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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE ESOMEPRAZOLE MAGNESIUM TRIHYDRATE LOADED FLOATING FILMS

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ABSTRACT

The present study was aimed to develop film which could float on gastric fluid in stomach by releasing the Esomeprazole magnesium trihydrate. It may act as site specific drug delivery system for treatment of Peptic ulcers and GERD. Floating films were prepared by Solvent Casting method varying the Different Conc. of Film former (HPMC K 15 M), Effervescent agent (Sodium bicarbonate) and plasticizer (PEG 400). The Prepared films were Characterized and evaluated for various parameters like FTIR and Film thickness, weight variation, Folding endurance, tensile strength, drug content, *in-vitro* dissolution studies, Buoyancy, floating time and lag time. From obtained results It can be concluded that Formulation EF6 demonstrated a lag time of roughly 57 seconds, a floating time of 12hrs in 0.1N HCL and also Shown retardance in *In-vitro* drug release studies of about 88% in 12hrs. So this formulation provides Gastroretentive property for the films in 0.1N HCL.

KEYWORDS: Floating films, Tensile strength, Lag time.

INTRODUCTION

The traditional Oral drug delivery system have several limitation such as limited targeting ability, Short retention time in the gastrointestinal (GI) tract and low bioavailability.[1] To overcome the problems associated with the conventional dosage form Gastro-retentive drug delivery system were used to formulate a dosage form and it Provides Improved Bioavailability, Improved Half life, Improved stability, provides Sustained/Prolonged Release, Increase Gastric Retention Time and Reduced drug waste.[2]

These Properties can be achieved by various gastro retentive dosage form, like floating systems, mucoadhesive systems, expandable systems, and magnetic systems.[3]

Esomeprazole Magnesium trihydrate is one of the most effective proton pump inhibitor which is S-isomer of omeprazole that suppresses gastric acid output and is used to treat GERD, Peptic ulcer, heal erosive esophagitis, and eliminate H. pylori to reduce the risk of repeated duodenal ulcer outbreaks. Esomeprazole Magnesium trihydrate belong to a BCS Class II drug (low solubility, high permeability),[4] with half-life of 1.2 hours and Variable bioavailability of 50-90%. Hence it is important to enhance bioavailability of the drug by floating drug delivery system.[5]

In floating drug delivery system mainly there are 2 type of system, Non-effervescent system and effervescent system, effervescent system floats by generation of CO_2 With the inclusion of effervescent agents.[5] Among the GRDDS formulation Floating film drug delivery system has expanding its advancement as compared to traditional dosage forms.[6] Floating film offers advantages like Ease of preparation of film, Time saving, Economically beneficial and reduced chance of cross contamination. Gastro retentive floating films consists of drug loaded sustain release layer along with film forming agent, plasticizer and suitable solvent.[7] Few attempts have been made by researchers to enhance bioavailability of Esomeprazole Magnesium trihydrate. But from literature survey it was found that less attempts has been made to increase bioavailability of drug by Floating Film drug delivery system. Hence sincere efforts was made to enhance bioavailability of Esomeprazole magnesium trihydrate.

MATERIALS AND METHODS

Materials

Esomeprazole Magnesium trihydrate was purchased from Yarrow chem products, Mumbai, India. HPMC K 15 M, Ethyl cellulose and Sodium bicarbonate were purchased from Loba chemie Pharmaceuticals.

Methods

FTIR

To identify the chemical interaction, purity and compatibility study of Esomeprazole magnesium trihydrate and excipients were confirmed by FTIR. FTIR spectra of pure drug, Polymers and Physical mixture were analyzed in the range of 400 to 4000 cm^{-1} by KBr Pellet method.[8]

Preparation of Esomeprazole magnesium trihydrate loaded floating films

HPMC K 15 M and Etshyl cellulose were Individually dissolved in water and Ethanol respectively in the ratio of 1:6. The respective solutions were mixed by placing container on a magnetic stirrer at 850 RPM then drug(Esomeprazole magnesium trihydrate) and sodium bicarbonate(Effervescent agent) were dispersed into solution mixture followed by addition of Plasticizer(PEG 400) film mixtures were stirred vigorously for one and half hour until to get Consistency of solution to form film. Then the solution was casted on petri plate and dried overnight at room temperature.[9]

Table 1: Composition of Esomeprazole magnesium trihydrate loaded film.

Ingredients	Formulation Code					
	EF1	EF2	EF3	EF4	EF5	EF6
Esomeprazole magnesium trihydrate (mg)	42.5	42.5	42.5	42.5	42.5	42.5
HMPC K 15 M (mg)	100	150	200	100	150	200
Ethyl cellulose (mg)	100	100	100	100	100	100
Sodium bicarbonate (mg)	30	30	30	75	75	75
PEG 400 (ml)	0.5	0.5	0.5	1	1	1
Water:Ethanol	1:6	1:6	1:6	1:6	1:6	1:6

EVALUATION OF PREPARED GASTRO-RETENTIVE FLOATING FILMS

Film Thickness

The thickness were measured using screw gauge at six different places by taking three films of each formulation then mean value was calculated and recorded. It is important to ensure that uniformity in the thickness. As the film thickness is directly related to the accuracy of the dose in the strip.[10]

Film weight variation

For each formulation, three randomly selected films were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

Folding endurance

Folding endurance is another procedure to estimate the mechanical properties of a film. It is measured by repeatedly folding a film at the same point until it breaks. Folding endurance value is number of times the film is folded without breaking. Higher folding endurance value depicts the more mechanical strength of a film.

The folding endurance was measured manually for the prepared films. A strip of film (3 x 3 cm^2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.[11]

Tensile Strength

Tensile strength of the film is the total weight which is necessary to break or rapture the film and was done by a device that has rectangular frame with two plates made up of Plexiglas. The one plate is in front and the other is the movable part of the device and can be pulled by the loading weights on the string, which is connected to the movable part. The testing procedure was performed the 3×3 cm^2 films were fixed between the stationary and movable plate. The force required to fracture the films was determined by measuring the total weight loaded in the string.[12]

$$\text{Tensile strength} = \frac{(\text{Load at failure} \times 100)}{(\textit{Strip thickness} \times \textit{Strip width})}$$

Determination of drug content

Drug content was determined by dissolving the films in 0.1N HCL, filtered through Whatman filter paper and Absorbance of the sample was measured using Shimadzu UV 1800 Spectrophotometer at a wavelength of 301 nm against 0.1 N Hcl as blank. The experiments were carried out in triplicate and average values were reported.[13]

***In vitro* dissolution studies**

The *In-vitro* drug release of Esomeprazole magnesium trihydrate loaded Floating film filled in capsule were conducted using USP type II paddle dissolution apparatus (TDT 08L, Electrolab, Mumbai, India). 900 ml of 0.1N Hcl was used as a dissolution medium at the rotation speed of 50rpm, kept at 37±0.5°C. The samples were withdrawn at predeteremined time interval and replaced with same amount of fresh buffer medium to maintain sink condition. Withdrawn samples were analysed for drug release using a Shimadzu UV 1800 Double beam spectrophotometer at 301nm.[14]

Buoyancy and floating test

Buoyancy test was carried out by placing a film into Container containing 250ml of 0.1N Hcl and monitored the time taken by the film to buoyant from the bottom to top of the Container, it represents lag time. The film's time to stay float was considered as floating duration.[15]

Drug release kinetics

To study the kinetics behaviour, The obtained drug release studies value were fitted for different release kinetics model like Zero order, First order, Peppas model, Higuchi model.[16]

FTIR

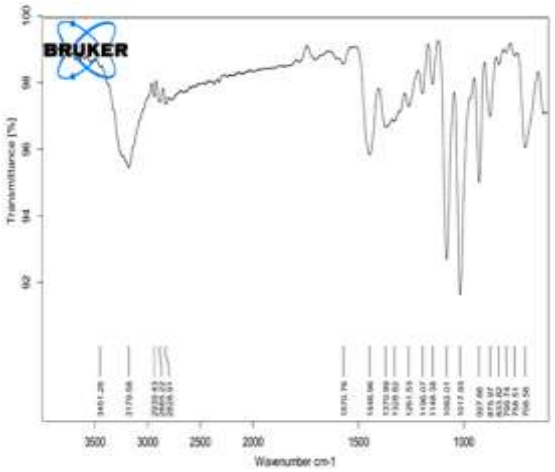

Fig 1: FTIR Spectra of pure Esom eprazole magnesium trihydrate drug.

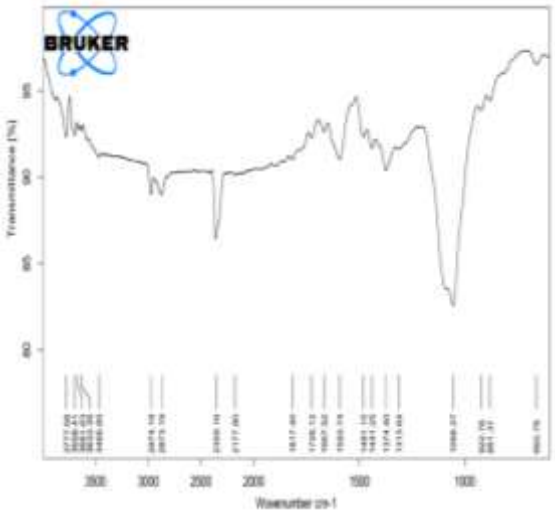

Fig 2: FTIR Spectra of Ethylcellulose.

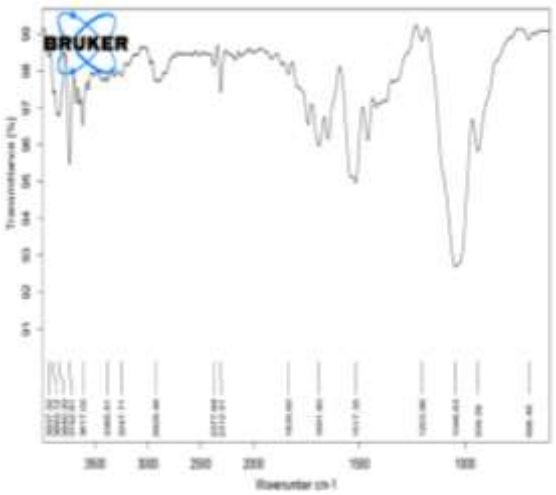

Fig 3: FTIR Spectra of HPMC K 15.

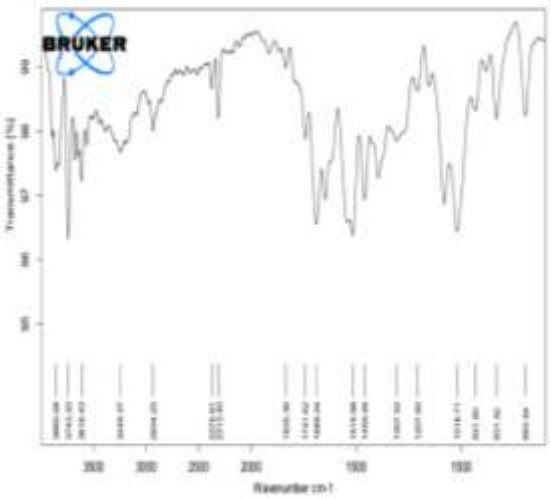

Fig 4: FTIR Spectra of Physical mixture (Drug + HPMC K 15 M + Ethylcellulose + $NaHCO_3$)

Evaluation parameters for floating films

Floating films were evaluated by organoleptic properties, Thickness, weight variation, folding endurance, tensile strength, drug content and *In-vitro* dissolution studies.

Table 2: Evaluation of Esomeprazole magnesium trihydrate loaded floating films.

Formulation code	Thickness (mm) ± S.D.	Weight uniformity (%) ± S.D.	Folding endurance ± S.D.	Tensile strength (M pa)± S.D.	Drug content (%) ± S.D.	Floating Characteristics	
						Floating time (Hrs)±S.D	Lag time (Secs)±S.D.
EF1	0.156±0.36	135±0.65	135±0.25	1.27±0.35	92.36±0.27	6.9	52
EF2	0.239±0.65	150.5±0.42	123±0.61	1.44±0.14	91.76±0.63	7.4	54
EF3	0.315±0.95	180.5±0.51	115±0.35	2.12±0.28	94.54±0.73	7.2	58
EF4	0.164±0.54	131±0.65	141±0.15	1.15±0.37	93.43±0.46	10.9	54
EF5	0.245±0.23	155.6±0.35	125±0.47	1.30±0.29	94.72±0.81	11.5	53
EF6	0.328±0.21	178.5±0.74	110±0.65	2.36±0.64	96.91±0.94	12	57

***In-vitro* dissolution studies**

Table 3: *In-vitro* Dissolution studies for EF1 to EF6.

Time (hrs)	% Drug release $\bar{X}$±SD (%) (n=3)					
	EF1	**EF2**	**EF3**	**EF4**	**EF5**	**EF6**
0	0	0	0	0	0	0
1	12.69±0.032	11.56±0.023	9.62±0.056	10.36±0.071	9.65±0.059	8.45±0.046
2	15.86±0.012	16.98±0.042	15.67±0.027	15.52±0.018	14.85±0.024	14.56±0.078
3	19.85±0.042	21.74±0.036	19.85±0.034	20.91±0.059	19.53±0.056	19.87±0.026
4	23.56±0.052	23.64±0.025	24.72±0.051	29.72±0.052	23.82±0.074	23.96±0.028
5	28.36±0.023	29.21±0.029	29.58±0.019	35.74±0.061	31.59±0.042	29.46±0.065
6	31.45±0.056	34.74±0.035	31.75±0.042	41.53±0.029	39.75±0.074	36.45±0.084
7	43.89±0.015	44.68±0.074	42.45±0.038	50.87±0.087	48.15±0.059	43.68±0.015
8	52.72±0.045	53.73±0.054	51.79±0.035	58.64±0.063	57.65±0.065	49.58±0.073
9	65.98±0.023	67.82±0.037	63.52±0.064	67.45±0.058	68.24±0.034	57.69±0.015
10	74.53±0.089	75.54±0.045	72.81±0.072	75.87±0.017	74.79±0.047	65.75±0.035
11	85.69±0.059	86.84±0.096	83.94±0.059	86.95±0.026	83.89±0.049	81.61±0.056
12	93.75±0.045	91.26±0.081	90.67±0.018	93.45±0.038	92.25±0.075	88.46±0.062

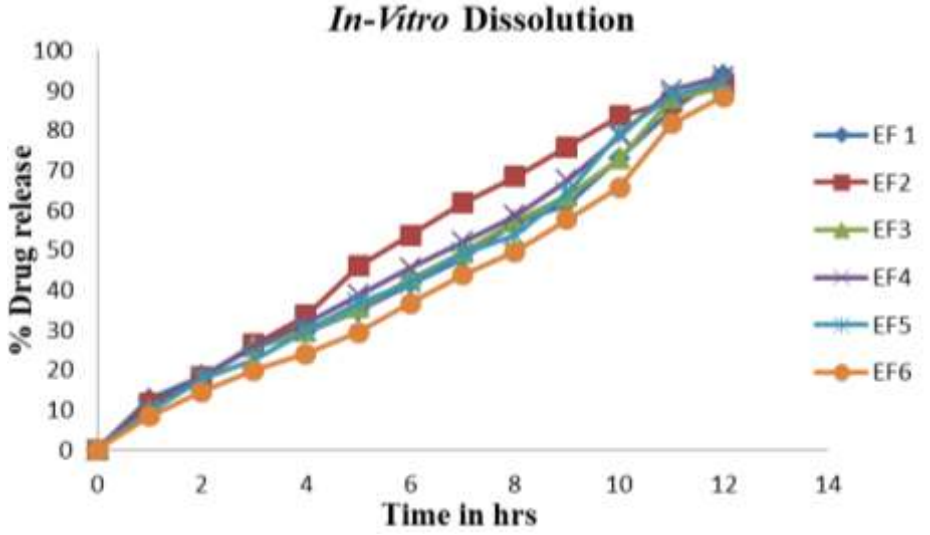

Fig 6: In-vitro Dissolution studies for EF1 to EF6.

Table 4: Regression co-efficient(R2) values and 'n' values of Esomeprazole magnesium trihydrate loaded Floating films Formulation according to different Drug Release kinetics model.

Formulation code	Zero order		First order		Higuchi	Peppas	
	R^2	n	R^2	n	R^2	R^2	n
EF1	0.9694	7.672	0.9604	0.226	0.9793	0.9942	0.7433
EF2	0.9773	7.566	0.8489	0.181	0.8739	0.9832	0.9271
EF3	0.9907	7.358	0.8529	0.177	0.9057	0.9912	0.8911
EF4	0.9938	7.643	0.8479	0.200	0.9129	0.9935	0.8835
EF5	0.9860	7.584	0.8401	0.191	0.8902	0.9867	0.9079
EF6	0.9799	7.034	0.8323	0.152	0.8663	0.9805	0.9412

DISCUSSION

In present study Esomeprazole magnesium trihydrate loaded Floating films were prepared by Solvent casting method varying the Film former concentration, Effervescent Concentration and plasticizer concentration. Prepared films were evaluated for Thickness, weight uniformity, Tensile strength, Drug content, Floating time, Lag time and *in-vitro* dissolution studies.

FTIR

FTIR Spectra of drug, polymers and Physical mixture with drug and polymer were represented in **Fig 2-5. And Table 3** Drug, polymer and its Physical mixture exhibited characteristic absorption peaks in corresponding IR regions. It was observed that difference of peaks between drug and Physical mixture is negligible and is well within the permissible range. So it shows that drug and polymer are compatible with each other.

Evaluation of Esomeprazole magnesium trihydrate loaded floating films

Thickness

Thickness of Six Formulations were varied from 0.156-0.328mm. as increase in Concentration of polymer increase in thickness can be observed so Polymer concentration and thickness are directly proportional to each other. Results depicted in **Table No 6.**

Weight Uniformity

Weight uniformity of Formulations EF1-EF6 were in range of 135-178.5 mg. weight variation provides information regarding uniform distribution of drug and polymer in formulations. Increase in weight of film can be observed when polymer concentration of polymer has been increased Results are depicted in **Table No 6.**

Folding Endurance

The folding endurance of all six formulations was found to be 110-141 times. Highest folding endurance was shown and lowest folding endurance was shown by EF1. As Plasticizer concentration increases there is increase in thickness so more number of folds can be observed in folding endurance. Results are represented in **Table No 6.**

Tensile Strength

The tensile strength of EF1-EF6 formulations was found to be **1.15-2.36 M Pa.** from the obtained results it was observed that increase in concentration of plasticizer shows less tensile strength. Although increase in concentration of Polymer(HPMC K 15 M) Showed higher tensile strength. Results are depicted in **Table No 6.**

Drug Content

Drug content of Six formulations was found to be **91.76-96.91%.** EF6 has shown a highest drug content and EF2 has shown lowest drug content.

Floating time

The floating time of EF1-EF6 Formulations was found to be in range of **6.9-12hrs. as concentration of effervescent agents increases, increase in floating time can be observed.**

Lag time

Lag time of EF1-EF6 Formulations was found to be in range of **52-58 Secs.** It was observed that increasing the ratio of cellulose derivative polymer increases floating lag time.

***In-vitro* dissolution studies**

The *in-vitro* dissolution rate of Esomeprazole magnesium trihydrate was performed to analyse the release rate of different formulation. From results it was observed that increase in concentration of polymer will retard the release of drug from polymeric layer of films significantly. This may be due to fact that increasing polymer concentration the film matrix got thicker and drug took more time to release from matrix of films. Hence Sustained release of drug can be achieved that increases Gastric residence time. Results are depicted in Table 7.

Release kinetics

The results obtained from dissolution studies of different batches was analysed using different mathematical models. EF1-EF6 most of the formulations follows Peppas model with the highest degree of correlation coefficient. R^2 value of EF1, EF2, EF3, EF4, EF5 and

EF6(R^2) 0.9942,0.9832,0.9912,0.9867 and 0.9805 respectively. And 'n' value of EF1, EF2, EF3, EF4, EF5 and EF6 0.7433, 0.9832, 0.9912, 0.9935, 0.9867 and 0.9412 respectively(n). hence all batches of formulation follows Peppas model by fitting to the Non-Fickian mechanism because the values are in between(0.7433-0.9412).

CONCLUSION

Gastro retentive Esomeprazole magnesium trihydrate loaded floating films were successfully prepared by solvent casting method. Varying polymer concentration has shown significant effect on thickness and in-vitro drug release, varying the concentration of plasticizer exhibited effect on tensile strength, varying the concentration of effervescent agent would affected on Floating time as well as lag time.

Formulation EF6 revealed that it has desirable Floatability, Thickness and *in-vitro* release rate which are necessary to sustain a release of drug. due to less availability of Esomeprazole magnesium trihydrate Floating drug delivery system, Hence an attempt was made to enhance its bioavailability.

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