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Investigation on the Effect of Different Disintegrants on the Orodispersible Tablets of Rabeprazole

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Abstract: In the present study, an attempt was made to formulate orodispersible tablets of rabeprazole. Tablets were prepared by direct compression method using diluent and various disintegrants. Tablets were also prepared using treated agar (TAG) powder as one of the disintegrant. A total number of ten formulations were prepared and evaluated. Along with physicochemical parameters, the tablets were also evaluated for special parameters like wetting time, *in vitro* dispersion time, *in vitro* disintegration and *in vitro* drug release. The results of wetting time, *in vitro* dispersion time and *in vitro* disintegration signify that as the concentration of disintegrant increases the time required for disintegration decreases. A better disintegration was observed in formulation OT1, OT2, OT5 and OT6 containing crospovidone and croscarmellose sodium. The correlation and slope values obtained after performing *in vitro* release studies indicated that all the ten formulations followed first order release rate kinetics.

Key words: Orodispersible tablets, rabeprazole, disintegrants, direct compression

INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drugs (Suresh *et al*., 2008). Patients often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have swallowing problems encounter difficulties in taking tablets (Koizumi *et al*., 1997) particularly pediatric and geriatric patients. Recent developments in the technology have prompted scientists to develop Orally Disintegrating Tablets (ODTs) with improved patient compliance and convenience (Abdelbary *et al*., 2005). The ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and without need of water (Yoshio *et al*., 2008). Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Such problems can be resolved by means of orodispersible tablets. These tablets disintegrate instantaneously when put on tongue, releasing the drug, which dissolves or disperses in the saliva (Dandagi *et al*., 2005). United States Food and Drug Administration (FDA) defined ODT as a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue. The disintegration time for ODTs generally ranges from several seconds to about a minute

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(Abdelbary *et al*., 2009). Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form Seager (1998). Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts (Masazumi *et al*., 2008). However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing (Abdelbary *et al*., 2004).

Rabeprazole belongs to a group of drugs called Proton Pump Inhibitors (PPIs). The proton pump is the site within the stomach cell where hydrochloric acid is actually made and pumped out into the stomach. The PPIs block the formation of acid in the stomach from 80 to over 90% if enough of the drug is taken. Rabeprazole is used for almost any condition where stomach acid is causing a problem or tissue injury. These include peptic ulcers in the stomach and duodenum and especially gastro esophageal reflux disease where acid splashes back into the food pipe causing injury. Rabeprazole is also used along with antibiotics to cure or eradicate a stomach infection caused by *Helicobacter pylori*. These bacteria have been shown to cause peptic ulcers.

The main criteria for krodispersible tablets is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 to 60 sec, without need of water and should have pleasant mouthfeel za (Indurwade *et al*., 2002). The disintegrants used should fulfill the criteria by disintegrating the tablets in specified limit time. In the present study a variety of disintegrants like crospovidone, croscarmellose sodium, pregelatinized starch, TAG and L-HPC were selected and tablets were prepared by direct compression method using other additives. The main objective of our study is to select best disintegrant for the preparation of rabeprazole orodispersible tablets that can be used in the treatment of hyperacidity and peptic ulcer without need of water of when water is not available.

MATERIALS AND METHODS

Rabeprazole was procured from Saga Laboratories, Ahmedabad as a gift sample. Aspartame, Avicel PH 102 (Dr. Reddys Laboratories Ltd., Hyderabad), crospovidone, croscarmellose sodium, pregelatinized starch and L-HPC (Zydus Cadila Health Care Ltd., Ahmedabad) were procured as gift samples for the research work. The present research work was carried out at KLES College of Pharmacy, Hubli during the period June 2007 to July 2008.

Preparation of Tag Powder

Ten gram of agar powder was added to a 250 mL beaker containing 100 mL of distilled water and agitated using a stirrer for one day. During this time the agar swells by absorbing water. The mixture removed and spread on a tray, at room temperature for three days. By this the drying process will be completed. After drying the agar mixture was transferred to grinding apparatus for fine grinding. The grinded powder was passed through sieve and collects the fine powder; this was used as TAG (Akihiko and Masayasu, 1996).

Preparations of Tablets

The tablets were formulated employing direct compression method using 9.5 mm flat-faced punches. It is the process by which tablets are compressed directly from mixtures

of the drug and excipients without preliminary treatment such as granulation. Calculated quantity of drug, filler, disintegrant, lubricant and glidant were weighed separately. Next the ingredients were uniformly mixed in mortar. Then uniformly blend the powder and subject for compression into tablets. The same procedure was adopted for the preparation of tablets in all the formulations.

The prepared tablets were evaluated for physicochemical parameters like uniformity of thickness using a dial-caliper (Mitutoya, Japan) and hardness test using Monsanto hardness tester. Randomly selected tablets from all the ten formulations were also evaluated for friability test (using Roche Friabilator), weight variation test and drug content uniformity (Gilbert and Neil, 1987).

In vitro Disintegration Test

The *in vitro* disintegration time was determined using Disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds (Gilbert and Neil, 1987).

Wetting Time

The method reported by Bi *et al.* (1996) was followed to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH (Peh and Wong, 1999), a tablet was put on the paper (Fig. 1) and the time for complete wetting was recorded. Three trials for each batch were performed and standard deviation was also determined.

In vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 mL of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

In vitro Dissolution Studies

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII. One tablet of known drug content from each formulation was taken for the release rate studies. Fine hundred milliliter of 0.1 N HCl was used as dissolution medium maintained at 37±1°C with 50 rpm. At every 3 min, 2.5 mL of sample was withdrawn, diluted suitably and

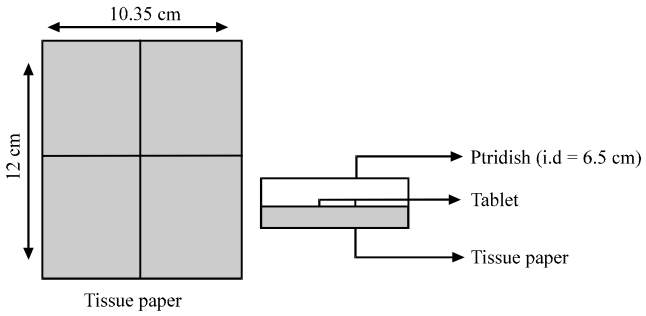

Fig. 1: Simple method for the measurement of wetting time of a tablet

analyzed spectrophotometrically at 235 nm. Further the cumulative percentage drug release determined was subjected to check the order of kinetics (Gilbert and Neil, 1987; Costa and Lobo, 2001).

Stability Studies

Stability studies were carried out at 25°C/60% RH and 40°C/75% RH for a specific time period up to 30 days for selected formulations according to ICH guidelines. After 10, 20 and 30 days, the formulations were taken and subjected for evaluation like hardness, drug content uniformity and *in vitro* disintegration to determine any significant changes (Zade *et al*., 2009).

RESULTS

The present study was carried out to prepare rabeprazole orodispersible tablets using various disintegrants like crospovidone, crocarmellose sodium, pregelatinized starch, TAG and L-HPC in 5 and 10% concentration, along with other additives. Direct compression method was used for the preparation of tablets. A total number of ten formulations were prepared and evaluated. Composition of all the formulations is shown in Table 1.

Tablets mean thickness (n = 3) was almost uniform in all the ten formulations. The thickness varies between 2.84 to 2.95 mm. The hardness was maintained to be within 3 to 4 kg cm^{-2}, as these tablets are rapidly disintegrating. In all the ten formulations (n = 3) the hardness was uniformly maintained and it was found to be 3.5 kg cm^{-1}. No variation in the hardness was found which clearly indicates that the blending was uniform. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Percent friability was less than 1% in the entire ten formulations and the values obtained lies between 0.16 and 0.36.

All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weight variation in all the ten formulations was found to be 193 to 212 mg, which was in pharmacopoeial limits. The percentage drug content of all the tablets was found to be between 95.38 and 99.13% of rabeprazole, which was within the acceptable limits. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the mean content of the drug present in the respective tablet.

Further the tablets were subjected for the evaluation of *in vitro* disintegration time. The *in vitro* disintegration time for all the ten formulations varied from 10.1±0.12 to 15.3±2.16 sec.

Table 1: Composition of rabeprazole orodispersible tablets

	Formulation code (mg)									
Ingredients	OT1	OT2	OT3	OT4	OT5	OT6	OT7	OT8	OT9	OT10
Rabeprazole	20	20	20	20	20	20	20	20	20	20
Crospovidone	10	---	---	---	---	20	---	---	---	---
Croscarmellose sodium	---	10	---	---	---	---	20	---	---	---
TAG	---	---	10	---	---	---	---	20	---	---
Pregelatinized starch	---	---	---	10	---	---	---	---	20	---
L-HPC	---	---	---	---	10	---	---	---	---	20
Avicel PH 102	157	157	157	157	157	147	147	147	147	147
Aspartame	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1

The wetting time for all the ten formulations was performed in triplicate. The values lie between 13.3±2.02 to 33.0±0.47 sec (Table 2).

In vitro dispersion is a special parameter in which the time taken by the tablet to produce complete dispersion is measured. The time for all the ten formulations varied between 11.9±1.15 and 34.0±2.64 sec (Table 2).

Formulations OT1, OT2, OT3, OT4 and OT5 which contains 5% disintegrant concentration releases 87.64, 82.15, 80.56, 81.15 and 80.35% drug respectively, at the end of 15 min. An increase in the drug release was observed when 10% disintegrant concentration was used in formulations OT6 to OT10. The drug release was found to be 99.26, 94.85, 89.12, 90.88 and 89.91%, respectively for the formulations OT6, OT7, OT8, OT9 and OT10 at the end of 15 min. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. In all the ten formulations the drug release was almost up to 80-100%, after 15 min. Formulations OT6 to OT10 shows almost 100% drug release at the end of 15 min. This signifies that disintegrant concentration in 10% is suitable for the formulation of orodispersible tablets of rabeprazole.

Further, the release rates obtained were subjected for kinetic treatment to know the order of release. The correlation coefficient and slope values obtained for all the ten formulations are shown in Table 3.

Stability studies were conducted for the formulations OT6 and OT7. The reason for selection is, these two formulations have shown good results in *in vitro* disintegration, wetting time and *in vitro* drug release studies. The tablets were analyzed for hardness, uniformity of drug content and *in vitro* disintegration time at a time interval of 10 days till a period of 30 days.

Table 2: Data of different disintegration properties of rabeprazole orodispersible tablets

	Time (sec)		
Formulation code	*In vitro* disintegration (n = 6)	Wetting (n = 3)	*In vitro* dispersion (n = 3)
OT1	11.6±1.15	14.5±2.18	12.1±1.19
OT2	12.1±2.10	16.2±4.15	14.8±3.12
OT3	15.3±2.16	33.0±0.47	34.0±2.64
OT4	12.3±2.15	19.4±1.18	15.3±1.15
OT5	13.1±1.05	21.2±1.15	18.3±2.31
OT6	10.1±0.12	13.3±2.02	11.9±1.15
OT7	11.5±1.05	15.1±1.09	13.3±2.10
OT8	14.6±2.27	25.3±1.27	24.8±3.51
OT9	11.9±1.21	17.0±2.15	14.9±3.10
OT10	12.6±1.19	19.8±1.90	16.8±3.25

Data are expressed as Mean±SD

Table 3: *In vitro* release of kabeprazole from prepared formulations and kinetic treatment

		Log cumulative % drug retained vs. time	
Formulation code	Cum. % drug released after 15 min	Correlation coefficient	Slope
OT1	87.64	0.9531	-0.0095
OT2	82.15	0.9445	-0.1236
OT3	80.56	0.9341	-0.2312
OT4	81.15	0.9353	-0.0212
OT5	80.35	0.9238	-0.1251
OT6	99.26	0.9971	-0.0012
OT7	94.85	0.9984	-0.0015
OT8	89.12	0.9932	-0.0031
OT9	90.88	0.9915	-0.0021
OT10	89.91	0.9908	-0.0013

DISCUSSION

In the present study, rabeprazole orodispersible tablets were successfully prepared using various disintegrants like crospovidone, crocarmellose sodium, pregelatinized starch, TAG and L-HPC in 5 and 10% concentration, along with other additives. TAG was prepared in the laboratory as mentioned in the methodology section and the same was used for the study. The well known super disintegrants were used and the comparative study was performed using rabeprazole as a model drug. The concentration 5 and 10% was finalized after following trial and error method and the tablets were prepared by using direct compression technique.

The thickness of all the tablets prepared was acceptable without much variation. Hardness of the tablets was uniform and indicated proper blending of the mixture for the preparation of the orodispersible tablets. Hardness is one important factor in concern to orodispersible tablets. The results of friability indicated that the integrity of the particles present in the tablets was good without much breakdown of the particles when friability test was performed. The tablets did not show any chipping or unnecessary breakdown of the particles. The weight variation test indicated that all the formulations were within pharmacopoeial limits with free flow of the powder blend and demonstrating the efficiency of compression of particles into tablets. Results of uniformity of drug content gave an indication that all the formulations were up to the mark containing the drug nearer to 100% with appropriate mixing and distribution of the drug in the blend.

The rapid disintegration was seen in the formulations containing crospovidone and croscarmellose sodium. Croscarmellose sodium swells rapidly absorbing more quantity of liquid when comes in contact with water. It has got a fibrous nature which allows inter particulate and intra particulate wicking property which helps in absorbing large quantity of water at low or high concentration level. The wicking property of crospovidone is more than croscarmellose which entertains the water up to a maximum extent which allows the disintegration rapidly because of the clean interaction of the particle arrangement of the super disintegrant. It was also noticed that as the disintegrant concentration was increased from 5 to 10% the time taken for disintegration was reduced. The water absorbing capacity of pregelatinized starch, L-HPC and TAG was less when compared to the super disintegrating croscarmellose sodium and crospovidone, hence they take little more time for disintegration.

The wetting time was rapid in crospovidone followed by croscarmellose sodium, Pregelatinized starch, L-HPC and TAG. Here also it was observed that as the concentration of disintegrant increased the time taken for wetting was reduced. The time taken by all the tablets to produce a uniform dispersion was within the limits. The *in vitro* dispersion was rapid in crospovidone followed by croscarmellose sodium, Pregelatinized starch, L-HPC and TAG. The same sequence was observed in all the three parameters related to disintegration. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. This signifies that disintegrant concentration in 10% is suitable for the formulation of orodispersible tablets of rabeprazole. The values obtained signify that the release rate follows first order kinetics. Good correlation of 0.9971, 0.9948 and slope values of -0.0012, -0.0015 was obtained in case of formulations OT6 and OT7, respectively. Both the formulations showed no significant variations in all the parameters and were stable for a period of 30 days.

CONCLUSION

In conclusion, overall results suggest that a 10% disintegrant concentration is suitable for the preparation of rabeprazole orodispersible tablets and the tablets containing disintegrants crospovidone (OT6) and croscarmellose sodium (OT7) are the best. The comparative study of several disintegrants yielded a conclusion that Crospovidone and croscarmellose sodium are very suitable for the preparation of rabeprazole orodispersible tablets which will satisfy all the criteria and official limits.

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