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Original Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF OMEPRAZOLE

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ABSTRACT

Objective: The aim of present study is to formulate mouth dissolving tablet of omeprazole, the drug will be directly absorbed into systemic circulation through buccal mucosa and lead to produce immediate action.

Methods: Mouth dissolving tablets of Omeprazole were prepared by wet granulation method. Required quantity of drug and other excipients were weighed and sieved from sieve no.60 for finding homogenous mixer, then a damp mass of mixer was prepared by using distilled water as a solvent, Damp mass was passed through sieve no. 10 and dried the granules at 50 °C till moisture remaining less than 2%

Results: All the formulated tablets met the pharmacopoeias standard of uniformity of weight, percentage friability, thickness, and drug content. The *in vitro* disintegration and dispersion studies were also performed, which shows very good bioavailability and drug release profile.

Accelerated stability studies were done for four weeks and found that no significant change in drug content and other parameters like hardness and *in vitro* dispersion time after four weeks even at 50 °C. It may be predicted that formulation will be stable for more than one year.

Conclusion: The present investigation successfully formulated mouth dissolving tablets of omeprazole with improved drug release profile. The formulation was chosen because it showed good results in terms of cumulative drug release, disintegration time, hardness and friability. The dissolution study of this formulation showed an increase in the cumulative % drug release.

Keywords: Mouth dissolving tablets, Omeprazole, Bioavailability, Hepatic first pass metabolism, Wet granulation method, Carr's index

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INTRODUCTION

Mouth dissolving tablets is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. MDT is also known as an orally disintegrating tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet[2]. Fast disintegrating dosage form has been successfully commercialized, and the growing importance was highlighted recently when the European Pharmacopoeia adapted the term 'Or dispersible tablets' as a tablet to be placed in the mouth where it disperses rapidly before swallowing [1, 2].

MDTs are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need for chewing the tablet, swallowing an intact tablet, or taking the tablet with water. Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for the treatment of patients when compliance may be difficult (e. g. psychiatric disorders). MDT has previously been distinguished as a separate dosage form because of the specific, intended performance characteristics of such products, which are rapid oral disintegration in saliva with no need for chewing or drinking liquids to ingest these products [3, 4].

Advantages of MDTs

1. Improved patient compliance.

2. Pregastric absorption can result in improved bioavailability, reduced dose, and improved clinical performance by reducing side effects.

3. Easy to administer in patients having difficulty in swallowing.

4. Useful for pediatric, geriatric and psychiatric patients.

5. Suitable during traveling where water may not be available.

6. Free of the need of measuring the dose, an essential drawback in liquids. So accurate dosing as compared to liquids can be achieved.

Ideal properties of MDTs [5, 6]

They should

1. Do not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.

2. Allow high drug loading.

3. Be compatible with taste masking and other excipients.

4. Have a pleasing mouth feel.

5. Leave minimal or no residue in the mouth after oral administration.

6. Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.

7. Exhibit low sensitivity to environmental conditions such as humidity and temperature.

8. Be adaptable and amenable to existing processing and packaging machinery.

9. Allow the manufacture of tablets using conventional processing and packaging equipment at low cost.

MATERIALS AND METHODS

Materials

Omeprazole drug was obtained as a gift sample from CIPLA Ltd., Mumbai. Potassium Chloride purified, LR Grade Potassium dihydrogen Orthophosphate Purified, Potassium Hydroxide (Pellets), LR Grade obtained as gift sample from CDH Ltd., Mumbai. Cross Carmellose Calcium was gift sample from Hiraniya cellulose product, Hdb. Hydroxy Propyl Methyl Cellulose was gift sample from Sigma Life Science, U. S. A. Hydroxy Propyl β-Cyclodextrin was gift

sample from Otto Chemie Pvt. Ltd., Mumbai. All chemicals and reagents used were of analytical grade.

Preparation of mouth dissolving tablets

Tablets were prepared by Wet Granulation method.

Table 1: Formulation of omeprazole mouth dissolving tablets

Tablet Ingredients(mg)	Formulation code								
	FA_1	FA_2	FA_3	FA_4	FA_5	FA_6	FA_7	FA_8	FA_9
Omeprazole	10	10	10	10	10	10	10	10	10
Mannitol	30	30	30	30	30	30	30	30	30
Lactose	33	33	33	33	33	33	23	13	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Hydroxyl Propyl β-Cyclodextrn	50	50	50	50	50	50	60	70	80
Crosscarmellose calcium	21	20	18	14	12	9	18	18	18
Hydroxy Propyl Methyl Cellulose	3	4	6	10	12	15	6	6	6
Total	150	150	150	150	150	150	150	150	150

It included the following steps

1. Accurately weighed the quantity of omeprazole, super disintegrant, mannitol, lactose, HPMC (15cps) and Hydroxypropyl β-Cyclodextrn were taken in a Mortar, mixed well and sifted through 60 mesh screen.

2. Step 1 materials were granulated with water.

3. The wet mass was sieved through 10 mesh screen and granules obtained were air-dried in the oven at 50 °C for 2 h. Dried granules were sifted through a 12-mesh screen.

4. Moisture contents of dried granules were controlled and maintained between 1-2 %.

5. Above blend with the target weight of 100 mg was compressed by using 6 mm normal concave punches and 1.5% Talc and 1.5% magnesium stearate was used as a lubricant. Tablets were prepared using the rotary tablet machine. Compression force was constant for all formulations are showed in table 1.

Pre compression parameters

All the parameters are determined, and results reported in table 2.

Table 2: Physical properties of powder blend

Formulation code	Bulk volume (cm3)	Bulk density (gm/cm3)	Tapped volume (cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner's ratio
FA_1	22.5	0.444	19.1	0.523	15.1	1.178
FA_2	21.7	0.46	18.9	0.529	13	1.15
FA_3	22.8	0.438	19.1	0.523	16.25	1.194
FA_4	20.8	0.48	17.5	0.571	15.93	1.189
FA_5	19.9	0.502	17.1	0.585	14.19	1.165
FA_6	20.9	0.478	17.6	0.568	15.84	1.188
FA_7	22.3	0.448	19.2	0.521	14.01	1.163
FA_8	21.9	0.457	18.7	0.535	14.58	1.171
FA_9	22.1	0.452	19.3	0.518	12.74	1.146

Angle of repose [9]

The angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured, and angle of repose was calculated using formula.

$$\theta = tan{-}1\ (h/5)$$

Where, θ is the angle of repose, h is the height of pile and r is the radius of the base pile.

Bulk density

Apparent bulk density was determined by pouring blend into a graduated cylinder. The bulk volume (Vo) and weight of powder (M) was deter-mined. The bulk density was calculated using the formula.

Apparent bulk density =weight of the powder (M)/volume of the packing (Vo)

Tapped density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight of powder blend (M) as measured. The tapped density was calculated using the formula.

Tapped Density = weight of the powder (M)/tapped volume of the packing (Vt)

Carr's compressibility index

The simple way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (C) which is calculated by using the following formula.

C = [(tapped density–bulk density/tapped density)]×100

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula**.**

Hausner ratio = tapped density/bulk density

Lower Hausner ratio (<1.25) indicate better flow properties than higher ones (>1.25).

Post compression parameters

Tablet's size and thickness [12]

3 tablets of each batch were selected randomly, and thickness and diameter of tablets were measured in mm by vernier calliper.

Tablet's hardness

The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of

a tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablets of each formulation was determined in Kg/cm^2 by the Monsanto hardness tester.

Table 3: Evaluation data of the prepared omeprazole mouth dissolving tablets

Formulat-ion code	Thick-ness (mm)	Dia-meter (mm)	Weight variaton (±%)	Hardness (Kg/cm^2)	Fria-bility (%)	Uniformity of content (%)	*In vitro* Disintegration time (sec.)
FA_1	2.93	6.0	Pass	2.23	0.904	91.92	49
FA_2	3.00	5.9	Pass	2.27	0.827	99.68	51
FA_3	2.98	6.0	Pass	2.86	0.723	93.65	53
FA_4	2.98	5.89	Pass	3.26	0.609	94.77	75
FA_5	3.00	6.0	Pass	2.4	0.591	94.61	92
FA_6	2.86	6.0	Pass	3.56	0.577	93.96	116
FA_7	3.03	5.99	Pass	2.83	0.724	93.31	54
FA_8	2.96	6.0	Pass	2.93	0.713	95.86	54
FA_9	2.91	5.90	Pass	2.9	0.716	94.03	53

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in table 3.

Tablet's friability

Friability of the tablet was checked by using Roche Laboratory friabilator. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 6 tablets was placed in a friabilator, which was then operated for 100 revolutions. Tablets were dusted and re weighed, the loss in the weight of the tablet is the measure of friability and is expressed in percentage as:

% friability = [(Initial Weight-Final Weight)/Initial Weight]*100

Weight variation

20 tablets of each batch were selected randomly and weighed after that single tablet weighed and calculated % deviation with respect to average weight of 20 tablets by using this formula:

% deviation = [(Individual Wg.-Avg. Wg)/Avg. Wg.] X 100

***In vitro* dispersion time**

The tablet was added to 10.0 ml of phosphate buffer, pH 6.8 at 37±0.5 °C. The time required for complete dispersion of a tablet was observed.

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10-cm diameter. Ten milliliters of water-soluble dye (eosin) solution was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

***In vitro* disintegration time**

The *in vitro* disintegration time was determined by using USP 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 palatable mass remaining in the apparatus was measured in seconds.

Drug-content

Five tablets were weighed individually and powdered. The powder equivalent to the average weight of tablets was weighed and extracted, and concentration was determined by measuring absorbance at 300.60 nm by a UV-visible spectrophotometer.

Dissolution test

The dissolution studies were carried out using USP 2 paddle apparatus. Paddles were allowed to rotate at 50 rpm and 900 ml of phosphate buffer pH 6.8 were used as dissolution medium. The temperature of dissolution medium was 37±0.5 °C. The duration of dissolution studies were for 24 min and samples (10 ml) were withdrawn at 4 min time intervals (subsequently 10 ml dissolution medium was replaced) and filtered through 0.45 µm Whatman membrane filter paper. The concentration of dissolving drug from tablets was determined spectrophotometrically at a wavelength, 300.60 nm. The dissolution study for each batch was carried out with three randomly selected tablets.

Stability studies

Stability studies were conducted for checking chemical breakdown or interactions between tablet components which may alter tablet physical properties and changing the bioavailability of a tablet system. Stability study was done by accelerated study testing method.

Accelerated Stability studies were conducted by storing the tablets at 25 °C, 40 °C, and 50 °C for four weeks. The hardness, dispersion time and drug content of tablets were tested weekly for four weeks.

Characterization of omeprazole tablet FT-IR studies

The infrared spectrum was taken for the pure omeprazole. FT-IR studies were carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy (FTIR) (Shimadzu Model–IRAFFINITY-1, Serial No. A21374600405).

RESULTS AND DISCUSSION

Omeprazole tablets were prepared by Wet Granulation method. Accurately weighed quantity of Omeprazole, super disintegrant, Mannitol, lactose, HPMC (15cps) and Hydroxypropyl β-Cyclodextrn.% of Moisture Content of granules of all batches were lies between 1 to 1.7 %. The angles of repose of granules of all batches were lies between 24.37 to 27.96 show good flows. Bulk density and tapped density: range from 0.438 to 0.502(gm/cm3) and 0.518 to 0.585 (gm/cm3) respectively. Compressibility index and Hausner ratio range from 12.74 to 16.25 and 1.15 to 1.194 respectively. Tablet thickness and diameter range is 2.86 to 3.03 mm and 5.89 to 6.09 mm respectively. The results indicate that the tablets are suitable for handling, counting and packing of tables and lies within limits as per specifications. The hardness of tablet was found to be between 2.23 to 3.56 kg/cm^2. The results indicate that the tablets are mechanically strong and are in the limit. Friability ranges .577 to .904 %. the results indicate that the percentage losses were not more than 1.0%. So tablet complies as per IP specifications. Weight variation test range from 148.76 mg to 151.26 mg as per IP specification. Disintegration time in between 49 to 54 second the results indicate that disintegration time of tablets is within 1 minute. Wetting time: in between 52 to 120 second and *in vitro* dispersion time was found to be 50 to 119 sec. drug content range in between 95 to 99% which show that tablets of all batches had content uniformity. Dissolution Study in 6.8 pH phosphate buffer: formulation of FA_1, FA_2,FA_3,FA_4,FA_5 and FA_6 have a recorded drug release 89.818%, 87.910%, 87.121%,

83.848%,,81.127% and 79.695 % at the end of 24 min the results was showed in fig. 1,

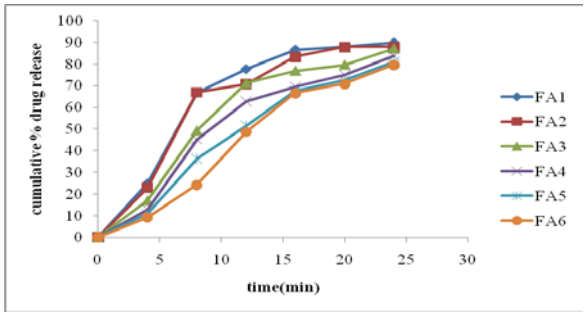

Fig. 1: *In vitro* drug release of FA_1, FA_2, FA_3, FA_4, FA_5 and FA_6 tablet formulations

Formulation F6, F7, F8 and F9 have a recorded drug release 89.799%, 98.127%, and 98.425% at the end of 24 min the result was showed in fig. 2.

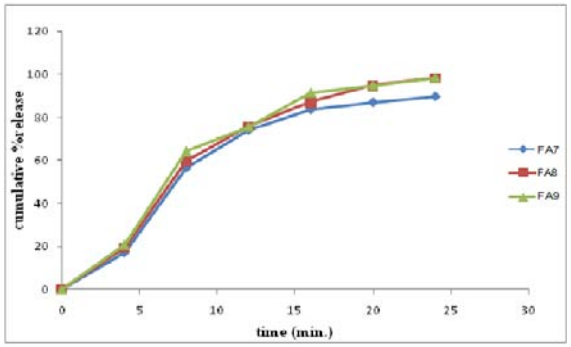

Fig. 2: *In vitro* drug release of FA_7, FA_8, and FA_9 tablet formulations

FTIR studies: The FTIR spectra of the pure drug were recorded in between 4000 to 600 cm-1. Characteristics peak and chemical group present in IR spectrum of omeprazole were showed in fig. 3,

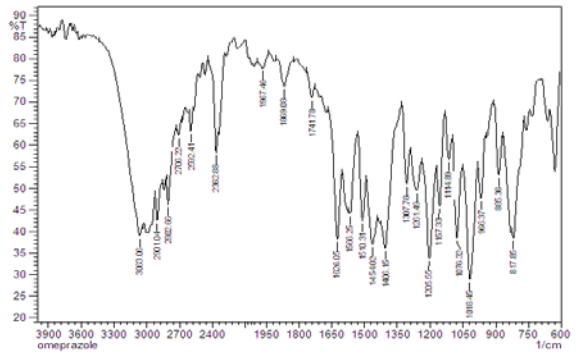

Fig. 3: FTIR spectra of omeprazole

C-H Stretching of alkane at 1261 cm^{-1}, Ar-C=N-Stretching at 1626.05 cm^{-1},-C-O-Stretching of (Ali. ether) at 1114.89 cm^{-1}, S=OStretching of (sulfone) at 1307.78 cm^{-1}. Storage condition: Tablets were stored at a temperature at 40 °C and RH-75% for a storage period of 1 w, 2week, 3week, and 4week. Hardness was decreased with time increases but in all cases, hardness was within the limit. Disintegration time: at various storage conditions increases but maximum 40 second which is less than 1 min (specification of IP). Dissolution studies shows there was no significant difference in dissolution data of formulations at initial and after specified storage period.

CONCLUSION

Mouth dissolving tablets of Omeprazole were prepared by wet granulation method using selected super disintegrants for the better patient compliance and effective therapy and Improved bioavailability of the drug by increasing disintegration rate and dissolution rate of omeprazole drug. Omeprazole tablets provided rapid onset of action with a minimum dose of the drug.

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CONFLICT OF INTERESTS

Declare none

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