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Formulation development, characterization and evaluation of rabeprazole sodium buffered formulation

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Abstract
Rabeprazole Sodium buffered Formulation were successively prepared and evaluated by performing the preformulation studies, formulation development and optimization and stability studies. The colour, odour, nature and taste of the drug were evaluated. It was found to be as per the monograph. Rabeprazole sodium was found to be very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n- hexane. Drug excipients compatibility study with and without FTIR spectroscopic analysis of drug with excipients showed that the drug was compatible with excipients which were used in the formulation. Rabeprazole buffer tablets were prepared by direct compression method and table in tablet technology. The prepared powder blend was evaluated for parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The obtained results indicated that it has good flow property for direct compression method. Tablets formulations were evaluated for hardness, thickness, weight variation, friability, assay and disintegration time. All these parameters were found to be within the pharmacopoieal limits. The drug release was found to be above 99 % within 60 mins when RT6 formulation *In vitro* dissolution study was performed. The *in vitro* acid neutralizing capacity of formulations study of all formulation showed good results. The stability studies of RT6 formulation at 40 ^{o}C/75% RH for a period of 3months indicated that there was no significant change in description, disintegration time, drug content and *in vitro* dissolution profiles.

Keywords: buffer tablet, fast dissolving tablet, rabeprazole sodium, neutralizing efficiency

Introduction

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-dissolving dosage forms. [1, 2, 3]

These tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption. To fulfill these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of the matrix. Different technological techniques, such as freeze drying or moulding or direct compression are currently employed to prepare the formulations of this type present on the pharmaceutical market. [4]

Honda and Nakano reported that a half of the patients surveyed experienced difficulty in taking medication and felt that a tablet was a better and easier formulation compared to other formulations such as capsules or powders. Sugihara reported that the degree of ease when taking a tablet depended on its size. He reported that the size of tablet that was easiest to swallow was 7–8 mm, but the size easiest to handle was one larger than 8 mm. [5]

Advantages of Fast Dissolving Drug Delivery System (FDDS) [6, 7]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients, mentally ill, disabled and uncooperative.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of FDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Rapid dissolution of drug and absorption, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.

- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects. [8]

Material and Methods

Drug Profile

Selected Drug: Rabeprazole Sodium
IUPAC Name: 2 - [4- (3 methoxy propoxy-3 – methyl – 2 - pyridinyl] - methyl] sulfinyl] – 1 H - benzimidazole sodium salt
Empirical formula: $C_{18}H_{20}N_3O_3SNa$
Molecular weight: 381.43
Melting point: 140-141^{0}C

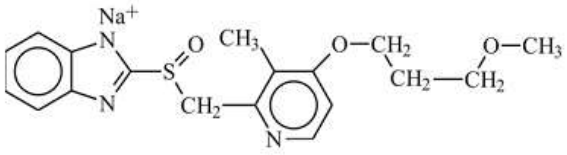

Fig 1

Materials

Rabeprazole sodium, Methanol, Ethanol, Tween 80, Dichloromethane, Potasium dihydrogen, Hydrochlric acid, Sodium hydrogen phthalate, Mannitol, Hydroxy Propyl Cellulose, Colloidal silicon dioxide Crospovidone, Magnesium stearate, Sodium bicarbonate, Iron oxide red, Sodium bicarbonate, Trisodium phosphate, Magnesium hydroxide. All the chemicals and materials were purchased from S D Fine chemical Ltd, Mumbai.

Methods

Preformulaion study [9, 10]

The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance.

Description

It is the initial evaluation during preformulation studies which assess the colour, odor and taste of the substance.

Solubility

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy. Solubility of Rabeprazole Sodium was determined in water and methanol, ethanol, chloroform and ethyl acetate. (Liberma & Lachman, 1991)

Melting point determination

Melting point of Rabeprazole Sodium was determined by Open capillary method.

Determination of partition coefficient

50 mg of drug was taken in three separating funnels. The separating funnels were shaken for 2hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated by using formula: K_{PC}= Concentration of Drug in Oil Phase/ Concentration of Drug in Water Phase

Determination of λmax

A solution of Rabeprazole Sodium containing the concentration10 µg/ ml was prepared in 0.1 N HCl. The solution was scanned in the range of 200 – 400 nm UV spectrum using Systronic double beam spectrophotometer.

Drug: Excipient Interaction Studies

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. The blends were stored at accelerated condition of 40 °C ±2 °C/ 75% ±5% RH for 30 days. The samples were compared with initial samples data after the 2nd and 4th week of the study.

FTIR spectra matching approach was also used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a shimadzu FTIR spectrophotometer.

The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks. (Mahajan *et al.*, 2004)

Table 1: Formulation Development of Inner Core Tablet

S. No.	Composition	Ratio (Drug: Excipient)
1.	Rabeprazole sodium	1:1
2.	Rabeprazole sodium + Mannitol anhydrous	1:1
3.	Rabeprazole sodium + Copovidone	1:1
4.	Rabeprazole sodium + Light magnesium oxide	1:1
5.	Rabeprazole sodium + Hydroxy propyl cellulose	1:1
6.	Rabeprazole sodium + Colloidal silicon dioxide	1:1
7.	Rabeprazole sodium + Magnesium stearate	1:1
8.	Rabeprazole sodium + Sodium bicarbonate	1:1
9.	Rabeprazole sodium + Iron oxide red	1:1

Preparation of standard calibration curve

100 mg of Rabeprazole Sodium was accurately weighted into 100 ml volumetric flask, dissolved in 0.1M HCL and volume was made up with 0.1M HCL. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with 0.1M HCL and marked as Stock. From this Rabeprazole Sodium standard stock solution (1000µg/ml), 1ml solution was diluted to 10 ml using 0.1M HCL solution to get concentrations of 100 µg/ml. from this solution, aliquots of, 0.5 ml, 1.0 ml, 1.5 ml,2.0 ml,2.5 ml,3.0 ml from standard drug solution were diluted to 10 ml with 0.1M. The absorbance of these solutions was measured at 275.43 nm 0.1N HCL as a blank.

Formulation Development of Rabeprazole Sodium Buffered Tablets [11, 12]

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. 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. [13]

Formulation of inner core tablet

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 for5 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

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 needed with impeller and chopperboth at fast speed and dried in hot air oven at 50 ^{0}C till the loss on drying of the dried granules become not more than 2% at 105 ^{0}C. 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. [14]

Table 2: Formulation Development of Inner Core Tablet

S. No	Ingredients	IC1	IC2	IC3	IC4
1.	Rabeprazole sodium	20	20	20	20
2.	Mannitol	49.6	49.8	48.8	47.8
3.	Hydroxy propyl cellulose	4	4	2	2
4.	Crospovidone	4	4	5	6
5.	Colloidal silicon dioxide	0.5	0.5	1.5	1.50
6.	Magnesium stearate	1.2	1.5	2	2
7.	Sodium bicarbonate	20	20	20	20
8.	Iron oxide red	0.7	0.7	0.7	0.7
9.	Total weight	100	100	100	100

Formulation of Tablet-in-Tablet

Formulation of Tablet in tablet is shown in Table 2. Selected punches and dies (12 mm round SC) were 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.

Evaluation of Tablets [15, 16, 17]

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, drug content and *in vitro* dissolution study.

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

S. No	Ingredients	RT1	RT2	RT3	RT4	RT5	RT6
1.	Inner core tablet	IC4	IC4	IC4	IC4	IC 4	IC4
2.	Sodium bicarbonate	300	300				
3.	Trisodium phosphate			200	250	200	250
4.	Magnesium oxide (heavy)	250	300			250	300
5.	Magnesium hydroxide			300	350		
6.	Mannitol	83.5	22.	113.5	6.5	152	52
7.	Hydroxy propyl cellulose	28	31.5	35	38.5	42	42
8.	Crospovidone	28	35	38	42	42	42
9.	Colloidal silicon dioxide	3.5	4.5	6	6	7	7
10.	Magnesium stearate	7	7	7	7	7	7

Result and Discussion

Preformulation Studies

Description

The colour, odour, nature and taste of the drug were evaluated. It was found to be as per the monograph.

Table 4: Description of Rabeprazole Sodium

S. No.	Tests	Results
1	Colour	White
2	Odor	Unpleasant
3	Nature	Crystalline
4	Taste	Bitter

Solubility study

Rabeprazole sodium was found to be very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and in soluble in ether and n-hexane.

Table 5: Solubility Study of Rabeprazole Sodium

Drug	Soluble in
Rabeprazole Sodium	Water
	Methanol
	Ethanol
	Chloroform
	Ethylacetate
	Ether
	N-hexane.

Melting point determination

The melting point of Rabeprazole Sodium was found to be 140.5 ^{o}C.

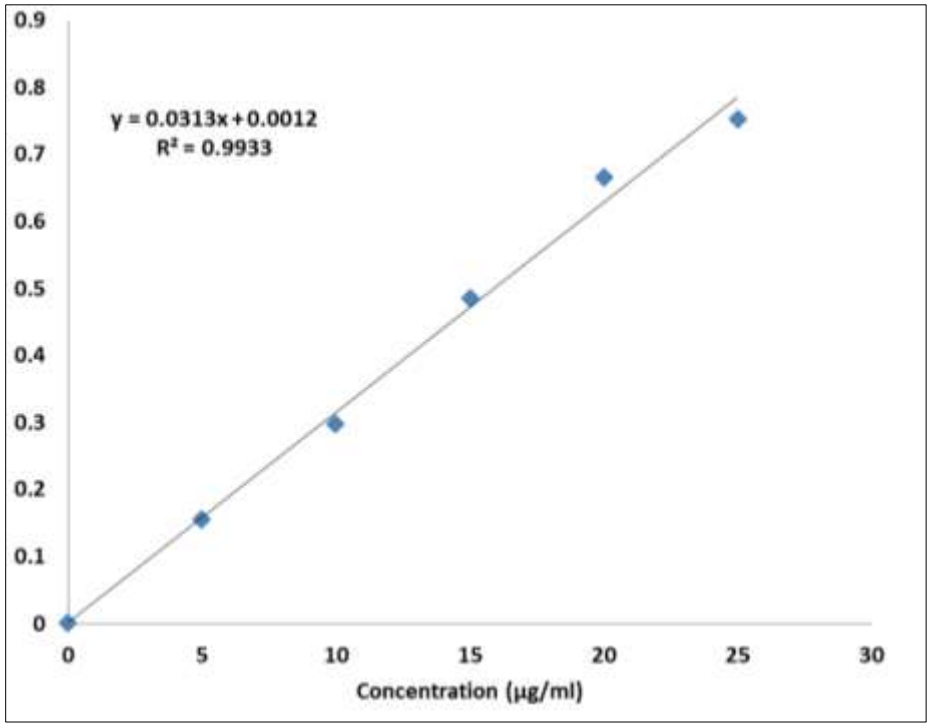

Fig 1: Standard calibration curve of Rabeprazole Sodium in 0.1NHCl

Drug Excipients Compatibility Study

Table 6: Drug Excipients Compatibility Study

S. No.	Composition	Ratio (Drug: Excipient)	I Week	II Week	III Week	IV Week
1.	Rabeprazole sodium	1:1	No Change	No Change	No Change	No Change
2.	Rabeprazole sodium +Mannitol anhydrous	1:1	No Change	No Change	No Change	No Change
3.	Rabeprazole sodium + Copovidone	1:1	No Change	No Change	No Change	No Change
4.	Rabeprazole sodium +Light magnesium oxide	1:1	No Change	No Change	No Change	No Change
5.	Rabeprazole sodium +Hydroxy propyl cellulose	1:1	No Change	No Change	No Change	No Change
6.	Rabeprazole sodium +Colloidal silicon dioxide	1:1	No Change	No Change	No Change	No Change
7.	Rabeprazole sodium +Magnesium stearate	1:1	No Change	No Change	No Change	No Change
8.	Rabeprazole sodium +Sodium bicarbonate	1:1	No Change	No Change	No Change	No Change
9.	Rabeprazole sodium + Iron oxide red	1:1	No Change	No Change	No Change	No Change

From the drug excipients compatibility study, it was observed that there was no change between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Rabeprazole sodium. [18] From the spectra of Rabeprazole.

Physical mixture of drug and selected ingredients it was observed that all characteristic peaks of Rabeprazole, were present in the combination spectrum, thus indicating compatibility between drug and selected ingredients. FTIR Spectra shown in Figure and table.

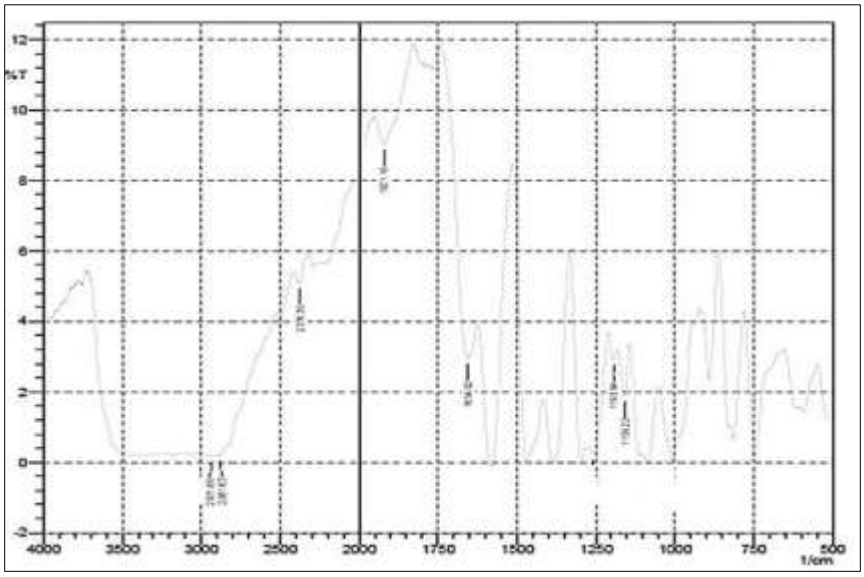

Fig 2: FTIR spectra of Rabeprazole Sodium

Table 7: FTIR Spectral Data of Rabeprazole Sodium

S. No	Wave Number(cm-1)	Peaks (cm-1)
1.	S=O	1159.22
2.	C-N	1193.94
3.	C=N	1654.92
4.	C-H (Aromatic)	3049.46
5.	C-H (Aliphatic)	2931.80
6.	OCH3	2285.65

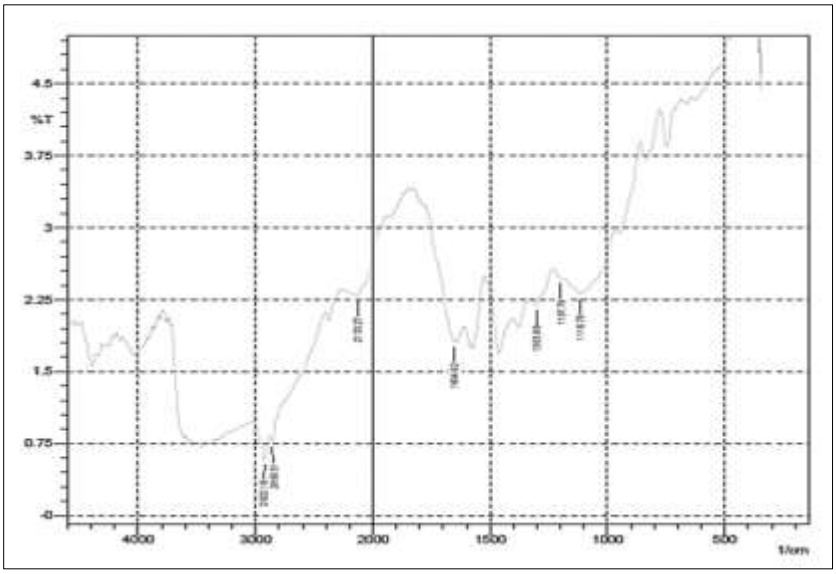

Fig 3: FTIR spectra of Rabeprazole Sodium Tablet

Table 8: FTIR Spectral Data of Rabeprazole Sodium Tablet

S. No	Wave Number(cm-1)	Peaks (cm-1)
1.	1298.09	S=O
2.	1091.71	C-N
3.	1647.21	C=N
4.	2924.09	C-H (Aromatic)
5.	2858.51	C-H (Aliphatic)
6.	2368.51	OCH3
7.	1298.09	S=O

Evaluation of Powder Blend

Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. Based on angle of repose it was observed that F6 showed excellent flow properties than the rest of formulations. Hausner's factor values were in the range of 1.16. The powder blend of the all designed formulations containing Rebeprazole sodium were evaluated for parameters like angle of repose was found to be 29.5±0.1, 27.6±0.4, 26.1±0.3 and 25.0±0.2, Bulk density was found to be 0.68±0.2, 0.76±0.2, 0.72±0.1and 0.77±0.4, tapped density 1.18±0.1, 1.12±0.2, 1.27±0.4 and 1.06±0.2 g/cm3, Hausner's ratio 1.16, 1.15, 1.15 and 1.16, Carrsindex26.34±0.2, 25.25±0.4, 25.23±0.5 and 26.85±0.3 were found for IC1, IC2, IC3 and IC4 formulation respectively and reported in table. Based on the results obtained we can conclude that IC4 showed excellent flow.

Table 9: Evaluation of Precompression Parameters of Rabeprazole Sodium Powder Blend

Formulation Code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility index (%)	Hausner's ratio
IC 1	29.5±0.1	0.68±0.2	1.18±0.1	26.34±0.2	1.16
IC 2	27.6±0.4	0.76±0.2	1.12±0.2	25.25±0.4	1.15
IC 3	26.1±0.3	0.72±0.1	1.27±0.4	25.23±0.5	1.15
IC 4	25.0±0.2	0.77±0.4	1.06±0.2	26.85±0.3	1.16

Rabeprazole Sodium buffered Formulation were successively prepared and evaluated by performing the preformulation studies, formulation development and optimization and stability studies.

- The colour, odour, nature and taste of the drug were evaluated. It was found to be as per the monograph.
- Rabeprazole sodium was found to be very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n- hexane.
- Drug excipients compatibility study with and without FTIR spectroscopic analysis of drug with excipients showed that the drug was compatible with excipients which were used in the formulation.
- Rabeprazole buffer tablets were prepared by direct compression method and table in tablet technology.
- The prepared powder blend was evaluated for parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The obtained results indicated that it has good flow property for direct compression method.
- Tablets formulations were evaluated for hardness, thickness, weight variation, fri ability assay and disintegration time. All these parameters were found to be within the pharmacopoieal limits.
- The drug release was found to be above 99 % within 60 mins when RT6 formulation *In vitro* dissolution study was performed.
- The *in vitro* acid neutralizing capacity of formulations study of all formulation showed good results.
- The accelerated stability studies of RT6 formulation at 40 ^{o}C/75% RH for a period of 3months indicated that there was no significant change in description, disintegration time, drug content and *in vitro* dissolution profiles.

Conclusion

It has been observed that buffered formulation is an effective approach for acid labile drugs. There are many formulations which could enhance the acid stability of the drugs but buffered formulation approach is the most effective and low cost approach. Drug delivery of acid labile like Rabeprazole Sodium is successively formulated. The main strategy was to develop a formulation giving protection to Rabeprazole Sodium as well as safe and effective release so as to impart its action in an effective manner. So first of all conventional formulations were designed having drug and buffer part compressed together (Tablet in Tablet), along with alkalizing agent. So It can be concluded that disintegrates concentration, granulation technique and both core play a key role in the development and optimization of the buffer tablet in tablet of Rabeprazole sodium. The satisfactory drug release profile of Rabeprazole sodium buffer tablet dosage form provides an increased therapeutic efficacy. So in future in situ buffered approach will play an important role in the advancement of medicinal field especially in case of instability of the drug due to gastric environment of the body.

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