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FORMULATION AND EVALUATION OF SUPERPOROUS HYDROGEL TABLETS OF RABEPRAZOLE SODIUM AS A GASTRORETENTIVE SYSTEM

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ABSTRACT

The present study intends to carry out the formulation and evaluation of gastro retentive drug delivery system based on superporous hydrogel tablet using rabeprazole sodium. Rabeprazole sodium belongs to the class of anti-secretory compounds which suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme. The drug rabeprazole sodium has low bioavailability of 52%, superporous hydrogel have fast swelling property, minimized rupturing, increased gastric residence time and also increased solubility, so to increase bioavailability and also to increase gastric residence time it is designed as a gastro retentive superporous hydrogel system. Superporous hydrogel swells rapidly in the stomach. The prepared superporous hydrogel may withstand various types of stress like compression, mechanical strength, stability in acidic condition of stomach and also gives effective pore size larger than 10 micrometre. Gastro retentive superporous hydrogel are generally characterized by their size, morphology, Scanning electron microscopy (SEM), porosity measurement, determination of void fraction, water retention capacity, and determination of drug content. Advantage of converting into superporous hydrogel tablet is to achieve improved therapeutic advantage, such as ease of dosing administration, patient compliance and flexibility in formulation.

KEYWORDS: Gastroretentive drug delivery system, Superporous hydrogel, Swelling, Gastric residence time.

1. INTRODUCTION

Oral route is the most accepted and convenient route of drug delivery for the last three decades. It has been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, flexibility in formulation and patient compliance.[1] Drugs which are easily absorbed from gastrointestinal tract (GIT) and those having shorter half-lives are quickly eliminated from the systemic circulation, so that frequent dosing of such drugs is very important to achieve the therapeutic activity. To avoid this limitation oral controlled release formulation is an attempt to slowly release the drug towards the gastrointestinal tract and maintain an effective drug concentration for a long time. But these dosage forms suffer from two adversities: short gastric retention time and unpredictable gastric emptying time, which lead to incomplete drug release from the dosage form. To avoid this site- specific dosage form need to be formulated to achieve gastric residence time as well as gastric emptying time.[2]

Gastroretentive drug delivery system is a new approach to prolong gastric residence time, thereby targeting site – specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects.[3] This dosage form can remain in the stomach for a longer period and hence prolong the gastric retention time. Several approaches has been developed for the gastroretentive drug delivery for the last few decades such as high density system, low density system, mucoadhesive system, superporous hydrogel system, magnetic system etc. Current study is to develop a superporous hydrogel in order to overcome all the problems of conventional marketed products and to provide a localised and sustained release of drugs.

Superporous Hydrogels (SPH) are three dimensional networks of cross-linked polymers which are chemically and physically bonded. Hydrogels having effective pore size of more than 10µm are known as superporous hydrogel.[4] They are network of hydrophilic polymers that are not soluble and absorb large amount of water in short period due to presence of interconnected microscopic pores. Due to its porous structure SPHs possess more surface area and shorter diffusion distance. Due to this they swell rapidly in contact with water. These system not only have the property of fast swelling they also have properties like slipperiness, biodegradability, biocompatibility, high mechanical strength, stability in acidic conditions of stomach etc. The swollen hydrogels are capable of bearing pressure more than 50-70 cm water pressure. Due to this property

they give extended gastric residence time.[5] Even though, sustained release medicaments of Rabeprazole sodium available in the market, there is a necessity to formulate newer sort of drug design that might have superior in control of drug delivery system. Therefore, the current study, have decided to adopt the controlled drug delivery system in the form of Rabeprazole sodium, superporous hydrogel tablet.

2. MATERIALS AND METHODS

2.1. Pre- formulation studies

2.1.1. Preparation of calibration curve

The standard solution of Rabeprazole was prepared by accurately weighing 25mg of Rabeprazole which was dissolved in 0•1M sodium hydroxide and made up the volume to 25ml in a volumetric flask. From the above solution 10ml was taken and diluted up to 100ml to produce 100µg/ml. From this solution 0.2, 0.4, 0.6, 0.8,1 ml was taken as stock solution and transferred to 10ml volumetric flask and made up the volume with 0.1M sodium hydroxide. The drug solution was scanned (200-400 nm) against reagent blank i.e. 0.1M sodium hydroxide and the absorption spectrum was recorded. The absorption maximum (λmax) was observed at 284nm. A graph was plotted by taking the concentration of the drug solutions on the x-axis and the corresponding to the absorbance values on the y-axis.[6]

2.2.1. Preparation of superporous hydrogel

First step is the preparation of hydrocolloid polymer solution by stirring 0.1M glacial acetic acid in a homogenizer until the polymer completely dissolves in acid. To this solution 10% w/w aqueous polyvinyl alcohol solution was prepared and mixed. Above solution was then treated with 0.2ml formaldehyde. Further to the above prepared solution 0.2ml of tween 80 was added and mixed thoroughly followed by the addition of 50mg of sodium bicarbonate. The mixture was then stirred well and kept aside overnight.[7]

2.2.2. Preparation of drug loaded superporous hydrogel

10ml of 0.1N HCL was taken and to the solution 20mg of drug and 100mg of superporous hydrogel which was previously kept overnight was added and mixed for 1hr at 50°C. To the above solution 2ml of acetone was added and the hydrogel was repeatedly washed with distilled water for the removal of unreacted material. The formed superporous hydrogel was then dried at 40°C for 24hr. Finally the dried superporous hydrogel was powdered and stored in a well closed container. By following the above mentioned procedure three other batches of superporous hydrogel were prepared and named F1, F2, F3, F4, F5 and F6 respectively.[8]

Composition of superporous hydrogel (F1) Chitosan 1mg, Poly vinyl alcohol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium Bicarbonate 50mg, Rabeprazole 20mg.

Composition of superporous hydrogel (F2) Pectin 2mg, Polyvinyl alcohol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium Bicarbonate 50mg, Rabeprazole 20mg.

Composition of superporous hydrogel (F3) Sodium carboymethycellulose 3mg, Polyvinyl alcochol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium bicarbonate 50mg, Rabeprazole 20mg.

Composition of superporous hydrogel (F4) Poly vinylpyrollidone 4mg, Polyvinyl alcohol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium bicarbonate 50mg, Rabeprazole 20mg.

Composition of superporous hydrogel (F5) Sodium alginate 5mg, Polyvinyl alcohol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium Bicarbonate 50mg, Rabeprazole 20mg.

Composition of superporous hydrogel (F6) Poly vinyl acetate 4.5, polyvinyl alcohol 4ml, Formaldehyde 0.2ml, Tween 80 0.2ml, Sodium bicarbonate, 50mg Rabeprazole 20mg.

2.3. Evaluation of drug loaded superporous hydrogel

2.3.1. Porosity measurement[9]

The previously dried hydrogel was immersed overnight in ethanol and then weighed after the removal of excess ethanol. The porosity was calculated using above equation:

Porosity = $V_T/_{VP}$ (VT = SPH total volume; VP = Pore volume)

2.3.2. Water retention capacity

Equation for the determination of the water retention capacity is as follows:

Wrt = (Wp – Wd) / (Ws – Wd)

Wd = Weight of dried superporous hydrogel; Ws = Weight of fully swollen superporous hydrogel; Wp = Weight of superporous hydrogel after exposure of 6hr.

2.3.3. Determination of drug content[10]

5mg of superporous hydrogel was weighed and transferred to 100ml volumetric flask containing 10ml of 0.1N HCL of pH 1.2 and made up to the volume. The mixture was then filtered and taken to determine UV-visible spectroscopy at 284nm.

2.3.4. Scanning electron microscopy

The shape and surface characteristics of Rabeprazole sodium superporous hydrogel were determined by SEM (scanning electron microscopy) Samples were dusted onto a double-sided tape on an aluminum stub. The stubs containing the sample were coated with gold using a cool sputter to a thickness of 400Å. Photomicrographs were taken at the accelerated voltage of 20 kilo volt and chamber pressure of 0.6 mmHg. SEM is taken for F5

formulation since its drug releasing rate is quite high compared to rest of the formulations.

2.3.5. Procedure for the preparation of superporous hydrogel tablet 20mg of drug loaded superporous hydrogel was taken and mixed along with magnesium stearate and talc into a clean mortar and pestle. The powder blend was mixed for five minutes and then magnesium stearate was added and again mixed for few more minutes. The formed blend was then passed through sieve no 60. Finally the prepared powder blend was then compressed into tablets.[11]

2.3.6. Composition of superporous hydrogel tablet
The quantity of ingredients mentioned were for single tablet formulation, whereas for 20 tablets making has given in bract is as follows. Drug + superporous hydrogel 45mg (9g); Magnesium stearate 2mg (0.4g); Talc1mg (0.2g); Sodium bicarbonate 8mg (1.6g); Microcrystalline cellulose 44mg (8.8g).

2.4. Evaluation of superporous hydrogel tablet
2.4.1. Precompression characterization[12] the powder blend of rabeprazole sodium superporous hydrogel was evaluated for various physiochemical parameters such as: Bulk density, Tapped density, Angle of repose, Carr's index.

2.5. Pro compression parameters
2.5.1. Weight uniformity test: Previously punched 20 tablets were taken and determined there weight individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

2.5.2. Hardness
Hardness test was determined by using Monsanto hardness tester by taking 6 tablets from each formulation and applied force to the tablet with the help of inbuilt spring.

2.5.3. Friability
Friability test was performed using Roche friabilator as per IP 2010.

2.5.4. Swelling Index
The swelling index of the tablets was determined in 0.1N HCL (pH 1.2) at room temperature. This property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was 0.1N HCL, 900 ml, rotated at 50rpm. The medium temperature was maintained at 37 ± 0.5°C throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. The swelling characteristics of the tablets were expressed by the following equation. Swelling index = weight of the swollen tablets - initial weight of the tablet/ initial weight of the tablet,/ ×100.[13]

2.5.5. *In – vitro* drug release study[14]
This study was performed using dissolution apparatus at 37 ± 0.5°C in 900ml 0.1N HCL dissolution medium at 50 rpm. At various time interval 5ml of sample was withdrawn and replaced with fresh dissolution media. The samples withdrawn were filtered and diluted and monitored at 284 nm by using UV- spectrophotometer. Percentage of drug release had calculated by the equation obtained from the calibration curve.

2.5.6. Interpretation of data
The order of drug release from superporous hydrogel tablet has measured by using graphical Method. The dissolution data of a graph was plotted with % drug release Vs. Time.[15] The dissolution profiles of all the batches were fit to zero order, first order, Korsmeyer‑Peppas model.

2.5.7. Stability studies
Three month stability studies were done as per ICH guidelines by using temperature 45°C, on the SPH hydrogel tablet of six formulations.[16]

4. RESULTS

4.1. Standard graph preparation
The standard graph of the drug was plotted by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis.[17]

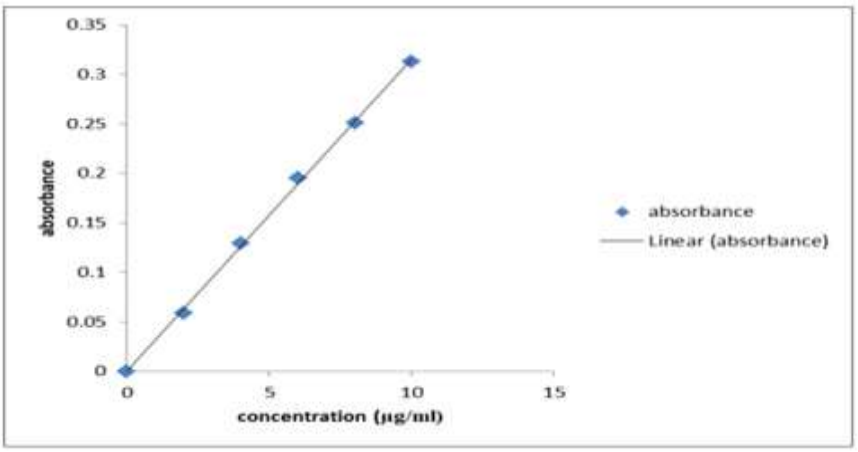

Fig. 1: Standard graph of Rabeprazole Sodium.

4.2. Formulation of superporous hydrogel

Superporous hydrogel were prepared by dissolving different concentrations of polymeric solution with 10% poly vinyl alcohol, 0.2ml formaldehyde and 0.2 ml tween 80 followed by the addition of sodium bicarbonate for the release of carbon dioxide which lead to the formation of a pale yellow colour gel.

4.3. Evaluation of drug loaded solid nanoparticle

The porosity of F1 to F6 formulations were 32.85,46.6, 51.8, 67.52 and 84.72 and 71.12 respectively, on the other hand, water retention capacity of SPH (F1 to F6) formulations has found to be 0.32, 0.40,0.52 and 0.61, and 0.73and 0.66. Porosity of superporous hydrogel depends on cross linking agent added. The porosity increases with decrease in polymer to cross linking agent. More penetration of water into the SPH enhances the water retention capacity.[18] Hence we can conclude that the porosity and water retention capacity is more for the F5 formulation.

4.3.1. Drug content

Drug content of SPH formulations (F1 to F6) was found to be 1.06mg, 1.75mg and 2.47mg, 2.70 mg and 3.25 mg and 3.00mg.

4.3.2. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) of the three formulations F1 to F6 were performed to elucidate the morphology of the superporous hydrogel. The particle size range of superporous hydrogel was found by using the instrument A JEOL JSM- 840 scanning electron microscopy.

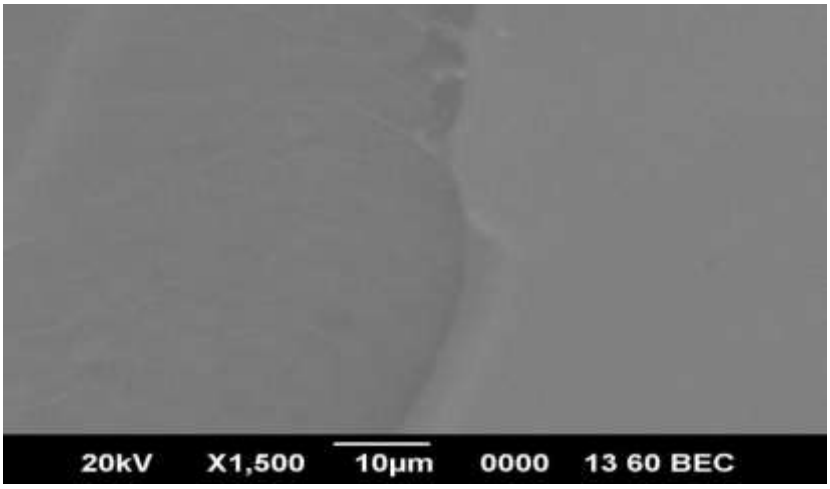

Fig. 2: SEM Image of F5 Formulation.

This image illustrated that the F5 formation showed a good particle range as compared with the other five formulations, so we can conclude that F5 formulation showed a strong SPH as compared with the other five formulations.

4.4 Evaluation of superporous hydrogel tablet

4.4.1. Pre compression characterization of powder

The flow properties of all the six formulations were found to be good as the Carr's index value was in the range of 5-15 which stated that powder flow property was excellent. There was no segregation, flooding or irregular flow observed during the test.

Table 1: Shows the pre compression characterization of powder.

Formulations	Angle of repose	Bulk density	Tapped density	Carr's index
F1	20.6	0.52	0.42	13.05
F2	22.4	0.53	0.43	14.25
F3	23.8	0.55	0.44	14.28
F4	25.4	0.56	0.45	14.31
F5	26.9	0.58	0.47	14.41
F6	26.3	0.57	0.47	14.37

4.4.2. Post- compression parameters of SPH tablet formulations

Table 2 illustrated that the percentage weight variation was within the Pharmacopoeial limits of the tablet weight. The hardness shown by F5 formulation was considered to be good as the tablet batch variation was found to be 3-4 kg/cm2. Friability values were found to be less than 1% and F5 formulation containing sodium

alginate was found to have better friability than other five formulations.

Table 2: Post compression parameters of SPH formulation.

Formulations	Weight uniformity (mg)	Hardness kg/cm^2	Friability %
F1	95.4	3.5	0.21
F2	96.3	4.3	0.24
F3	96.4	4.4	0.26
F4	96.2	4.2	0.22
F5	96.1	4.4	0.30
F6	96.3	4.4	0.23

4.4.3. Swelling index of SPH tablet formulation

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. The gel layer helps in governing drug release. Swelling is important because the gel layer is formed due to the permeation of water within the gel and also it is a factor for ensuring floating.[19] The Swelling index % of F1 to F6 formulations were 42.15, 43.24 and 46.72 and 44.30 and 46.20, and 45.32. The F5 formulation containing sodium alginate is having good swelling index due to this the penetration of water to the gel layer is more and thereby increases the water retention property, so that moisture uptake by the F5 formulation can be also increased.

4.4.4. *In- vitro* drug release

Table 3: Cumulative % drug release of SPH tablet.

Time(h)	F1	F2	F3	F4	F5	F6
1	21.7	20.6	24.2	22.6	27.3	23.6
2	28	28.0	28.4	26.0	40.5	26.0
3	34.3	28.7	37.5	38.7	50.9	39.8
4	42.2	34	45.7	44.5	59.3	47.12
5	46.9	41	48.2	47	64.1	51.2
6	54.7	56.2	54.2	56.2	74.52	58.9

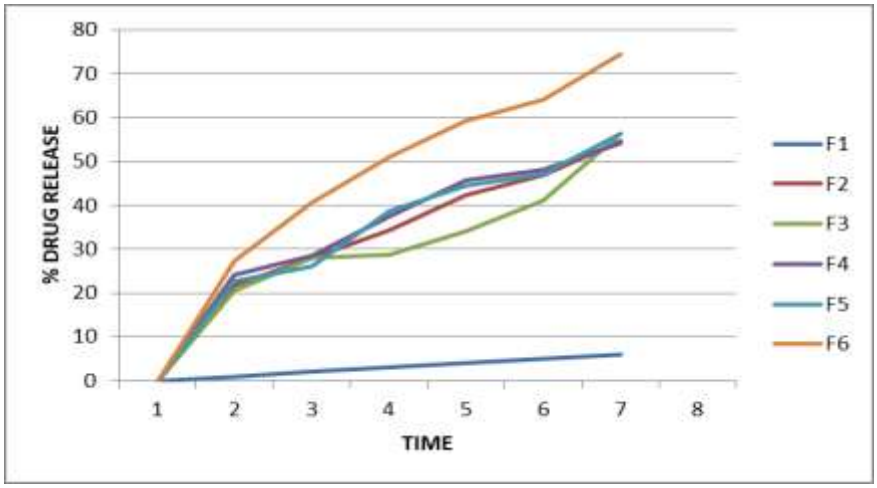

Fig. 3: Cumulative % SPH drug release v/s time graph for F1 to F5 Formulations.

Formulation F1 showed drug release at 54.7% in the sixth hour, F2 and F4 formulation showed release at 56.2%, F3 showed drug release at 54.2% and F6 formulation showed a release of 58.9% but the formulation F5 showed a complete drug release of 74.52% in the 6th hr. stating that F5 formulation containing sodium alginate showed a good drug release compared to other five formulation.

4.4.5. Interpretation of data

In vitro drug release study data of all three formulations were subjected to goodness of fit test by linear regression analysis according to Zero order, first order kinetics and Korsmeyer-Peppas model to ascertain the mechanism of drug release. The korsemeyer –Peppas release exponent range more than 1 is assumed to be zero order release which can be achieved when drug diffusion is rapid. It also helps in demonstrating transport of swell-able polymers.

4.4.9. Stability Studies

Stability study of optimized formulation at accelerated condition (40±2^{0}C, 75±5% RH) was carried out for three month. Drug content was found to be 49.76, 49.53,

49.31, 49.23, and 49.54. It did not show any changes in physical appearance when compared to freshly prepared formulation. The percentage drug content was evaluated and shows that there are no significant changes in the drug content during storage.

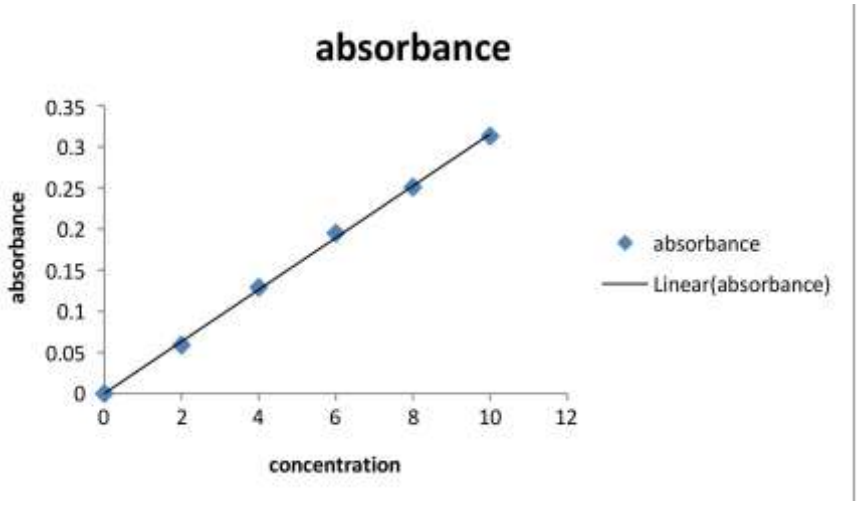

Fig. 1: Standard graph of Rabeprazole Sodium.

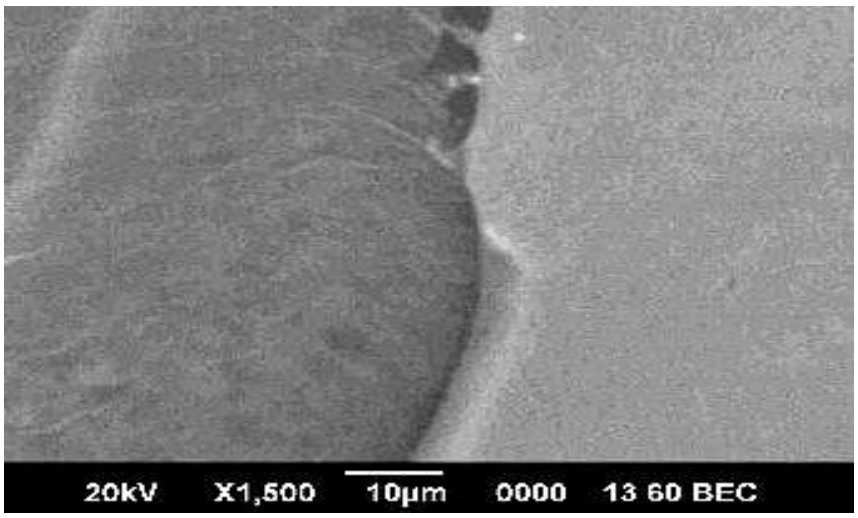

Fig. 2: SEM Image of F5 Formulation.

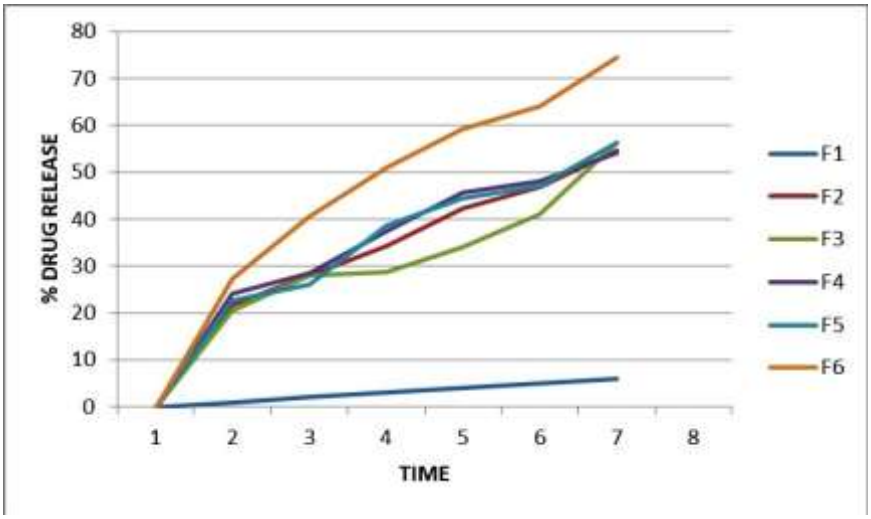

Fig. 3: Cumulative % SPH drug release v/s time graph for formulations F1 to F5.

5. CONCLUSION

The present study intends to carry out the formulation and evaluation of gastro retentive drug delivery system based on superporous hydrogel tablet using rabeprazole sodium. Rabeprazole sodium belongs to the class of anti-secretory compounds which suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme. The drug rabeprazole sodium has low bioavailability of 52%, superporous hydrogel have fast swelling property, minimized rupturing, increased gastric residence time and also increased solubility, so to increase bioavailability and also to increase gastric residence time it is designed as a gastro retentive superporous hydrogel system. Major goal in designing gastro retentive drug delivery system is to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects.

Superporous hydrogel swells rapidly in the stomach. Gastric contraction pushes the dosage form towards pylorus and due to larger size of dosage form it slips over the surface of the system and pushes back to the stomach. In present study superporous hydrogels are prepared by dissolving third generation superporous hybrids pectin and sodium alginate in glacial acetic acid by using polyvinyl alcohol and formaldehyde. Further sodium bicarbonate is used to accelerate the process and foam formation. The prepared superporous hydrogel may withstand various types of stress like compression, mechanical strength, stability in acidic condition of stomach and also gives effective pore size larger than 10 micrometre. The drug was incorporated into prepared superporous hydrogel by heating.

Gastro retentive superporous hydrogel are generally characterized by their size, morphology, Scanning electron microscopy (SEM), porosity measurement, determination of void fraction, water retention capacity, and determination of drug content. Advantage of converting into superporous hydrogel tablet is to achieve improved therapeutic advantage, such as ease of dosing administration, patient compliance and flexibility in formulation. The prepared tablet is then subjected to usual tablet characterization. The study shows that F5 formulation showed the best particle range of 10µm increased swelling index of 46.72% and drug release rate of 74.5%.

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Declarations of interest: None.

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