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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF OMEPRAZOLE FAST DISSOLVING TABLETS

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ABSTRACT

Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), Gastroesophageal reflux disease (GERD), laryngopharyngeal reflux disease (LPR) and Zollinger-Ellison syndrome. The present study deals with the formulation of omeprazole fast dissolving tablets utilising cross linked alginic acid and calcium silicate as super disintegrates and a total of 8 formulation batches were prepared. All the pre compression and post compression parameters are studied and the results comply with in the limits. *In vitro* dissolution studies explained that the optimised F7 formulation with super disintegrants Cross linked alginic acid at low ratio and Calcium silicate at high ratio showed a cumulative release of 99.6 % of drug at the end of 12 minutes and also exhibited first order kinetics with Higuchi mechanism of drug release.

Keywords: Omeprazole, Fast dissolving tablets, calcium silicate, cross linked alginic acid.

INTRODUCTION

The Centre for Drug Evaluation and Research (CDER), US FDA[1] defined fast dissolving tablets (FDT) as "A solid dosage form containing medicinal substances, which disintegrate or dissolve rapidly, usually within a matter of seconds, when placed upon the tongue".[2] FDTs disintegrate and / or dissolve instantaneously in the saliva without the use of water. However some patients, particularly paediatrics and geriatric patients have trouble in swallowing or chewing solid dosage forms (conventional dosage forms). To avert the impediments accompanying with dosage forms like the dry syrups and effervescent tablets which require water for their action whereas the chewable tablets have the problem of bitter tasting or unpleasant taste of the drug and injections are not preferred due to their intrusiveness. So, the development of an appropriate dosage form is most desirable. The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. The elementary methodology in development of FDT is the use of super disintegrants like croscarmellose, sodium starch glycolate, cross linked alginic acid etc, provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva[3,4]. Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), Gastroesophageal reflux disease (GERD), laryngopharyngeal reflux disease (LPR) and Zollinger-Ellison syndrome. It is a selective and irreversible proton pump inhibitor which suppresses the gastric acid secretion by specific inhibition of hydrogen-potassium adenosine triphosphatase (H^+-K^+-ATPase) enzyme system found at the secretary surface of the parietal cells. The systemic bioavailability is 60 % for repeated doses and the absorption is completed within 3-6 h[5,6]. The purpose of the contemporary study is to formulate Omeprazole fast dissolving tablets using super disintegrants cross linked alginic acid and calcium silicate and study there *in vitro* performance.

MATERIALS AND METHODS

Omeprazole is a gift sample obtained from In ventis Pharma Pvt Ltd, Hyderabad, India Super disintegrates Cross linked alginic acid and calcium silicate were acquired from Rhom Pharma. Micro crystalline Cellulose, sodium saccharin, magnesium stearate were obtained from Signet chemicals. Aerosil was obtained from Aurobindo Pharma limited. All the reagents used are of analytical grade.

Construction of Standard Calibration Curve for Omeprazole

An accurately weighed 100 mg of omeprazole drug was dissolved in 100 ml of 0.05 N HCl[7] and used as primary stock solution. From the primary stock, concentrations of 2, 4, 6, 8, 10 µg / ml were prepared and the absorbance was measured at 302 nm using UV-Visible spectrophotometer. A plot was drawn taking concentration on x-axis and absorbance on y-axis and regression was determined as in Figure1.

Physical Evaluation of Powder blend

The powder blend was studied for angle of repose, bulk and tapped densities, compressibility index and Hausner's ratio[8,9].

Determination of Angle of Repose

The flow property was determined by the angle of repose which is the maximum angle that can be attained between the free surfaces of a powder heap with its horizontal plane. The formula for calculating angle of repose was:

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

Where, h = height of the pile; r = radius of the pile

Values of θ less than 40° indicate reasonable flow property to the powder and value greater than 50° indicates difficulty in flow.

Determination of Bulk and Tapped Densities, Compressibility Index and Hausner's ratio

A fixed amount of powder (W) was placed in a measuring cylinder and is allowed to fall under its own weight onto a

hard surface from a 2.5 cm height at 2 sec time interval. The tappings were continued until there were no void spaces and the final volume was noted. The bulk density and tapped density were calculated using the following formulas:

$$\text{Bulk density} = W / V_0$$
$$\text{Tapped density} = W / V_f$$

Where, W = weight of the powder; V_0 = initial volume; V_f = final volume.

Carr's Compressibility Index

It is measured from bulk and tapped densities. Calculated using the formula,

$$\text{Compressibility index, (CI)} = 100 (V_0 - V_f) / V_0$$

Hausner's ratio

It measured as the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = \text{tapped density} / \text{bulk density}$$

Method of Tablet Preparation

All the ingredients were accurately weighed and sieved through mesh # 36. Except aerosil and talc all the others were mixed geometrically. The blend was lubricated later with talc and aerosil. Tablets of 200 mg were compressed using 9 mm flat face circular punches which were fixed to the 16 station single rotary tablet compression machine (Cadmach, Ahmedabad, India). The prepared tablets were evaluated for several post compression parameters like hardness, thickness, weight variation, friability, drug content, disintegration time and *in vitro* dissolution studies. Table 1 illustrates the list of formulation batches.

Evaluation of Post Compression Parameters

Thickness[10-12]

The thickness of tablets was estimated using vernier callipers expressed in mm.

Hardness

The formulated tablets were evaluated for hardness using a Monsanto hardness tester. The force is applied diametrically and is expressed as kg/cm^2. Three tablets for each formulation were evaluated.

Friability

The tablets were subjected to combined effects of abrasion and shock by placing them in a roche friabilator that revolves at 25 rpm for about 4 minutes. Pre-weighed tablets (W_i) were subjected to 100 revolutions and later de dusted with a muslin cloth and the tablets weight (W_f) was noted. The friability (F) can be calculated using

$$F = \frac{W_i - W_f}{W_f} \times 100$$

Weight Variation

Twenty tablets from each formulation were taken and the average weight was noted. The individual weight was compared with the average weight.

Wetting Time

A petri dish of internal diameter 6.5 cm was taken containing 10 ml of water with a soluble dye like eosin in which a tissue paper folded twice and placed. On the top of it a tablet was positioned and the time for complete wetting was noted. Three trials were performed for each batch.

***In vitro* Disintegration Test**

The *in vitro* disintegration was implemented in USP disintegration apparatus. The set-up was done by employing six tablets in each tube and the time necessary for the complete disintegration with no palpable mass was noted in seconds.

***In vitro* Dissolution Study**

In vitro dissolution was done in USP dissolution type II (paddle) apparatus with 900 ml of phosphate buffer pH 6.8 as the medium at 100 rpm and the temperature was maintained at 37 ± 0.5°C. 5 ml aliquots were withdrawn at specified time intervals of 2, 4, 6, 8, 10 minutes and replaced with equal amount of buffer to sustain sink conditions. The samples were withdrawn and examined spectrophotometrically at 302 nm using UV-Visible spectrophotometer.

Table 1: List of Ingredients in Formulation Batches (F1-F8)

S. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
1	Omeprazole	20	20	20	20	20	20	20	20
2	Cross linked alginic acid	10	20	-	-	10	20	10	20
3	Calcium silicate	-	-	40	80	40	80	80	40
5	Sodium saccharin	2	2	2	2	2	2	2	2
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Aerosil	4	4	4	4	4	4	4	4
8	Microcrystalline cellulose	161	151	131	91	121	71	81	111
Total weight (mg)		200	200	200	200	200	200	200	200

Table 2: Results of Pre-Compression Parameters

Formulation batch	Angle of repose (°) Mean ± S.D	Bulk density (gm/cc) Mean ± S.D	Tapped density (gm/cc) Mean ± S.D	Compressibility index (%) Mean ± S.D	Hausner's ratio Mean ± S.D
F1	28.5 ± 0.85	0.55 ± 0.06	0.65 ± 0.06	15.5 ± 0.52	1.02 ± 0.55
F2	26.5 ± 0.50	0.45 ± 0.06	0.67 ± 0.05	17.5 ± 0.42	1.05 ± 0.25
F3	29.7 ± 0.35	0.51 ± 0.03	0.71 ± 0.08	19.8 ± 0.1	1.1 ± 0.15
F4	28.9 ± 0.85	0.52 ± 0.04	0.65 ± 0.04	16.4 ± 0.55	1.03 ± 0.5
F5	26.6 ± 0.55	0.49 ± 0.05	0.70 ± 0.06	15.6 ± 0.06	1.15 ± 0.15
F6	30.5 ± 0.15	0.52 ± 0.02	0.66 ± 0.05	16.9 ± 0.60	1.23 ± 0.12
F7	31.5 ± 0.65	0.56 ± 0.08	0.63 ± 0.07	15.8 ± 0.25	1.2 ± 0.06
F8	29.9 ± 0.45	0.55 ± 0.05	0.62 ± 0.06	18.8 ± 0.15	1.22 ± 0.15

*All values are calculated as Mean ± S.D

Table 3: Results of Post-Compression Parameters

Formulation batch	Thickness (mm) Mean ± S.D	Hardness (kg/cm^2) Mean ± S.D	Friability (%) Mean ± S.D	Weight variation (mg) Mean ± S.D	Wetting time (sec) Mean ± S.D	*In vitro* disintegration (sec) Mean ± S.D
F1	3.24 ± 0.5	3.8 ± 0.65	0.54 ± 0.5	202 ± 0.5	35 ± 0.52	20 ± 0.25
F2	3.0 ± 0.15	3.74 ± 0.55	0.75 ± 0.15	205 ± 0.6	39 ± 0.25	30 ± 0.33
F3	3.2 ± 0.26	3.95 ± 0.5	0.64 ± 0.5	195 ± 0.5	36 ± 0.52	22 ± 0.65
F4	2.9 ± 0.52	3.7 ± 0.15	0.44 ± 0.25	198 ± 0.2	35 ± 0.36	24 ± 0.55
F5	2.96 ± 0.33	3.9 ± 0.55	0.77 ± 0.6	196 ± 0.6	36 ± 0.92	22 ± 0.45
F6	3.1 ± 0.65	4.2 ± 0.05	0.65 ± 0.55	204 ± 0.8	42 ± 0.6	28 ± 0.66
F7	3.3 ± 0.25	4.0 ± 0.35	0.62 ± 0.4	200 ± 0.5	32 ± 0.8	22 ± 0.33
F8	3.0 ± 0.55	3.95 ± 0.15	0.59 ± 0.15	1992 ± 0.7	37 ± 0.45	27 ± 0.75

*All values are calculated as Mean ± S.D

Table 4: Kinetic Values Obtained from *in vitro*-Release Data for Formulations F1-F8

Formulation code	Zero order	First order	Higuchi	Korsmeyer Peppas	
	R value	R value	R value	R value	'n' value (release exponent)
F1	0.9715	0.9856	0.9598	0.9558	0.4758
F2	0.9254	0.9563	0.9755	0.9705	0.4561
F3	0.9156	0.9936	0.9896	0.9567	0.4785
F4	0.8993	0.9748	0.9963	0.9562	0.4963
F5	0.9602	0.9686	0.9875	0.8965	0.5444
F6	0.9795	0.9856	0.9845	0.9561	0.6654
F7	0.9525	0.9758	0.9777	0.9687	0.5893
F8	0.9103	0.9315	0.9658	0.9581	0.5677

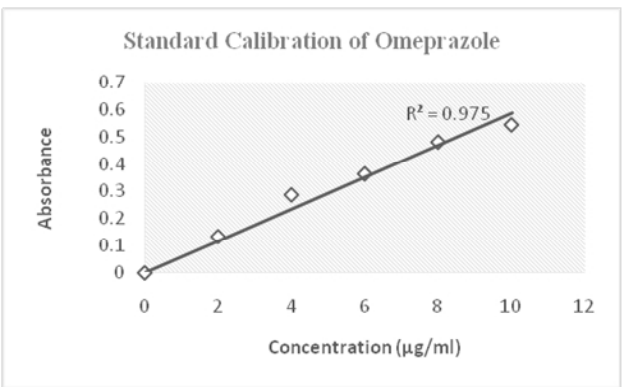

Figure 1: Standard Calibration Curve of Omeprazole

Figure 2: Wetting Time Evaluation of Omeprazole FDTs

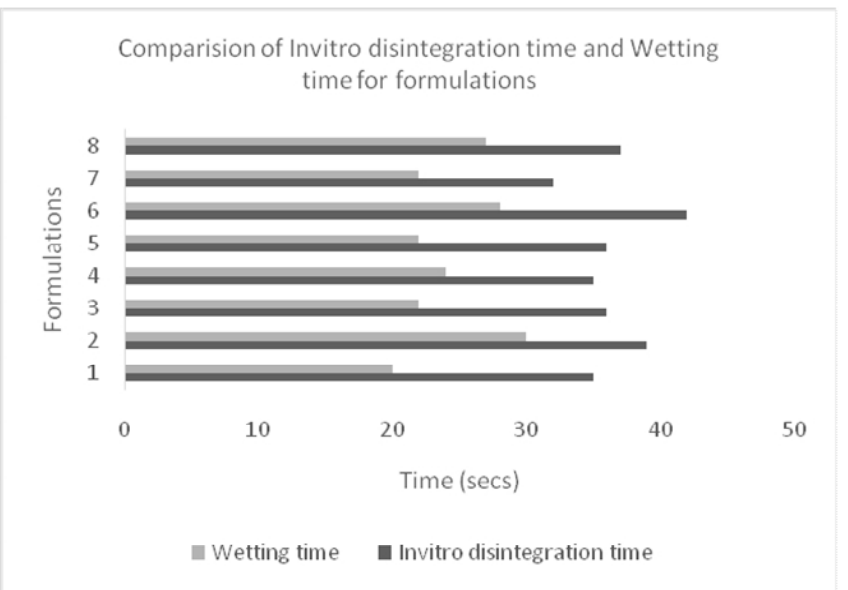

Figure 3: Comparison of *in vitro*-Disintegration Time and Wetting Time for Formulations F1-F8

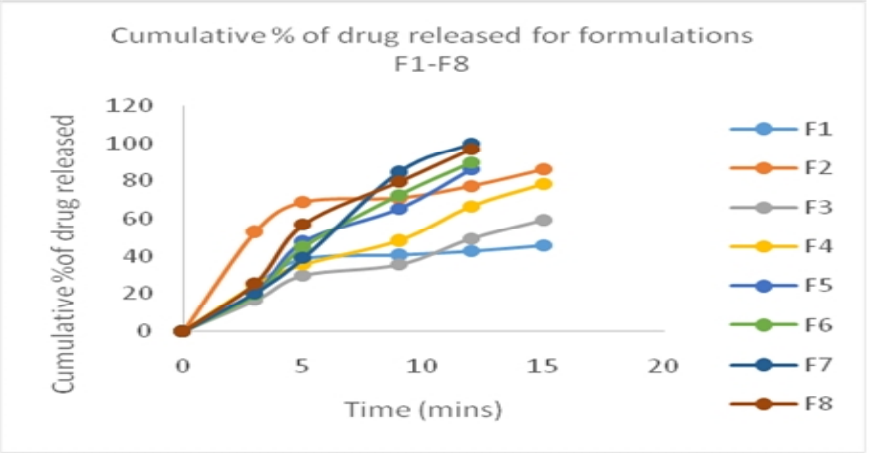

Figure 4: Cumulative % of Drug Released for Formulations F1-F8

RESULTS AND DISCUSSION

The fast dissolving omeprazole tablets were designed using two super disintegrants Cross linked alginic acid and calcium silicate. A total of 8 formulations were prepared and the various quality control tests were adopted in tables 2 and 3. There was no significant weight variation observed within average weight and individual weight. The % friability of the tablets was well within the tolerable range. The tablet thickness ranged from 2.9 ± 0.52 to 3.3 ± 0.25. The hardness of tablets ranged from 3.7 ± 0.15 to 4.2 ± 0.05. The % friability ranged from 0.44 ± 0.25 to 0.77 ± 0.6. Wetting time corresponds to the time taken for the tablet for the tablet to disintegrate when kept motionless on the tongue. The wetting time ranged from 32 ± 0.25 to 42 ± 0.6. The *in vitro* disintegration time for the formulated tablets ranged from 20 ± 0.25 to 30 ± 0.33.

In vitro Dissolution Studies

All the 8 formulations were subjected to *in-vitro* dissolution studies by using phosphate buffer as dissolution medium. *In-Vitro* release studies of all formulations were plotted and shown in the Figure 4. Formulations F1, F2 contained low and high concentrations of cross linked alginic acid showed cumulative drug release of 45.5 % and 65.9 % respectively at the end of 15 minutes. Formulation F3 and F4 contained low and high concentrations of calcium silicate showed cumulative drug release of 59.5 % and 78.5 % respectively at the end of 15 minutes. Formulations F5, F6, F7 and F8 showed 85.9 %, 89.5 %, 99.6 %, 96.8 % respectively at the end of 12 minutes. Out of all eight, F7 showed 99.6 % release within 12 minutes. The cumulative % of drug release for all formulations was shown in Figure 4. The drug release followed first order kinetics for all formulation batches. (F1-F8) on the basis of regression value (R value is greater for first order). To ascertain the mechanism of drug release the data was subjected to Higuchi and korsmeyer Peppas equations and the kinetic date was depicted in Table 4. Formulations F1- F8 showed Higuchi mechanism of drug release. The optimised F7 formulation with super disintegrants Cross linked alginic acid at low ratio and Calcium silicate at high ratio exhibited first order kinetics with Higuchi mechanism of drug release.

CONCLUSION

The use of super disintegrants cross linked alginic acid and calcium silicate showed faster disintegration and dissolution profile. Ideally F7 formulation was considered as optimized which showed 99.6 % drug release at the end of 12 minutes. All the formulations followed first order kinetics with higuchi mechanism of drug release (F1-F8).

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