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Research Article

Formulation Development and Evaluation of Hydrogel Based Gastroretentive Drug Delivery System of Antihypertensive Drug

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ABSTRACT

Site specific drug delivery has become the important aspect of research. In present study focused has been made to formulate gastroretentive drug delivery (GRDDS) of drugs having narrow absorption window or having good absorption at proximal part of gastrointestinal tract (GIT) to deliver at stomach site. Hydrogel based gastroretentive formulation of ramipril were prepared by gas blowing technique with the help of using monomers like acrylamide and acrylic acid; bisacrylamide (BIS) as cross linker; pluronic F-127 as foam stabilizer; ammonium per sulphate (APS) as redox initiator; N, N, N', N'-tetramethylethylenediamine (TEMED) as catalyst and sodium bicarbonate ($NaHCO_3$) as foaming agent. Chitosan was taken as secondary polymer to enhance the mechanical properties of formulation. Hydrogel were characterized with respect to various parameters such as swelling ratio, mechanical strength, apparent density, porosity, void fraction, drug entrapment and *in vitro* drug release. Further scanning electron microscopy (SEM) and stability studies of formulation were carried out. Study showed the influence of chitosan various concentration on mechanical strength and also on swelling properties. The drug release from chitosan based hydrogel showed for prolonged period of time. Stability studies showed no change in physical appearance and insignificant difference in entrapment efficiency. Thus prepared formulation could be a better targeting for gastroretentive drug delivery.

Keywords: Chitosan, swelling, mechanical strength, gastric retention.

INTRODUCTION

In today's era targeting of drug at particular site has become the important part of pharmaceutical research. But various issues are observed while targeting of drug molecule at specific sites such as fast elimination, degradation and short residence time. Over the last few decades, the focused has been made in designing of device that can retain in the upper part of the gastrointestinal tract (GIT) in terms of enhancing drug residence time of drug at targeting sites. There are various technologies have been used for gastroretentive device such as low-density systems[1], high density systems[2], bioadhesive systems[3] and expanding systems[4]. But these systems are affected by various factors such as gastric fluid contents, harsh gastric environment, gastric contraction and food content. These factors result in reducing gastric retention time. Hydrogels based GRDDS have been designed by many researchers as a gastric retention device. They have the characteristics to absorb considerable amount of water and swell due to having hydrophilic functional group in their structure. This swelling property is responsible to keep the formulation in stomach for prolonged period of time. Thus on the basis of good swelling and mechanical properties porous hydrogel were prepared. These have elastic property due to incorporation of hybrid agent like alginate, polyvinyl pyrrolidone and chitosan. They can withstand for considerable period of time. Ramipril (RAM) is angiotensinogen convervting enzyme (ACE) inhibitor belonging to the antihypertensive category of drug. ACE is an enzyme which is responsible for the conversion of angiotensin I to the angiotensin II which is a vasoconstrictor and also stimulates the adrenal cortex for secretion of aldosterone secretion and thus result in reducing vassopressure activity. After oral administration, peak plasma concentration achieved within a short period of time. Its biological half life is 2-4 hrs. Its absolute bioavailability is 28 %[5]. Ramipril is lipophilic in nature and it has poor solubility in water. Ramipril is stable in acidic media but undergoes degradation in alkaline medium[6]. Thus ramipril hydrogel were prepared for gastroretentive delivery.

MATERIAL AND METHODS

Ramipril was obtained as a gift sample from Dr. Reddy's laboratories. Chitosan (Medium molecular weight), Acrylic acid (AA), acrylamide (AM), N, N'-methylenebisacrylamide (Bis), ammonium persulphate (APS), N, N, N', N'-tetramethylethylenediamine (TEMED), were obtained from Sigma Aldrich. Sodium bicarbonate, hexane, sodium chloride and sodium hydroxide (analytical grade) were from Fine chemicals.

Synthesis of ramipril hydrogel

Ramipril hydrogel formulation were synthesized by using gas blowing technique[7]. For this monomer solution of Acrylamide (50%), acrylic acid (50%), bisacrylamide

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Table 1: Composition of hydrogel formulations at various concentrations of monomers

Ingredients	Formulation code		
	F_A	F_B	F_C
Acrylamide (50%w/v)	200 µl	200 µl	200 µl
Acrylic acid (50%v/v)	200 µl	200 µl	200 µl
BIS (%w/v) (70 µl)	2.5	2.5	2.5
Water	100 µl	100 µl	100 µl
PF-127 (10%w/v)	100 µl	100 µl	100 µl
Chitosan(%w/v) (200 µl)	1.0	2.0	3.0
APS (20% w/v)	25 µl	25 µl	25 µl
TEMED (20% w/v)	25 µl	25 µl	25 µl
$NaHCO_3$(mg)	100 mg	100 mg	100 mg

(BIS) (2.5%) as a cross linker, distilled deionized water, pluronic F-127 (10%w/v) as a foam stabilizer were prepared. Chitosan were taken at different concentration i.e. 1.0, 2.0 and 3.0 % w/v as a secondary polymer, ammonium per sulphate (APS) (20% w/v) as a redox initiator and N, N, N', N'-tetramethylethylenediamine (TEMED) were taken as a catalyst. Monomer solutions were added in test tubes and the test tubes were shaken after every ingredient added for proper mixing. Chitosan of different concentration were added in respective test tube. Then redox initiator and catalyst were added in the test tube. RAM (mg) was added to the test tube and mix well to ensure mixing. After that sodium bicarbonate (100 mg) was added as a foaming agent in the composition. During adding all ingredients, shaking is done for proper mixing and distributing gas bubble throughout the formulations. After gelation formulation were treated with ethanol and take out from test tubes and then kept at 60 °C in oven for overnight. Amount of chitosan were varying in the formulation to evaluate the various parameters of hydrogel like swelling properties, apparent density, porosity, void fraction mechanical strength, drug loading efficiency and in vitro release of drug. Ingredients used for developed formulation were given in table 1.

Characterization of Superporous hydrogel

Swelling Ratio

To determine the swelling ratio, a completely dry, disc-shaped hydrogel was weighed and then immersed in excess of swelling medium. Swelling ratio was determined in 0.1 N HCl. At various time intervals, the hydrogel disc was removed from the medium and weighed after excessive swelling medium on the surface was blotted. Measurements were carried out in triplicate. Swelling ratio for the entire formulation batch with respect to changing concentration of BIS and chitosan were calculated. Results were calculated according to the following equation:

$Q = (M_s - M_d)/ M_d$

Where Q is the swelling ratio, M_s the mass in the swollen state and M_d the mass in the dried state[8].

Determination of Apparent density, porosity and void fraction

Apparent density

Solvent displacement method was used for determination of apparent density of all formulations. Firstly, hydrogel formulations in dried form were kept in specified volume of hexane. After that hexane volume increased and was noted. Density was calculated by following equation:

Apparent density (ρ) = M_d/V_h

Where M_d is the mass of dried hydrogel and V_h is the displaced volume of hexane by hydrogel formulation[9].

Porosity

For porosity measurement, dried hydrogel was kept in hexane overnight. Then weighed hydogel after excess of hexane was blotted. Porosity was calculated from following equation:

Porosity = V_P/V_T

Where V_P (V_T - V) is the pore volume of hydrogel and V_T is the total volume of hydrogel which is the dimension of swollen hydrogel[10].

Void space

Void fraction determination of hydrogel was done by placing it in 0.1 N HCl overnight and dimension of swollen hydrogel was calculated. After that subtract the weight of dried hydrogel from weight of swollen hydrogel for determination of total volume of pores[11]. Void fractions were calculated by following formula:

$$\text{Void fraction} = \frac{\text{Dimensional volume of hydrogel}}{\text{Total volume of pores}}$$

Mechanical Strength

Mechanical strength of hydrogel was determined by using hardness tester with slight modification. For determination of mechanical strength, fully swollen hydrogel was placed in the tester and force was applied until hydrogel break. After that compressive strength was determined by dividing compressive force to break hydrogel with cross sectional area[12].

Estimation of drug content

Multiple extraction procedure was used for determination of drug content in hydrogel. For this, RAM hydrogel was kept in a beaker containing 50 ml of 0.1 N HCl for extraction and stirring was carried out during extraction period. Process was carried out many times until of drug were not extracted[13]. After that solution was filtered and drug content was estimated by using UV-VIS

Table 2: Determination of apparent density, porosity and void space

Formulations	Apparent density (g/cm^3)	Porosity	Void space
F_A	0.39 ± 0.01	46.29 ± 0.23	1.85 ± 0.04
F_B	0.48 ± 0.03	39.17 ± 0.11	1.67 ± 0.07
F_C	0.56 ± 0.01	33.46 ± 0.41	1.48 ± 0.09

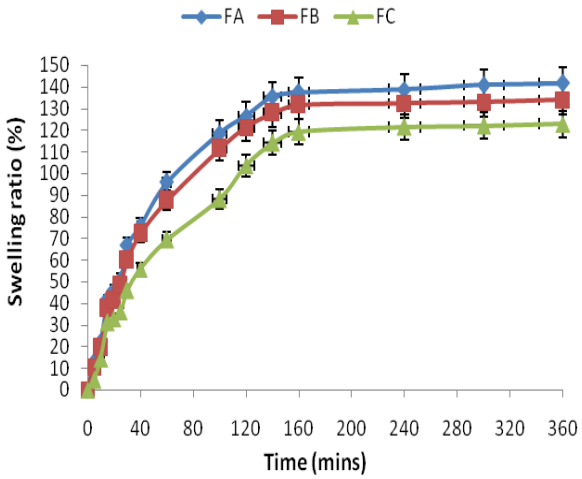

Figure 1: Swelling ratio of hydrogel formulations in 0.1 N HCl

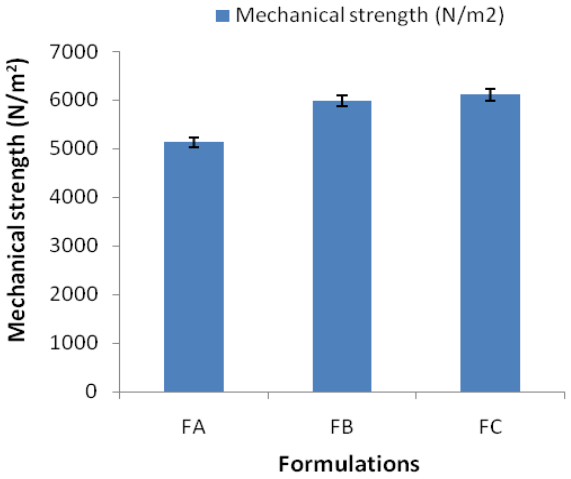

Figure 2: Determination of mechanical strength of all formulations

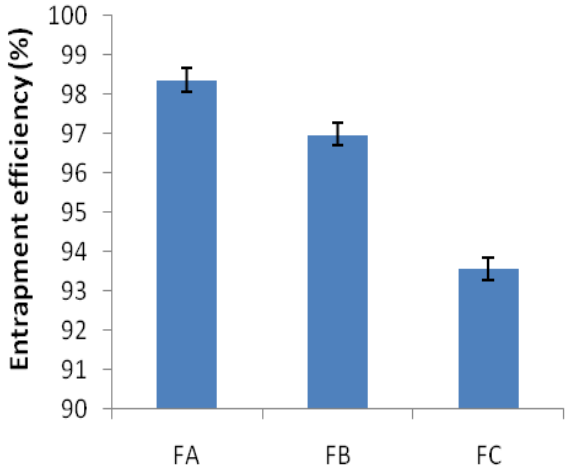

Figure 3: Entrapment efficiency of formulations

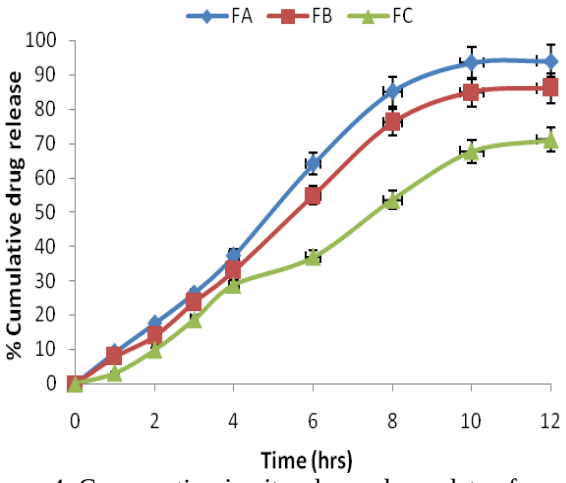

Figure 4: Comparative *in vitro* drug release data of hydrogel formulations

Table 3: Stability profile of selected formulation (F_A) at different storage conditions

Storage conditions	Time intervals (Months)	Physical appearance	Drug content (%)
	0	No change	98.36±0.07
25 ^{0}C ± 2 ^{0}C/60 ± 5 % RH	3th	No change	98.18±0.04
	6th	No change	96.77±0.03
	12th	No change	95.03±0.09
	0th	No change	98.36±0.05
30 ^{0}C ± 2 ^{0}C/65 ± 5 % RH	3th	No change	97.78±0.03
	6th	No change	96.03±0.04
	12th	No change	94.71±0.07
	0th	No change	98.36±0.09
40 ^{0}C ± 2 ^{0}C/75 ± 5 % RH	3th	No change	96.89±0.02
	6th	No change	93.24±0.08

spectrophotometer at 210 nm.

In Vitro release study

The release of drug from prepared RAM hydrogel was determined by using USP dissolution apparatus II (Paddle type) at 37 ± 0.5 ˚C in 250 mL of 0.1 N HCl buffer for 24 hrs. The paddle was rotated at 100 rpm and withdrawing 10 ml aliquot from the medium at predetermined time of interval. The withdrawing samples were replaced with fresh media of 0.1 N HCl buffer. The aliquots sample was filtered through 0.45 µm filter membrane and assayed spectrophotometrically at 210 nm (14). All experiments were carried out in triplicates.

Release kinetics data of drugs

On the basis of swelling ratio, mechanical strength, drug loading capacity and *in vitro* release profile, final formulation was selected for further studies. Kinetic studies of drug release for selected hydrogel formulation was carried out with respect to various kinetic models

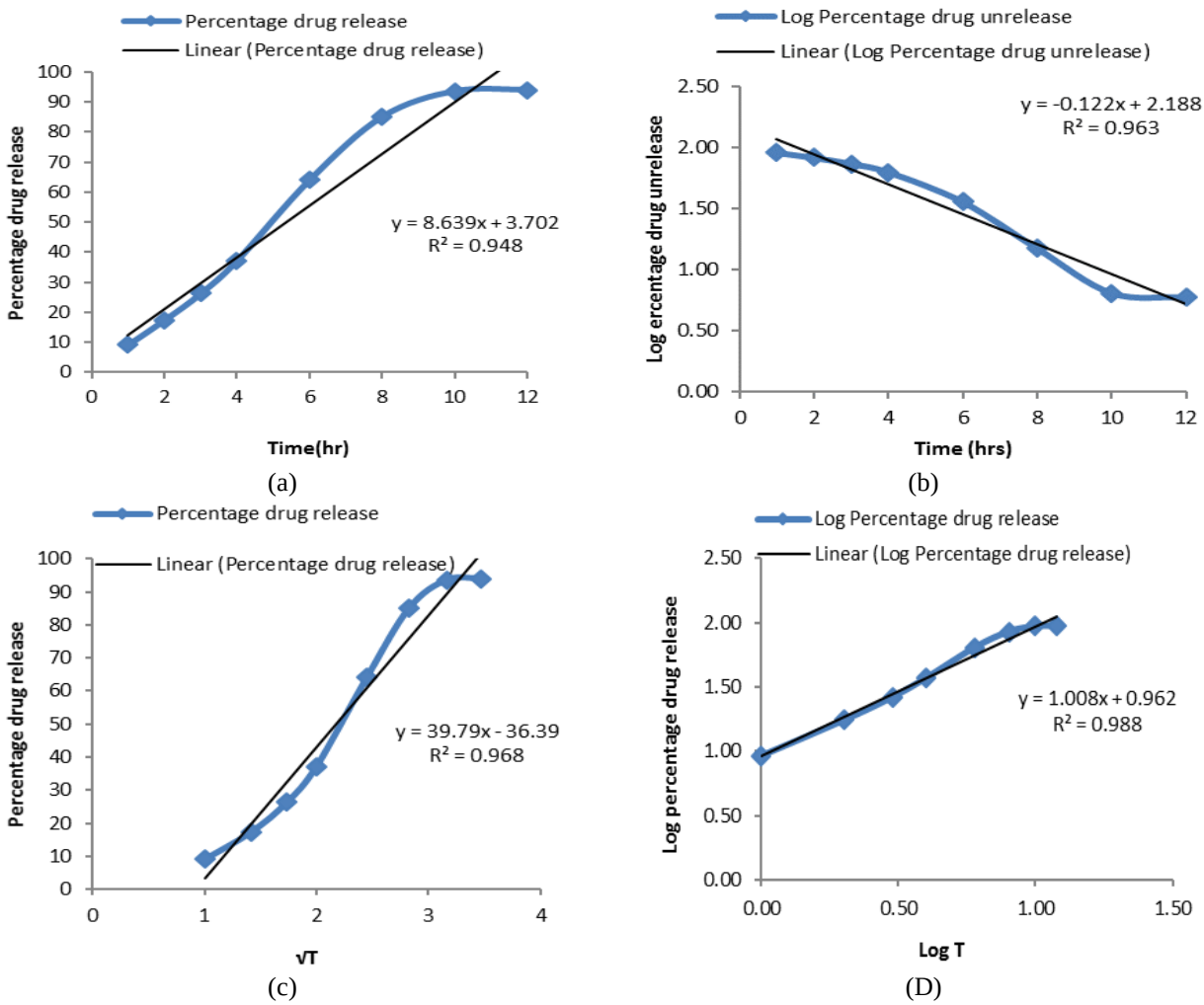

Figure 5: Drug release kinetics of selected formulation (F_A) a) Zero order; b) First order; c) Higuchi model; d) Korsemeyer peppas model.

viz; Zero order kinetics, First order kinetics, Higuchi model and Korsmeyer peppas model. After that regression analysis (R^2) was determined and diffusion coefficient (n) was also calculated.

Release kinetic graphs were plotted for selected formulation in various models by putting them in following equations as:

Qt =Kot (Zero order release kinetics)

Where Qt is the percentage drug release at time t and graph was plotted between Qt Vs t

$\ln Q_t = \ln Q_0 - K_1 t$ (First order release kinetics)

$Qt = Kh\ t^{1/2}$ (Higuchi model)

$M_t / M_a = K_p t^n$ (Korsmeyer peppas model)

Scanning electron microscopy (SEM)

Formulation was morphologically studied by using SEM. For this dried hydrogel disc sample were taken and cut to expose their internal structure. The sample for formulation was prepared separately on sample holders. The holders were coated with gold palladium using sputter coater for one minute under argon gas before electron microscope scanning.

Stability studies

Final formulation was further studied to confirm its stability profile. For this purpose, formulation was kept in different conditions as mentioned below:

Temperature: 25 ^{0}C ± 2 ^{0}C and 60 ± 5 % Relative Humidity (RH) for 12 months

Temperature: 30 ^{0}C ± 2 ^{0}C and 65 ± 5 % Relative Humidity (RH) for 12 months

Temperature: 40^{0}C ± 2 ^{0}C and 75 ± 5 %Relative Humidity (RH) 6 months (Accelerated condition)

Stability of final formulation was confirmed on the basis of physical appearance and drug loading efficiency.

RESULTS AND DISCUSSION

Swelling Ratio

It was observed from the fig. 1 that swelling ratio of hydrogel was affected with varying concentration of chitosan. It was found that swelling ratio was decreased with increasing the chitosan concentration from 1.0 to 3.0 % w/v. Reduction in swelling ratio was due to high viscosity of the solution after increasing the concentration of chitosan above 1.0 % w/v[15]. Due to high viscosity slow amount of water can penetrate inside polymeric network that resulted in reducing swelling ratio.

Apparent density, Porosity and void fraction

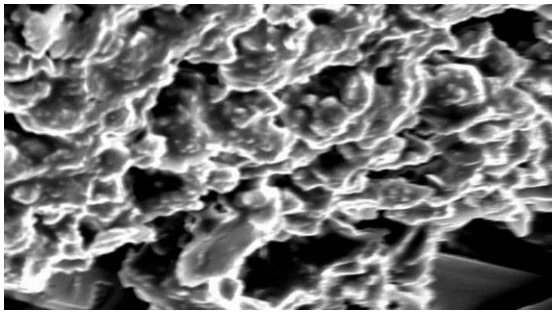

Figure 6: SEM image of F_A 1000x magnification

Apparent density

It was observed that with increment in chitosan concentration there was also increasing in apparent density. It was due to fact that with increasing chitosan concentration from 1.0 to 3.0% w/v caused increasing viscosity of the solution and there occurred accumulation at pore periphery that slightly increased apparent density.

Porosity

It was observed from the table 2 that with increasing chitosan concentrations there become more stiff structure around the void space due to denser network formation between interpolymeric networks and hence less space available for pore formation. This result in reduce porosity with increasing chitosan concentration.

Void space

It was observed that with increasing chitosan concentration, viscosity formulation increased that accumulated at polymeric space and thus reduces void space[16].

Mechanical strength

Mechanical strength of hydrogel was affected with respect to change in chitosan concentration. Mechanical strength of all formulation of hydrogel was found to be in the range of 4400-6300 N/cm^2. It was found that incorporation of chitosan in formulation produce elasticity to the hydrogel and there was insignificant change in mechanical strength was observed. Results were shown in fig. 2.

Estimation of drug loading

Drug content analysis revealed that drug was distributed in all hydrogel uniformly and various chitosan concentration affecting the drug loading in formulation. It was found that drug loading efficiency was slightly reduced on increasing chitosan concentration from 1.0 % to 2.0 % but there occurred sharp reduction in drug loading efficiency on further increasing the chitosan concentration from 2.0 to 3.0 % w/v. It could be due to the fact that with increment of chitosan concentration from 1.0 to 2.0 % w/v result in slight increment in viscosity due to changing concentration occurred. But at 3.0 % w/v concentration of chitosan, solution become too viscous that is difficult for drug molecule to pass through network structure and also there is very less porosity of hydrogel at this chitosan concentration caused less drug loading[15]. Results were shown in fig. 3.

In vitro release study

It was observed from the data as shown in fig. 4 that chitosan solution concentration affected the percentage release of drug from the dosage form. It was found that cumulative drug release from formulation was reduced insignificantly when chitosan concentration increased from 1.0 to 2 % w/v. Further release of drug from formulation was retarded significantly on further increasing the concentration of chitosan from 2.0 to 3.0 % w/v. It was due to the fact that with chitosan at concentration of 1.0% w/v showed good porosity and swelling ratio that allowed the better absorption of buffer media through polymeric network and hence release was prolonged upto 12 hrs. At chitosan concentration 2.0 and 3.0 % w/v polymeric structure so formed are somewhat rigid due to increasing viscosity of solution. Hence resist diffusion of buffer media in hydrogel polymeric network[15].

Drug release kinetics

It was found that F_A formulation possessed good swelling ratio, considerable mechanical strength, better entrapment of drug loading and drug release studies. Thus F_A formulation was analysed for released kinetic studies. Kinetic studies of hydrogel formulation by fitting them various mathematical models such as zero order; first order; higuchi model; korsmeyer model. Regression (R^2) analysis of all formulation were determined and shown in fig. 5. It was observed from data as shown in fig. 5 that best fit model was korsmeyer peppas model and having higher R^2 value than other models i.e. 0.988. Further n value from the Korsmeyer-Peppas equation was determined and was found to be 0.635 i.e. $0.45 > n$ value < 1.0 in the drug release profiles, hence the release mechanism showed anomalous transport.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was carried out for the determination of morphological characterization of hydrogel. It was observed from the fig. 6 that hydrogel possessed porous structure which provides faster swelling to hydrogel. Highly porous structure of hydrogel is responsible for better water penetration through the pores and that cause the effective drug release.

Stability studies

It was observed from the data shown in table 3 that there were insignificant differences in drug loading efficiency of formulation of all storage condition. Physical appearance also showed no change in formulation. Thus Stability studies of final formulation suggested that hydrogel formulation were less prone to degradation in different atmospheric conditions and hence were stable.

CONCLUSION

Chitosan based hydrogel were prepared by gas blowing technique that showed good swelling in acidic media. This was because chitosan swell at acidic pH due to protonation of amino group. But further swelling of hydrogel reduced due to high viscosity of chitosan solution at higher concentration. Chitosan concentration also enhances the mechanical strength of polymeric network that is suitable to withstand at harsh gastric environment. It was due to the fact that with increase

chitosan concentration more stiff structure was formed and thus also reduces porosity due to resist in pore formation. Thus optimum concentration of chitosan is required to meet that all desired characteristics. Chitosan concentration also affects the drug loading efficiency and drug release profile. It was observed from the study that at optimum chitosan concentration maximum drug was loaded in hydrogel network and drug was released in controlled manner upto 12 hrs. Thus it was concluded that chitosan based hydrogel could be a better targeting of drug for gastroretentive drug delivery.

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