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DESIGN & DEVELOPMENT OF GASTRORETENTIVE SUPERPOROUS HYDROGEL TABLETS OF ESOMEPRAZOLE

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ABSTRACT

Super porous hydrogel were designed to retain drug in gastric medium. These systems swell very rapidly in stomach & maintain their integrity for longer period even in acidic environment of stomach while releasing pharmaceutical ingredient. The present work focused on the concept to formulate super porous hydrogel tablets of esomeprazole using effervescent approach for gastro retentive drug delivery system to improve its bioavailability. The rate retarding polymers like chitosan, xanthum gum & tamarind gum along with other suitable excipients were used by direct compression method. The prepared tablets were evaluated for apparent density porosity, swelling studies, scanning electron microscopy, *in vitro* drug release, FTIR studies & stability studies. The results revealed that the selected formulation (**F6** containing xanthum gum) successfully showed expected criteria for gastro retentive drug delivery system based on super porous hydrogel is promising for stomach specific delivery of esomeprazole.

KEYWORDS: Gastro retentive, Super porous hydrogel, Swelling studies & Stability studies.

INTRODUCTION

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performance.[1] Despite tremendous advantages in drug delivery, the oral route remains the most preferred route for the administration of therapeutic agents because of the low cost of therapy and ease of administration leads to high-level of patient compliance. On the other hand, this high-throughput screening process has done little to address the issue of poor bioavailability of orally administered drug candidates. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the

active substance can be released over a defined period of time at a predetermined and controlled rate.[2-4] Oral drug delivery system (oral DDS) has been known for decades as the most widely utilized route for drug administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. More than 50% of drug delivery systems available in the market are oral DDS.

Esomeprazole is a proton pump inhibitor with a bioavailability of 50- 90%. Its metabolism is mainly by liver and excretion by renal and fecal. It acts by irreversibly blocking the (H+K+) ATPase enzyme system of the gastric parietal cell. Its half-life is 1-1.5 hrs with poor absorption may be because of degradation and poor solubility. The solubility and absorption can be improved with an increase in the gastric residence time and also by creating basic pH with incorporation of carbon dioxide. The present work was aimed to formulate Superporous Hydrogel tablets of Esomeprazole using an effervescent approach for gastro retentive drug delivery system to improve its bioavailability.[5] by using different rate retarding polymers like chitosan, xanthan gum and Tamarind gum, along with suitable excipients. All the formulations were prepared by direct compression method.

MATERIALS AND METHODS

Esomeprazole gift sample from Cadila Pharmacuticals, Chitosan, Xantham gum, Tamarind gum, microcrystalline cellulose were purchased from BMR Chemicals, Hyderabad.

METHODOLOGY

Preparation of drug loaded SPHs

Hydrocolloid polymer solution (2%w/v) was prepared by stirring in 0.1M glacial acetic acid solution using a homogenizer until the chitosan dissolves in acid completely. A 10% w/w aqueous PVA solution was prepared and mixed to the polymer solution. To this solution, 0.2 ml of formaldehyde solution (10% w/w of the dry weight of chitosan) was mixed thoroughly followed by 50 mg of sodium bicarbonate. The prepared mixture was stirred well and kept aside overnight. 10 ml of 0.1 N HCl was taken. To this 20 mg of drug and 100 mg of superporous hydrogel were added and mixed for 1 h at 50°C. Then acetone of 2ml was added and the hydrogel was repeatedly washed with distilled water to remove any unreacted material. Further it was dried at 40°C for 24h, finally powdered and stored in a well closed container. The super porous hydrogel formulations other than chitosan were prepared by using distilled water. Different formulations are shown in table 1.

Table 1: Formulations of super porous hydrogel tablets of esomeprazole Prepared by Direct compression method.

Ingredients(mgs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Esomeprazole	20	20	20	20	20	20	20	20	20
Formaldehyde(ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
PVA (%)	10	10	10	10	10	10	10	10	10
Chitosan (%)	2	3	4	-	-	-	-	-	-
Xanthan gum (%)	-	-	-	2	3	4	-	-	-
Tamarind gum (%)	-	-	-	-	-	-	2	3	4
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg.stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Tablet weight	150	150	150	150	150	150	150	150	150

Evaluation of tablet (Pre & Post compression parameters)

Tablets are evaluated for its parameters like various quality control tests such as tablet thickness and diameter, hardness, friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for GRDDS like swelling studies & release rate of drug.[6-9]

Tablet thickness and diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers. The tablet thickness should be controlled within a ± 5% variation of a standard value. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. It is expressed in millimeters (mm).

Weight variation

Twenty tablets were selected randomly from each batch were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

Hardness

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. The hardness of the tablets was determined using pfizer hardness tester (cisco). Six tablets were picked randomly from each formulation for measurement. It is expressed in Kg/cm^2. The force required to break the tablet is measured in kilograms/cm^2 and

a crushing strength of 4 kg/cm^2 is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg/cm^2; However, hypodermic and chewable tablets are usually much softer (3 kg/cm^2) and some sustained release tablets are much harder (10 -20 kg/cm^2).

Friability

The friability test was carried out to evaluate tablet surfaces and/or show evidence of lamination or capping when subjected to mechanical shock or attrition. The friability of tablets was determined by using roche friabilator (Lab India, FT 1020) and expressed in %. Twenty tablets dedusted tablets were initially weighed [$W_{(initial)}$] and transferred to friabilator and are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were weighed again [$W_{(final)}$]. The friability (f) was calculated by the formula,

$$f = \left[\frac{W_{(initial)} - W_{(final)}}{W_{(initial)}} \right] X\ 100$$

Values from 0.8-1.0% are regarded as the upper limit of acceptability.

***In-vitro* Drug release studies**

In-vitro drug release of the samples was carried out using USP– type II dissolution apparatus (paddle type). The dissolution medium, 900 ml 0.1N HCl solution, was placed into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5^{o}C using 50 rpm. One Esomeprazole tablet was placed in each paddle of dissolution apparatus. The apparatus was allowed to run for 12hours. Samples measuring 5 ml were withdrawn at regular intervals upto 12 hours using 5 ml syringe. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity (5ml) of dissolution medium. Collected samples were suitably diluted with 0.1N HCl and analyzed at 222 nm using 0.1N HCl as blank by using a double beam UV spectrophotometer (T60 UV-VISIBLE spectrophotometer).

Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding

the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

Scanning electron microscopy

The dried superporous hydrogels were used for scanning electron microscopy (SEM) studies to determine the morphology of the dried samples. A JEOL JSM-840 scanning electron microscope (Jeol USA, Inc., Peabody, MA) was used after coating the samples with gold using a Hummer Sputter Coater (Technics, Ltd.). Images were captured using a digital capture card and Digital Scan Generator 1 (JEOL).

RESULTS AND DISCUSSION

Evaluation of dry mixed powder blend for pre-compressional parameters

Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density and tapped density of powder blend was found (Table 2) to be between 0.532 ± 0.03 to 0.559 ± 0.02g/cm^3 and 0.399 ± 0.03 to 0.471 ± 0.03 g/cm^3. This indicates good packing capacity of powder blend. Carr's index evaluated interparticulate cohesive properties with angle of repose measurements and studied the effects of packing geometry of solids with bulk and tapped density.

This ratio, percent compressibility, was used as an index of flow. Adhesive/cohesive forces of particles are related to flow behaviour. Values of Carr's index below 15% usually show good flow characteristics, but readings above 25% indicate poor flow ability. Carr's index was found to be between 13.05 ± 1.21 to 14.93 ± 0.78. Hausner's ratio is simple method to evaluate stability of powder column and to estimate flow properties. Hausner's ratio was found 1.11 ± 0.11 to 1.18 ± 0.21.

Table 2: Flow properties of tablet blend.

Formulation code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	32.58±0.512	0.533±0.03	0.407 ±0.013	14.18±0.19	1.16±0.11
F2	30.36±0.731	0.537±0.01	0.418 ±0.017	14.13±0.41	1.16±0.45
F3	34.21±0.629	0.541±0.03	0.454 ±0.021	14.11 ±0.32	1.17 ±0.19
F4	32.46±0.321	0.532±0.03	0.399 ±0.073	15.03±0.84	1.18±0.02
F5	33.67±0.631	0.539±0.08	0.407 ±0.066	14.05±0.71	1.16 ±0.07
F6	3122±1.731	0.559±0.02	0.471±0.033	13.50 ±1.21	1.16 ±0.12
F7	31.06±0.622	0.554±0.08	0.399 ±0.091	14.93 ±0.78	1.17±0.03
F8	32.58±0.55	0.538±0.02	0.422 ±0.038	13.05 ±1.21	1.16±0.12
F9	33.36±0.621	0.554±0.08	0.443 ±0.031	14.28 ±0.23	1.18±0.02

Evaluation of Prepared tablets post compressional parameters

The tablets prepared of all formulations were evaluated for quality control parameters, Weight variation, Hardness, Friability, Drug content uniformity, and thickness. All formulations had weight variation in the range of 93.3 ± 1.2 to 98.7 ± 3.2 and thickness was within 4.4mm. The hardness of tablets varied from 4.9-6.5 kg/cm^2. The friability of tablets is also depends on type of filler and moisture contents in it. The friability was in range of 0.201±0.04 to 0.703± 0.35 and finally friability was less than 0.8% Drug content uniformity of all tablets was in the range of 98.84±0.69-99.9±0.5 indicating good content uniformity in the all formulations. The reading complies as per I P. That indicates drug was uniformly distributed throughout the tablet shown in Table 3.

Table 3: Evaluation of Prepared Esomeprazole Superporous Hydrogel Tablets.

Formulation Code	Weight variation (%)	Drug content (%)	Thickness (mm)	Hardness (Kg/cm^2)	Friability %
F1	96.5±2.5	88.95±0.88	4.2 ± 0.02	5.8 ±0.13	0.501±0.04
F2	94.5±1.2	90.1±0.83	3.9 ± 0.02	5.9±0.19	0.502±1.15
F3	98.7±2.7	96.73±0.87	3.8 ± 0.07	6.2±0.21	0.201±0.04
F4	93.4±2.5	92.8±0.64	3.9 ± 0.05	5.7 ±0.11	0.571±0.08
F5	97.3±3.2	97.4±0.58	4.3 ± 0.03	5.0 ±0.63	0.520±0.06
F6	98.4±3.5	99.24±0.8	3.9 ± 0.07	4.9±0.30	0.460±0.06
F7	96.2±3.2	94.8±0.42	4.2 ± 0.05	5.9 ±0.16	0.501±0.04
F8	98.4±3.5	98.9±0.58	4.4 ± 0.24	6.2±0.26	0.602±0.03
F9	97.3±3.2	99.62±0.69	3.9± 0.05	6.5±0.18	0.703± 0.35

Dissolution studies

From the *in vitro* drug release studies it was observed that the formulations of gastroretentive superporus hydrogel tablets of esomeprazole formulated by using chitosan (2%, 3%, and 4%)

shows maximum drug release at the end of 10hours (Fig 1). So the further trails were carried by using xanthan gum using same concentrations as in case of chitosan. It shows maximum % drug release at the end of 12hours with 4% of xanthan gum. Then to identify the best polymer for the formulation of superporus hydrogel tablets of esomeprazole another natural gum was used (tamarind gum) and it shows 81.62% of drug release at the end of 12hours. By observing the all 9 formulations it was concluded that the maximum drug release was found in the F6 formulation containing xanthan gum with 4% concentration. So the drug release kinetics were evaluated for the F6 formulation.

The prepared tablets of all the formulations were evaluated for physical characters, assay, *in-vitro* drug release, swelling index, hardness and friability. The main aim was to optimize the formulation for 1-12 hours *in-vitro* release. Optimized formulation F6 containing 4% of xanthan gum was consider as the best product with respect to *in vitro* drug release for 12 hours release action and improved site- specific action[10-12] The results showed that the drug release rate was decreased as the viscosity of the polymer was increased. The drug release kinetics was performed for the optimized formulation and it shows zero order with super case transport drug release.

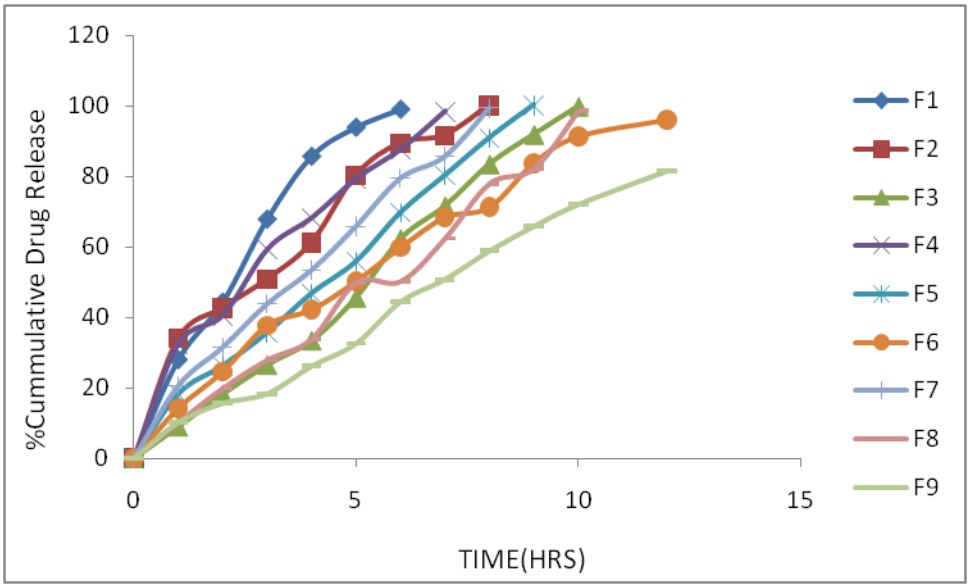

***Fig. 1: In vitro* drug release profiles of F1-F9.**

The *In vitro* dissolution data for best formulation F6 were fitted in different kinetic models i.e, zero order, first order, higuchi and korsemeyer-peppas equation (Fig 2). Optimized formulation F6 shows R^2 value 0.978. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the

higuchi and peppas plot, if n = 0.45 it is called Case I or fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-fickian transport, n = 1.27 for case II transport and n > 0.89 for Super case II transport.[13-14] The 'n' value is 0.826 for the optimised formulation (F6) i.e., n value was > 0.89 this indicates Super case transport. The release kinetics for the optimized formula are shown in table 4.

Fig. 2: Zero order plot for the optimized formulation.

Table 4: Correlation coefficient values of selected formulation by kinetic plots.

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer – Peppas**	**Korsmeyer-Peppas (n)**
F6	0.978	0.906	0.963	0.734	1.27

Scanning electron microscopy

The SEM images of SPH possessed large numbers of interconnected pores, indicating that formation hydrogel with the superporous structure. In the structure of SPH the inner surface contained large numbers of the pores connected to each other. It can be observed in the SEM image which shows structures with a great penetration of the medium into the system with pores that form connections (channels) with the interior of the structure.[15] The capillary channels were clearly observed from SEM image and this may enable water to enter into the hydrogel networks or drug molecules to diffuse out of them. The scanning electron microscopic photograph of superporous hydrogel shown in Figure 3, clearly shows the

presence of pores on the surface. The superporous hydrogel has high porosity and is responsible for faster swelling of superporous hydrogels. The mechanical strength was significantly increased.

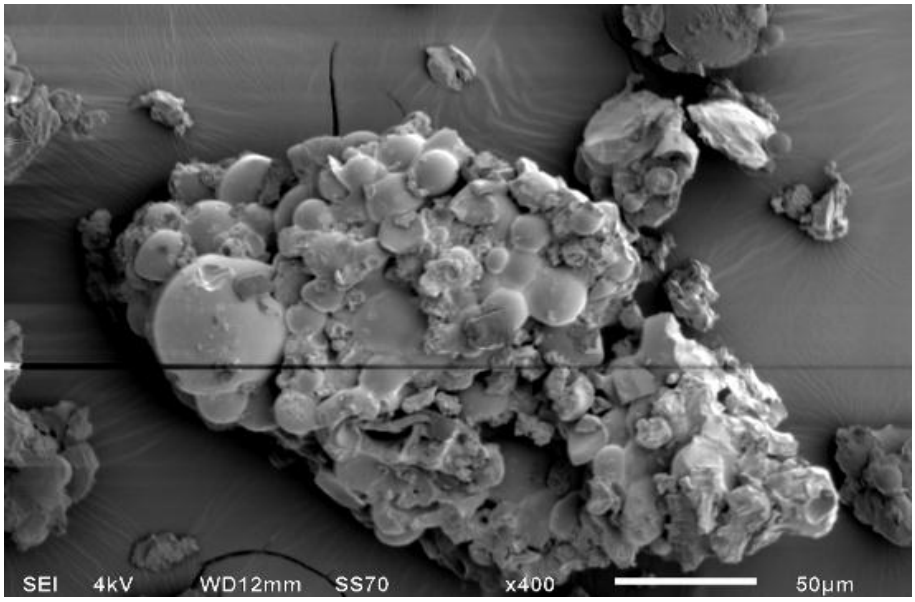

Fig. 3: Scanning electron microscopic photograph of F6 recorded at 400X magnification with scale bar of 50µm showing porous surface.

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FTIR analysis of pure drug with that of various excipients used in the formulation. The spectral peaks in Fig 4a & 4b indicates that there is no incompatibility between pure drug and optimized formulation, indicating suitability of drug and selected ratios and ingredients without effecting the stability.

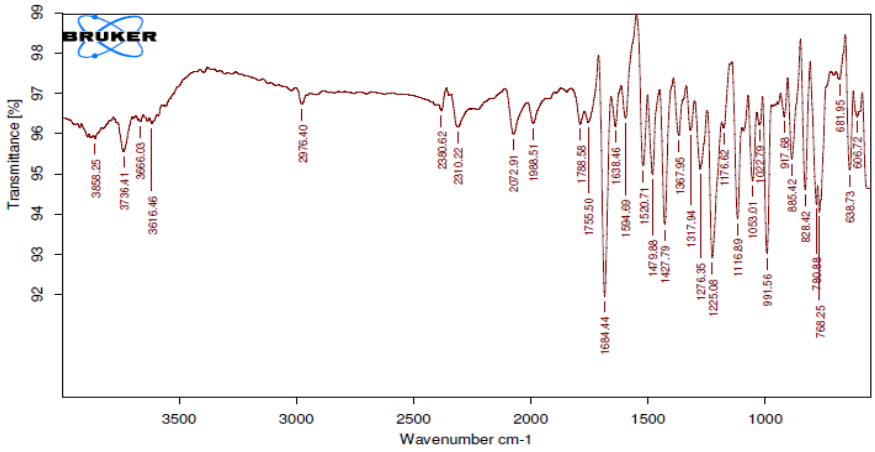

Fig. 4a: FT-IR spectra of pure drug.

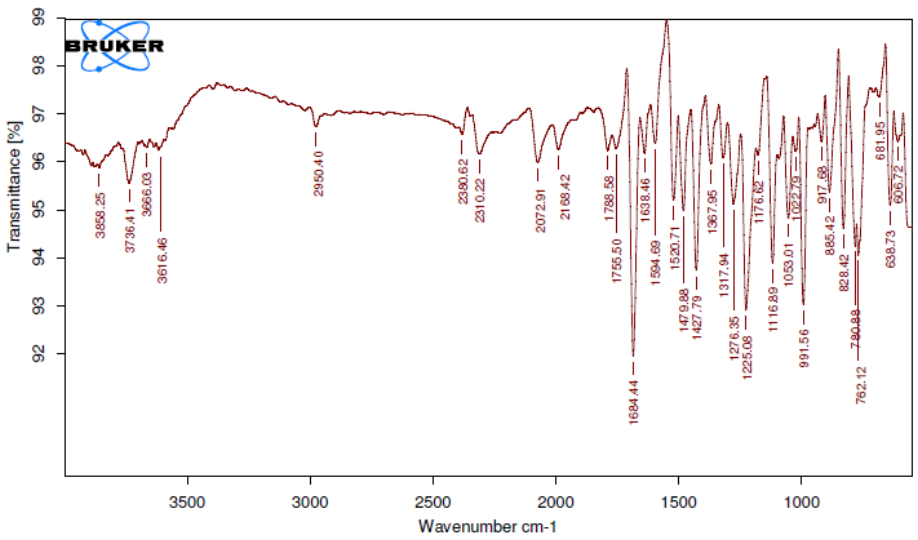

Fig. 4b: FTIR Spectra of optimized formulation.

CONCLUSION

Superporous Hydrogel tablets of Esomeprazole were prepared by direct compression method. The directly compressed formulations exhibited better *in-vitro* drug release profiles. The formulation F6 prepared by direct compression containing xanthan gum-formaldehyde prepared by cross-linking technique exhibited good swelling index and maximum rate of drug release. So, this formulation was considered to be the optimized formulation.

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