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Formulation and evaluation of delayed release tablet of Esomeprazole Magnesium

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ABSTRACT

The objective of the current investigation was to formulate delayed release tablets of esomeprazole that could control the release of the drug thereby reducing its dosing frequency and improving the bioavailability. The objective was accomplished by preparation of the matrix tablets using HPMC, carbopol 934 and Eudragit RLPO as the matrix forming polymers. The angle of repose for all formulations was found to be within the range from 25°16 to 27°22. This indicates that good flow property of powder blend. The bulk density and tapped density values were found to be within the range from 0.48 to 0.57 and 0.54 to 0.66 respectively. The Hausner's ratio values were found to be within the range from 1.10 to 1.21. Swelling study was performed on all the formulation for 9 h and was found to be in the range of 1.29 to 5.06. Results lead to conclusion that the formulation F6 and F8 were the best formulation that exhibited the desired sustained release, tablet qualities as well as the swelling properties that are desired by a matrix tablet.

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Introduction

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals (Vyas and Khar, 2002). The most preferred route of drug administration for systemic delivery of drugs is orally. More than 50% of drug delivery systems available in the market are oral drug delivery systems. Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. It is helpful in prolonged delivery of a therapeutic dose, thus reducing the number of times that a patient needs to take their medication while maintaining a steady state of drug in the bloodstream, and time-delayed release introduces a lag time before dose release, providing pulsatile delivery of drug to specific sites, such as the colon, or at a specific time (Borguist et al, 2006). Matrix tablet excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form (Jantzen and Robinson, 1995). Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of the H+ / K+ ATPase in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid. It is used in the treatment of dyspepsia and peptic ulcer disease. Approximately 80% of the administered dose of esomeprazole is excreted as metabolites in urine and the remaining 20% is excreted in feces. It has a short half life of 1 to 1.5 hours (drugbank, 2021). Since Esomeprazole is a potent drug used in the treatment of Peptic ulcer and has a short half life its dosing intervals generally varies based on the intensity of the ulcers. Hence to decrease the number of dosing intervals and to sustain the drug Esomeprazole sustain release dosage forms are being designed. The main objective of the work is to develop a simple, cost effective oral sustained release dosage form of Esomeprazole using natural polymers, which shows good stability and sustainability of the drug thus decreasing the number of dosing intervals and increasing the patient compliance.

Material and Methods

Esomeprazole was obtained as a generous gift sample from Edmund Healthcare Pvt. Ltd., India. All reagent and chemical were procured from chemical supplier and were of analytical grade.

Preformulation Studies (Martin 2006)

Organoleptic properties

A small quantity of pure esomeprazole powder was taken in a butter paper and viewed in well illuminated place to observe its color; the taste and odor were observed using tasting and smelling the drug.

Solubility analysis

Solubility of esomeprazole was determined in water, methanol, ethanol, 0.1N hydrochloric acid. Solubility studies were performed by shaking small amount of esomeprazole in test tubes containing the solvent and observing for undissolved particles (if any).

Melting point

The melting point of esomeprazole was determined by open capillary method. The pure drug was filled in a capillary tube sealed at one end and placed in the melting point apparatus to observe the temperature at which melting occurs.

Loss on drying

It was determined by drying the pure drug in an oven at 100°C to 105°C for 3 h. The percent loss of moisture was calculated by the difference between the initial and final weight of the drug.

Formulation of esomeprazole delayed release tablets

A 2^3 factorial approach was used for preparing eight formulations in various combinations of the matrix forming polymers. Each polymer (independent variable) was used as two levels, high and low or presence and absence (table 1).

The formulation of the matrix tablets was performed using direct compression method by employing HPMC, carbopol 934 and Eudragit RL/PO as the matrix forming polymers (Table 2). Magnesium stearate was used as the lubricant in 2.5% concentration of total weight of the polymers and esomperazole (Niaz et al, 2018).

The quantity of the drug, matrix forming polymers and all other excipients was accurately weighed and passed through sieve no. 22. The ingredients were mixed together manually using tumbling action in large poly bags. The powder blend was again passed through sieve no. 22 and mixed with magnesium stearate. The blend was evaluated for precompression parameters and compressed into 5 mm tablets using single punch tablet punching machine.

Evaluation of precompression blends (Nagaich et al, 2014)

Angle of repose, Carr's Index, Bulk density, Tapped density and Hausner's ration were determined to assess the flow ability of the prepared granules.

Evaluation of delayed release tablets (Roy et al, 2013)

Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula

Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tab-

lets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 10 mg of drug was dissolved in 0.1M HCl and volume was made up to 100 ml using 0.1M HCl. 10ml of the filtrate was made up to 100ml with 0.1M HCL. 10µg/ml solution was prepared from the above solution and analyzed for drug content.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated matrix tablets. The dissolution media used consisted of 900 mL of phosphate buffer pH 6.8 and distilled water. 5 mL of samples were collected at time points of every hour until 12 h and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 295 nm.

Swelling Index

One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed (Radhika et al, 2009). The weighing was continued for every 2 hr, till the end of 9 h. The % weight gain by the tablet was calculated by formula

Where, S.I = swelling index, M_t = weight of tablet at the time (t) and M_0 = weight of tablet at time 0.

$$S.I = \frac{Mt - Mo}{Mo} * 100$$

Results and Discussion

Preformulation study

The organoleptic properties were observed using the sense organs. Esomperazole was found to be bitter, odorless, white powder with a melting point of 157-159°C. It was soluble in water and 0.1N HCl, slightly soluble in ethanol, methanol and had a LOD of 0.21%.

Precompression characterization of the blend

The delayed release tablets were prepared using HPMC, Eudragit RL/PO and carbopol 934 as the release retarding matrix polymers. Angle of repose for all formulations was examined and the values were found to be within the range from 25°16 to 27°22. This indicates that good flow property of powder blend. The bulk density and tapped density values were found to be within the range from 0.48 to 0.57 and 0.54 to 0.66 respectively. The Hausner's ratio values were found to be within the range from 1.10 to 1.21. All these parameters indicate that the powder blend had good flow property and is suitable for compression in to tablets. The compressibility index for formulations exhibited good compaction characteristics of the blends.

Evaluation of matrix tablets

The thickness of all formulation was ranged in between 4.8 to 4.9 mm. Hardness of tablet of all formulation ranged from 4.1 kg/cm^2 and 4.4 kg/cm^2. The hardness of all formulation showed variation because of formulation combination and powder properties. The friability of all formulation was in the range of 0.42% to 0.62%. All formulation exhibited less than 1% friability and hence passed the test for friability. The weight variation of all formulation was in the range of 1.8 to 3.1 %.

Swelling study was performed on all the formulation for 9 h. The results of swelling index were shown in table. All formulation was in the range of 1.29 to 5.06. The highest degree of swelling was achieved by F8 that contained equal amounts of all the three polymers (Table 3).

The dissolution study was done in pH 6.8 phosphate buffer medium to check the release control profile of the matrix. It was observed that of all the formulations F1, F2, F3 and F4 could not control the release for even up to 6 h. On the other hand, the formulation F5 and F7 were able to release almost 100% of the drug at the end of 9 h duration whereas formulations F6 & F8 were able to sustain the drug release upto 11 and 21 h respectively (Figure 1 and 2).

Conclusion

The results obtained from the study indicate that use of HPMC, carbopol 934 and Eudragit RLPO in equal ratio as the matrix forming substance could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments. Further *in vivo* release studies are needed to support for the conclusion of the present investigation.

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Table 1 Design of formulations

Factor	Level	
	High (+)	Low (-)
HPMC	10 %	3.33 %
Carbopol 934	10 %	3.33 %
Eudragit RL/PO	10 %	3.33 %

Table 2 Composition of matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Esomperazole	40	40	40	40	40	40	40	40
HPMC	-	40	-	20	-	20	-	13.33
Carbopol 934	-	-	40	20	-	-	20	13.33
Eudrgit RL/PO	-	-	-	-	40	20	20	13.33
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table 3 Quality parameters of delayed release tablets of esomeprazole

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (%)	Friability (%)	Swelling Index	Drug content (%)
F1	4.9	4.4	2.3	0.53	1.29	98.7
F2	4.8	4.1	1.8	0.42	2.16	98.1
F3	4.9	4.3	2.2	0.52	2.31	98.6
F4	4.9	4.3	1.9	0.48	3.18	99.1
F5	4.8	4.4	2.1	0.52	3.22	98.9
F6	4.9	4.2	3.1	0.58	3.46	98.7
F7	4.9	4.3	2.9	0.54	4.44	99.1
F8	4.8	4.4	2.6	0.62	5.03	99.1

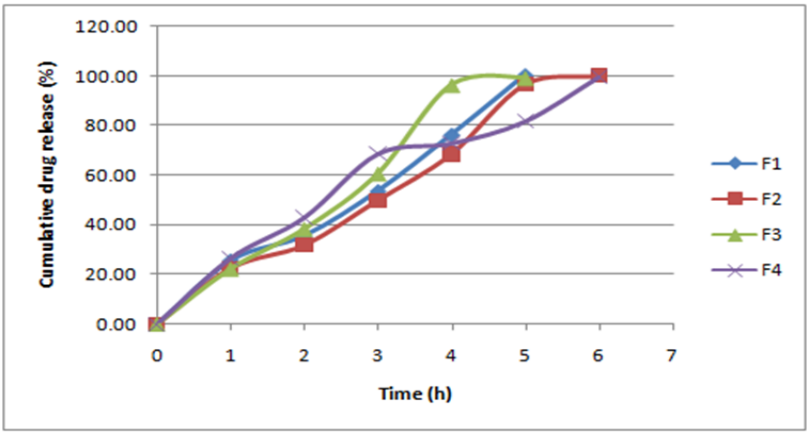

Figure 1 Release of esomeprazole from F1-F4

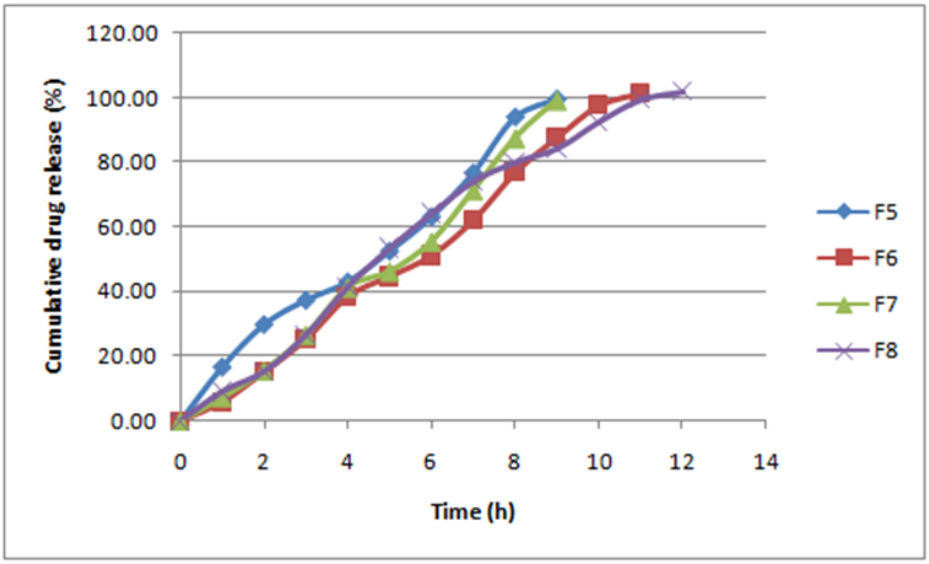

Figure 2 Release of esomeprazole from F5-F8

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