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FORMULATION OF IMMEDIATE RELEASE TABLETS OF RABEPRAZOLE SODIUM BY USING TABLET IN TABLET TECHNOLOGY

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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*

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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 Hetro Pharma, 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].

Table 1: Formulation of Rabeprazole sodium tablets

Sl.no	Ingredients	F 1 mg/tab	F 2 mg/tab	F 3 mg/tab	F 4 mg/tab	F 5 mg/tab	F 6 mg/tab
1	Rabeprazole sodium	20	20	20	20	20	20
2	Sodium bicarbonate	250.00	300.00				
3	Trisodium phosphate			200.00	250.00	200.00	250.00
4	Magnesium oxide (heavy)	300.00	300.00			250.00	300.00
5	Magnesium hydroxide			300.00	350.00		
6	Mannitol	180.00	26.50	119.50	12.50	159.00	59.00
7	Hydroxy propyl cellulose	23.00	31.50	35.00	38.50	42.00	42.00
8	Crospovidone	20.00	35.00	38.50	42.00	42.00	42.00
9	Magnesium stearate	7.00	7.00	7.00	7.00	7.00	7.00
	Total weight	800	800.00	800.00	800.00	800.00	800.00

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.

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 500C till the loss on drying of the dried granules become not more than 2% at 1050C.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.

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.

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.

***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 370± 0.50C. 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: 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:

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. 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.

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. 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.. 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%.

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). 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 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. 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 .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.

Table 2: Evaluation parameters of tablet blends

S.No	Parameter	F 1	F 2	F 3	F 4	F 5	F 6
1	Bulk density(gm/ml)	0.615	0.611	0.629	0.622	0.617	0.624
2	Tapped density(gm/ml)	0.719	0.723	0.728	0.724	0.715	0.725
3	Carr's index (%)	14.46	15.49	13.59	14.68	13.70	13.79
4	Hausner ratio	1.16	1.18	1.15	1.16	1.15	1.16
5	Flow property	Good	Good	Good	Good	Good	Good

Table 3 Evaluation parameters of tablet blends

S.No	Parameter	F 1	F 2	F 3	F 4	F 5	F 6
1	Drug content (%)	98.04%	100.07%	99.35%	101.20%	98.92%	99.02%
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

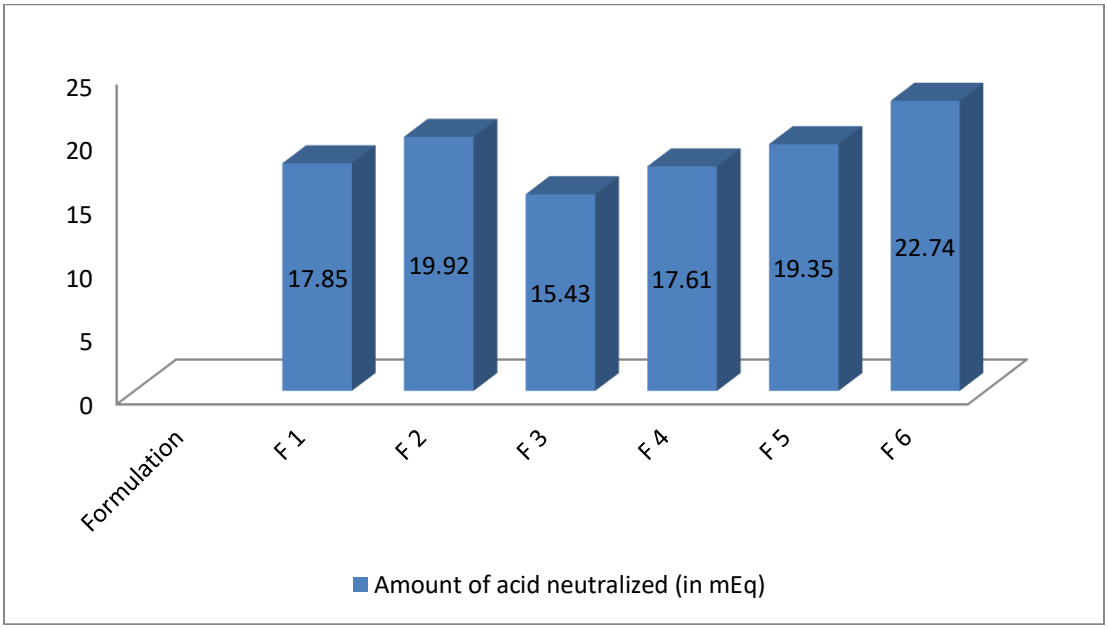

Fig: 1. Test for acid neutralizing capacity

Table: 4 Dissolution study in Simulated Gastric Fluid (SGF)

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

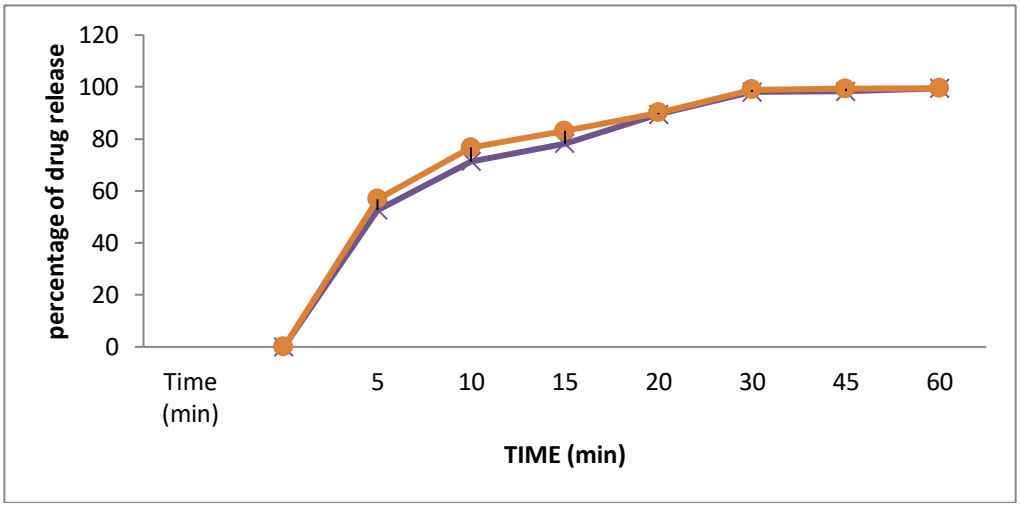

Fig:2. Comparative Dissolution study of Reference product andFormulation 6 in Simulated Gastric Fluid (SGF)

Fig:3. Comparative Dissolution study of Reference product andFormulation 6 in pH 7.4 Phosphate buffer

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

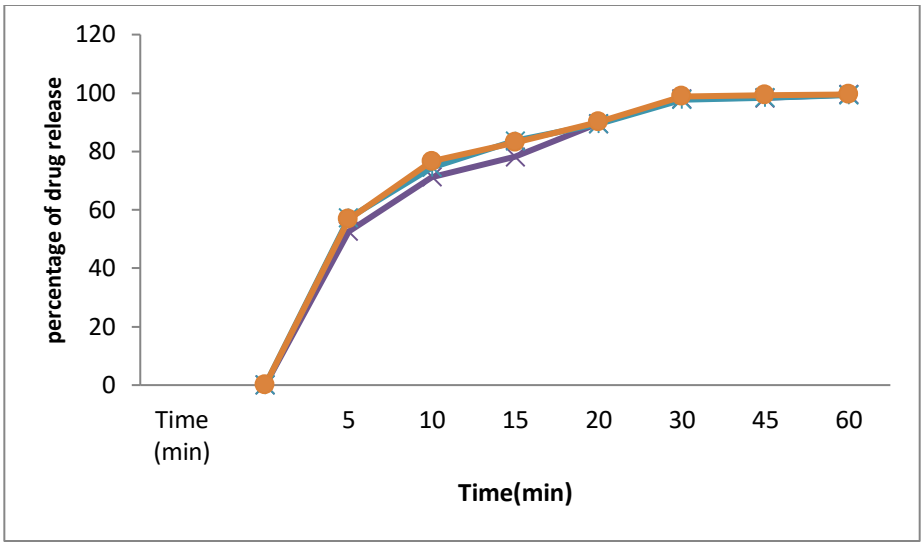

Fig:3. Comparative Dissolution study of Reference product andFormulation in pH 7.4 Phosphate buffer

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