Original Article

Antacids incorporation in immediate release tablets failed to improve the stability of omeprazole in acidic media

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Abstract

Background: The stability of omeprazole (OMZ) decreases in acidic medium. In this investigation, attempts have been made to develop oral tablet containing antacids/buffers to increase the pH of dissolution media for certain time. **Materials and Methods:** Tablet formulations were prepared by the direct compression technique. For the selection of superdisintegrant, Croscarmellose sodium, used initially was replaced with other superdisintegrants. The prepared tablets were evaluated for hardness, weight variation, thickness, friability, drug content, disintegration time and *in vitro* drug release studies. During the *in vitro* drug release studies, the pH of dissolution media was measured. **Results and Discussion:** All batches showed very short disintegration time, within 0.5-2 min except F1 and S5. Batch F7 was able to provide the immediate drug release. The study showed that the incorporation of antacid improved the pH of dissolution media, but failed to maintain it. Even though the high quantities of antacids were incorporated; the stability of drug in media was not improved. Other superdisintegrants did not show any significant changes in drug release or disintegration time. Bath F7 was stable for the period of 6 months at 40°C / 75 %RH. **Conclusions:** Incorporation of higher quantities of antacids failed to retain the stability of OMZ in acidic media.

Key words: Antacids, immediate release tablets, omeprazole, superdisintegrant, superporous hydrogel particles

INTRODUCTION

Omeprazole (OMZ) is a potent inhibitor of gastric acid secretion by selectively interacting and inhibiting the gastric parietal cell proton pump.[1] OMZ was widely used in the treatment of active duodenal ulcer, active benign gastric ulcer, gastroesophageal reflux disease, erosive esophagitis and other pathological hypersecretory conditions.[2] The drawbacks are mainly related to the physicochemical instability to heat, light and acidic media, even with coated formulations. Moreover the low aqueous solubility of OMZ, ~0.4% at 25 °C, is responsible for small dissolution rates and so low bioavailability.[3] The stability of OMZ decreases in acidic medium, when it comes in contact of acidic medium leads a significant degradation of the drug and hence reduced bioavailability.[4-6] Due to its low bioavailability, short biological half life[7] and hepatic first pass metabolism, various oral formulation of OMZ such as enteric-coated granules[8,9] and tablets[10,11] have been developed with a subsequent 40% increase in oral bioavailability[12] of OMZ but have a wide individual variation of plasma concentration in human.[8-11] To overcome this problem, alternative dosage forms such as rectal suppository[13] and buccal adhesive tablets[14] were also developed. But all the dosage form of OMZ gives only systemic effect.

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In this investigation, attempts have been made to develop oral tablet containing antacids/buffers to increase the pH of dissolution media for certain time which provides stability to the drug temporarily, meanwhile the drug gets released.

MATERIALS AND METHODS

Materials

OMZ was generous gift from Cadila Pharmaceuticals Pvt Ltd., Ahmedabad, India. Sodium bicarbonate, magnesium hydroxide, croscarmellose sodium microcrystalline cellulose, acrylic acid, N,N'-Methylene-bis-acrylamide, Span 80, ammonium persulphate, and N,N,N',N'-Tetramethylethylenediamine were purchased from SD Fine Chem. Ltd, Mumbai, India. Acrylamide was obtained from Burgoyne Burbidges and Co. Pvt. Ltd., Mumbai, India. Double distilled water and 0.1N HCl were prepared in laboratory. All other chemicals used were of analytical grade and used as obtained.

Preparation of immediate release tablets

Tablet formulations were prepared by the direct compression technique. The drug and additives were passed through 80# sieve, and mixed thoroughly by geometric mixing. Croscarmellose sodium was used as a superdisintegrant. Talc and magnesium stearate were then added as glidant and lubricant, respectively. The blend was compressed using flat-faced round-shaped punch (11 mm diameter) for tablets with weight 700 mg (F1-F3) and deep concave capsule shaped punch for tablets with weight more than 700 mg (F4-F9) using a rotary tablet compression machine (Rimek, Ahmedabad, India). Each tablet contained 40 mg OMZ. The composition for single tablet is shown in Table 1.

Batch F1-F9 was prepared to select best immediate release formulation. Thereafter for the selection of superdisintegrant that provides fast immediate release, the superdisintegrant, Croscarmellose sodium, used in selected batch from F1-F9 was replaced with other superdisintegrants, as shown in Table 2 (Batch S1-S5). Other superdisintegrants used were sodium starch glycolate, starch 1500, cross povidone and superporous hydrogel particles. Superporous hydrogel particles were prepared as reported in our previous studies.[15-17] Batch S5 was prepared as a control batch without addition of superdisintegrant.

Evaluation of tablets

The prepared tablets were evaluated for hardness, weight variation, thickness, friability, drug content and disintegration time. For each formulation, the hardness (5 tablets) and friability (10 tablets) of OMZ tablets were determined using the Pfizer type hardness tester (Janki Impex, Ahmedabad) and the Roche friabilator (Electrolab, India), respectively. The thickness of the tablets was determined using a thickness gauge (Mitutoyo, Japan). Five tablets from each batch were used, and average values were calculated. To study weight variation 20 tablets of each formulation were weighed and the test was performed according to Indian Pharmacopoeia 2007. For estimation of drug content, 10 tablets were crushed, and the aliquots of powder equivalent to 100 mg of drug were extracted in 0.1N HCL. The solutions were passed through 0.45-µm membrane filter and after suitable dilutions the absorbance was measured at 302 nm using the UV-1800 UV/Vis Double Beam Spectrophotometer (Shimadzu, Japan). The disintegration time test was carried out on the 6 tablets using the Disintegration Test Apparatus USP (Electrolab, India). Distilled water and 0.1N HCL at 37 °C ± 2 °C were used as disintegration media. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

In vitro drug release studies

The release rate of OMZ from immediate release tablet (n = 3) was determined using USP XXIV Dissolution Testing Apparatus II (dissolution tester model TDT-08 L, Electrolab, India). The dissolution test was performed using 900ml of 0.1N HCL at 37 ± 0.5 °C and 100 rpm. At the regular time interval of 5 min samples (5 ml) were withdrawn from the dissolution apparatus for 1 hr; and the fluid removed was replaced with fresh dissolution medium, immediately. The samples were filtered and diluted to suitable concentrations with 0.1N HCL. The absorbance

Table 1: Composition for single immediate release Omeprazole tablet

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Omeprazole	40	40	40	40	40	40	40	40	40
Sodium bicarbonate	250	250	250	500	500	500	750	750	750
Magnesium hydroxide	170	257	343	170	257	343	170	257	343
Croscarmellose sodium	14	14	14	19	19	19	24	24	24
Microcrystalline cellulose	205	118	32	193	106	20	180	93	7
Talc	14	14	14	19	19	19	24	24	24
Magnesium stearate	7	7	7	9	9	9	12	12	12
Total weight	700	700	700	950	950	950	1200	1200	1200

of these solutions was measured at 302 nm using UV-1800 UV/Vis Double Beam Spectrophotometer. The cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

pH check for dissolution media

OMZ is unstable at acidic pH.[4-6] If the pH of dissolution media is raised beyond 4 the stability of drug can be improved up to certain extent. And so, in prepared tablets antacids were used to maintain the pH of dissolution media above 1.2. During the *in vitro* drug release studies, the pH of dissolution media was also measured at the time of each sampling up to 45 min.

Stability studies

The optimized batch was kept in airtight containers and stored in stability chamber (TH-90S, Thermolab, India) at 40°C/75%RH for 6 months.[18] Results for *in vitro* dissolution studies obtained after 6 months were compared with the data obtained at the time of preparation. The similarity factor (f_2) was applied to study the effect of storage on optimized batch. The f_2 value is calculated from the equation 1:

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{j=1}^{n} |Rj - Tj|^2]^{-0.5} \times 100\} \quad (1)$$

RESULTS AND DISCUSSION

Preparation of immediate release tablets

To accommodate the different weights of tablets *viz.* 700, 950 and 1200 mg, tablets with two shapes were prepared by the direct compression technique. All tablets with weight 700 mg were compressed using flat-faced round-shaped punch. And tablets with weight 950 mg and 1200 mg were compressed using deep concave capsule-shaped punch.

Table 2: Composition for single immediate release Omeprazole tablet containing different superdisintegrants

Ingredients (mg/tablet)	F7	S1	S2	S3	S4	S5
Omeprazole	40	40	40	40	40	40
Sodium bicarbonate	750	750	750	750	750	750
Magnesium hydroxide	170	170	170	170	170	170
Croscarmellose sodium	24	-	-	-	-	-
Cross povidone	-	24	-	-	-	
Starch 1500	-	-	24	-	-	-
Sodium starch glycolate	-	-	-	24	-	-
Superporous hydrogel particles	-	-	-	-	24	-
Microcrystalline cellulose	180	180	180	180	180	204
Talc	24	24	24	24	24	24
Magnesium stearate	12	12	12	12	12	12
Total weight	1200	1200	1200	1200	1200	1200

Evaluation of tablets

The evaluation parameters for tablets are shown in Table 3. The thickness of the tablets ranged from 4.02 ± 0.03 to 6.23 ± 0.04 mm. The hardness and percentage friability of the tablets of all batches ranged from 4.0 ± 0.21 to 4.2 ± 0.16 kg/cm^2 and 0.74 ± 0.04 to 0.89 ± 0.05, respectively. For weight variation test, the average percentage deviation of 20 tablets of each formulation was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 98.38 ± 0.04 to 99.65 ± 0.05. Disintegration time was ranged from 30 ± 3 to 106 ± 7 and 58 ± 4 to 211 ± 9 second in distilled water and 0.1N HCL, respectively. Batch F9 was found to be fast disintegrating formulation. Disintegration time was on of the important parameters in case of immediate release formulation. All batches showed very short disintegration time, within 0.5-2 min except F1 and S5.

In vitro drug release studies

The drug release profiles (n=3) from batches containing different proportions of antacids, and different superdisintegrants are shown in Figures 1 and 2, respectively. Although Batch F9 was fast disintegrating, however, Batch F7 was able to provide the immediate drug release as was able to release more than 90% of drug within 40 min. Except Batch F5 and F9, all other batches showed immediate release and release more than 99% of OMZ within 60 min.

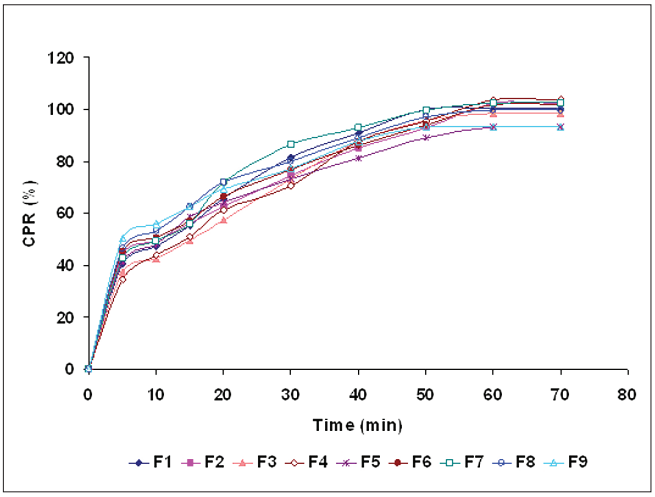

Figure 1: Drug release profiles from immediate release Omeprazole tablets (n = 3)

Here an attempt was made for the selection of superdisintegrant that provides fast immediate release. The superdisintegrant, Croscarmellose sodium, used in Batch F7 was replaced with other superdisintegrants. Other superdisintegrants *viz.* cross povidone, sodium starch glycolate, starch 1500, and superporous hydrogel particles[15] were not shown any significant changes in drug release or disintegration time. The presence of superdisintegrant provided less disintegration time in distilled water and 0.1N HCL compared to control batch S5. Compared to commonly used superdisintegrants, superporous hydrogel particles, newly tried and recently reported, played an equivalent and important role as a superdisintegrant. The superporous hydrogel particles, having a high tendency of swelling and hence impart quick breakage of tablets as the dissolution media penetrates, may be other option for a superdisintegrant for future formulations.

pH check for dissolution media

It is reported that OMZ degrades very rapidly in aqueous solutions at low pH values.[4-6] In aqueous solutions, the degradation rate proceeds with a half life of less than 10 min at pH values below 4, 18 h at pH 6.5 and about 300 days at pH 11.[19] The process of OMZ degradation

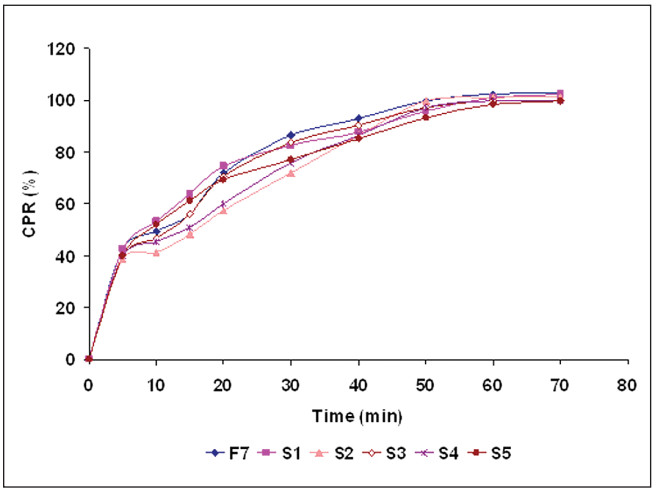

Figure 2: Drug-release profiles from immediate release Omeprazole tablets containing different superdisintegrants ($n = 3$)

Table 3: Evaluation parameters for Omeprazole matrix tablets

Batch	Thickness[a] (mm)	Hardness[a] (kg/cm²)	Friability[b] (%)	Deviation in weight variation test[c] (%)	Drug content[b] (%)	Disintegration time[d] (sec)	
						Distilled water	0.1N HCL
F1	4.02 ± 0.03	4.1 ± 0.11	0.76 ± 0.07	3.25 ± 0.04	98.38 ± 0.04	103 ± 6	145 ± 9
F2	4.02 ± 0.04	4.2 ± 0.14	0.74 ± 0.04	3.34 ± 0.07	98.82 ± 0.06	45 ± 3	113 ± 6
F3	4.06 ± 0.03	4.2 ± 0.09	0.85 ± 0.05	3.29 ± 0.06	98.67 ± 0.05	36 ± 3	100 ± 5
F4	5.21 ± 0.05	4.1 ± 0.13	0.83 ± 0.06	3.32 ± 0.08	98.89 ± 0.06	51 ± 4	110 ± 6
F5	5.23 ± 0.04	4.0 ± 0.21	0.76 ± 0.04	3.18 ± 0.06	99.18 ± 0.08	40 ± 3	80 ± 5
F6	5.20 ± 0.06	4.1 ± 0.14	0.79 ± 0.07	3.62 ± 0.04	98.92 ± 0.06	32 ± 3	65 ± 5
F7	6.18 ± 0.06	4.1 ± 0.07	0.89 ± 0.05	3.32 ± 0.07	98.82 ± 0.05	45 ± 4	95 ± 7
F8	6.23 ± 0.04	4.2 ± 0.16	0.88 ± 0.07	3.61 ± 0.09	99.65 ± 0.05	38 ± 3	76 ± 5
F9	6.19 ± 0.05	4.2 ± 0.12	0.81 ± 0.04	3.39 ± 0.03	98.53 ± 0.08	30 ± 3	58 ± 4
S1	6.20 ± 0.07	4.1 ± 0.08	0.83 ± 0.06	3.38 ± 0.05	99.08 ± 0.08	49 ± 4	98 ± 7
S2	6.19 ± 0.05	4.1 ± 0.08	0.76 ± 0.05	3.33 ± 0.06	99.11 ± 0.06	48 ± 4	99 ± 6
S3	6.21 ± 0.03	4.1 ± 0.05	0.80 ± 0.04	3.36 ± 0.07	98.71 ± 0.04	42 ± 4	89 ± 8
S4	6.15 ± 0.04	4.1 ± 0.07	0.78 ± 0.06	3.39 ± 0.06	98.89 ± 0.03	53 ± 3	102 ± 8
S5	6.11 ± 0.07	4.1 ± 0.03	0.77 ± 0.05	3.40 ± 0.03	99.11 ± 0.08	106 ± 7	211 ± 9

[a]Mean ± SD, n = 5, [b]Mean ± SD, n = 10, [c]Mean ± SD, n = 20, [d]Mean ± SD, n = 6

Table 4: Average pH of dissolution media at the time of each sampling

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	1.92	2.03	2.07	1.66	1.71	1.75	1.80	1.78	1.79
10	1.86	1.97	1.99	1.64	1.68	1.71	1.80	1.76	1.74
15	1.81	1.92	1.93	1.63	1.65	1.69	1.78	1.73	1.71
20	1.76	1.89	1.89	1.62	1.61	1.65	1.76	1.70	1.67
30	1.70	1.82	1.85	1.60	1.59	1.60	1.75	1.66	1.62
40	1.62	1.75	1.78	1.56	1.58	1.57	1.71	1.62	1.59
45	1.61	1.75	1.78	1.55	1.58	1.55	1.67	1.61	1.57

n = 3

is acid catalyzed. An increase in the pH values decreases the rate of degradation. In this formulation this stability problem was tried to minimize/overcome by addition of buffers/antacids in the formulation which help in providing and maintaining the pH of dissolution media beyond 4. Here immediate formulation was tried, so the drug was immediately released in this media and hence might be have less chance of degradation. Table 4 shows the pH of dissolution media at the time of each sampling up to 45 min. Incorporation of antacids, sodium bicarbonate and magnesium hydroxide, helped in raising the pH of dissolution media beyond 1.2 for all batches. However, the antacids failed to raise it beyond 4, which was necessary to improve the stability of drug in media. As the disintegration of tablet proceeded, the antacids were released in dissolution media which raised the pH beyond 1.2 initially, but afterwards as the time passed it gets lowered, but still beyond 1.2. Antacids were able to raise the pH but failed to maintain it. Different proportions of antacids changes the pH of dissolution media, but was not able to provide significant difference.

Stability studies

Batch F7 was selected for reference in order to calculate similarity factor (f_2). After 6 months of applied stability conditions Batch F7 showed the similarity factor 83.64. The stability studies showed that there were no significant changes observed for *in vitro* dissolution studies after 6 months. Bath F7 was stable for the period of 6 months at 40°C / 75%RH.

CONCLUSIONS

The study showed that the incorporation of antacid improved the pH of dissolution media, but failed to maintain it. Even though the high quantities of antacids were incorporated; the stability of drug in media was not improved. Croscarmellose sodium was the best suited superdisintegrant suitable for the immediate release OMZ tablet. Replacement of croscarmellose sodium with the other superdisintegrants did not show any improvement in drug release. From this study, both the parameters dissolution and disintegration time are very important and play an important role in the immediate release formulations.

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