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REVEIW ARTICLE

FORMULATION AND OPTIMIZATION OF ORO DISPERSIBLE TABLET OF RABEPRAZOLE SODIUM AS PROTON PUMP INHIBITOR

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ABSTRACT

Rabeprazolea proton pump inhibitor the most effective pharmacotherapy for treating acidity related disorders. The main objective of the study is to formulate and optimize an orodispersible tablet of rabeprazole sodium. The tablets were prepared by direct compression method by using varying concentration of Crosspovidone as superdisintegrants. Theprepared formulations were evaluated for various parameters like, hardness, weight variation, friability, *in vitro* dispersion time, water absorption ratio, drug content uniformity and *in vitro* release study. The prepared tablets were dispersed in the range of 7.9±0.5- 12.2±1.5 seconds, the water absorption ratio was 122.5±2.2-157.9±3.2%. All the formulations exhibited fairly uniform drug content92.7±0.4-99.5±0.8%and 85.6-95.2% of drug release was observed in 10 min, among this different formulation, the formulation containing 7.5% of Crosspovidone has shown maximum of 95.2±0.7% of the drug release. Stability study of optimized formulation revealed no significant change and its found to be a stable. The overall result indicated that the formulation F3 containing Crosspovidone 7.5% is fulfilling the needs of the orodispersible tablets.

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INTRODUCTION

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies hasbeen increasing dramatically. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new dosage forms for existing drugs with improved safety and efficacy with reduced dosing frequency**.** To fulfil these needs, the pharmaceutical technologists have developed a novel dosage form known as Orally Disintegrating Tablets ODTs (Hirani J J *et al*.,2009). The Orally Disintegrating Tablets are also called as oro dispersible tablets, fast dissolving tablets, porous tablets etc. The Centre for Drug Evaluation and Research, US FDA defined orally disintegrating tablet as "A solid dosage form containing medicinal substances, which disintegrate or dissolve rapidly, usually within a matter of seconds, when placed upon the tongue" (Missula S *et al*.,2013). The demand for development of orally disintegrating tablets (ODTs) has enormouslyincreased as it has significant impact on the patient compliance, as they offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of populations(Modi J *et al*.,2013). The proton pump inhibitors are a group ofdrugs that reduce the secretion of gastricacid. They act by binding withthe enzyme H+, K (+)-ATPase, hydrogen/potassium adenosine triphosphates,which is sometimes referred to as the protonpump. This enzyme causes parietal cells of the stomach lining to produce acid. Although they perform much of the activity similar to the histamine H-2 receptor blockers, the protonpump inhibitors reduce stomach acid more andover a longer period (Gencarelli DM.2005).Purpose Proton pump inhibitors are used totreat ulcers; gastro oesophageal reflux disease(GERD), a condition in which backward flow of acid from the stomach causesheartburn and injury of the foodpipe(oesophagus); and conditions in which the stomach produces too much acid, such asZollinger-Ellison syndrome (Kirchheiner *et al*., 2009). Proton pumpinhibitors may be used to protect againstthe ulcerogenic effects of non-steroidal anti-inflammatory drugs

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and to help heal ulcerscaused by these drugs (Mansuri N *et al*., 2016). Rabeprazole sodium a proton pump inhibitor, Chemically 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]sulfinyl]-1H-Benzimidazole sodium salt. Its molecular formula is $C_{18}H_{20}N_3NaO_3S$ (Gouda M M *et al*., 2010). A substituted benzimidazole that inhibits gastric acid secretion. The stability of rabeprazole sodium is function of pH; it is rapidly degraded in acid media, and is more stable under alkaline condition (VL. Kulkarni *et al*., 2006). It belongs to a class of antisecretory compounds that do notexhibit anticholinergic or histamine H2 –receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ ATPase at the secretory surface of the gastric parietalcell. Because this enzyme is regarded as the acid proton pump within parietal cell, rabeprazolehas been characterized as a gastric proton –pump inhibitor (Abraham S *et al*.,2010) Rabeprazole blocks the final steps of gastric acid secretion, which when placed in the tongue disintegrates or dissolves rapidly in the saliva without water. As tablet disintegrates in the mouth, this could enhance the clinical effect of the drug through pregastric absorption from the mouth, pharynx and oesophagus. This leads to an increase in bioavailability by avoiding first pass liver metabolism. The drug releases from the rabeprazole due to the action of super disintegrates like Crosspovidone and Microcrystalline cellulose in the formulation. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. As an effect of swelling of superdisintegrant, the wetted surface of the carrier increases, which promotes wettability and dispersibility of the system and thereby enhance the disintegration and dissolution. Hence rabeprazole has been developed by direct compression method with the goal of speeding absorption and rapid onset of action.

MATERIALS AND METHODS

Materials

Rabeprazole was obtained as a gift samples from Yarrow Chem Products, Mumbai, India. Crosspovidonewere procured from S.D chemical, Mumbai. All other ingredients used were of analytical grade.

Compatibility studies

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer by comparing with the standard FT-IR spectrum of the pure drug.

Pre-Compression Parameters (Munde A V *et al*.,2015)

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum con height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated as follows.

$\theta = \tan^{-1} (h / r)$

Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder was determined.

Tapped density

The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus -II. The minimum volume occupied by the powder after tapping was measured.

Tapped density = weight/tapped volume

Compressibility Index

Compressibility index is calculated as follows. The value below 15% indicates a powder with good flow characteristics where as above 25% indicates poor flow ability

Tapped density - Bulk density/ Tapped density*100

Haussner's ratio

It is an indirect index of ease of powder flow, it is calculated as follows. Haussner's ratio < 1.25 indicates good flow properties, where as > 1.5 indicates poor flow ability.

Tapped density /Bulk density

Preparation of Orodispersible tablets (Munde *et al*., 2015)

Rabeprazole Orodispersible tablets were prepared by direct compression method of various formulation by using additives in varying concentrations and the detailed composition was shown in the Table 1. All the ingredients were powdered separately in a clean and dry porcelain mortar and then they were passed through # 60 mesh sieve. The drug and the additives were mixed thoroughly in an inflated polyethylene pouch in a geometric ratio of their weight. Then the powder mixture was compressed in to tablets of 100 mg weight using 6 mm flat round punches.

Table 1. Formulation design of Rabeprazole Orodispersible tablets

Ingredients	F1	F2	F3	F4
Rabeprazole	20	20	20	20
Crosspovidone	2.5	5	7.5	10
Microcrystalline cellulose	45.5	43	40.5	38
Mannitol	30	30	30	30
Mg. Stearate	1	1	1	1
Talc	1	1	1	1
Total weight	100	100	100	100

Evaluation tests for tablets

Weight Variation (Kamble D S *et al*.,2016): To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness and Friability (Kamble D S *et al*., 2016): For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.

Drug Content uniformity test (Munde A V *et al*.,2015): Twenty tablets were weighed and powdered. An amount of powder equivalent to 10 mg of Rabeprazole was dissolved in

100 ml of phosphate buffer pH 6.8, filtered, diluted suitably and analysed for drug content at 284nm using UV-Visible spectrophotometer (Shimadzu corporation, Japan). From the absorbance values, amount of drug present in the given tablet was calculated. Procedurewas repeated by using two more tablets from the same formulation and the average value of all three tablets were calculated.

Water Absorption ratio (Tekade N P *et al*., 2010): A piece of tissue paper folded twice was placed in a small Petridish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

Wa- weight of tablet after water absorption
Wb- weight of tablet before water absorption

***In Vitro* Dispersion Time (Tekade N P *et al*., 2010):** *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of phosphate buffer pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in vitro* dispersion timewas performed.

***In Vitro* Dissolution Studies (Pimple S *et al*., 2014):** *In vitro* drug release studies for the Rabeprazole Orodispersible tablets was studied using dissolution test apparatus II USP XXVII model [Paddle type] for the fabricated batches with the rotation speed of 50 rpm using phosphate buffer pH 6.8 as the dissolution medium maintained at a temperature of 37 ± 0.5^{0}C. Samples were withdrawn at predetermined time interval and filtered through Whatman filter paper, diluted suitably and analysed at 284 nm for cumulative drug release using Schimadzu UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate.

Stability studies: Stability study of optimized formulation was carried out at 25^o/60% and 40^o/75% RH for a period of three months. During stability study the tablets were analysed for drug content.

RESULTS AND DISCUSSION

FT-IR spectrum: Infra-red spectra of pure drug Rabeprazole and combination of drug with polymers (Crosspovidone) were obtained ad shown in Figures1. All the characteristic peaks of Rabeprazolewere present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of the drug.

Physical Characteristics of Powder Blends: The prepared powder blendswere evaluated for various pre-compression parameter as explained earlier.

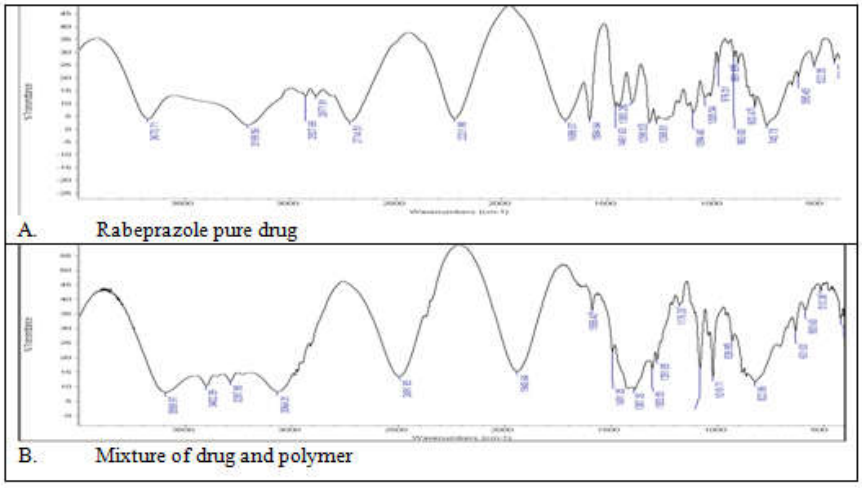

Figure 1. A. FT-IR spectrum for pure drug B. FT-IR spectrum for pure drug with polymer

Table 2. Physical Characteristics of Powder Blends

Formulation code	Angle of repose (degree)	Bulk density (gm./cc)	Tapped density (gm./cc)	Carr's index (%)	Hausner's ratio
F1	22.16 ±0.2	0.38 ±0.2	0.50 ±0.1	10.11 ±4.9	0.88 ±0.1
F2	23.27 ±0.4	0.43 ±0.3	0.55 ±0.4	12.52 ±2.2	1.06 ±0.3
F3	23.14 ±0.4	0.49 ±0.1	0.58 ±0.1	16.26 ±2.2	1.27 ±0.1
F4	24.22 ± 0.6	0.50 ± 0.4	0.60 ± 0.2	19.33 ± 4.5	1.33 ± 0.1

***In Vitro* Disintegration Time (Pimple *et al*., 2014):** The disintegration time of the tablets was determined as per Indian Pharmacopoeial monograph. The time required for disintegration of six tablets from each batch placed in each tube of disintegration test apparatus were measured at 37 ± 0.5ºC using 900 ml of distilled water. The time required to obtain completedisintegration of all the six tablets was noted.

The Bulk density was found in the range of 0.38 – 0.50G/CC and the tapped density was found to be in the range of 0.50 – 0.60G/CC. Using the above two density data, the Carr's compressibility index were calculated, the compressibility index was found to be in the range of 10.1 – 19.3% the compressibility and flow ability data indicated good flow properties for all the blended formulation. The better flow

property of all powder blends was also evident from angle of repose. The angle of repose was range of 22.16- 24.22^0. Angle of repose below 30º indicates good flow property. In the present study, all powder blends showed good flow property. The results are shown in the Table (2).

Post- Compression evaluation parameters

Weight Variation: The formulations were evaluated for their uniformity of weight according to the procedure and they show maximum weight of 105.2 mg and the minimum weight of 99.5mg from F1 to F4formulations were observed. The maximum allowed percentage weight variation for tablets 100 mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus, all the formulations were found to be complying with the given standards, and the results are shown in Table 3.

Hardness: All the tablet formulations were evaluated for their hardness as per procedure and all the formulations have an average hardness in the range 3.52 ± 0.11- 3.90 ±0.15 Kg/cm^2.which was found to be acceptable and the results are shown in the Table 3.

Friability: The Orodispersible tabletswere evaluated for their percentage friability as per the standards the average percentage friability for all the formulations were found be 0.91% to 0.95%, which is observed to be within the limit and the results showed that tablet possess enough resistance to with stand the mechanical shock and abrasion during handling and transportation and the results are tabulated in Table 3.

Drug Content: The formulations were evaluated for their uniformity of drug content according to the procedure to determine the amount of drug in all the formulation. The percentage of drug was found to be in the range of 95.14 to 99.13% w/w. The maximum drug content of 99.13 % w/w for F3 and the minimum of 95.14 % w/w for F2 formulations was observed. The results are tabulated in the Table 3. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

Table 3. Post compression parameters

Formulation code	Weight Variation (mg)	Diameter (mm)	Hardness (Kg/cm2)	Friability (%)	Drug Content (%)
F1	100.3±0.6	6	3.52 ± 0.1	0.95	97.02 ± 0.4
F2	99.5 ±0.1	6	3. 77± 0.1	0.92	95.14 ± 0.1
F3	101.1±0.4	6	3.90 ± 0.1	0.95	99.13 ± 0.7
F4	105.2±0.6	6	3.88 ± 0.1	0.91	97.11 ± 0.5

Wetting time and water absorption ratio

Wetting time and water absorption ratio of thetablets were measured and it was found to be in the range of 134 ± 3.9 - 157 ± 3.2% and wetting time of 11.2±0.8- 18.6±0.5 sec indicating suitability of formulation for fast dissolving tablet and the results are tabulated in the Table 4.

***In-Vitro* Disintegration Time**

The disintegration time of the tablets was determined by using disintegration test apparatus were measured at 37 ± 0.5ºC using 900 ml of distilled water. According to the pharmacopoeial standards the dispersible tablet must disintegrate within 3 min. but all formulated batches have shown very low disintegration time i.e. 9.7±0.6 to 14.05±0.5 sec indicating suitability of formulation for fast dissolving tablet and the results are shown in the Table 4.

Table 4. Evaluation of Orodispersible Tablets

Formulation code	Water Absorption Ratio (%)	Wetting Time(sec)	*In-Vitro* Disintegration Time (sec)	*In-Vitro* Dispersion Time(sec)
F1	134 ± 3.9	18.6±0.5	14.5±0.5	12.2±1.5
F2	145 ± 1.8	12.7±1.2	10.2±0.5	9.6±0.3
F3	157 ± 3.2	11.2±0.8	9.7 ±0.6	7.9 ±0.5
F4	122 ± 2.2	14.1±0.5	11.9±0.5	10.3±0.4

***In-vitro* Dissolution studies**

The drug release pattern was studied for all formulations for by using paddle type dissolution apparatus inphosphate buffer pH (6.8). The percentage cumulative drug release profile from formulation F1 to F4 was found to be in the range of 85.69% to 95.31% respectively. In this the maximum release was found to be 95.31% from F3 formulation this may be due to presence of (7.5%) of cross povidone & minimum release of 85.69 % in F4 (10%) formulation. From the above study, it can be concluded that by increasing the concentration >7.5% of superdisintgrant there may be reduced in the drug release from the formulations and the results are shown in Figure2.

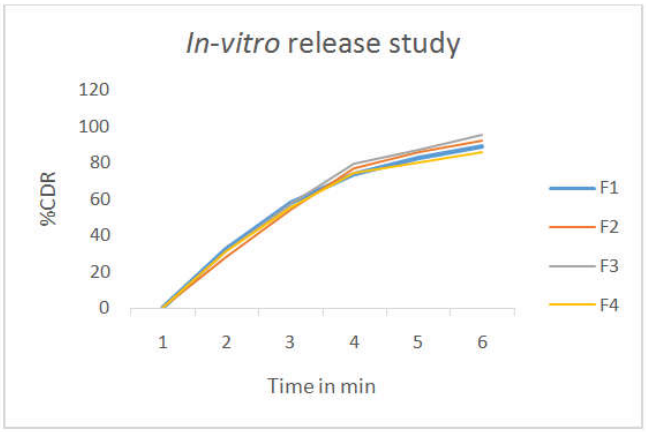

Figure. 2. In-vitro release study

Stability study

The selected formulation F3 was subjected to accelerated stability studies for three months at 25º/60% and 40º/75% RH, the samples were evaluated for any physical changes & drug content. And the subjected formulation was found to be stable.

Conclusion

Overall, the results suggest that suitably formulated orodispersible tablet of Rabeprazolecontaining 7.5% Crosspovidone as super disintegrant (F3) can be achieved. The tablets exhibited good i*n vitro* dispersion and wetting properties in presence of superdisintigratingagent, &better disintegration and drug release time when compared to other formulation. The prepared tablets were disintegrated within few seconds without need of water; thereby enhance absorption leading to increased bioavailability. Thus, the

present study demonstrated potentials for rapid absorption and improved bioavailability.

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