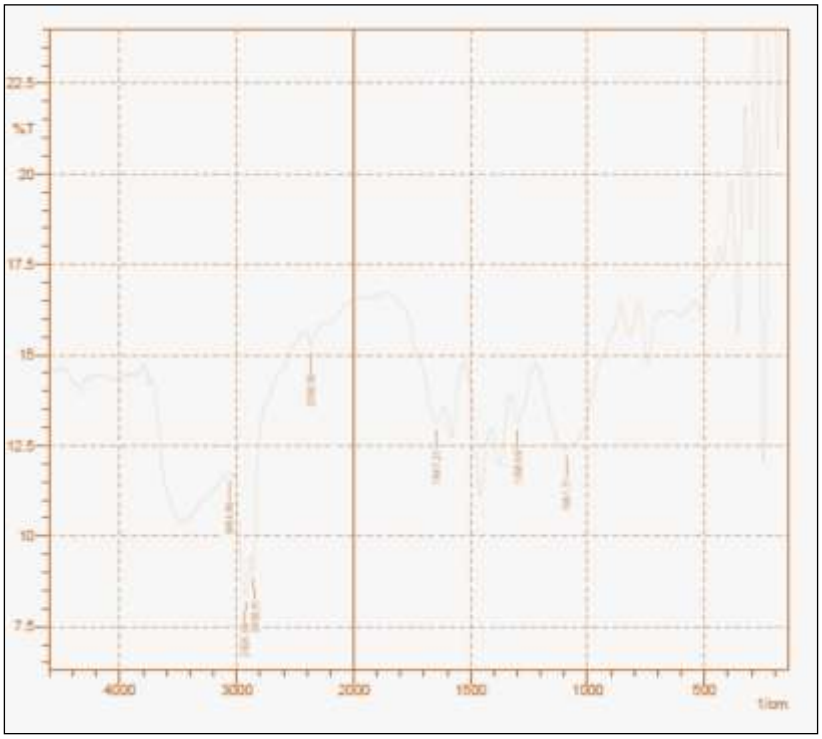

Figure 7: IR spectrum of RS + CCS

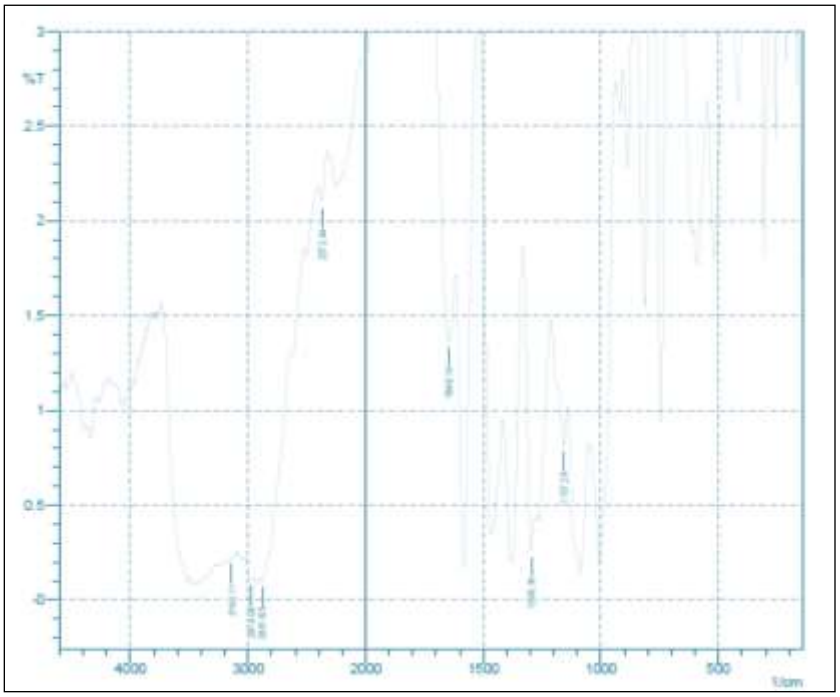

Figure 8: IR spectrum of Drug + all excipients

Table 4: FTIR studies for drug and drug-excipients mixture

Sr. No.	Interpretation	IR absorption bands (cm^{-1})			
		RS	RS + HPMCK15M	RS +EC	Formulation
1	N-H	3397.09	3397.96	3395.19	3461.09
2	O-H	3361.12	3358.17	3330.28	3297.86
3	CH2	3157.39	3162.98	3176.53	3048.08
4	CH3	2968.46	2973.76	2951.36	2857.83
5	C-O	1590.86	1586.59	1595.02	1587.38
6	S=O	1126.38	1113.06	1117.90	1116.72

Evaluation

Pre-compression parameters

The results obtained in pre-compression studies are summarized in table below.

Table 5: Pre-compression parameters of formulations

Formulation code	Bulk density (gm/ml) ±SD	Tapped density (gm/ml) ±SD	Carr' index (%)±SD	Angle of Repose (θ) ±SD
C1	0.37±0.78	0.44±0.45	21.64±0.16	21.31±0.45
C2	0.38±0.04	0.46±0.09	14.98±0.46	34.78±0.17
C3	0.37±0.43	0.43±0.34	17.79±0.31	31.16±0.74
C4	0.39±0.17	0.42±0.74	16.37±0.73	22.61±0.14
C5	0.38±0.58	0.45±0.19	11.43±0.74	26.43±0.48
C6	0.36±0.26	0.46±0.26	19.68±0.18	31.01±0.55

Post compression parameters

The results obtained for post-compression parameters are summarized in the table 6.

Table 6: Post-compression parameters of formulations

Formulations	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight uniformity (mg)	Percent drug content
C1	3.67	6.5±0.09	0.83±0.09	210.14±1.13	98.72±0.8
C2	3.87	6.8±0.21	0.39±0.02	194.54±1.31	98.61±0.12
C3	3.50	5.7±0.47	0.77±0.07	192.09±0.97	99.21±0.5
C4	4.04	6.6±0.06	0.91±0.12	197.17±2.28	97.92±0.9
C5	3.51	6.1±0.87	0.59±0.08	200.64±1.12	99.96±0.7
C6	3.29	5.5±0.52	0.78±0.13	207.66±0.91	99.43±0.6

***Mean ± S.D.**

Optimized formulation

From all the prepared formulations, the best formulation (C5) was selected based on physiochemical and compression parameters.

Stability study

The optimized formulation (i.e. C5) was packed in aluminum pouch and charged for accelerated stability studies at 40°C and 75% RH, for 1 month. The tablets were evaluated for their physical appearance and post-compression parameters at specified intervals of time. Formulation C5 was found to be stable during the stability study of 1 month without any significant changes in post compression parameters as shown in table 7.

Table 7: Stability study parameters obtained before and after a period of 1 month

Sr. No.	Parameters	Initial	After 15 days	After 1 month
1	Physical appearance	White to off white	No change	No change
2	Weight variation (mg)	200.64±1.12	200±1.17	200±1.53
3	Friability (%)	0.59±0.08	0.59±0.03	0.58±0.07
4	Thickness (mm)	3.51±0.75	3.51±1.54	3.51±1.11
5	Hardness	6.1±0.87	6.1±0.34	6.1±0.94

***Mean ± S.D.**

In-vitro drug release studies

In-vitro drug release of RS from compression coated tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml HCl buffer (pH 1.2) which was replaced with phosphate buffer (pH 6.8) after two hours. Temperature was maintained at 37± 0.50°C. The speed of rotation of paddle was set at 50 rpm. At a predetermined time interval of 15 minutes, 5 ml samples were withdrawn, filtered through Whatman filter paper. The system released the drug rapidly after a certain lag time due to the rupture of the HPMC K15M and ethyl cellulose (5Cps) film as shown in table 8. Absorbance of solution was checked by UV spectrophotometer and drug release was determined from standard curve. The optimized

formulation C5 was found to give maximum cumulative drug release of 99.97% in 195 minutes. The drug release profiles from various formulations are shown in figure 9.

HPMC K15M was chosen because of its swelling nature and its eroding behavior and was applied by direct compression method. The rupturable coating consisted of a plasticized mixture of EC as it forms a mechanically weak and semipermeable film, which could rupture easily upon exposure to the dissolution media and was water insoluble. Water influx was through the semipermeable rupturable outer coating which led to rupture of the outer coating and drug was released within a short time after a definite lag time period.[28]

Table 8: *In-vitro* drug release study

Time (min)	**% Cumulative Drug release from formulations**					
	C1	**C2**	**C3**	**C4**	**C5**	**C6**
0	0	0	0	0	0	0
15	0	0	0	0	0	0
30	0	0	0	0	0	0
45	0	0	0	0	0	0
60	0	0	0	0	0	0
75	0	0	0	0	0	0
90	11.5±0.15	0	0	0	0	0
105	78.21±0.23	18.27±0.28	24.31±0.23	0	0	0
120	81.09±0.38	77.19±0.34	75.89±0.35	9.13±0.27	5.95±0.69	4.76±0.34
135	83.12±0.36	81.56±0.39	84.93±0.42	73.67±0.43	89.62±0.19	88.78±0.38
150	87.89±0.17	86.45±0.17	87.45±0.49	86.91±0.46	93.46±0.36	90.71±0.23
165	88.67±0.31	88.63±0.46	88.85±0.25	89.65±0.31	95.54±0.39	94.17±0.31
180	88.91±0.62	89.13±0.35	88.94±0.51	91.78±0.19	98.04±0.17	96.08±0.18
195	89.83±0.46	89.97±0.41	90.78±0.16	93.70±0.34	99.97±0.51	97.46±0.43

***Mean ± S.D.**

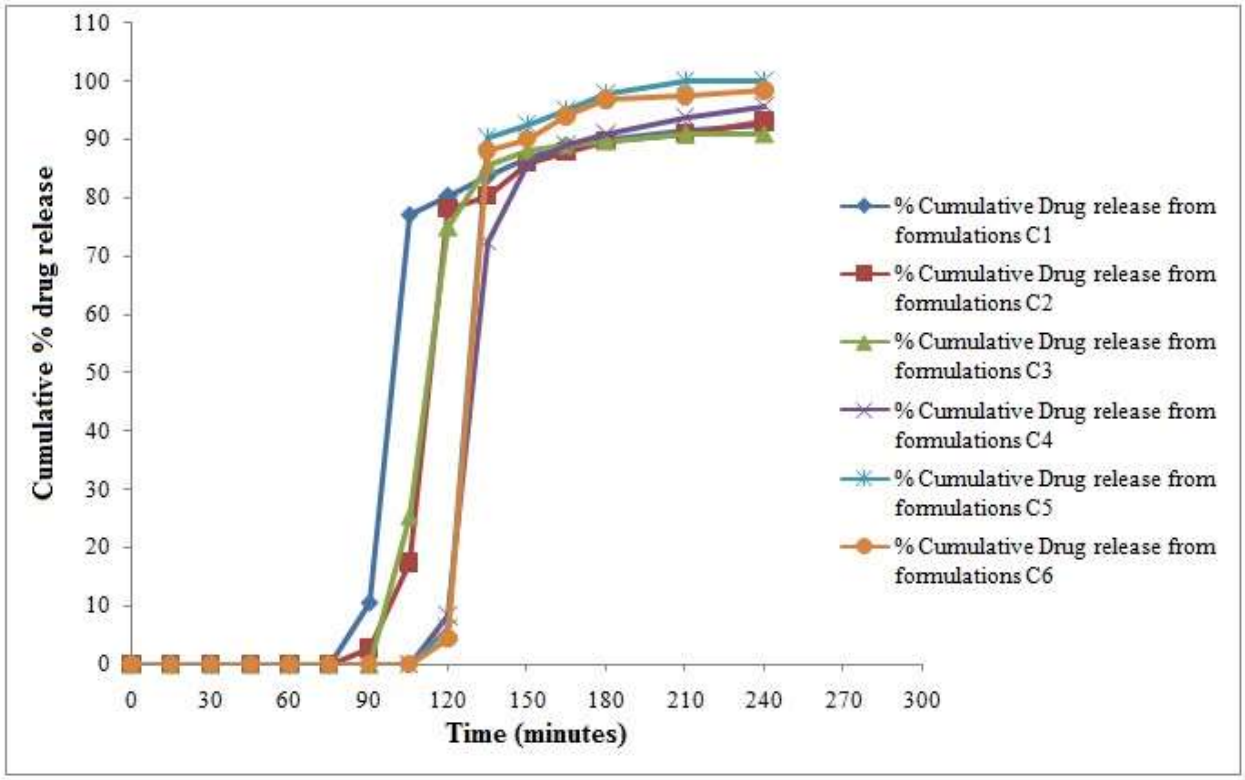

**Figure 9: *In-vitro* drug release profile of RS from C1-C6 formulations **

Drug release kinetics

Data of drug release kinetics is shown in table 9. 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 C5 was found out according to zero order equation 0.812, first order equation 0.123, higuchi model 0.762 and korsmeyer peppas model 0.981. 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 is described in table 9. On the basis of n value the best formulation C5 exhibited non fickian type drug release

Table 9: Release kinetics data for different formulations of Rabeprazole Sodium

Batch	Zero order		First order		Higuchi		Korsmeyer pappas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) (M/L).S	R^2	K_H	R^2	N
C1	0.945	14.89	0.019	0.161	0.844	36.45	0.938	0.78
C2	0.934	14.72	0.032	0.113	0.812	34.57	0.926	0.73
C3	0.926	14.55	0.054	0.136	0.864	35.78	0.934	0.79
C4	0.932	14.33	0.046	0.154	0.738	35.11	0.943	0.72
C5	**0.812**	**12.78**	**0.123**	**0.243**	**0.762**	**34.87**	**0.981**	**0.81**
C6	0.801	14.33	0.034	0.187	0.745	32.56	0.967	0.78

CONCLUSION

In the present study, pulsatile drug delivery system of Rabeprazole sodium for effective treatment of Peptic Ulcer was formulated. Each tablet contained 20 mg of drug. The study includes preformulation of drug and excipients, formulation, evaluation and stability studies of pulsatile release tablets. The pulsatile tablets prepared by compression coating method consisted of two different parts: a core tablet, containing the active ingredient along with superdisintegrant, and an erodible outer coating layer composed of HPMC K15M and ethyl cellulose along with Karaya gum as binder. The effect of formulation composition on the barrier layer comprising both polymers, excipients on the lag time of drug release was investigated. The compression coated tablets were further evaluated for weight variation test, thickness, hardness, friability, lag time and dissolution study. Stability studies were conducted for the optimized formulation at 40ºC/75% RH (accelerated stability testing) for 1 month. During study, 6 formulations of RS were developed amongst which formulation C5 was observed to possess the best result in terms of compression parameters as well as cumulative percentage drug release. The system released the drug rapidly after a certain lag time due to the rupture of the HPMC K15M and EC film. The release profile of optimized formulation C5 was close to korsmeyer peppas model. Irrespective of the polymer type and its concentration, the prepared optimized pulsatile tablets showed non fickian (anomalous) release. Since the formulation was developed to be taken at bedtime, the tablet would be expected to 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. Thus the novel time controlled chronotherapeutic pulsatile drug delivery system for oral use was successfully developed and evaluated; the concept, however, needs to be further confirmed with *in-vivo* studies.

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