ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation of Immediate Release Tablets of Rabeprazole Sodium by Using Tablet in Tablet Technology.

Arti Mohan*, and Rohit Gundamaraju.

RGR Siddhanthi College of Pharmacy, Bolton Road, Secunderabad - 500015, Telangana, India.

ABSTRACT

Rabeprazole provided effective control of gastric acid in patients with symptoms of gastroesophageal reflux. The present work was carried out to improve the therapeutic efficacy of Rabeprazole by expediting its onset of action. Rabeprazole is unstable in acidic environment which requires the drug in immediate release tablet to be delivered in an alkaline environment to enhance the in vivo stability of Rabeprazole. The tablets were prepared by using Tablet-in-Tablet technology, in which the drug was present as inner core and the buffer as the outer layer. A total of four inner core formulations were prepared by direct compression method and evaluated for their physical parameters. Outer core formulation was prepared using wet granulation method. A total of six tablets in tablet formulations were prepared using A4 as the best inner core formulation depending upon its disintegration time. The prepared tablets were film coated by using Insta moist shield film coating material, to protect the formulation from moisture absorbance. All the six formulations were evaluated and Batch F6 was selected as best formulation and compared with the reference product. The developed tablets were found to be superior to the existing immediate release formulations by providing macro pH environment instead of micro pH ambience with less buffer content.

Keywords: Acid neutralizing capacity, Buffer, Direct compression, immediate release, Proton pump inhibitor.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Despite the dramatic success of pharmacological acid suppression in healing peptic ulcers and managing patients with gastro-esophageal reflex disease (GERD), a number of challenges remain in the management of acid related disorders. Several new drugs are currently being investigated to provide a significant advance over current treatments. These include new drug formulations, novel proton pump inhibitors (PPIs) as well as potassium-competitive acid blockers (P-CABs), which have already reached clinical testing [1].

Rabeprazole at the standard dose of 20 mg once daily provided effective control of gastric acid in patients with symptoms of gastroesophageal reflux. A rapid onset of action would be desirable in prevention and management of nonvariceal upper gastrointestinal bleeding and may be important in patients taking nonsteroidal anti-inflammatory drugs. The present work was carried out to improve the therapeutic efficacy of Rabeprazole by expediting its onset of action. Rabeprazole is unstable in acidic environment which requires the drug in immediate release tablet to be delivered in an alkaline environment to enhance the in vivo stability of Rabeprazole.

MATERIAL AND METHODS

Material

Rabeprazole sodium was obtained as a gift sample from Metro chemicals, Hyderabad. Buffers like Tri sodium Phosphate and Sodium bicarbonate were purchased from FMC Bio polymer, U.S.A. Magnesium hydroxide and Magnesium oxide from Hindustan Magnesium products Pvt. Ltd, Hyderabad. Coating material like Insta moist shield was purchased from Ideal cures Pvt. Ltd, Mumbai. All other reagents used were of analytical grade.

Methods

Moisture uptake study by Rabeprazole at different relative humidity

One gm Rabeprazole sodium was taken in a glass petridish and spread uniformly in a thin layer. The petridish was then placed in the 75% relative humidity (RH) chamber. The weight increase due to moisture absorption was measured by taking weight at different intervals such as 10, 20, 30, 60, 90, 120, 150 and 180 minutes by an electronic balance. The process repeated at 50% and 25% RH chamber and amount of moisture absorbed determined [2].

Formulation Development

Selection of buffers

Water soluble buffers such as sodium bicarbonate and trisodium phosphate as well as water insoluble buffers as magnesium oxide, magnesium hydroxide and calcium carbonate were tested for their acid neutralizing capacity by adding a fixed dose of the buffer to a sample of artificial gastric juice. The basal stomach fluid contains 9.6 ml of 0.1 N HCl and releases 0.5 ml of 0.1 N HCl per minute [2,3] The buffer was added to the basal simulated gastric fluid containing 9.6 ml of 0.1 N HCl + 210 ml of water and titrated with excess acid (0.1 N HCl) at the rate of 0.5 ml/ minute for a period of 1 hour (total volume = 250 ml).. The buffer(s) which maintained a pH above 6.0 at the excess acid secretion were selected [4].

Formulation of inner core tablet of the tablet-in-tablet

Method: Direct compression

Rabeprazole sodium, sodium bicarbonate, mannitol, hydroxy propyl cellulose, crospovidone as shown in Table 1 were co-sifted through 40 # sieve on a vibratory sifter and collected. Iron oxide red was sifted through 100 # sieve and collected. The sifted materials were loaded into the octagonal blender and mixed for 5 minutes. To the above mixed blend, colloidal silicon dioxide and magnesium stearate were added, blended for

5 minutes and compressed by using 7 mm, round shaped flat- faced punches on a Rimek 16 station rotary compression machine with "B & D" tooling.

Table 1: Formulation of Inner core tablet

Sr.no	Ingredients	A 1 mg/Tab	A 2 mg/Tab	A 3 mg/Tab	A 4 mg/Tab
1	Rabeprazole sodium	20.00	20.00	20.00	20.00
2	Mannitol	49.60	49.80	48.80	47.80
3	Hydroxy propyl cellulose	4.00	3.00	2.00	2.00
4	Crospovidone	4.00	4.00	5.00	6.00
5	Colloidal silicon dioxide	0.50	1.00	1.50	1.50
6	Magnesium stearate	1.20	1.50	2.00	2.00
7	Sodium bicarbonate	20.00	20.00	20.00	20.00
8	Iron oxide red	0.70	0.70	0.70	0.70
	Total weight	100.00	100.00	100.00	100.00

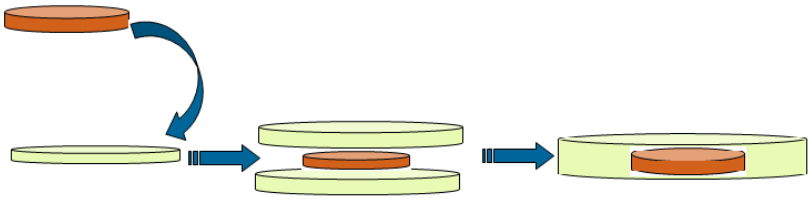
Formulation of outer layer buffer blend of the Tablet-in-Tablet

Method: Wet granulation

Sodium bicarbonate, magnesium oxide, mannitol were co-sifted through 40 # sieve. Hydroxyl propyl cellulose, crospovidone and aerosil were sifted individually through 40 # sieve and collected separately. Magnesium stearate was sifted through 60 # sieve. Binder solution was prepared by adding half quantity of hydroxy propyl cellulose to the weighed quantity of water (350 ml/1000 tab) under constant stirring for 30 minutes. The sifted sodium bicarbonate, magnesium oxide, mannitol and half quantity of crospovidone were loaded into the Rapid Mixer Grinder bowl and mixed for 10 minutes by keeping impeller slow and chopper off. The binder solution was slowly added to the dry mix and the wet mass was kneaded with impeller and chopper both at fast speed and dried in hot air oven at 50^0C till the loss on drying of the dried granules become not more than 2% at 105^0C.Semidried granules were sifted through 20 # sieve. To the dried granules the remaining half quantity of hydroxyl propyl cellulose and crospovidone were added and blended for 5 minutes in the octagonal blender. Colloidal silicon dioxide and magnesium stearate was added to the pre-lubricated blend and mixed for 5 minutes.

Formulation of Tablet-in-Tablet

Formulation of Tablet –in –tablet is shown in Table 2. Selected punches and dies (12 mm round SC) was fixed to the compression machine. 350 mg of buffer composition was filled into the die cavity of rotary press and core tablet was placed at the center and filled with remaining 350 mg of buffer composition then finally compressed into a tablet.



ISSN: 0975-8585

Table 2: Formulation of Tablet-in-Tablet

Sl.no	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6
		mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
0	Inner core tablet	A 4	A 4	A 4	A 4	A 4	A 4
1	Sodium bicarbonate	300.00	300.00				
2	Trisodium phosphate			200.00	250.00	200.00	250.00
3	Magnesium oxide (heavy)	250.00	300.00			250.00	300.00
4	Magnesium hydroxide			300.00	350.00		
5	Mannitol	83.50	22.00	113.50	6.50	152.00	52.00
6	Hydroxy propyl cellulose	28.00	31.50	35.00	38.50	42.00	42.00
7	Crospovidone	28.00	35.00	38.50	42.00	42.00	42.00
8	Colloidal silicon dioxide	3.50	4.50	6.00	6.00	7.00	7.00
9	Magnesium stearate	7.00	7.00	7.00	7.00	7.00	7.00
	Total weight	800.00	800.00	800.00	800.00	800.00	800.00

Film coating of Tablets

Tablet coating is the application of a coating composition Insta Moist Shield (A21D00062) to a moving bed of tablets with concurrent use of heated air to facilitate the evaporation of solvent. Moist shield film coating was applied to protect formulation from the moisture absorbance. These prepared tablets were examined for post compression parameters such as weight variation, hardness, thickness, friability, disintegration [5,6]. The tablets were also checked for acid neutralizing capacity [7], content uniformity [5] and In vitro dissolution tests [8].

Evaluation of Prepared tablets

Physical parameters

The physical parameters of inner core tablets of all trials, tablet-in-tablet and coated tablets were evaluated .

Acid neutralizing capacity

Accurately weighed quantity, equivalent to the minimum labelled dosage of tablet in tablet was transferred to a 250 ml beaker, to this 10 ml of water was added, and swirled gently. The walls of the beaker were washed with 60 ml of water and mixed on the magnetic stirrer for 1 minute. 30 ml of 1 N HCl was pipetted out into the test preparation and stirred continuously for 15 minutes and excess hydrochloric acid was titrated with 0.5 N NaOH to attain a stable pH of 3.5. The number of mEq of acid consumed was calculated by the formula [7]:

Total mEq = (30 x Normality of HCl) – (Volume of NaOH x Normality of NaOH)

Content Uniformity [5]

Ten tablets were assayed according to HPLC method [8].

Standard Preparation

20 mg Rabeprazole working standard was weighed and transferred into a 100 ml of clean, dry volumetric flask. To this about 10 ml of methanol was added, sonicated and volume was made up with water. 5 ml of above solution transferred into a 50 ml volumetric flask and the volume made up with water.

Sample preparation

20 tablets were weighed and crushed into a powder. The crushed powder equivalent to 2 mg of drug was taken and transferred into 100 ml volumetric flask. 10 ml methanol was added ,sonicated and volume made up with water.

Procedure

The blank preparation was injected, Five replicate injections of standard preparation were injected and chromatograms were recorded The compliance of system suitability parameters was checked. The sample preparation was injected in singlet and the chromatograms were recorded. Response for the analyte peak was measured.

Percentage Purity was calculated as:

Amount preset in the given sample: $= \frac{\text{sample area}}{\text{standard area}} \times \frac{\text{standard diluton}}{\text{sample dilution}} \times \frac{\text{potency}}{100} \times \text{Average weight} \times 1000$

$$\text{Percentage purity} \quad = \frac{Amount\ present}{Labelled\ claim} \times 100$$

In-vitro Drug Dissolution study [8]

The dissolution study for the tablets of all trials and the reference product was carried out using simulated gastric fluid and phosphate buffer pH 7.4.

- Dissolution study in Simulated Gastric Fluid (SGF)
- Comparison of Micro Environment pH and Macro Environment pH concept
- Dissolution study in Phosphate buffer pH 7.4

In vitro dissolution studies were carried out on USP Type II dissolution apparatus. The stated volume of dissolution medium Simulated gastric fluid (900 ml) or pH 7.4 phosphate buffer (900 ml) was placed in the vessels at temperature $37^0 \pm 0.5^0$C. One dosage unit of each trial and reference product was placed in each of the vessels and operated the apparatus at 75 rpm and samples analyzed at 5, 10, 15, 20, 30, 45, 60 minutes by using HPLC method. The amount of drug dissolved in the medium was calculated by using the following formula:

$$\%\ of\ Rabeprazole\ sodium\ Dissolved = \frac{At \times Ws\ \times 5\ \times 900\ \times P\ \times 100}{As \times 100 \times 50 \times 1 \times 100 \times L}$$

At = Area of Rabeprazole peak in the test solution.
As = Area of Rabeprazole peak in the standard solution.
Ws = Weight of Rabeprazole standard taken.
P = Potency of Rabeprazole working standard used.
L = Labelled claim of Rabeprazole per tablet, in mg.

Stability Studies [9]

For the prepared tablets, the stability studies were carried out at intermediate and accelerated conditions for a period of one month. At the end of study period the samples was analyzed by appropriate methods to determine the stability of formulation.

RESULTS

Study of Hygroscopic nature of Rabeprazole

This experiment indicates that % RH of manufacturing environment has a great effect on the moisture level of Rabeprazole tablets as Rabeprazole absorbs maximum amount of moisture at higher % RH. This higher moisture level is responsible for various physical stability problems of Rabeprazole tablets. (Table 3)

ISSN: 0975-8585

Table 3: Physical characteristics of Inner core tablet of Tablet-in-Tablets

S.No	Parameter	A 1	A 2	A 3	A 4
1	Appearance	Brick red colour, round shaped tablets			
2	Weight variation (mg)	101 ± 5.0	98 ± 5.0	102 ±5.0	99 ± 5.0
3	Thickness(mm)	2.2 ± 0.3	2.1 ± 0.3	2.2 ± 0.3	2.0 ± 0.3
4	Hardness (kg/cm^2)	3.0-4.0	2.0-3.0	2.0-3.0	2.0-3.0
5	Friability (%)	0.04	0.07	0.05	0.06
6	Disintegration(min)	4.0-5.0	3.5-4.0	2.5-3.0	2.5-3.0

Formulation Development

Based on their acid neutralizing capacity, buffers were individually evaluated for their acid neutralizing capacity. The buffers which gave an immediate rise in pH and able to sustain pH of the medium above 6.0 with time, compatibility of buffer with drug and minimum quantity of the buffer required to neutralize the stomach acid are important attributes of the buffer selection. Based on the above results Tri sodium phosphate and Magnesium oxide were found to be effective in their acid neutralizing capacity. (Figure 1 & 2)

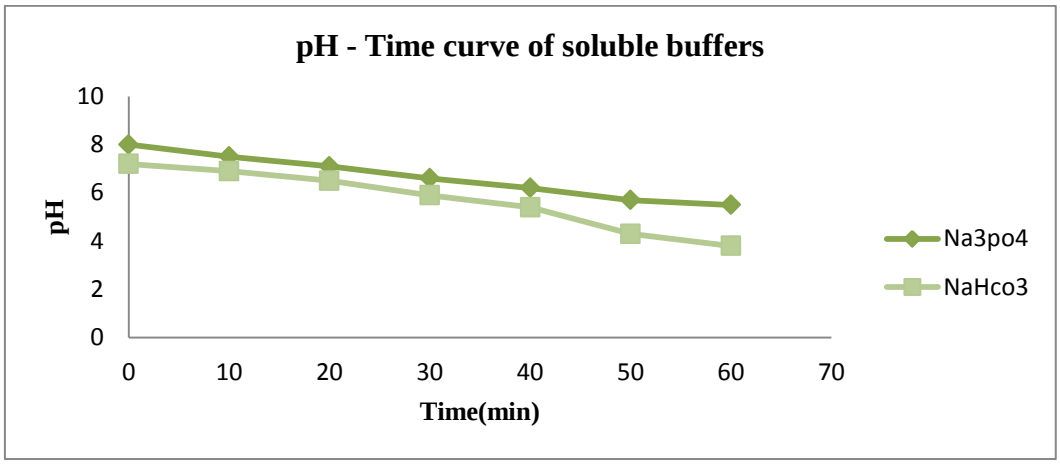


Figure 1: pH - Time curve of soluble buffers

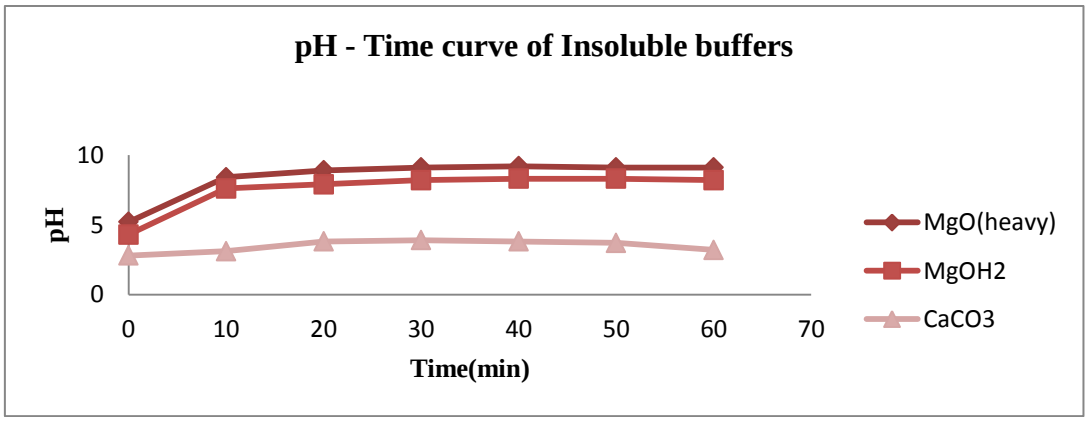


Figure 2: pH - Time curve of insoluble buffers

Evaluation of physical characteristics of Tablets

The physical parameters of inner core tablets of all trials were found to be within the fixed limits except disintegration time. The disintegration time of A 3 & A 4 batches was found to be within the specified time. It was achieved by increasing the disintegrant concentration and A4 was chosen as the best formulation.

ISSN: 0975-8585

The tablets [10] were compressed to an average weight of 800.0 mg. The weight of tablets was acceptable showing weight variation of 5%, as per pharmacopoeial limits. The hardness of formulation batches F 4, F 5, F 6 was found to be optimum. Friability values of all batches was within the pharmacopoeial limits except batch F1 due to less hardness. The disintegration time of F6 was found to be good as per the requirement of dosage form and subjected to coating**.** (Table 4, 5,& 6)

Table 4: Physical characteristics of Tablet-in-Tablets

S.No	Parameter	F 1	F 2	F 3	F 4	F 5	F 6
1	Appearance	White colour, round shaped, biconvex uncoated tablets					
2	Weight variation (mg)	802 ± 5.0	799 ±5.0	804 ±5.0	803 ±5.0	798 ±5.0	801 ±5.0
3	Thickness (mm)	5.5 ± 0.3	5.3 ± 0.3	5.5 ± 0.3	5.4 ± 0.3	5.3 ± 0.3	5.4 ± 0.3
4	Hardness (kg/cm^2)	5.0-6.0	8.0-9.0	7.0-8.0	8.0-9.0	8.0-9.0	8.0-9.0
5	Friability (%)	1.08	0.82	0.80	0.63	0.37	0.36
6	Disintegration (min)	7.0-8.0	6.0-7.0	5.0-6.0	4.0-5.0	4.0-5.0	4.0-5.0

Table 5: Physical characteristics of coated Tablet-in-Tablets

S.No	Parameter	Result
1	Appearance	Yellow colour, round shaped, biconvex film coated tablets
2	Average weight (mg)	825.06
3	Thickness(mm)	5.58
4	Hardness (kg/cm^2)	8.0-9.0
5	Disintegration(min)	4.0-5.0

Table 6: Hygrscopic study of Rabeprazole

Humidity condition	% of Moisture Content Absorbed			
	30 min	1 hr	2 hr	3 hr
30% RH	0.3	0.5	0.6	0.8
50% RH	1.7	2.5	3.2	4.1
75% RH	3.8	4.0	5.1	6.8

Content Uniformity

All the formulation trials were evaluated for the percentage of drug content present. The acquired results were found to be within the limits i.e 98.0 – 102.0%. **(Table 7)**

Table 7: Percentage of drug content

Formulation	F 1	F 2	F 3	F 4	F 5	F 6
Drug content (%)	98.04%	100.07%	99.35%	101.20%	98.92%	99.02%

Test for acid neutralizing capacity

All the formulation trials were evaluated for their Acid-Neutralizing Capacity. Among all the batches F2 and F6 gave good results. F2 contains 600 mg of buffer and F6 contains 550 mg of buffer and the acid neutralizing capacity were found to be 19.92 and 22.74 respectively. So the formulation F6 was found to have better acid neutralizing capacity with less quantity of buffer**.** (Figure 3)

ISSN: 0975-8585

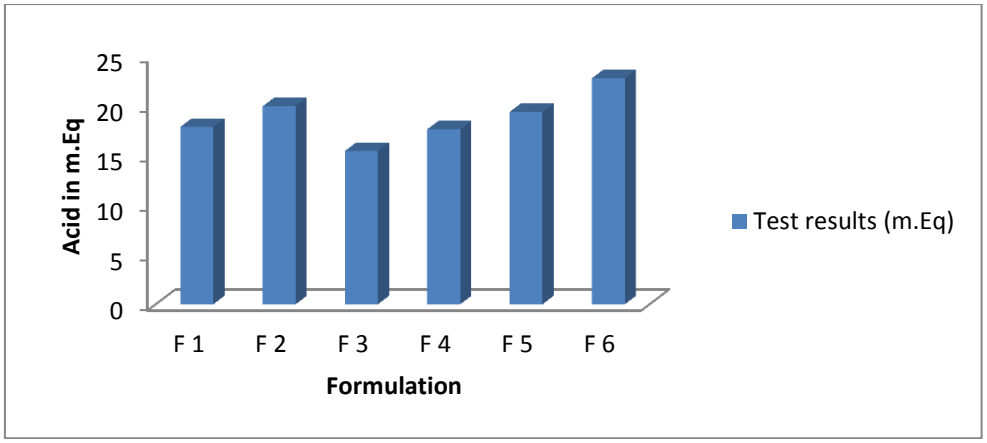


Figure 3: Test for acid neutralizing capacity

Dissolution Study

Table 8: Dissolution study in Simulated Gastric Fluid (SGF)

Time (min)	Mean % drug release						
	Reference	F 1	F 2	F 3	F 4	F 5	F 6
5	62.6	41.8	47.4	51.4	52.6	57.2	56.8
10	71.3	56.6	65.3	78.2	71.3	74.5	76.6
15	80.8	62.6	76.2	80.8	78.2	83.6	83.1
20	83.5	75.5	84.8	86.6	89.5	89.4	90.1
30	85.1	88.9	93.7	95.9	98.1	97.8	98.9
45	87.4	95.6	98.1	97.8	98.3	98.4	99.3
60	88.2	97.8	98.9	99.1	99.5	99.3	99.5

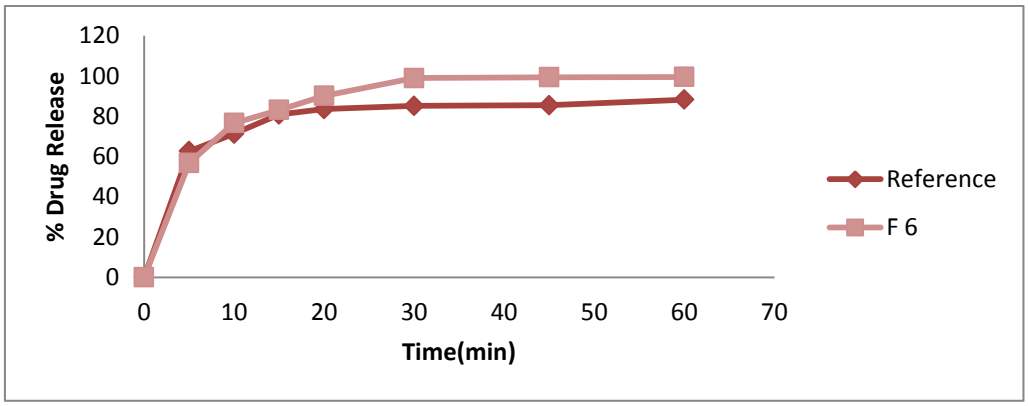


Figure 4: Comparison of Micro Environment pH and Macro Environment pH Concept

Table 9: Dissolution study in pH 7.4 Phosphate buffer

Time (min)	Mean % drug release						
	Reference	F 1	F 2	F 3	F 4	F 5	F 6
5	71.4	45.2	47.1	52.5	51.6	55.4	54.3
10	80.2	67.8	76.6	74.6	71.8	78.1	77.9
15	89.5	79.6	83.6	89.3	81.9	88.5	90.1
20	94.7	84.1	89.5	91.2	90.4	94.9	97.4
30	97.5	95.6	95.9	98.4	97.8	99.2	99.5
45	97.9	98.5	98.7	99.2	98.9	99.8	99.6
60	99.2	99.3	99.4	99.3	99.5	100.6	99.8

ISSN: 0975-8585

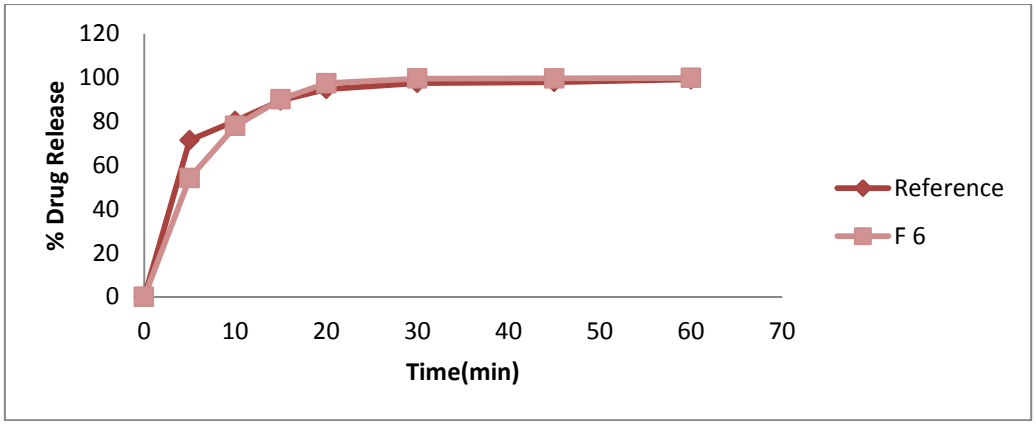


Figure 5: Comparative Dissolution study of Reference product and Optimized formula F6

The comparative in-vitro dissolution study was carried out for both optimized batch(F6) and the reference product. The percentage of drug release was found to be 99.8 % and 99.2 % at 30 minute for batch F6 and reference product respectively.

In the reference product the drug and buffer will release at a time, as a result it did not give an initial rise in pH thereby leading to partial degradation of the Active Pharmaceutical Ingredient in the medium which indicates that the microenvironment pH fails to protect the drug from degradation. But in the present formulation the buffer will create alkaline environment before the drug comes in contact with the medium as a result of which drug was found to be stable due to macro environmental pH [11].

Stability Studies

Stability testing was conducted to know how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. In the present stability study of the optimized batch, all the results were found to be satisfactory and within limits. There were no significant changes after the period of 1 month study. (Table 10)

Table 10: Stability studies

Test name	Initial	1 Month	
		30^0 C/65 % RH	40^0 C/75 % RH
Description	Yellow colour, round shaped, biconvex film coated tablets	Yellow colour, round shaped, biconvex film coated tablets	
Average weight (mg)	825.06	825.33	825.51
Thickness (mg)	5.58	5.58	5.58
Hardness (kg/cm)	8.0-9.0	8.0-9.0	8.0-9.0
Disintegration (min)	4.0-5.0	4.0-5.0	4.0-5.0
Assay (%)	99.07	99.03	99.08
Water content (%)	4.84	4.78	4.86
Dissolution Time (min)	% Drug Release		
5	66.8	54.5	57.3
10	76.6	79.3	77.1
15	83.1	85.2	83.8
20	90.1	90.6	89.9
30	98.9	99.1	98.5
45	99.3	99.4	99.2
60	99.5	99.4	99.5

CONCLUSION

The present work was carried out to improve the therapeutic efficacy by expediting the onset of action of Rabeprazole. It may be concluded that the formulation development of the once daily immediate release tablet-in-tablets of Rabeprazole sodium could be accomplished with the use of selected buffering agents and other additives. The present formulation contains Rabeprazole sodium along with buffers. The buffers in tablet neutralize the acid in stomach within few minutes. This result in faster relief from hyperacidity symptoms, mean time the absorption of drug takes place. The increase in the gastric pH by the buffers results in increased gastrin secretion, which in turn causes the activation of greater number of proton pumps making them available for inhibition by rabeprazole in the parietal cell canaliculi [8]. Thus, *Rabeprazole sodium immediate release* tablets provide immediate neutralization followed by prolonged acid suppression. The prepared tablets were suitable for administration with or without food with a rapid onset of action. In this respect the developed tablets were found to be superior to the existing immidiate release formulations by providing macro pH environment instead of micro pH ambience with less buffer content.

REFERENCES

[1] Text book of Gastroenterology (Lippincott Williams & Wilkens,New York) volume 1, 1999, p-no. 284-285.
[2] Tushar S Deshpande, Ms Sadhana, P Gautam. Int J Pharm Invent 2011;1(2):26-32.
[3] C Lentner Basle, CIBA GEIGY, Units of measurement, body fluids, composition of the body, Nutrition, Geigy Scientific tables (1981) 1:123-133; Yamada, Tadataka (ed.)
[4] Muneera Mohamed Shafee, Ruckmani Kandasamy; Immediate Release Compositons of Acid labile drugs, United States Patent, 2011.
[5] Indian Pharmacopoeia, The Controller of Publications, Delhi, 2010, Volume 1, 187-193.
[6] Edward M R, Joseph B S, Oral solid dosage forms, The Science and Practice of Pharmacy, Pharmaceutical manufacturing (Lippincot Williams and Wilkins, New York) 889-899.
[7] United States Pharmacopoeia, NF 26 (616), 2125-2126
[8] In House Specifications, Analytical Development Laboratory, Bioplus Life Sciences Ltd.
[9] Stability testing of new drug substances and products,'Stability test guidelines' European test for evaluation of medical products, London,2003.
[10] S Brito Raj et al. J Pharm Res 2011;4(10):3585-3589.
[11] Howden CW, Ballard ED, Koch FK, Gautille TC, Bagin RG. J Clin Gastroenterol 2009;43(4):323-6