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FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

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ABSTRACT

The current work emphasises the significance of esomeprazole magnesium trihydrate floating polymeric microsphere formulation and assessment. EMT containing microspheres were successfully made using the solvent evaporation process using polymers EC & HPMC and ethanol with dichloromethane in 1:1 ratio as an organic solvent. Drug polymer compatibility was checked using FTIR and a standard curve of EMT was obtained using ethanol as solvent. The prepared formulations were then assessed for various evaluation characteristics. The best prepared formulation F_3 showed % entrapment efficiency 79.98%, percentage yield of 81.7%, buoyancy study 83%, drug content 83.19%. Thereby, it could be concluded that EMT microspheres may be able to reduce the frequency of administration as well as the dose-dependent adverse effects. There was no drug-polymer interaction discovered, and formulations remained stable over time. Thus, floating microspheres of EMT with good buoyancy and sustained release were obtained.

Keywords :- Floating microspheres, ethanol, dichloromethane, preformulation, sustained release.

INTRODUCTION

The recommended method of administration of a dosage form is the oral method where the drug is taken orally. It, generally, is majorly as well as easiest route in case of administration of drug among many other dosage forms[1]. However, substances with an absorption window narrower than others, drug delivered just before and close in reference to absorption window is only accessible in case of absorption. And then, following passage through the absorption window, drug which was released, is thrown out with negligible absorption. This event reduces the period available for medication absorption following it, resulting in lower bioavailability[2]. There have been several attempts to retain the dose form in the stomach in order to lengthen retention time. The most often used of them have been floating dosage formulations. Since, hydrodynamically controlled systems are such made with a bulk density lesser compared to stomach fluids, these systems float in the stomach for an extended duration and do not affect gastric emptying rate. As this system remains buoyant over the surface of contents in stomach, then the drug, slowly, is discharged at required rate. Once drug is released, the stomach's contents are emptied[3]. GERD or Gastroesophageal reflux disease is a chronic upper gastrointestinal disorder and in this, the stomach contents runs up into the oesophagus on a regular basis, causing symptoms and/or difficulties.[4] Proton Pump Inhibitors are suggested to be used to treat such acid reflux diseases. Esomeprazole magnesium Trihydrate was used drug in the current study for producing floating drug loaded microspheres which afloat on the gastric contents and provide a sustained release of drug. Esomeprazole is well tolerated, and 40mg of esomeprazole is more successful in controlling acid than twice the normal omeprazole dose. When compared to an equivalent dosage of omeprazole, plasma concentration studies indicated that the favourable

hepatic metabolism of esomeprazole leads in a higher supply of acid suppressant to the systemic circulation. The floating microspheres were formulated using the method of solvent evaporation. In which, polymer selected is dissolved using the selected organic solvent, which is further emulsified in an aqueous solution. Stable emulsion is formed which is then followed by the evaporation of the organic solvent by stirring, resulting in formation of floating microspheres[5]. By continuous drug release, fluctuation can be avoided in the plasma drug concentration hence bioavailability is increased[6].

MATERIALS & METHODS

The Materials Used

EMT procured from Windlas Biotech Limited, Dehradun. The polymers Ethyl cellulose and HPMC; the organic solvents ethanol and dichloromethane; liquid paraffin an surfactant span 80 were obtained from Central Drug House Pvt. Ltd.

Methods

A. PREFORMULATION STUDIES

1. Organoleptic Properties

This involves documenting the drug's physical attributes, such as its flavour, aroma, and colour. These characteristics are crucial and helpful for appropriate batch specifications[7].

2. Flow Characteristics

- **Bulk Density**: This property is the relationship between the powder mass and the volume of the powder in bulk. This density is calculated, determining the volume of taken quantity of the powder fed through a screen and into a volume measuring device. Bulk density = Mass/Volume in Bulk
  i.e., B= M/V.[8]

- **Tapped Density:** The bulk density apparatus is also used to measure the tapped density. The granules of the powder are placed in the apparatus and then the volume of powder which is the total volume, is noted. The cylinder is then tapped up to a 100 times and again the cylinder volume is measured. Tapped density is the mass of the powder by the total volume of powder after 100 tapping.
  3 readings were recorded and an average was calculated. (n=3)[9]

- **Compressibility index**: The next flow property i.e., compressibility index was calculated by filling a measuring cylinder with powder granules and noting the volume (V0) before tapping. Volume (V) was measured again after 100 taps.
  Compressibility index =[BD-TD /BD] x 100.
  3 readings were recorded and an average reading of compressibility index was calculated.

- **Angle of repose:** This is calculated by the height and radius of powder pile determined as the powder bed was formed by pouring the it into the funnel placed upon a graph sheet. A 4-inch funnel was attached to the stand with a clamp, with the funnel stem set approximately at height of 2-3 cm above the graph sheet below. The funnel then filled with powder and was left to flow freely into the graph sheet. Using a pencil, the area covered by the powder bed was marked by making a circle around it and then the radius and height of heap were measured and recorded using a scale. The radius was measured 3 times as r1,r2 and r3 and an average was noted. (n = 3).
  Tan ø = h /r
  4 readings were recorded and an average was calculated. (n=3)[10]

3. Study of solubility

Esomeprazole magnesium trihydrate solubility in many distinct solvents is determined by taking an excess of the drug and dissolving it in 20ml of distilled water and other various solvents. The solution is then filtered

using filter paper. 1ml filtered solution is taken and is diluted with solvent to equal 100ml.UV spectrometric analysis is used to determine the amount of drug dissolved[11].

4. Determining the melting point

The melting points of the medications were calculated by inserting a little amount of drug in the capillary tube with one of its end closed in Theil's melting point apparatus and recording the melting temperature of the powder. The average of three readings was recorded.

5. Partition Coefficient

The Partition Coefficient of the drug sample is calculated, applying the flask shake method. In a glass stoppered flask, water, or phosphate buffer of a pH 7.4 was added in same amount of n-octane. The drug (10mg) was placed in this flask, and the resulted mixture was then shaken vigorously. Two phases are formed, which are then separated by a separating funnel, and then the amount of drug in the n- octanol phase is calculated by subtracting the conc. in the aqueous from the total amount of drug.

Log P = drug conc.in organic phase/ drug conc.in aqueous phase[12].

6. Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum was used as to identify the test drug and to assess the compatibility between the polymer used and the drug. Individual peaks of only the drug sample were compared to polymer and a physical drug:polymer (1:1) mixture. The potassium bromide (KBr) dispersion method can be used for FTIR analysis. To achieve this, combine floating polymeric microspheres of esomeprazole with KBr and compress with a force (hydrostatic)to form a uniform pellet. Scan the pellet at a resolution of 4cm3 and a scanning range of 400 to 4000 cm^3.[13]

7. Development of standard curve of Esomeprazole

Preparing the stock solution.

100 milligrams of drug is placed in a flask i.e. a100ml volumetric flask. To the 100ml volumetric flask, ethanol was added and with the addition of ethanol, the capacity was increased to 100ml.

Preparation of standard solution

From the above stock solution, 1ml was pipetted and put in small volumetric flask of 10ml and ethanol was then added to make up the volume to 10ml. Pipette out O.4ml, O.8m l, 1.2ml, 1.6ml, and 2.0ml solution from standard stock solution in five 10ml volumetric flasks the volume was made up with ethanol to get 4g/ml, 8g/ml, 12g/ml, 16g/ml, and 20 g/ml concentration. At 301 nm, the absorbance of the above-mentioned standard solution was determined, and a graph plotted with concentration and absorbance on the X and Y axis respectively[14].

B. PREPARATION OF FLOATING MICROSPHERES OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE

Solvent Evaporation Method

The Floating Microspheres of EMT was formulated by using the solvent evaporation method. In this, a mixture of ethanol and dichloromethane in varying ratio were prepared and the required quantity of drug ,Ethyl cellulose and HPMC was weighed and dissolved in the organic solvent at room temperature. The solution was then poured into 100ml of liquid paraffin. 0.1% of the surfactant span 80 was added to it. It was then stirred at 800rpm using a propeller type agitator till whole of the organic solvent is evaporated and microspheres were obtained. The microspheres were then filtered, washed in petroleum ether, and allowed to overnight at room temperature.

Table No.1 Formulation of floating polymeric microsphere of Esomeprazole

Formulation	EMT	ETHYL CELLULOSE	HPMC	DC: ETHANOL	LIQUID PARAFFIN	SPAN 80
F1	100mg	100mg	-	1:1	100ml	0.1%
F2	100mg	200mg	-	1:1	100ml	0.1%
F3	100mg	300mg	-	1:1	100ml	0.1%
F4	100mg	-	100mg	1:1	100ml	0.1%
F5	100mg	-	200mg	1:1	100ml	0.1%
F6	100mg	-	300mg	1:1	100ml	0.1%

C. EVALUATION OF PREPARED FLOATING POLYMERIC MICROSPHERES OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE.

1. Percentage Yield

The microspheres prepared ,dried and the percentage yield calculated : Percentage yield = weight of microspheres formed / weight of drug and polymer (total) X 100.

2. Buoyancy Percentage

Floating microspheres were taken in a solution of 0.1 M HCL and span 80 was added to it. This solution was then further stirred for 5-6 hours. some of the microspheres were floating and some of them were settled down. The floating microspheres were then collected and taken out separately. The particles which settled down were separated and collected by filtration process. Particles were then dried to calculate the buoyancy percentage buy the given formula,

Buoyancy percentage = WF / WF +WS X 100

3. Drug content

Microspheres of Esomeprazole Magnesium Trihydrate were precisely weighed and crushed. The powdered microspheres were put in a volumetric flask of 100ml, which was filled with pH 6.8 phosphate buffer and stored for 24 hours. The solution was then filtered using No. 44 Whatman filter paper. The solution was diluted with new solvent, and absorbance at 210 nm was measured with a UV spectrophotometer and the percent drug content was calculated.

4. Drug entrapment efficiency

The prepared esomeprazole floating microspheres Entrapment efficiency was investigated. Prepared formulation was taken in same quantity of 7.2 phosphate buffer. The suspension was then ultracentrifuged at 17000rpm for 40 minutes. The free concentration of the drug in the supernatant was determined using spectrophotometry. Entrapment efficiency is calculated by the following equation,
% Entrapment efficiency= W-w/w X 100.

5. In vitro release of drug studies

The USP type II dissolving paddle assembly was used to measure the medication release rate from floating microspheres. In 900 ml of 0.1 N HCI (pH 1.2), floating microspheres corresponding to 100 mg medication was disseminated maintained at 37°C and rotated at 100 rpm. After each withdrawal, a 5 ml sample was removed and filtered, and an equivalent amount of dissolving media was put in the vessel to provide constant sink state. The obtained samples were diluted with 0.1 N HCI and spectrophotometrically measured at 276 nm to estimate the drug content in the dissolving media.

RESULTS AND DISCUSSION

1. Preformulation study conducted on Esomeprazole Magnesium Trihydrate powder.

1.1 Organoleptic properties

The organoleptic Properties of drug sample were observed as shown in table 2. It was observed that the organoleptic properties of the drug compliance with standards. This can be used as preliminary identification tool for drug.

Table No.2 Organoleptic Properties of Drug

S.No.	Organoleptic Properties	Standard	Observation
1.	Appearance	Crystalline powder	Crystalline powder
2.	Odour	Odourless	Odourless
3.	Colour	White	White

1.2 Flow Properties

The Bulk density was found, **0.187 gm/ml.**

The tapped density was found, **0.214 gm/ml.**

The compressibility index was found to be **12.6%** which indicates an excellent flow.

Hausnier's ratio was found to be **1.144** which suggests good flowing property.

Angle of repose was **29.79**^{o} i.e. the powder has an excellent flow.

1.3 Solubility Studies

It was observed that the drug was found to be freely soluble in Phosphate buffer solution with a pH of 7.4, methanol, ethanol, water.

The order of solubility was :

Table No. 3 Solubility Analysis

S.No.	Solvent	Extent of Solubility
1.	Phosphate buffer pH 7.4	0.551 mg/ml
2.	Methanol	1.213 mg/ml
3.	Water	0.016 mg/ml

1.4 Melting Point

Melting point observed of the powder substance discovered within a range that indicates its purity. The melting point was found to be 178^{0}C.

1.5 Partition Coefficient

PC of the drug was calculated using flask shaking method and the observed value was found to be 2.39 which was within the standard range. The observed value of the test drug shows that is lipophilic in nature.

1.6 Identification of drug by means of FT-IR

The acquired FT-IR of the medication (Fig 1) demonstrates the identification of distinct functional groups that were compared with the reference spectra, and no significant difference was seen, confirming the purity of the powder of Esomeprazole Magnesium Trihydrate.

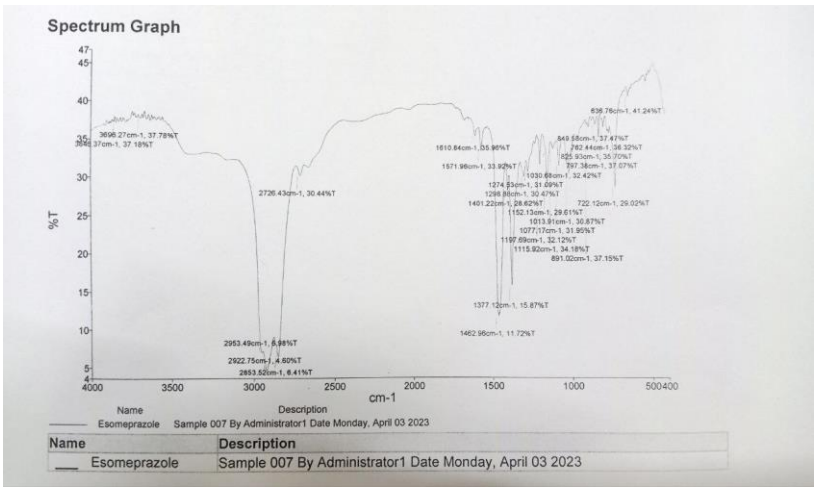


Fig.1

1.7 . Estimation of Esomeprazole as API by U.V. Spectroscopy

Drug exhibited absorbance maxima at 301nm as shown in fig 2.

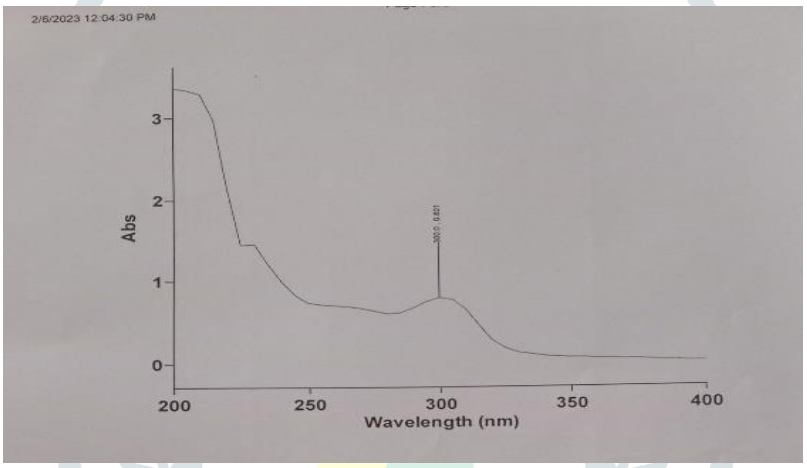


Fig 2.

Standard curve of Esomeprazole at 301nm

The standard curve of drug was prepared in ethanol. The Beer's Lambert law was in the concentration range 5-20 µg/ml at 301nm as shown in table 7.4.A straight line indicates compliance with Beer's law within the working range.

Table No.4 Standard curve of Esomeprazole at 301nm

S. No.	Concentration(µ/ml)	Absorbance(nm)
1.	0.4	0.2397
2.	0.8	0.4709
3.	1.2	0.7078
4.	1.6	0.9508
5.	2.0	1.1799

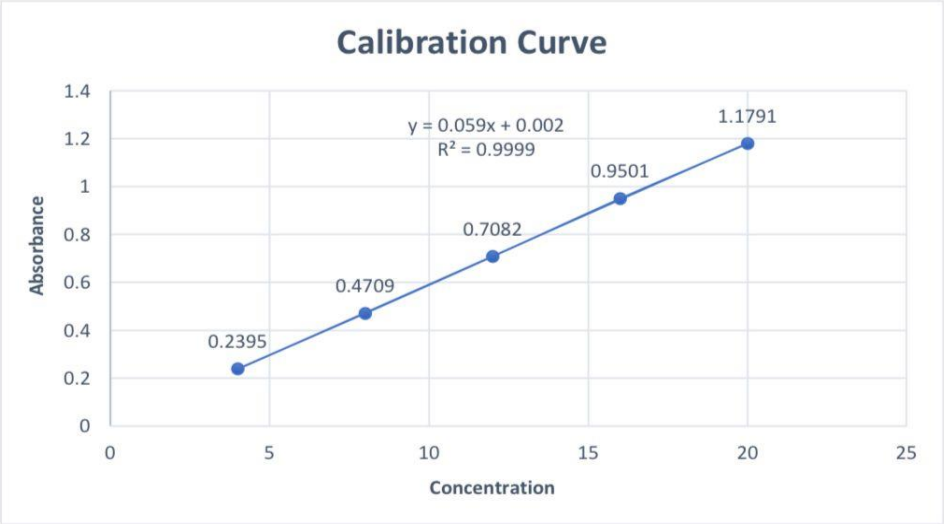


Fig 3.

2. Characterisation of floating microspheres

2.1 Percentage Yield

The yield of the formulations were calculated; the highest percentage yield was determined in the F_6 i.e. the 6^{th} formulation.

Table No. 5 Percentage yield (%)

S.No.	Formulation Code	% Yield
1.	F_1	77.2%
2.	F_2	82%
3.	F_3	81.7%
4.	F_4	76%
5.	F_5	79%
6.	F_6	82.9%

2.2 Buoyancy Percentage

It was found that as the polymer quantity increases, the buoyancy time was also increased. The formed microspheres were floating on the dissolution surface medium for a long time of time.

Table No.6 Buoyancy percentage

S.No.	Formulation Code	Buoyancy percentage
1.	F_1	69%
2.	F_2	77%
3.	F_3	83%
4.	F_4	74%
5.	F_5	79%
6.	F_6	81%

2.3 Drug Entrapment Efficiency

All formulations' % entrapment efficiency was assessed; it was between 71.2 – 79.11%.A rise in entrapment efficiency was seen when polymer concentration rose because more drug particles were coated, resulting in better encapsulation efficiency as can be seen from Table no. 7.

Table No.7 Drug Entrapment Efficiency

S.No.	Formulation Code	Entrapment efficiency
1.	F_1	73.77 %
2.	F_2	79.45%
3.	F_3	79.98%
4.	F_4	66%
5.	F_5	72.46%
6.	F_6	77.8%

2.4 Drug Content

Table No. 8 Drug Content

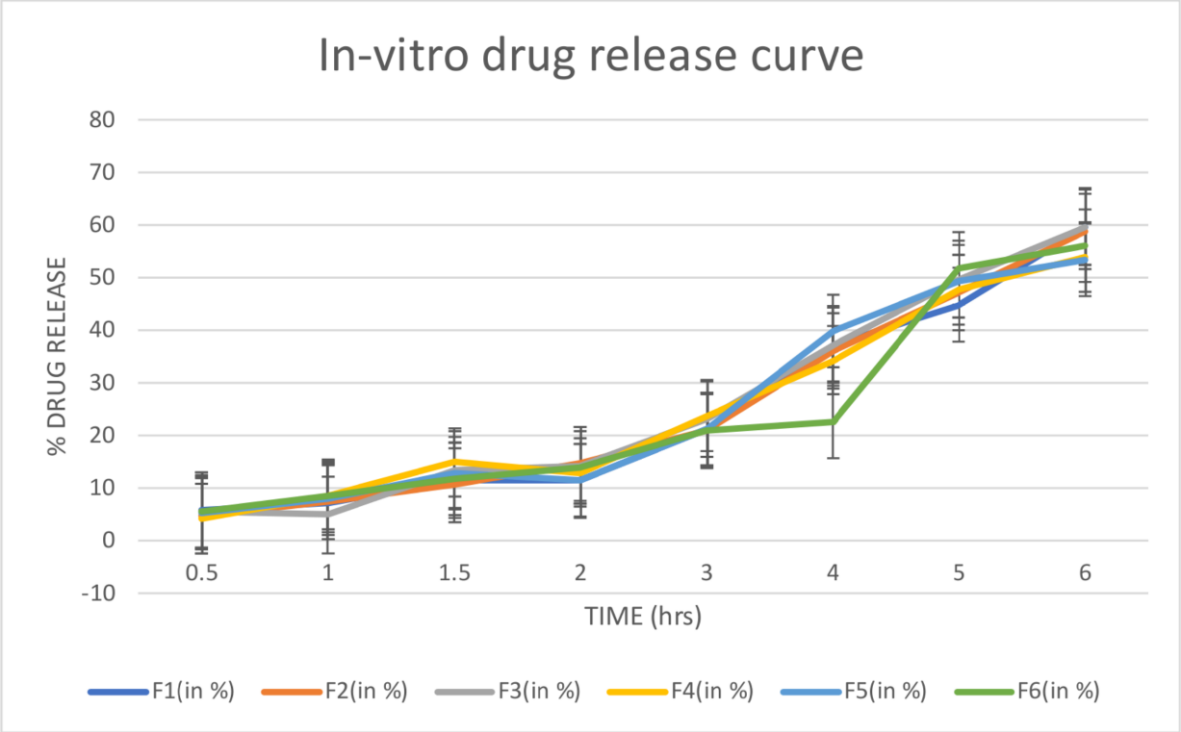
S.No.	Formulation Code	Drug Content
1.	F_1	72.53
2.	F_2	79.28
3.	F_3	83.19
4.	F_4	68.62
5.	F_5	76.765
6.	F_6	79.9

2.5 In vitro Drug Studies

Best prepared F_3 exhibited 59.81 drug release at 07 hours. The microspheres were able to sustain release due to high polymer content.

Table No 9 In vitro drug release

S.No.	Time (in hrs)	F_1(in %)	F_2(in %)	F_3(in %)	F_4(in %)	F_5(in %)	F_6(in %)
1.	0.5	2.45	2.6	2.41	1.22	1.89	2.98
2.	1	5.81	4.72	5.6	4.2	5.33	5.6
3.	1.5	7.21	7.43	4.90	8.61	7.94	8.59
4.	2	11.47	10.54	13.42	14.89	12.84	11.75
5.	3	11.38	14.62	14.22	12.97	11.39	13.96
6.	4	21.11	20.93	23.15	23.65	21.33	21.08
7.	5	37.27	36.09	37.30	34.36	39.98	22.57
8.	6	44.85	47.20	49.79	47.78	49.34	51.93
9.	7	59.68	58.91	59.81	54	53.52	56.06



CONCLUSION

Finally, the current work emphasises the significance of esomeprazole magnesium trihydrate floating polymeric microsphere formulation and assessment. EMT containing microspheres were successfully made using the solvent evaporation process. The best prepared formulation F_3 showed % entrapment efficiency 79.98%, percentage yield of 81.7% , buoyancy study 83%, drug content 83.19%.Thereby, it could be concluded that EMT microspheres may be able to reduce the frequency of administration as well as the dose-dependent adverse effects.. There was no drug-polymer interaction discovered, and formulations remained stable over time. Thus, floating microspheres of EMT with good buoyancy and sustained release were obtained.

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