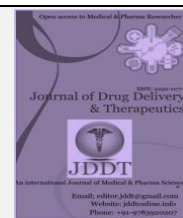
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Research Article

## Formulation and *In-Vitro* Evaluation of Enteric Coated Tablet Incorporating Rabeprazole

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### ABSTRACT

The objective of the work is to try and assess the applicability and manufacturing possibilities to optimize an enteric coated tablet formulation containing Rabeprazole sodium as the drug aiming at the anti-acidity activity with desired drug release properties. Enteric coated tablet was chosen as dosage form being a cost-effective technology for pharmaceutical industry requiring fewer procedures. Before the implementation of the pharmaceutical technological aims, analysis of critical factors influencing the manufacture was carried out. Reproducible manufacturing processes are required to achieve suitability and tablets uniformity to achieve the uniform properties of tablets, which could influence experimental parameters. Rabeprazole in core content of tablet is blended with HPMC (different grades), xanthan gum, PVPK30, mannitol, croscopolidone, Sodium starch glycolate, Colloidal silicon dioxide to formulate the product. Prepared formulation was tested for weight and content uniformity, physical characteristics, *in vitro* dissolution behaviour, acid resistance and accelerated stability studies. All studies performed resulted and revealed for assurance of such enteric coated tablet formulation for drug Rabeprazole with optimum characteristics, concluding it as a promising approach to enhance drug release characteristics.

**Keywords:** Rabeprazole, HPMC, enteric coated tablets, *In Vitro* evaluation.

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## 1. INTRODUCTION

Oral site-specific drug delivery systems have attracted a great deal of interest recently for the local treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach. However, the micro environment in the gastrointestinal tract and varying absorption mechanisms generally causes hindrance for the formulation scientist in the development and optimization of oral drug delivery.<sup>1</sup> Delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH-sensitive drug release and time-controlled drug release. Among these, the time-controlled release systems such as sustained or delayed-release dosage forms are very promising. Nevertheless, due to the potentially large variation of gastric emptying time of dosage forms in humans, these dosage form may show high inter patient variability in the site of drug delivery. On the other hand, pH-

sensitive delivery systems such as enteric-coated dosage forms offer a simple and practical means for intestinal drug delivery. Rabeprazole sodium<sup>2</sup> is a classical example of proton pump inhibitors and is approved by FDA for the treatment of symptomatic gastro esophageal reflux disease, long-term treatment and maintenance of erosive esophagitis. The stability of Rabeprazole sodium decreases with a corresponding decrease in the pH of the media. Hence, the exposure of Rabeprazole sodium to the acidic contents of the stomach would lead to significant degradation of the drug and would result in reduced bioavailability. Few attempts have been made to deliver this drug by peroral route in the form of enteric coated granules, solid dispersion, and suspension and matrix tablets. A number of enteric coating polymers are available and capable of protecting the drug core from the aggressive environments of the stomach. Being soluble at higher pH values, these polymers dissolve in the intestine and release the core for ready action. These polymers include several synthetic polymers like cellulose acetate phthalate (CAP), hydroxy propyl methyl cellulose phthalate (HPMCP).

The aim of the present study was to compare the suitability of these renowned polymers to develop enteric coated tablets<sup>3</sup> of a very sensitive proton pump inhibitor Rabepazole sodium. Rabepazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfonyl)-1H-benzo[d]imidazole belongs to a class of proton pump inhibitors (PPIs). It suppress surface of the gastric parietal cell. Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach.<sup>4</sup>

## 2. MATERIALS AND METHODS

Rabepazole sodium is used as API in this study and was obtained as a gift sample from Incare Pharma Pvt. Ltd; hydroxy propyl methyl cellulose grade K15 and K100, xanthan gum, PVPK30, mannitol, croscopovidone, Sodium starch glycolate, Colloidal silicon dioxide are the other ingredients used for formulation of enteric coated tablets. Preliminary and optimization experiments have been carried out. Principal aim of the research work was the optimization of enteric coated tablet. The methods section contains all method descriptions, which were used either during preliminary or optimization studies.

### 2.1 Pre-formulation Studies<sup>5,6</sup>

The objective of pre-formulation studies is to develop a portfolio of information about the drug substance to serve as

a set of parameters against which detailed formulation design can be carried out. Pre-formulation investigations are designed to identify those physicochemical properties of drug substances and excipients that may influence the formulation design, method of manufacture, and biopharmaceutical properties of the resulting product.

Analysis of lubricated compression blend for pre compression parameters such as angle of repose, bulk and tapped densities, compressibility index, and Hausner ratio was done according to the procedure stated for characterization of Rabepazole.

### 2.2 Fourier transforms infrared spectroscopy (FT-IR) interpretation<sup>7,8,9,10</sup>

The infrared spectrum of rabepazole was recorded by using Perkin Elmer (Spectrum Bx) Fourier transform infrared spectroscopy. The sample was placed on the sample holder. The surface of the sample levelled. This sample holder was then placed in the analysis chamber and the spectrum was recorded.

### 2.3 Formulation batches<sup>11,12,13,14</sup>

Different formulation batches were formulated containing Rabepazole as the active ingredient along with other suitable ingredients as tabulated below in table 1. Various blends tried were named as Batch B1 to B9.

**Table 1.** Formulation of core tablet

S. No.	INGREDIENT	B1	B2	B3	B4	B5	B6	B7	B8	B9
1.	Rabepazole sodium	20	20	20	20	20	20	20	20	20
2.	HPMC K-100	20	-	-	30	-	-	15.5	-	-
3.	HPMC K-15	-	20	-	-	30	-	-	15.5	-
4.	Xanthan gum	-	-	20	-	-	30	-	-	15.5
5.	Mannitol	60.4	60.4	60.4	50.4	50.4	50.4	65.4	65.4	65.4
6.	Croscopovidone	30	30	30	30	30	30	30	30	30
7.	Providone (PVP-K30)	12	12	12	12	12	12	12	12	12
8.	Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9.	Magnesium stearate	5	5	5	5	5	5	5	5	5
10.	Sodium starch glycolate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
11.	Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

### 2.4 Procedure of granulation<sup>13</sup> (For batches B1 – B9)

Granules of the sustained release layer were formulated with dry granulation method using PVP K30 as granulating agent. Rabepazole & polymer were passed through 40# s.s. sieve. Mixed well for 15-20 minutes. PVP K30 was added to sufficient water under stirring to prepare granulating solution. This granulation solution

was added to drug mixture till good wet mass was formed. This mass was passed through 8# s.s. sieve. These granules were dried till LOD (loss on drying) was 2.0 – 2.5% and dried granules were passed through 20# sieve and the granules were lubricated with magnesium stearate and HPMC K-15, HPMC K100, Xanthan gum was also added in this step which were passed through 60# sieve prior to addition to granules.

**Table 2.** Formulation of enteric coated tablet

S. No.	INGREDIENT	B1	B2	B3	B4	B5	B6	B7	B8	B9
1.	HPMC-P	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6
2.	Triethyl citrate (5%)	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76
3.	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
4.	Dichloro- methane	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

**2.5 Procedure for preparation of sub-coating of the core tablets<sup>12</sup>**

Sub coating of the compressed tablets is achieved by standard coating pan technique. Coating solutions of OPADRY prepared separately with plasticizers in 5 % concentrations respectively. Thus solutions are applied over tablets using spray gun at appropriate pressure. The coated tablets are dried at 35-40°C for 10min. 1%, 2%, 3%, and 4% of sub coating percentage has been given to the core tablet.

**2.6 Procedure for preparation of enteric coating of the sub-coated tablets<sup>11</sup>**

The sub coated tablets are loaded into containing bed is warmed till the temperature reaches to 38°C - 40°C. Then spray gun is switched on to spray the enteric coating dispersion using HPMC-P in more than 8% of enteric coating percentage has been given to the sub coated tablets.

**2.7 Evaluation of lubricated blends of formulations**

**2.7.1 Pre-compression parameters of tablet<sup>9</sup>**

Analysis of lubricated compression blend for precompression parameters such as angle of repose, bulk and tapped densities, compressibility index, and Hausner ratio was done according to the procedure stated for characterization of Rabeprazole sustained release tablets.

**2.7.2 Post-compression parameters<sup>15,16,17,18</sup>**

The tablet compacts were tested for Description, Thickness, Hardness, Friability, Weight variation, Uniformity of drug content, *In-vitro* drug release of enteric coated tablets, Drug

Release Kinetic Studies, Accelerated Stability Studies. The results obtained are elaborated in the next section.

**3. RESULTS AND DISCUSSION**

**3.1 Pre-formulation study of the drug**

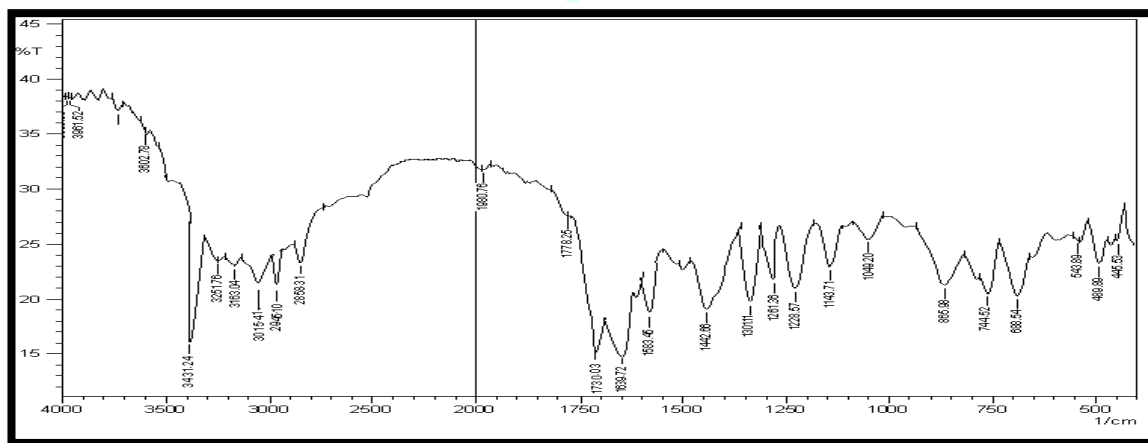
The flow property study of blend of all ingredients along with drug was carried out & all the parameters obtained within a range.

**Table 3.** Micromeretic properties of API

S. No.	Characteristics	Results
1	Description	Of white to pale yellow colour amorphous powder
2	Bulk Density	0.53gm/ml
3	Tapped Density	0.69gm/ml
4	Carr's Index	32.1%
5	Hausner Ratio	4.17
6.	Angle of Response	36

**3.2 Compatibility Study**

The results of FTIR analysis of pure drug and bend of drug with polymers used for the formulations were interpreted and revealed that there is no significant interaction between drug and polymers. This is an assuring result to use these ingredients with no alteration in physicochemical as well as therapeutic activity of the formulation. The Rabeprazole FTIR alone and in blend is presented as below in figures 1 to 4.



**Fig. 1** FT-IR of Rabeprazole

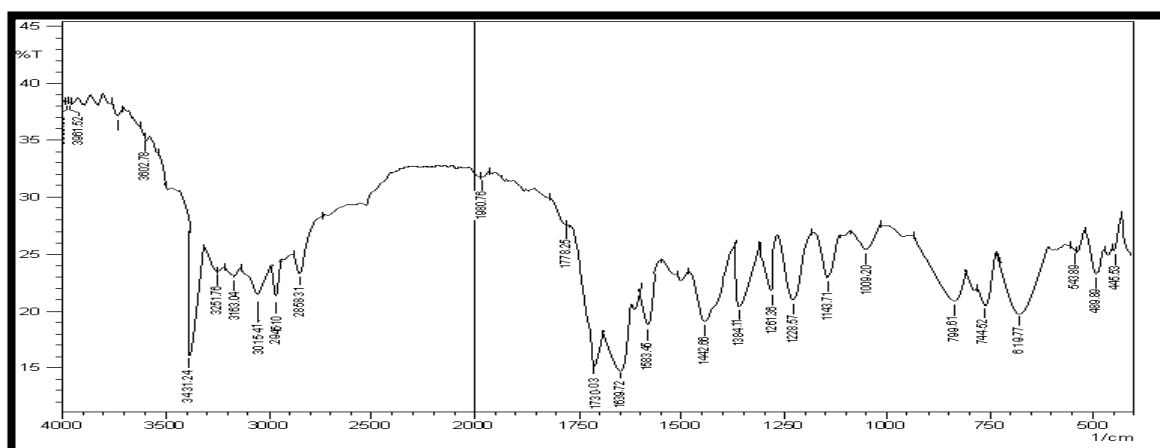


Fig. 2 FT-IR of Rabeprazole with HPMC K100

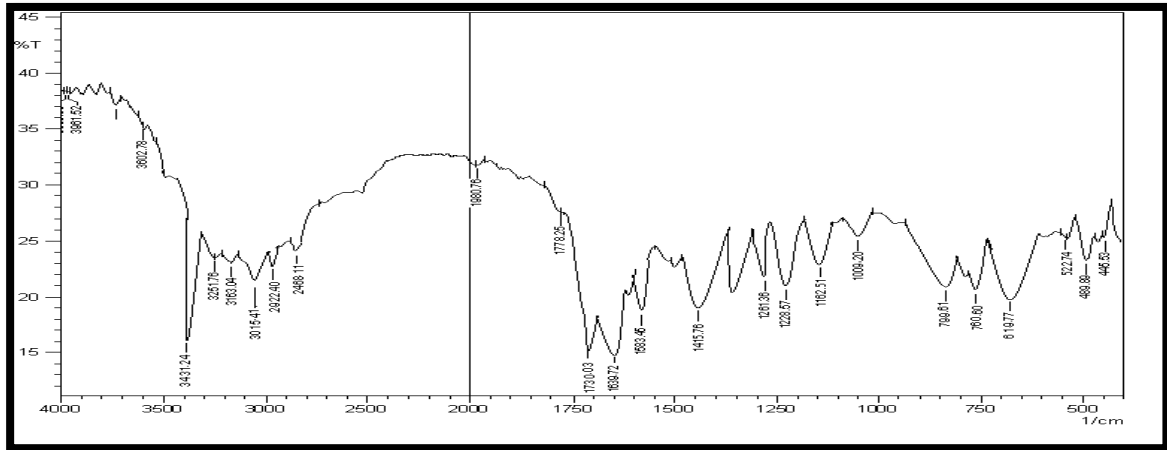


Fig. 3 FT-IR of Rabeprazole with xanthan gum

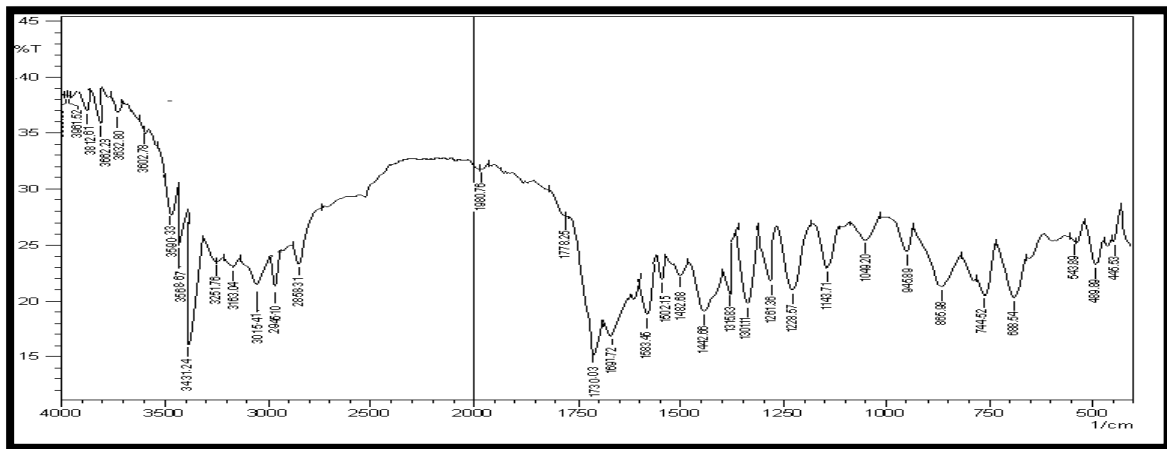


Fig. 4 FT-IR of Rabeprazole with HPMC K-15

3.3 Post Compressional evaluation of prepared tablets

Formulation batches B1 to B9 were evaluated for post compressional parameters such as Weight, Thickness,

Hardness, Friability and the results found are as tabulated below in table 4. Results obtained of all formulation within range as per official standard.

Table 4. Characteristics of formulation

Formulation Batch	Average wt (mg) ± (SD)	Thickness (m) ± (SD)	Hardness (kp) ± (SD)	Friability ± (SD)
B1	151.2 ± 5.16	4.0 ± 0.08	6 – 8 ± 0.18	0.75 ± 0.08
B2	149.5 ± 5.11	4.1 ± 0.08	6 – 8 ± 0.18	0.75 ± 0.08
B3	150.6 ± 5.09	4.0 ± 0.07	6 – 8 ± 0.28	0.64 ± 0.08
B4	151.4 ± 5.12	4.0 ± 0.08	6 – 8 ± 0.18	0.75 ± 0.08
B5	144 ± 5.15	4.1 ± 0.08	6 – 8 ± 0.22	0.60 ± 0.08
B6	152.6 ± 5.16	4.1 ± 0.08	6 – 8 ± 0.23	0.65 ± 0.08
B7	150 ± 5.17	4.0 ± 0.08	6 – 8 ± 0.31	0.71 ± 0.08
B8	145 ± 5.12	4.0 ± 0.08	6 – 8 ± 0.23	0.74 ± 0.08
B9	149 ± 5.10	4.0 ± 0.08	6 – 8 ± 0.33	0.75 ± 0.08

**3.4 Acid resistance test<sup>19</sup>**

To determine the effect of gastric environment the acid resistance study was carried out. All the formulation showed

resistance to acid. Formulations maintained their integrity in simulated gastric fluid. The formulations didn't disintegrate up to 45 min as per the official standard.

**Table 5.** Acid resistance test

Batch	B1	B2	B3	B4	B5	B6	B7	B8	B9
Acid resistance (%)	100	95	98	93	99.5	90	98.8	80	97
Disintegration of tablet in acid 0.1 N HCL(1hr)	NO	NO	NO	NO	NO	NO	NO	NO	NO

**3.5 In vitro Dissolution tests<sup>20,21,22</sup>**

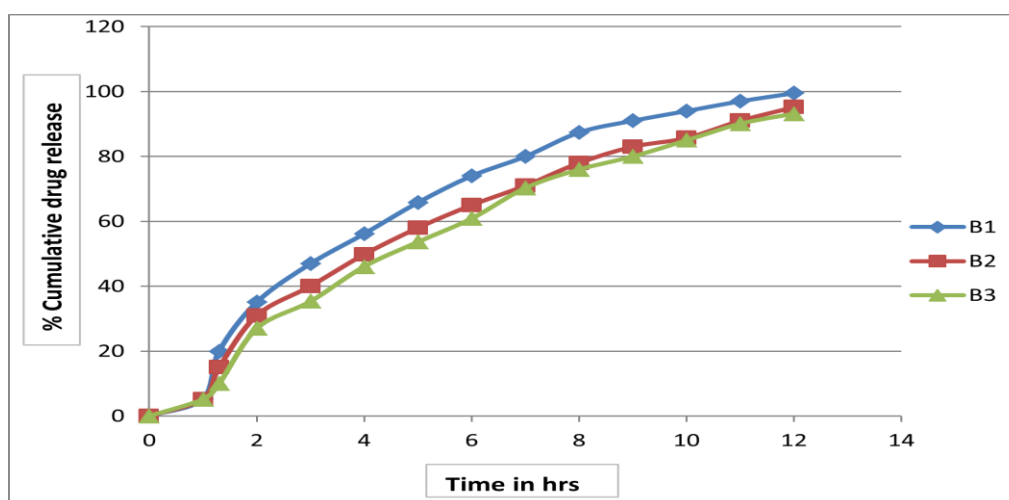
The dissolution for all the formulations was carried out according to US Pharmacopoeia for 2 h in 0.1N HCl and then media was changed into phosphate buffer of pH 6.8. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. The formulation B1 showed more percentage drug release (99.5%) as compared with other formulation. All the formulations showed optimum drug release as per the criteria of sustained drug release. From the results of the present study experiment, it

was concluded that by using the combination of HPMC K15 and HPMC K100, one can obtain the good control on the release profile of water soluble drug and sustained release formulation can be successfully prepared. HPMC K100 hydrates and forms gel at a higher rate as compared to HPMC K15 and is helpful for initially controlling the release rate of water soluble Rabeprazole sodium drug.

Table 6 depicts results of *in vitro* dissolution test. The *in vitro* drug release profiles B1 to B9 are diagrammed below in figures 5 to 7.

**Table 6.** *In vitro* drug release from the formulations B1 to B9

In vitro drug release from the formulation after time(hrs)	BATCH								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	00	00	00	00	00	00	00	00	00
1	5.3	5.22	5.21	5.2	5.18	5.21	5.21	5.21	5.21
1.30	20	15	10	16	13	12	13	16	14
2	35.1	31	27	30	25	21	30	24	25
3	46.96	40.05	35.35	39	33.65	30	40	38	35
4	56.17	49.81	46.08	50	42	37	55	53	51
5	65.8	58	53.66	59	51	45	60	63.66	63.66
6	74	65	60.89	67	58	53	70.89	70.89	70.89
7	80	71	70.3	71	64	60	73	75.3	73
8	87.4	78	76	76	68	70	80	82.21	81
9	91	83	80	80	73	79	82	86.29	86.29
10	94	85.7	85	83	80	84	85	90	88.29
11	97	91	90.1	88	85.25	88	90.1	95	90.1
12	99.5	95.2	93.2	92	91	89	96.7	98.1	96.7



**Fig. 5** *In vitro* drug release profile of batches (B1-B3)

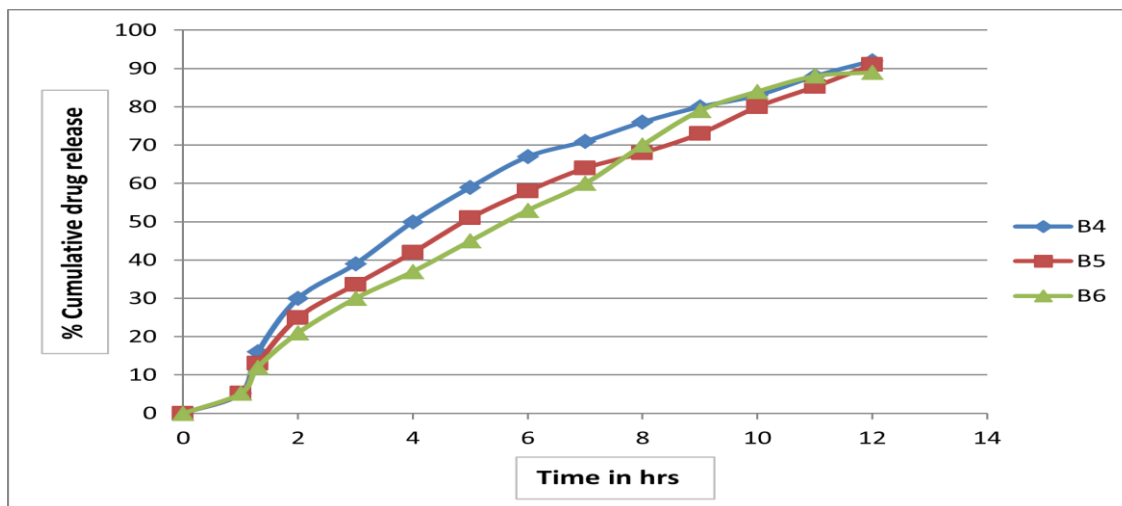


Fig. 6 In vitro drug release profile of batches (B4-B6)

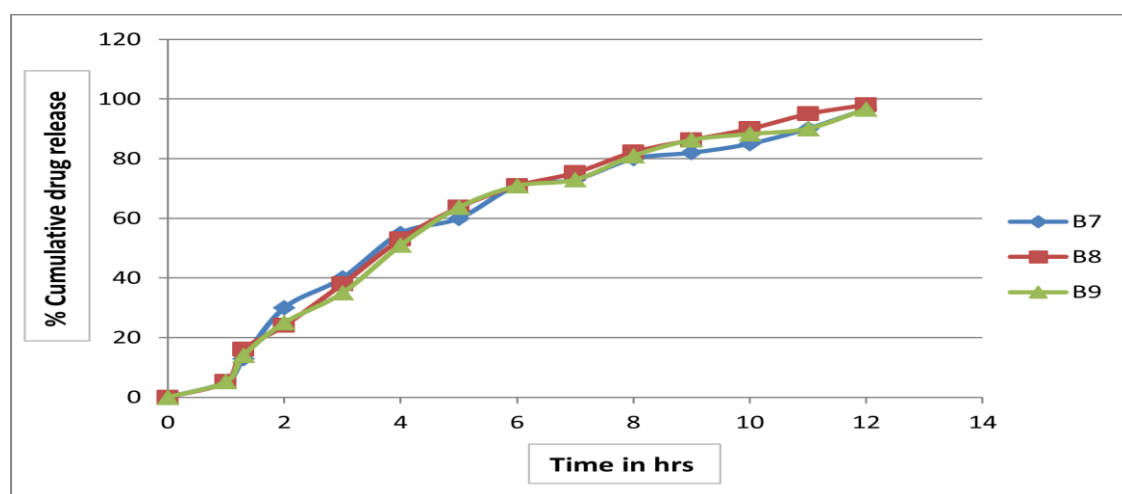


Fig. 7 In vitro drug release profile of batches (B7-B9)

3.6 Stability study<sup>23,24</sup>

In the present study, stability studies were carried out at  $40 \pm 2 \text{ }^\circ\text{C} / 75 \pm 5 \text{ \% RH}$  for a specific time period up to 1 month. The tablets from the selected and optimized batch (B-1) were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of one month. Each tablet was individually weighed

and packed in high-density polyethylene (HDPE) containers and put at above specified conditioned in a Stability chamber for one month. After one month, the formulation was observed for changes in physical appearance and chemical analysis. The optimized formulation B1 showed very good drug release behaviour even after undergoing accelerated stability studies which conformed to its optimum nature. Data is tabulated in table 7.

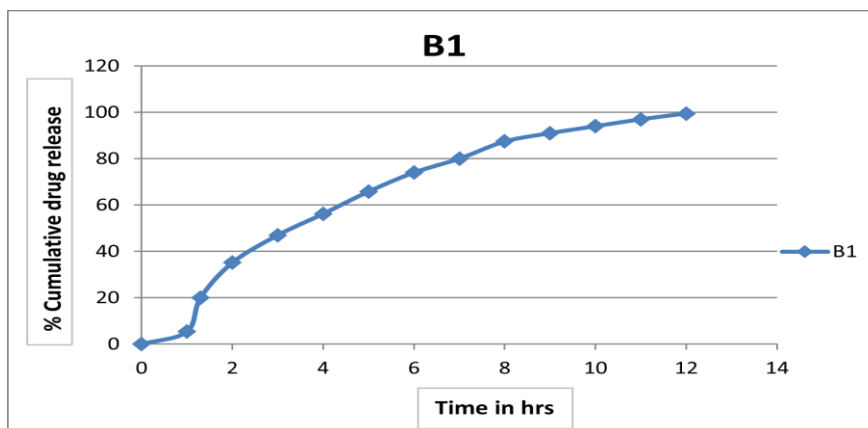


Fig. 8 Stability study curve

**Table 7.** Stability study of optimized batch (B1) in intestine PH (7.5)

Sampling time (Hr)	Colour change	Thickness	Change in integrity
0	No	4.1	No
2	No	4.3	No
4	No	4.7	No
6	No	4.8	No
8	No	4.10	No
10	No	4.13	No
12	No	4.15	No

### 3.7 Drug Release Kinetic Studies

To analyse the mechanism of drug release from the tablets, *in vitro* dissolution data were fitted in Zero Order, First

Order, Matrix Model, Korsmeyer-Peppas Model. The results are as tabulated below in table 8.

**Table 8.** Drug Release Kinetic Studies

Formulation Batch (Optimized)	Zero Order (R <sup>2</sup> )	First Order (R <sup>2</sup> )	Higuchi Model (R <sup>2</sup> )	Korsmeyer-Peppas's Model (n)
B1	0.9088	0.9612	0.9901	0.5345

The batch B1 is optimized in that R<sup>2</sup> values were higher for Higuchi model than for zero order model indicating that the drug release from the formulation followed Higuchi model, indicating that the drug release mechanism from the tablet was diffusion controlled. Obtained values of n is 0.5345 indicating non-fickian release kinetic, which is indicating of drug release mechanism involving, diffusion mechanism. Therefore, the release of drug from the prepared tablet is controlled by swelling of polymers followed by drug diffusion through the swelled polymer.

### 4. CONCLUSION

In the above view of findings it can be concluded that hydroxypropylmethylcellulose of grade K100M when combined with the grade K15M shows the desired sustained release effect and hence can be utilized as matrix forming agent to prolong the release of Rabeprazole. The overall frequency of administration of a drug candidate like Rabeprazole was successfully reduced, which generally requires dosing in 3 to 4 times a day in conventional tablet dosage form. Thus the improved patient compliance might be obtained by the administration of such a dosage form with the reduced dosing frequency and of attractive appearance. The release retardant materials are economical, readily available, safe, having wide regulatory acceptance and easy to handle. It may be beneficial to adopt such a technology for the commercial production of enteric coated sustained release tablet.

From the results of the present study experiment, it was concluded that by using the combination of HPMC K15M and HPMC K100M, one can obtain the good control on the release profile of water soluble drug and sustained release formulation can be successfully prepared. HPMC K100M hydrates and forms gel at a higher rate as compared to HPMC K15M and is helpful for initial controlling the release rate of water soluble Rabeprazole sodium drug. In all formulations, batch B1 shows better drug release (99.5%) in which polymer HPMC K100M -20mg is added.

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