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Formulation and Evaluation of Gastroretentive Floating Tablet of Esomeprazole Magnesium Dihydrate

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Sheri P. S[1], Anupama Jayaraj[2], Shahina.S[3], Shefna Hussain[4], Shilpa Chandran[5], Sisira Prasad[6]

[1]Professor, Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Alathara, Thiruvananthapuram, Kerala, India.[2]Associate professor, Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Alathara, Thiruvananthapuram, Kerala, India.[3]Research Scholar,Mar Dioscorus College of Pharmacy, Alathara, Thiruvananthapuram,Kerala, India.[4]Research Scholar, Mar Dioscorus College of Pharmacy, Alathara,Thiruvanathapuram, Kerala,India. [5]Research Scholar, Mar Dioscorus College of Pharmacy,Alathara,Thiruvanathapuram,Kerala,India.[6]Research Scholar, Mar Dioscorus College of Pharmacy, Alathara,Thiruvanathapuram, Kerala, India.

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ABSTRACT

The Floating tablet of Esomeprazole magnesium dihydrate was prepared by using direct compression method. A floating drug delivery system also called hydrodynamically balanced system is the class of gastroretentive drug delivery system. These have sufficient buoyancy to float over the gastric content and remain buoyant in the stomach. Xanthan gum, Eudragit, and Carbopol used as the independent variables. Sodium bicarbonate is used as gas generating agent. The compatibility of a drug with polymers was studied by FTIR Spectroscopy. Evaluation studies like physical parameters, swelling index, buoyancy studies, invitro dissolution, and drug content studies are carried out. This study proves that Gastro-retentive activity of Esomeprazole is facilitated by using Eudragit, Xanthan gum and Carbopol 940.

INTRODUCTION

Floating drug delivery systems are hydrodynamically controlled low-density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. It is especially used for achieving controlled plasma level as well as improving the bioavailability.

Esomeprazole is a substituted Benzimidazole, indicated for the treatment of gastroesophageal reflux disease in adults and children, risk reduction of NSAID-associated gastric ulcer, Helicobacter pylori eradication and control of pathological hypersecretory condition associated with Zollinger-Ellison syndrome. This dosage form will be very useful to deliver the narrow absorption window drugs which an oral administration prolongs its gastric residence time there by increasing bioavailability, diminishing the side-effect and enhancing patient compliance. The bioavailability of Esomeprazole magnesium dihydrate when given orally is 50-60%. The biological half-life of Esomeprazole magnesium dihydrate is 1-1.5 hours. The main absorption site is the upper part of the small intestine.

MATERIALS AND METHODS

MATERIALS

Esomeprazole was purchased from Yarrow Chem Mumbai, Xanthan gum, Eudragit, Carbopol 940, Microcrystalline cellulose, sodium bicarbonate, magnesium stearate and talc were purchased from Yarrow Chem.

METHODS

Floating tablets of esomeprazole Magnesium Dihydrate were prepared by using the direct compression method. The gas generating agent used is Sodium bicarbonate and which is helpful for floating. Accurately weigh each ingredient and pass it through 60 mesh sieves. All ingredients were blended uniformly in glass mortar except Magnesium stearate. After sufficient mixing, lubricant (Magnesium stearate) is added and mixed for 2-3 minutes. Before the tablet compression, the pre-compressional parameters such as angle of repose, bulk density, tapped density, %compressibility index and Hausner's ratio should be done. Then the tablets were compressed using tablet punching machine. In all formulations, the weights of all tablets should be kept constant. Preformulation studies were performed, the maximum absorbance of esomeprazole was determined by uv-visible spectrophotometer. Calibration

curve was also designed by measuring the absorbance. and FTIR studies of drug to polymers were performed by using FTIR spectrophotometer for pure drugs, polymers and formulations.

Table 1: Composition of floating tablet of Esomeprazole Magnesium Dihydrate

(All the quantities in mg)

Sr no.	Ingredients	F1	F2	F3	F4	F5	F6
1	Esomeprazole magnesium dihydrate	20	20	20	20	20	20
2	Xanthan gum	20	20	20	40	40	40
3	Eudragit	10	20	30	10	20	30
4	Carbopol 940	20	20	20	20	20	20
5	Microcrystalline cellulose	95	85	75	75	65	55
6	Sodium bicarbonate	30	30	30	30	30	30
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2
9	Total	200	200	200	200	200	200

EVALUATION PARAMETERS

PRE-COMPRESSION PARAMETERS

Angle of repose

The angle of repose is a parameter commonly used for the evaluation of interparticle force.it is used as an indirect method to determine the flow property of the powder mixture. Fixed funnel method is used. Here the funnel is secured with its tip with a height 2cm, above a plane paper kept on a flat horizontal surface. Powder is added while the funnel is closed until the apex of conical pile so formed just reaches the tip of funnel. Angle of repose was determined by putting the values of the base radius ‘r’ and height of the pile ‘h’ in the given following equation.

$$\tan\theta = h/r$$

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

where, **θ**=angle of repose

h=height of pile

r=radius of the pile

Table 2: Relationship between angle of repose and flowability

Angle of repose	**Flowability**
≤25	Excellent
25-30	Good
30-34	Acceptable
≥40	Very poor

Bulk density

Bulk density is the weight of a volume unit of a powder and is usually expressed in g/cm3, kg/m3, or g/100ml.Bulk density is usually determined by pouring an accurately weighed quantity of precompressed powder into a 25-graduated measuring cylinder. After that, the bulk volume was noted down, and repeated this three times as the mean values. And calculated the final volume as a result of bulk volume using the following formula:

$$\textbf{Bulk density} = \frac{\textbf{weight of powder}}{\textbf{Bulk volume of powder}}$$

Tapped density

Tapped density was determined by pouring the accurately weighed quantity of precompressed powder into a 25ml graduated measuring cylinder. Then the measuring cylinder was subjected to 100 tapping, and repeated for three times and take the mean values. And calculated the final volume as a result of tapped volume, using following formula:

$$\textbf{Tapped Density} = \frac{\textbf{Weight of powder}}{\textbf{tapped volume of powder}}$$

% Compressibility index

The compressibility index is used to evaluate the flowability of precompressed powder by comparing the bulk density and tapped density of the powder mixture.It is also called Carr's index. The percent compressibility index can be calculated by using the following formula:

$$\% CI = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Where, cl=compressibility index

Table 3: Correlation between % compressibility and flowability

% compressibility	flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
≥40	Extremely poor

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It provides an indication of the degree of densification that could result from vibration of the feed hopper, interparticulate interaction and settling property can be measured by Hausner's ratio.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 4: Hausner's ratio as an indication of powder flow.

Hausner's ratio	Flow property
≤1.18	Excellent
1.19-1.25	Good
1.3-1.5	Passable
≥1.5	Very poor

POST COMPRESSION PARAMETERS

The quality control test is conducted for the evaluation of the prepared floating tablets. The quality control test includes diameter, thickness, weight variation, hardness, friability, drug content uniformity, swelling index, in-vitro buoyancy, and in-vitro dissolution studies.

Diameter and Thickness

The diameter and thickness of the prepared floating tablet are evaluated by taking three tablets from each formulation. Diameter and thickness were measured by using a vernier calliper.

Weight variation test

A weight variation test is performed by taking twenty tablets from each formulation and tablets are individually weighed by using an electronic balance and the average weight is calculated. The % weight variation is determined by:

% weight variation = (WA – WI) x 100/WA

WA - Average weight of tablet

WI - the individual weight of tablet

Weight	% variation
Less than 80 mg	10%
80-250 mg	7.5%
Above 250 mg	5%

Tablet hardness

A hardness test is performed by taking tablets from each batch by using the Monsanto hardness tester. This test is performed to check if the tablet has hardness to prevent breaking during handling.it is measured in kg/cm^2.

Friability test

For performing the friability test twenty tablets were taken from each batch of formulation and weight is taken, then placed it inside the friabilator and operated up to 100 revolutions at 25 rpm for 3-5 minutes. Then again tablets are removed from the friability and weight is

taken again. Friability is the weight loss of tablet due to removal fine particles from the surface of the tablet in the containers. If any processing problem is occurred that tablet should be rejected. The % friability was calculated by:

$$\% \text{ friability} = (1-W/W0) \times 100$$

W0 – initial weight of tablet

W - final weight of the tablet

Swelling index

In this test tablets from each batch were taken and the weight was taken then it is placed in a beaker containing 200ml of distilled water. After that the tablet was removed from the beaker after each hour. Excess water present in the surface is soaked out using a filter paper and weight is taken and this process continues up to 5 hours.

The swelling index can be calculated by:

$$S.I = \{(Wt - Wo)/Wo\} \times 100$$

S.I = Swelling index

Wt. = weight of tablet at time t

Wo= weight of tablet before immersion

Drug content

In the test, three tablets were randomly selected from each batch, weighed, and powdered all the tablets using mortar and pestle. Then average weight of three tablets was taken. The amount of powder equivalent to 100mg was transferred into a 100ml volumetric flask and diluted with distilled water to make 100µg/ml concentration and filtered it. After taking 1ml filtered solution and make up the volume with 100ml distilled water to make concentration 10µg/ml and then absorbance was measured at 300nm using UV-visible spectroscopy. Each measurement was taken and mean was calculated. The drug concentration was calculated from the standard calibration curve of the drug.

In vitro buoyancy studies

By visual observation, buoyancy studies of prepared floating tablets were carried out. In this tablet was placed in a beaker containing 100 ml 0.1N HCL. Floating lag time is the time

taken for the tablet to emerge on the surface of the medium is calculated. Total floating time is the total time by which the tablet remain buoyant on the surface of the medium.

In vitro dissolution studies

A dissolution test apparatus (USP type 2) was used to carry out dissolution studies of all formulation batches(F1-F6).900ml of dissolution media contain 0.1N HCL, pH 1.2 for 9 hours at 50 rpm at 37±0. 5˚c.At different time intervals (0,0.25,0.5,1,2,3,4,5hours) 2ml of sample solution were withdrawn and filtered. Then 1ml of filtered sample solution was diluted up to 10ml with the same dissolution media. It is then analysed for drug content by using UV- Visible spectrophotometer at 300 nm. Before that 2ml sample was replaced in the vessel after each withdrawal to maintain sink condition. From the in-vitro dissolution studies percentage of drug release was calculated then the percentage drug release was plotted against the time to study the release pattern of the drug.

RESULT AND DISCUSSION

Pre-compression parameters

Angle of repose (θ):

The values obtained for angle of repose was found to be in the range in between ≤25.So it indicates that the excellent flow property of the powder mixture for the direct compression method.

Compressibility index:

The values obtained for the compressibility index ranges in between 23-35%, it indicates that the powder mixture has poor flow property.

formulation	Angle of repose	Loose bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's index	Hausner's ratio
F1	24.05	0.396	0.573	30.80	1.19
F2	25.18	0.405	0.555	26.91	1.17
F3	26.11	0.411	0.589	30.17	1.13
F4	25.08	0.411	0.589	30.17	1.23
F5	26.74	0.430	0.605	28.87	1.20
F6	28.81	0.389	0.528	26.36	1.24

Post compression parameters

Tablet dimensions:

The average thickness of tablets was uniform in all batches and was found in the range between 3.41-3.42mm, whereas the diameter of tablets ranges between 8.71-8.72mm.

Hardness test:

The hardness of prepared tablets ranges between 3.03-4.3kg/cm^2.

Friability test:

The friability test was carried out using a Roche friabilator. The% friability was less than 1% in all the formulation batches indicating tablets were mechanically stable.

Sl. No	batches	Tablet dimension		Hardness (kg/cm2)	Friability (%)
		Diameter(mm)	thickness(mm)		
1	F1	7.8	4.38	4.13	0.657
2	F2	7.7	4.38	4.16	0.454
3	F3	7.8	5.39	5.05	0.554
4	F4	7.8	4.39	4.14	0.452
5	F5	7.7	4.38	4.34	0.448
6	F6	7.7	5.38	5.27	0.543

Weight variation test

In tablet formulation weight variation test is an important parameter. This can be done by taking 20 tablets from each formulation is comparing them with individual weight of the tablet.

Buoyancy study

For a floating tablet buoyancy study is one of the important parameters. This is carried out in 0.1N HCL at 37±0.5˚c.

Sl.no	Batches	Weight variation test(g)	Buoyancy studies		Drug content
			Floating lag time (min)	total floating time (hrs)	
1	F1	208	4.2	>9	94.2
2	F2	205.5	4.1	>10	94.8
3	F3	200	4.5	>9	95.3
4	F4	201	4.4	>11	97.3
5	F5	198.5	4.6	>10	96.6
6	F6	201.5	4.8	>11	98.5

Swelling study:

Due to the hydrophilicity of the polymer, it absorbs the water so tablet get swells.

Sl.no	Time (Hrs)	Swelling index (%)					
		F1	F2	F3	F4	F5	F6
1	1	75	100	110	160	165	195
2	2	135	140	165	220	345	340
3	3	140	125	215	375	445	365
4	4	105	90	190	355	475	490

In vitro dissolution study:

A dissolution test apparatus was used to carry out dissolution studies using 0.1N HCL as a dissolution media. A dissolution study were carried out for 9 hours.it was found to be F6 batch shows better sustained release characteristics and floating lag time.

Time in hrs	F1	F2	F3	F4	F5	F6
0	8.52	9.51	10.51	9.01	8.06	10.51
0.25	21.52	10.52	23.02	19.52	14.01	18.02
0.5	30.53	21.03	29.53	24.02	29.04	27.53
1	36.25	32.76	34.03	36.05	36.56	31.03
2	40.42	44.41	40.06	42.08	43.57	45.56
3	43.17	55.43	55.07	58.58	53.58	56.58
4	47.43	64.21	60.58	64.09	68.58	66.09
5	54.12	68.31	64.59	71.60	70.09	73.10
6	66.07	72.41	72.54	77.51	75.98	77.53
7	76.58	75.08	76.42	80.82	77.15	80.41
8	85.59	79.58	78.58	84.09	78.58	86.09
9	91.1	81.59	84.59	91.60	84.09	93.10

Compatibility studies

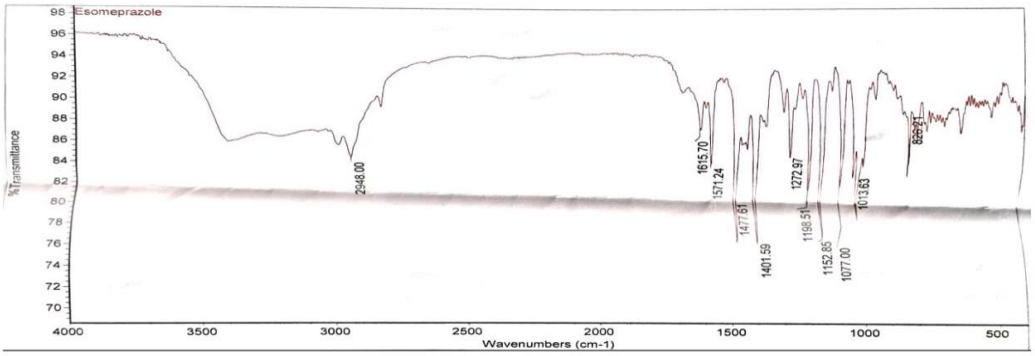

Figure 1-IR Spectrum of Esomeprazole Magnesium dehydrate

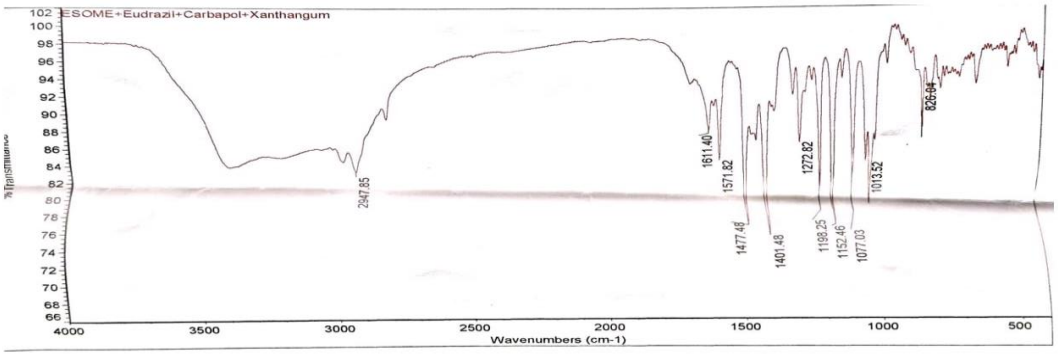

Figure 2-IR spectrum of Esomeprazole+Eudragit+Carbopol 940

DISCUSSION

The compatibility between the drug-polymer was carried out by using FTIR spectroscopy. The drug and polymer were found to be compatible, and hence this confirmed the absence of any chemical interaction or complexation between drug and polymer.

CONCLUSION

The prepared Esomeprazole magnesium dihydrate floating tablet shows a remarkable effect on Gastroretentive activity and the amount of Eudragit and Carbopol 940 had significant effect on drug release rate, floating lag time and total floating time.

F6 Batch gave the better-sustained release of drug and better floating lag time. So, this batch was selected as the best formulation.

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