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## AN INVESTIGATION OF *IN-VITRO* RELEASE OF RABEPRAZOLE SODIUM FROM PULSATILE RELEASE TABLETS CONTAINING HPMC-EC BLEND AS TIME LAGGED PRESS COATING

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### Keywords:

Rabeprazole sodium,  
Pulsatile release tablets, Time  
lagged press coating, Enteric coating

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**ABSTRACT:** To develop new pulsatile release tablets of Rabeprazole sodium (RS), that can suppress drug release in stomach and release the drug rapidly after a predetermined lag time for about 4 h in intestine, a multiple unit dosage forms was designed that contain, drug-containing core, a coating to achieve time lag in drug release and an outermost acid resistant enteric coating. Time lagged press coating was performed using ethyl cellulose (EC) and different grades of hydroxypropyl methylcellulose (HPMC) in different ratios. The press-coated tablets were optimized by the drug release study and finally the formulation F<sub>17</sub> containing 7:1 ratio of EC and HPMC K4M was selected as optimized formulation. This press coated tablet was further enteric coated with Cellulose acetate phthalate (CAP). The weight gain of the enteric coating was optimized based on the integrity of coating in an acidic solution for about 2 h. Formulation F<sub>21</sub> was finally selected with 10% weight gain and rupture time of 120 minutes in 0.1N HCl. Further, the drug release from F<sub>21</sub> formulation started after 270 minutes (4.5 h). The results indicate that the drug release was successfully suppressed till 4.5 hrs as per the need of pulsatile dosing of RS as the drug concentration needed between 12 am to 6 am. By considering the dosing time of 8: 00 pm, the formulation release only 15.1 % of the drug till 1 am (after 5 hrs) and 90 % of the drug release after 7.25 h.

**INTRODUCTION:** Rabeprazole Sodium (RS) is a proton pump inhibitor that blocks secretion of gastric acid from gastric parietal cells. This drug is used in the treatment of acid related diseases like gastric ulcer, peptic ulcer, duodenal ulcers, erosive or ulcerative gastro esophageal reflux disease (GERD), symptomatic GERD, pathological hyper-secretory conditions (Zollinger - Ellison).

The drug is chemically known as 2-[[[4 (3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole sodium, with empirical formula of C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>NaO<sub>3</sub>S. RS is very soluble in water and in alkaline media. The stability of RS is a function of pH; it is rapidly degraded in acid media, however it is more stable in alkaline conditions.

Therefore, exposure of rabeprazole to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability<sup>1,2</sup>. This research work focuses on to protect the drug from acidic environment by providing enteric coat along with the delivery of drug in a pulsatile manner in intestine at the required time.

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Pulsatile delivery system also known as time controlled system or sigmoid release system is a drug delivery system in which the drug should not be released at all during the initial phase of dosage form administration. In other words the drug should be released as a “pulse” after a lag time for meeting chronopharmaceutical need<sup>3</sup>. Chronopharmaceutics is a combination of chronobiology (study of biological rhythms) and pharmaceutics (deals with drug delivery). When the medical treatment is given in accordance with the biological rhythms, this is known as chronotherapy<sup>4-5</sup>. Various studies have shown potential benefits of chronotherapy in management of number of diseases which exhibit 24 h (circadian) rhythm such as asthma, diabetes mellitus, peptic ulcer, arthritis, cardiovascular diseases, attention deficient syndrome and hypercholesterolemia<sup>6-8</sup>.

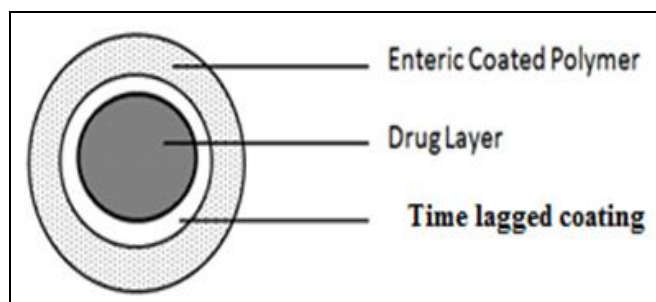
Many common gastrointestinal diseases like GERD heartburn and ulcer follow strong rhythms in their symptoms and response to medications. Normal gastric acid secretion follows circadian rhythmic patterns. Research studies showed gastric acid secretion is 2-3 times greater between midnight 22:00 and 02:00 than in the day<sup>9</sup>. The pulsatile delivery system provides chronotherapeutic effect by delivering the drug in time specific and site specific manner in the right amount. Various technologies have been developed for pulsatile release purposes. Several formulations based on coating, capsular and osmotic system have been developed. The formulation techniques for pulsatile drug delivery systems are commonly based on rupturable or erodible coatings/ matrices<sup>10-12</sup>.

A time-controlled delivery system named chronotropic® system is based on a dosage form containing a core (tablet with a drug) coated with three polymeric layers: the outer layer dissolves at pH > 5, then the second layer made of HPMC swells providing the delay phase and finally the third layer was made of an enteric coating material. In fact, the system is resistant to acidic environment, a non-release phase ending with a rapid release of the drug.

Various materials like HPMC, hydroxypropyl cellulose, polyethylene oxide, micronized ethyl cellulose, Eudragit® RS, behenic acid have been investigated as compression coatings material to

obtain time-controlled release. Bimodal drug release usually obtained with multilayered with compression-coated tablets<sup>13-15</sup>. The proposed pulsatile tablet of this work aimed to develop chronotherapeutic drug delivery system which can be administered just before going to bed making it convenient for achieving desired blood levels required at early mornings.

The developed formulation (**Fig. 1**) comprises three layers; a RS core tablet prepared by wet granulation method containing microcrystalline cellulose (MCC; Avicel PH 101), and a super disintegrating agent croscarmellose sodium (CCS), outer barrier layer (to achieve time lag in drug release) containing a hydrophobic polymer ethyl cellulose (EC) and a hydrophilic polymer such as hydroxypropyl methylcellulose (HPMC) in different weight ratios; and a top layer of enteric coating polymer like cellulose acetate phthalate (CAP).



**FIG. 1: DESIGN OF MULTILAYERED PULSATILE TABLET**

The coating to achieve time lag in drug release was developed using rupturable polymer EC in combination with an erodible polymer HPMC. HPMC is a water soluble polymer that swells in contact with gastrointestinal fluids. The other component of the barrier layer, EC is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release. It is postulated that when the barrier layer is exposed to dissolution media, the HPMC particles swell and erode, a process which is retarded to varying degrees depending upon the quantity of EC present, demonstrating that manipulation of both components controls the erosion rate<sup>16-18</sup>. The effect of the formulation of an outer shell comprising both hydrophobic polymer and hydrophilic excipients on the lag time of drug release is investigated. The time-release function should work more efficiently

in the small intestine as compared to the stomach. In the small intestine, drug carrier will be delivered to the target side and drug release will begin at a predetermined time point after gastric emptying. The lag-time and the release rate can also be well controlled by varying the composition (ratio HPMC/ethyl cellulose) and the amount (thickness) of the compression-coating. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release is investigated. The release profile of proposed tablet should exhibit a time period, without drug release (time lag) followed by a rapid and complete release phase according to chronopharmaceutical need.

### MATERIALS AND METHODS:

**Materials:** RS was obtained as gift sample from Sharon Bio-Medicine Limited, Dehradun, India. MCC (Avicel PH 101) and polyethylene glycol (PEG 400) were supplied from SD Fine Chemical Limited, Mumbai. Croscarmellose Sodium (CCS; Ac-Di-Sol<sup>®</sup>) and EC were obtained from Loba Chemie Pvt. Ltd., Mumbai. CAP was purchased from E-Merck India Ltd. Mumbai and HPMC from Yarrow Chem Products, Mumbai. All other reagents used in this study were of analytical grade.

### Methods:

**Drug-Excipients Compatibility Studies Using Fourier Transformed Infrared Spectroscopy (FTIR):** 100 mg of sample and 300 mg of KBr

(potassium bromide) were taken in mortal pastel and triturated. A small amount of triturate sample was taken in to pellet maker and were compressed at 10 Kg/cm<sup>2</sup>. The pallet was kept in sample holder and scanned from 4000 cm<sup>-1</sup> to 400 cm<sup>-1</sup>.

**Preparation of Tablet Cores:** The purpose of this study is to first formulate a core that can provide a burst release once the outer coating dissolves (**Table 1**). For this purpose, CCS (5% or 10% w/w) was used as a super disintegrant to achieve immediate release. MCC was also added to the composition of the core, which along with CCS will swell sufficient enough to disintegrate the tablet.

This may also help in rupturing the external polymer coating. The mixture for compression of core tablets was obtained by manually granulating the RS (20 mg), MCC, and lactose or CCS with 5 % cornstarch paste. Following drying and sieving, talcum powder and magnesium stearate was added in the external phase and then compressed to a theoretical weight of about 100 mg.

**Preparation of Press Coating of the Core Tablets/ Compression-coating of Tablet Cores:** The optimized core tablets (batch F<sub>1</sub>- F<sub>4</sub>) were compression-coated using various HPMC compression coating formulations (HPMC K4M, HPMC K15, HPMC K100) and ethyl cellulose in various ratios (**Table 2**).

**TABLE 1: FORMULATION OF CORE TABLETS OF RABEPRAZOLE SODIUM**

Ingredient	Formulation code			
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>
Rabeprazole sodium (mg)	20	20	20	20
Microcrystalline cellulose pH 101 (mg)	75	70	65	55
Starch paste (5%)	q.s	q.s	q.s	q.s
Lactose (mg)	-	-	-	15
Croscarmellose sodium (mg)	-	5	10	5
Talc (mg)	3.5	3.5	3.5	3.5
Magnesium stearate (mg)	1.5	1.5	1.5	1.5
Total (mg)	100	100	100	100

q.s. – quantum satis

**TABLE 2: COMPOSITION FOR PRESS COATING**

S. no.	Ingredients	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F <sub>9</sub>	F <sub>10</sub>	F <sub>11</sub>	F <sub>12</sub>	F <sub>13</sub>	F <sub>14</sub>	F <sub>15</sub>	F <sub>16</sub>	F <sub>17</sub>	F <sub>18</sub>
1	HPMC K4M (mg)	200	175	150	100	50	-	-	-	-	-	-	-	25	-
2	HPMC K15 (mg)	-	-	-	-	-	50	200	150	100	-	-	-	-	-
3	HPMC K100 (mg)	-	-	-	-	-	-	-	-	-	150	50	200	-	-
4	Ethyl Cellulose (mg)	-	25	50	100	150	150	-	50	100	50	150	-	175	200
5	Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Total weight of press coated tablet = 300 mg

The compression-coated tablets (core: coat, 1:2) were prepared by first filling one-half (100 mg) of compression-coated powders in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half (100 mg) of the polymer powder on top and then by compression. The effect of formulation composition on lag time of drug release was investigated.

**Enteric Coating of Press Coated Tablet/ Preparation of Enteric Coated Press Coated Tablet of Rabeprazole Sodium:** Different formulations of compression coated core tablet were tested for various evaluation parameters and the best formulation was then enteric coated with CAP 3 % w/v solution using isopropyl alcohol as a solvent and PEG 400 (1.25%w/v) as a plasticizer. The enteric coating was performed with 5%, 7.5% and 10% weight gain as shown in **Table 3**.

**TABLE 3: WEIGHT GAIN FOR ACID RESISTANT COATING LAYER**

Formulation code	% Weight gain of coating layer
F <sub>19</sub>	5
F <sub>20</sub>	7.5
F <sub>21</sub>	10

#### Evaluation:

**In-vitro Drug Release From Core Tablets and Press Coated Tablets:** Drug release for core tablets and press-coated tablets were studied in a paddle apparatus (USP XXIII type II) (VEEGO Mumbai India) with a rotation speed of 100 rpm and 900 ml of phosphate buffer pH 6.8 as a medium at  $37 \pm 0.5$  °C (n=6). Drug release was measured by UV spectrophotometer (SHIMADZU-1700) at a wavelength of 285.5 nm.

**Rupture Test:** Rupture test is used to check the integrity of the coating. It was determined visually by using the USP XXIII Type II dissolution apparatus (900 ml of 0.1 N HCl,  $37.0 \pm 0.5$  °C, 100 rpm, n = 3). In addition, the rupture behavior of pulsatile release tablets was photographed by a digital camera.

**In-vitro Drug Release From Enteric Coated Tablet:** *In -vitro* drug release was carried out using paddle apparatus (USP XXIII Type II) with a rotation speed of 100 rpm and 900 ml of medium at  $37 \pm 0.5$  °C (n=6). The dissolution media used hydrochloride solution with a pH of 1.2 for 2 h, and then replacing the medium with phosphate buffer

pH 6.8. The amount of rabeprazole sodium dissolved was assayed by UV-visible spectroscopic analysis of absorbance at a wavelength of 285.5 nm. The lag time ( $t_{10}$ ) was defined as the time in hrs when 10% of the drug contained in tablets was released.

#### RESULTS AND DISCUSSION:

**Drug-Excipients Compatibility Studies Using Fourier Transformed Infrared Spectroscopy (FTIR):** The drug and excipients compatibility study was performed by placing the samples as protocol. The physical mixture, drug and excipients were evaluated for physical observation i.e. liquefaction, color change and odor generation and finally by compression of their spectra. No observation of any new peak of drug was found in all of physical mixture of drug and excipients and all characteristic peaks of drug were found in physical mixture which revealed compatibility of drug with all of the excipients and polymer selected (**Fig. 2** and **Fig. 3**).

**Design of Pulsatile Release Tablet:** The pulsatile drug delivery system consisted of inner core tablet containing drug reservoir and outer compression coating with the combination of water insoluble polymer EC and water soluble polymer HPMC. EC was chosen because it forms a semi permeable film which ruptures on contact of dissolution medium. HPMC is a water soluble polymer that swells and eroded in the dissolution medium. These compression coated tablets were further enteric coated with CAP to protect the drug from acid environment of the stomach and release the drug in intestinal pH.

**In-vitro Drug Release:** The goal of this study was to protect the drug from the gastric environment by enteric coating and to obtain flexible extended drug release profiles (*e.g.* sigmoidal, pulsatile, increasing release rate with time) with HPMC- EC compression-coatings to the tablet.

**In-vitro Drug Release Profile of Core Tablets:** All tablet cores F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub> and F<sub>4</sub> (without compression-coating) resulted in complete drug release within 15 min (**Fig. 4**). Upon contact with dissolution medium, core tablet get erode and release the drug as given in **Fig. 4**. Among all four formulations, F<sub>3</sub> showed maximum release rapidly due to high amount of croscarmellose sodium a super disintegrating agent.

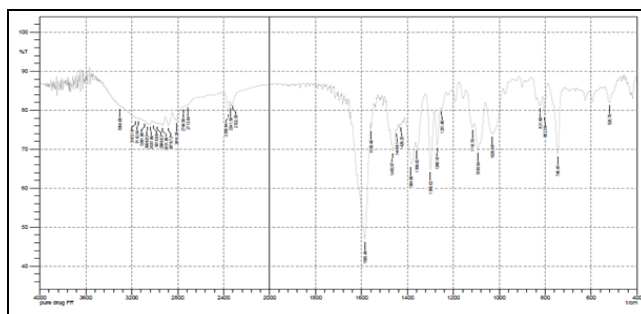


FIG. 2: FTIR SPECTRA OF RABEPRAZOLE SODIUM

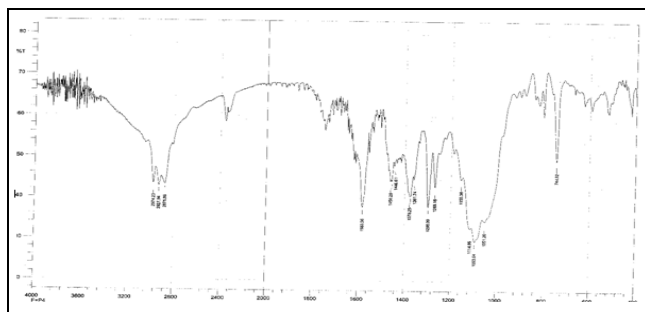


FIG. 3: FTIR SPECTRA OF RABEPRAZOLE SODIUM + AVICEL + CCS + HPMC + EC

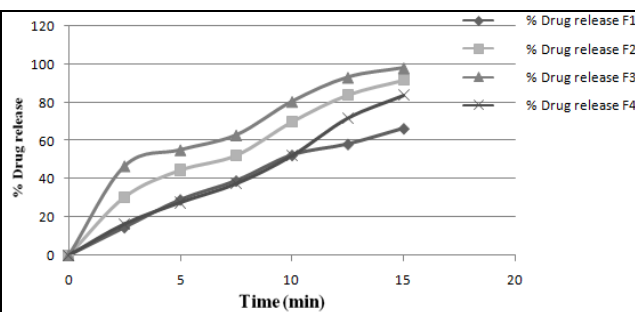


FIG. 4: IN-VITRO DRUG RELEASE PROFILE OF RS CORE TABLET

### **In-vitro Release Profile of Press Coated Tablets:**

Formulation F<sub>3</sub> which was selected as best formulation was then press-coated to find out the changes in the release rate of the RS. Press coating of the core tablet produces a lag time prior to drug release. Depending on the selection of coating agent (s), various release mechanisms can be involved, such as in the case of erodible, rupturable or diffusive reservoir systems<sup>19 - 20</sup>. When the dissolution medium reaches the core after eroding or rupturing the outer barrier layer, rapid drug release was observed. The compression coatings were done by using HPMC and ethyl cellulose in various ratios. Various grades of HPMC, *i.e.*, HPMC K 4 M, K15 and K100 were used. The HPMC compression-coating hydrated and swelled around the drug cores. The drug release through the compression coating depends on the type of polymers used and their ratio.

With HPMC alone depending on the solubility, drugs are released from HPMC matrix tablets by diffusion through and/or erosion of the gelled HPMC matrix. Water soluble drugs release faster because of an increasing diffusional release component with increasing drug solubility. Erosion occurs as the polymer chain becomes more hydrated, diluting the gel formed and gradually the gel gets diluted that disentanglement concentration is reached resulting in erosion<sup>21 - 23</sup>. The effect of

various changes in the HPMC compression coating on the drug release was investigated. It was shown by the drug release studies that high molecular weight HPMC forms a stronger gel and thus due to slower erosion the lag time is increased as in formulations F<sub>11</sub> to F<sub>16</sub>. The lower viscosity grade HPMC K4 M eroded faster and resulted in earlier completeness of drug release. The lag-time and the release rate could also be well controlled by varying the composition of HPMC and ethyl cellulose. Ethyl cellulose alone in F<sub>18</sub> showed highest lag time of 4 hours and with HPMC K4 M alone in F<sub>5</sub> showed lowest lag time of 45 min.

Increasing the ethyl cellulose amount and increasing the HPMC viscosity, prolonged the lag time and extended the release phase (less steep profiles) because of a higher gel strength (slower erosion) and a higher diffusional resistance. Ethyl cellulose a water insoluble polymer forms a mechanically weak and semi permeable rupturable film that rupture easily on contact of dissolution medium<sup>24</sup>. Drug was released after a definite lag time period on rupturing of the outer coating. Among all the formulations F<sub>6</sub>, F<sub>10</sub>, F<sub>11</sub>, F<sub>12</sub>, F<sub>13</sub>, F<sub>14</sub>, F<sub>15</sub> and F<sub>16</sub> showed extensively less drug release due to increased concentration of water insoluble polymer (ethyl cellulose) and high viscosity grade polymers *i.e.* HPMC K15 and HPMC K100 as compared to HPMC K4.

Formulations F<sub>5</sub>, F<sub>7</sub>, F<sub>8</sub>, F<sub>9</sub>, showed the drug release after 1 hr to 1 hr 30 min because of the faster erosion of the lower molecular weight HPMC K4M (Fig. 5). Formulations F<sub>17</sub> and F<sub>18</sub> showed drug release after 3 h and 4 h respectively (Fig. 5). F<sub>17</sub> showed best release profile when compared to others. Therapeutic level and time dependent pulsatile drug delivery system has been achieved from the tablet of formulation F<sub>17</sub> with lag time of 3 h and then 92.3 % drug release at 5 h which meets the demand of chronotherapeutic drug delivery.

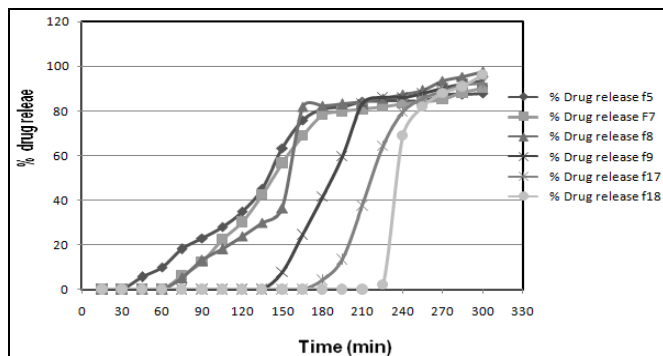


FIG. 5: *IN-VITRO* RELEASE PROFILE OF PRESS COATED TABLET

**Rupture Test:** The rupture test clearly revealed that F<sub>21</sub> formulation should be selected as compared to F<sub>20</sub> and F<sub>19</sub> as rupture time of enteric coating is 120, 105 and 75 min respectively (Table 4). So the F<sub>21</sub> formulation with 10% coating gain is optimized for enteric coating performance (Fig. 6).

#### *In-vitro* Release Profile of Enteric Coated Tablets:

A pulsatile release from HPMC - EC compression-coated tablets, is desirable for acid labile rabeprazole sodium. This can be achieved by introducing an enteric polymer layer of CAP after the compression-coating. The cap enteric coating eliminates the drug release in the acidic environment of the stomach and completely dissolves in intestinal pH-ranges/regions. Formulation F<sub>17</sub> was coated with 3% w/v solution of CAP in isopropyl alcohol using 1.5 % w/v PEG-400 as plasticizer. Three formulations *i.e.*, F<sub>19</sub>, F<sub>20</sub>, F<sub>21</sub> were developed with coating weight gain of 5 %, 7.5% and 10 %. All three formulation were evaluated for drug release in 0.1N HCl for 2 hrs and then in phosphate buffer pH 6.8. It was observed that there was no drug release of all three formulations in first 2 hrs in 0.1N HCl.

The drug release was started after 210 minutes in formulation F<sub>19</sub> with 5 % coating weight gain,

whereas for F<sub>20</sub>, 7.5 % drug release was started after 255 and after 270 minutes in F<sub>21</sub> with 10% coating weight gain (Fig. 7). The optimized formulation F<sub>21</sub> showed 95.4% drug release after 7.75 hours and it successfully inhibit drug release in initial hours.

TABLE 4: RUPTURE TEST

Formulation code	Time in minute
F <sub>19</sub>	75
F <sub>20</sub>	105
F <sub>21</sub>	120

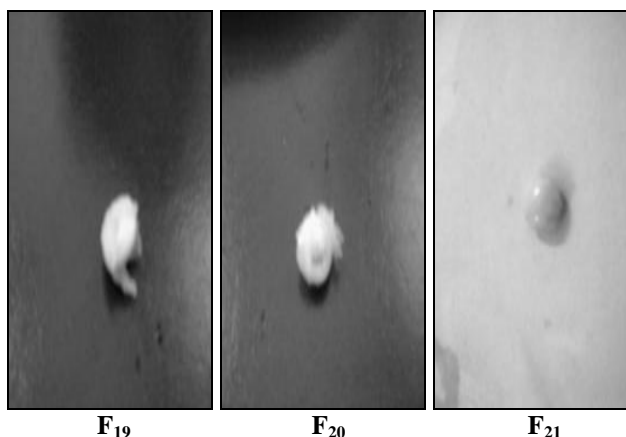


FIG. 6: RUPTURE TEST OF SELECTED FORMULATIONS

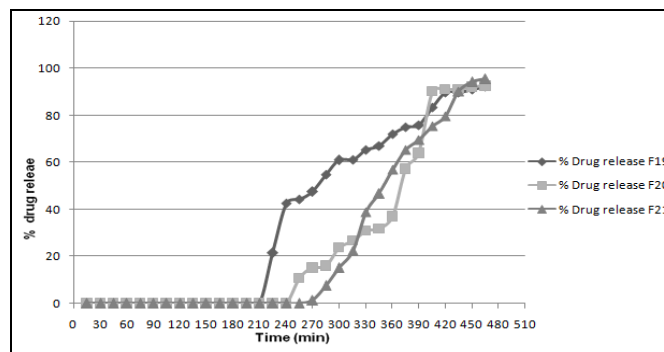


FIG. 7: *IN-VITRO* RELEASE PROFILE OF ENTERIC COATED TABLET

**CONCLUSION:** RS pulsatile release tablets were formulated to achieve the release of drug in intestine after a predetermined lag time. The influence of press coating using EC and various grades of HPMC on the release of drug was investigated. RS is acid sensitive therefore incorporation of CAP as an enteric coating polymer protects the drug from gastric pH and releases the drug in intestinal pH. The lag time of the tablet could be modified by several factors like grades of HPMC and the ratio of HPMC and EC. From the dissolution studies it was revealed that the drug is released rapidly after a predetermined lag time achieving the requirement of pulsatile delivery.

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**CONFLICT OF INTEREST:** The authors confirm that this article content has no conflict of interest.

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