Journal of Applied Pharmaceutical Science Vol. 7 (12), pp. 047-057, December, 2017
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2017.71206
ISSN 2231-3354

Crushed Puffed Rice-HPMC-Chitosan based Single-Unit Hydrodynamically Balanced System for the Sustained Stomach Specific Delivery of Metoprolol Succinate

Shashank Soni[1, 2*], Veerma Ram[1], Anurag Verma[2]

[*1, 2] School of Pharmaceutical Sciences, Sardar Bhagwan Singh PG Institute of Biomedical Sciences and Research, Balawala, Dehradun, India.
[2] School of Pharmaceutical Sciences, IFTM University, Moradabad, India.

ARTICLE INFO

Article history:
Received on: 04/10/2017
Accepted on: 27/11/2017
Available online: 30/12/2017

Key words:
Biodegradable polymer, Crushed puffed rice, Hydrodynamically Balanced System, Metoprolol Succinate, Zero order kinetics model.

ABSTRACT

Purpose: Developed and evaluated a Hydrodynamically Balanced System (HBS) capsule system using natural and novel biodegradable polymer used as Crushed Puffed Rice (CPR) alone and in combination with auxiliary polymers (High Molecular Weight Chitosan; HMWCH and Hydroxypropyl methylcellulose; HPMC K15) for stomach specific delivery.

Method: A total of nine formulations was prepared by manual shaking method and filled in colorless hard capsule shell size 1. The prepared capsule was evaluated for parameters such as drug content, *in vitro* buoyancy and drug release in 0.1M HCl, drug delivery kinetics.

Results: Average floating time for the formulation is 08 hours. CPR is used as a buoyancy imparting agent due to its floating behavior; it floats in 0.1 M HCl (pH 1.2) and remained unwetted for the time period of 05 hours. CPR, HPMC K15, and HMWCH have a significant effect ($p < 0.05$) on MS retarding. Formulation D1-D9 follows zero order model and Fickian diffusion which was confirmed by R^2 value and Akaike Information Criteria (AIC).

Conclusion: The data obtained from the study suggests that CPR in combination with HMWCH or HPMC K15 or HPMC K15 + HMWCH has sufficient potential to be used as a carrier for stomach specific drug delivery.

INTRODUCTION

Metoprolol Succinate (MS) is a β 1-selective adrenergic blocking agent (Sandberg *et al*., 1998). Since the half-life of MS is ~3 to 4 h (Kendall *et al*., 1991), multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MS absorption mainly takes place in the duodenum and jejunum and is directly proportional to the dose available (Jobin *et al*., 1985).

A gastroretentive is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments (Narendra *et al*., 2006). MS is highly soluble throughout the physiological pH. MS shows the several experimental properties like melting point 120 ^{0}C, water solubility 1.699 ± 004 mg/L (at 25 °C), log p 1.88, Caco2 permeability -4.59, log S - 2.8, pKa strongest acidic and basic 14.09 and 9.67 respectively, physiological charge 1, hydrogen acceptor and donor count 4 and 2 respectively, polar surface area 50.72 Å, rotable bond count 09, refractivity 76.7 m^3mol^{-1}.

* *Corresponding Author*
Shashank Soni, School of Pharmaceutical Sciences. Sardar Bhagwan Singh PG Institute of Biomedical Sciences and Research, Balawala, Dehradun, India. Phone: +919410572306,
Email: shashank_soni64 @ yahoo.com

It shows predicted ADMET properties like human intestinal absorption and Caco2 permeability positive behavior whereas negative effects on crossing blood-brain barrier (Blomqvist *et al*., 1988). It comes under the category of Biopharmaceutical Class System (BCS) I drug which states that it is extremely soluble and highly permeable. It is, therefore, a suitable candidate with the high solubility for an Hydrodynamically Balanced System (HBS) sustained delivery systems (Ravishankar *et al*., 2006; Wikstrand *et al*., 2003).

The present study involves the invention, development, and optimization of a novel gastroretentive floating, swellable, sustained release HBS capsules using CPR as a polymer for achieving gastroretention for MS by physical blending and filled in the hard gelatin capsule shell of size 01. None of the work till date is reported by using CPR in drug delivery and gastroretention technology also by using MS. Chemically, CPR contains carbohydrates (as rice starch) as the major constituent (Kizil *et al*., 2002). Since these are very crispy in nature, they can be crushed with ball mill ease into fine low-density powder which is not easily wetted by water and can float over the surface of the water for a prolonged period of time (figure 10 D). This property of puffed rice motivated us to use it as buoyancy imparting agent and if possible as a release retarding polymer also. The current investigation is, therefore, envisaged to investigate the potential of CPR as a buoyancy imparter agent. This HBS gastroretentive capsule contains three polymers with different concentrations: High Molecular Weight Chitosan (HMWCH) – rapidly hydrating, rate controlling polymer, Hydroxypropyl methylcellulose K 15 (HPMC K15) – gel-forming agent, and Crushed Puffed Rice (CPR) – buoyancy importer and drug delivery carrier alone and in combination with auxiliary biodegradable and biocompatible polymers; HMWCH and HPMC K15. Nature of HMWCH is cationic and it is reported that it enhances the transport of drug via opening the tight junction of epithelial cells of the stomach (Sonaje *et al*., 2012). The positive charge, with very high charge density, present on the amino group surface of Chitosan binds to the negative charge of stomach mucosal lining, which results in the formation of hydrogel complex which retards the release of MS from the matrixes of Chitosan molecules and HPMC K15 is nonionic, when these come in contact with the dissolution media they form a gelatinous glassy structure at the outer surface. Now, this outer surface acts as an obstruction barrier for the media to penetrate inside the glassy structure and acts as a rate-limiting step for the release of the drug. The gel strength is also a rate-limiting step for the sustaining of drug (Soni *et al*., 2016). The gel strength can be increased by increasing the viscosity and this is achieved by the changing in the grades, addition with some another polymer or change in the concentration (Bernkop-Schnürch *et al*., 2012; Garg *et al*., 2008; Boldhane *et al*., 2010). Selection of HPMC and HMWCH is based on the previously reported work by one of the authors of this study (Soni *et al*., 2016; Verma *et al*., 2012; Verma *et al*., 2017). The pooled result of CPR alone and in combination with auxiliary polymers on the floating behavior and on in vitro release pattern of the MS has also been studied and reported in this present research novel experimental work.

EXPERIMENTAL

Materials and Method

Metoprolol Succinate (MS), High Molecular Weight Chitosan (HMWCH; Degree of Deacetylation > 85 %, apparent viscosity > 400 mPas at 20 ^{0}C, Brookfield), Dialysis membrane (1000 Dalton molecular weight) was procured from Merck (formerly Sigma-Aldrich; St. Louis), USA. Hydroxypropyl methylcellulose (HPMC K4M, apparent viscosity 3000-5600 cps at 20 ^{0}C and K15M, apparent viscosity 11250-21000 cps at 20 ^{0}C) obtained as a gift sample from Colorcon Asia Private Limited, India. *Oryza Sativa* (crushed puffed rice) obtained from the local market of Dehradun, India. 0.45 µm membrane filter was procured from Rankem, India. Double distilled water was used throughout the experiment. All other chemicals and reagents used were of analytical grade.

Development of CPR powder

CPR was dried in the tray dryer at a temperature of 45 ^{0}C to remove the moisture from its pore till the equilibrium moisture content (EMC) was achieved followed by transfer in the ball mill for size reduction. After running time of 10 minutes the crushed CPR was collected over butter paper and passed over a sieve # 120 to get a monodisperse powder, undersize particles were collected and stored in an airtight glass vial to prevent the entry of moisture.

Preparation of Single-unit Hydrodynamically Balanced System (HBS) Capsules containing formulations by ordered mixing

Optimized formulations (Table 1) of HBS capsules were prepared to ordered mixing technique by placing the drug between layers of polymers in a glass vial (10 ml) and shaken vigorously manually by hand for 5 min., followed by encapsulation in colorless hard gelatin capsule shell (size 1) using laboratory capsule filling machine. The manual shaking procedure had advantages that it did not cause size reduction of neither drug nor polymer during mixing that would believe to affect the release profile of formulations during drug release studies (Soni *et al*., 2016).

Table 1: Formulation composition of MS with HPMC, HMWCH and CPR

Formulation Code	MS (mg)	CPR* (sieve#120) (mg)	HMWCH* (mg)	HPMC K15* (mg)
D1	25	75	---	---
D2	25	75	75	---
D3	25	75	---	75
D4	25	75	37.5	37.5
D5	25	---	75	---
D6	25	---	---	75
D7	50	75	75	---
D8	50	75	---	75
D9	50	75	37.5	37.5

MS: Metoprolol Succinate, CPR: Crushed Puffed Rice, HMWCH: High Molecular Weight Chitosan, HPMC: Hydroxypropyl Methylcellulose (Hypromellose). *Concentration of all the polymers were chosen on the basis of initial trials study conducted for efficient buoyancy.

Thermal characterization of CPR

Thermal characterization was performed on EXSTAR TG/DTA 6300 and it includes Thermo Gravimetric Analysis (TGA), Differential Thermal Analysis (DTA) and Derivative Thermo Gravimetric Analysis (DTG), having the sensitivity of 0.2 µg for TGA and 0.06 µV for DTA. It was carried out to study the determination of characteristic peaks (endothermic and exothermic) and heat of melting was recorded of a drug, excipient and drug-excipient mixtures in the present investigation. The study was carried out at 5 ^{0}C / min till melting point in the presence of inert nitrogen (N2) using a duplicate sample of 5 mg in the crimped aluminum pan. The flow rate of purge gas is 2ml/minute (Soni *et al*., 2016).

Functional group characterization of CPR by using Fourier Transform Infrared spectroscopy (FTIR) studies

Fourier Transform Infrared spectroscopy (FTIR) was performed by BX2, Perkin Elmer; Norwalk, USA. The FTIR analysis was carried out to confirm the presence of the functional group in the compound. The method involved is of direct compression technique by using potassium bromide (KBr). The KBr pellet of approximately 1 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of KBr in pressure compression machine. The sample pellet was mounted in FTIR compartment and taken the scan at wavelength 4000cm^{-1} – 400cm^{-1}.

All optical measurements were performed at room temperature under ambient conditions (Soni *et al*., 2016).

Stability studies of MS in 0.1 M HCl (pH 1.2)

Stability studies of MS were performed in 0.1M HCl (pH 1.2) were determined in order to assure that whether the drug will remain stable throughout the period of drug release in acidic pH. In this 2 mg/ml, 3 mg/ml and 4 mg/ml solution of MS is prepared in 0.1 M HCl (pH 1.2). The temperature of the system is maintained at 37 ± 0.5 ^{0}C. One ml of the sample was withdrawn periodically with the help of a syringe and at the mouth 0.45 µm filter membrane was placed, replaced by freshly prepared 0.1 M HCl (pH 1.2). The samples are suitably diluted by the same followed by sonication for 5 minutes and were measured at 224 nm (Shimadzu UV-1800) (Soni *et al*., 2016; Verma *et al*., 2012).

Determination of drug content in formulations

The drug concentration in each formulation was determined in triplicate by emptying each capsule containing formulation in 0.1 M HCl at 37 ± 0.5 ^{0}C. This mixture is stirred for 2 hours at 200 rpm and analyzed at 224 nm using UV-Vis spectrophotometer (Soni *et al*., 2016; Verma *et al*., 2012).

Effect of pH and temperature on swelling behavior of CPR and determination of swelling kinetics

In order to study the swelling behavior of CPR (approximately 1.00 g) were dispersed in the different solvent: pH 1.2 buffer solution (0.1 M HCl), and pH 6.8 buffer solution (phosphate buffer). The CPR was placed in the swelling solution using dialysis membrane (M.W:1000 Dalton) and the weights of the swollen samples were measured against time after the excess surface water over the dialysis membrane was removed with a help of dry piece of filter paper (Martinez-Ruvalcaba *et al*., 2009). The swelling ratio (Q) for each sample at the specified time was calculated. Temperature also plays an important role in swelling behavior of polymers. In this work investigation of the swelling behavior of CPR at *in vitro* body temperature (37 ± 0.5 ^{0}C) and at extreme temperature 50 ± 0.5 ^{0}C was performed using dialysis membrane (M.W:1000 Dalton) as per the procedure described by Gupta *et al*., 2012. The weighed amount of CPR was placed in a dialysis bag (M.W:1000 Dalton) in pH 1.2 buffer solution (0.1 M HCl) by keeping temperature 37 ± 0.5 ^{0}C and 50 ± 0.5 ^{0}C using dissolution apparatus USP XXIV type II (paddle) apparatus (Electrolab; TDT-08L, Mumbai; India). The weights of the swollen samples were measured against time after the excess surface water over the dialysis membrane was removed with a help of filter paper.

The swelling ratio (Q) at different time interval and swelling rate kinetics (K) was for each concentration of CPR at different pH was calculated and reported.

Water Holding Capacity (WHC) determination for formulations

WHC was defined as the ratio (%) of gel weight after centrifugation to the original gel weight and was determined in triplicate. It was determined by the method reported by (Huang *et al*., 2003; Verma *et al*., 2012) by making some slight modifications. Individual formulations were kept in a dialysis membrane (1000 Dalton molecular weight) by holding both the sides tied with the help of thread. These formulations containing dialysis bags were transferred into the dissolution vessels containing 900 ml 0.1 M HCl (pH 1.2) maintaining temperature 37 ± 0.5 ^{0}C (Electrolab; TDT-08L, Mumbai; India). At specified intervals of time formulations from the dialysis bag transferred out in a graduated centrifuge tube for centrifugation at room temperature at 10000 rpm for 10 minutes. These contents were removed out from the tube weight taken and compared with the initial weight and again transferred into the dialysis bags for the procedure.

***In vitro* buoyancy studies**

The HBS capsules were placed in 900 ml of in simulated gastric fluid, pH 1.2 in USP XXIV type II apparatus (Electrolab; TDT-08L, Mumbai; India) at 50 rpm maintained at 37± 0.5°C. The time during which the formulations remained buoyant was observed and was taken as the floating time (Soni *et al*., 2016; Verma *et al*., 2012).

***In vitro* release studies and drug delivery kinetics**

All the prepared ordered mixed HBS capsules were immersed in 900 ml of 0.1 M HCl using USP XXIV type II

(paddle type) apparatus (Electrolab; TDT-08L, Mumbai; India) at 50 rpm having temperature 37± 0.5°C. Aliquots of 1 ml as samples were withdrawn with the help of syringe fitted with 0.45 µm membrane filter for analysis and an equal amount of fresh 0.1 M HCl was replaced in the dissolution vessel to maintain the sink condition (Soni *et al*., 2016). Obtained samples were analyzed for their absorbance at 224 nm and the concentration was determined by the standard curve of MS.

In order to explain the drug release from the formulation, various equations are used like Zero Order, First Order, Higuchi model, and Korsmeyer-Peppas equation was used. The dosage form which follows zero order kinetics follows to a uniform rate of drug release from the solid dosage form. The dosage form which follows zero order kinetics provides maximum therapeutic value with minimum side effects. First order release relates the initial amount release rapidly followed by decrease/sustaining the release of drug from the polymeric reservoir. Such type of systems in plasma not maintains the plasma drug concentration profile uniformity. Higuchi mechanism relates the drug release from the matrix system by the diffusion mechanism which is given by

$$Q = K \sqrt{t} \ldots \textbf{(1)}$$

Where Q is the accumulative amount of drug release from the polymeric matrixes after coming to the dissolution medium in time t and K denominates the release constant. Apart from this Korsmeyer-Peppas equation was also applied to investigate mechanism which takes place from the swollen polymeric matrices which are given by

$$Mt / M \infty = K t_n \ldots \textbf{(2)}$$

Where Mt / M ∞ is the fraction of drug released in time t and K is the structural and geometrical constant, and n, is the release exponent. If n = 0.5 it follows Fickian diffusion mechanism, if it 0.5 < n < 1.0, the release follows Non Fickian diffusion and diffusion mechanism if n = 1.0 and more than 1.0 it follows super case II transport (zero order). Korsmeyer Peppas equation explains the mechanism of drug release by the dual effect of diffusion and relaxation of polymeric strands after coming to the dissolution medium. Apart from r2 value, Akaike Information Criteria (AIC) was also used to validate the release kinetics value. AIC value was calculated by KinetDS-3.0 software.

$$AIC = n*In (WSSR) + 2*p \ldots \textbf{(3)}$$

Where n is the number of dissolution points, p is the number of parameters of the exemplary to be calculated and WSSR is the weighed sum square residues. When compared with the several models from a given set of data, the model which has the smallest AIC value is regarded as a best-fit model. All the models are applied to the first 60% of drug release from the controlled release polymeric matrices (Soni *et al*., 2016; Soni *et al*., 2017; Verma *et al*., 2012).

Statistical analysis

All the data were analyzed by Students t test to determine statistical differences between the results. A probability value $p < 0.05$ was considered statistically significant. Statistical analysis of obtaining the data was performed by using Graphpad Instat® software.

RESULTS AND DISCUSSION

Thermal Characterization of CPR

Figure 1 represents the thermal behavior of CPR under experimental condition. DTA shows the narrow endothermic peak at 288 ^{0}C (enthalpy 25.9 mJ/mg) which represents the glass transition temperature of biopolymer used. The exothermic peak at 499 ^{0}C (enthalpy -921 mJ/mg) and 636 ^{0}C (enthalpy -1.05 J/mg) represents the slow degradation of biopolymer. DTG and TG thermogram represent the biopolymer are stable up to the temperature of 290 ^{0}C, exothermic peak at 633 ^{0}C represents the degradation of biopolymer and maximum loss of mass 41.6% occurs from temperature 253 ^{0}C to 316 ^{0}C and 4.7% loss of mass occurs at temperature 639 ^{0}C.

Functional group characterization of CPR by using Fourier Transform Infrared spectroscopy (FTIR) studies

Figure 2 shows the FTIR spectra of CPR. The peak at 3403.46 cm^{-1} corresponds to the alcohol (O-H) stretching having strong and broad absorption intensity. Sharp and broad peak intensity at 2927.16 cm^{-1} corresponds to the CH_2 deformation having medium absorption intensity. Broad and sharp peak intensity at 1649.58 cm^{-1} corresponds to the alkene (C=C) having medium peak intensity which represents the tightly bound water adsorbed in the region of starch (Santha *et al*., 1990; Wilson *et al*., 1991). The peak intensity at 1412.57 cm^{-1} represents the C-O-O stretch, CH2 bending. Peak intensity at 1380.21 cm^{-1} represents the C-O-H bending, CH_2-twisting. Small peak intensity at 1241.86 cm^{-1} represents the CH_2OH (side chain) related mode. Broad, sharp peak intensity at 1156.98 cm-1 represents C-O, C-C stretching mode, whereas, the peak intensity at 1085.85 cm^{-1} represents C-O-H bending and the peak intensity at 1022.02 cm^{-1} and 931.48 cm^{-1} represents anhydro-glucose ring at O-C stretching. A FTIR spectrum below 800 cm^{-1} represents complex vibrational modes due to the skeletal mode vibrations of the pyranose ring in the glucose ring (Kizil *et al*., 2002; Huang *et al*., 2007). All these peaks are present in the parent peaks of starch as investigated by authors (Kizil *et al*., 2002; Huang *et al*., 2007; Santha *et al*., 1990); since we are using CPR as a novel biodegradable polymer for drug delivery technology this puffed rice also contains starch as its main constituent. From this FTIR we can say that the basic constituent present in CPR is starch on the preliminary basis which is used as buoyancy imparting agent.

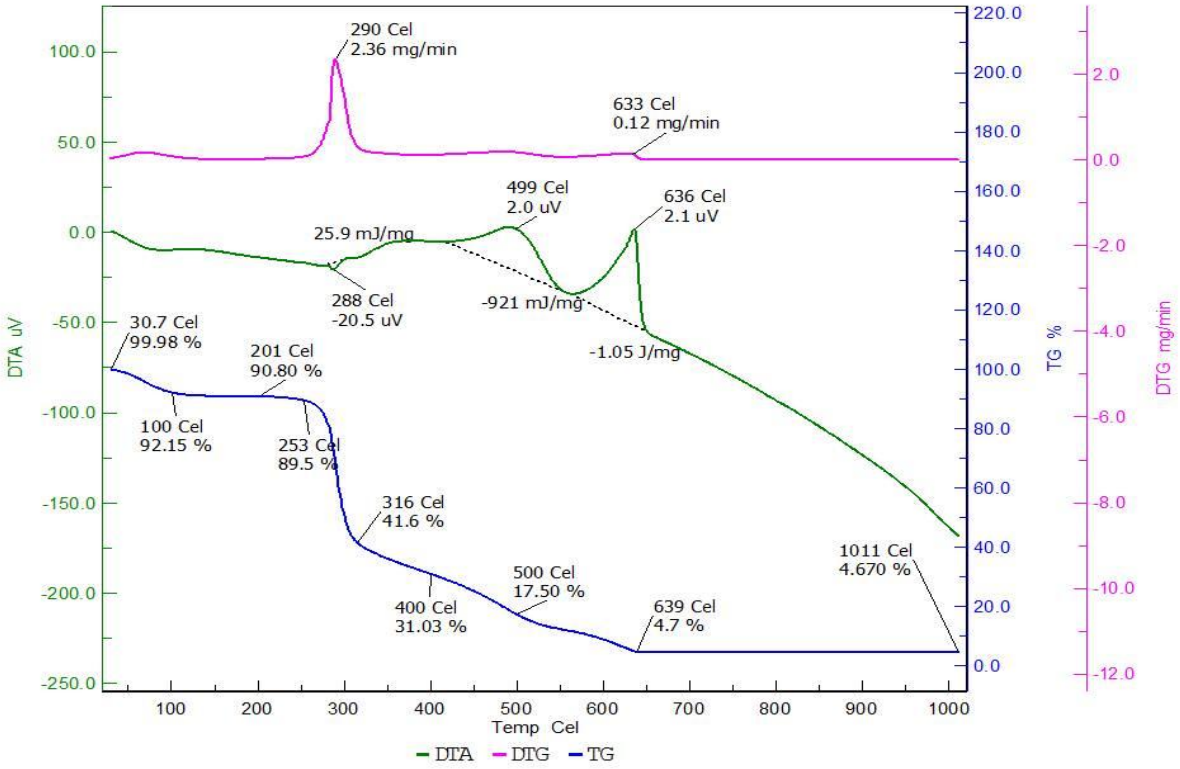

Fig. 1: Thermal characterization of CPR

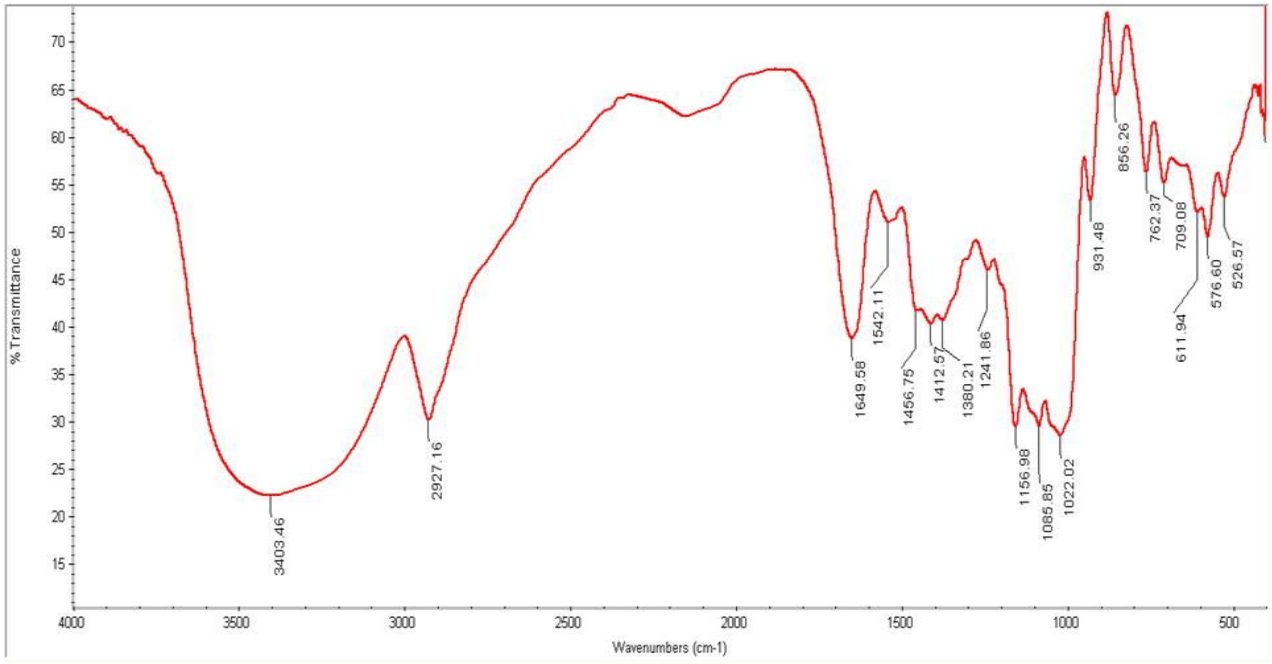

Fig. 2: FTIR spectra of CPR under wavelength of 4000cm-^{1} – 400cm-^{1}

Stability studies of MS in 0.1 M HCl (pH 1.2)

MS shows some degradation in 0.1 M HCl (pH 1.2) in the concentration range of 2 mg/ml, 3 mg/ml and 4 mg/ml but the degradation was not significantly found (figure 3) ($p > 0.05$). The debasement of the drug was not seen concentration dependent.

The debasement of the drug was not observed during drug release studies due to the formation of glassy polymeric structure in the dissolution media due to the nature of hydrophilic colloid it directly prevents the drug from the degradation. This assures the drug will be stable throughout the period of drug release in 0.1 M HCl (pH 1.2).

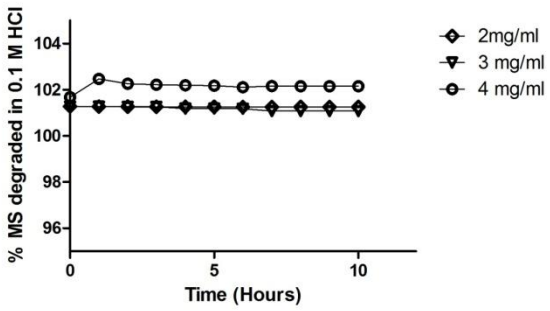

Fig. 3: % MS degradation in 0.1 M HCl (pH 1.2) (n=3, mean ± S.D)

Effect of pH and temperature on swelling behavior of CPR

During design and development of oral delivery of a drug (s), the formulator must consider the nature of pH throughout the gastrointestinal tract. It varies from acidic in the stomach to slightly alkaline in the intestine. The structure of the polymers with large numbers of pores connected to one another to form capillary channels is favorable for the easy diffusion of the swelling medium into the polymeric matrix and thus the rate limiting step for swelling of the polymers.

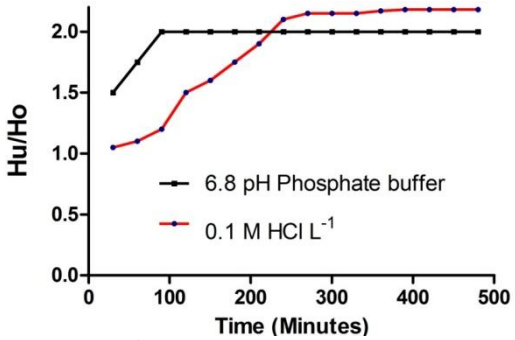

Fig. 4: Swelling index of CPR in 0.1 M HCl (pH 1.2) and 6.8 pH phosphate buffer (n=3, mean ± S.D)

Swelling of CPR in the pH 1.2 was significant good. Since CPR composed of carbohydrate group which can dissociate or get protonated at pH 1.2 of the swelling media, the degree of swelling of CPR underwent appreciable change (figure 4). At pH 1.2 slight swelling capacity of the CPR was observed due to the protonation of carbohydrate groups. The degree of ionization also caused an increase in ion osmotic pressure. Capillary wetting of interconnected open pores of CPR also responsible for a higher degree of swelling in the medium. When the pH reached 6.8, all the carbohydrate groups were converted to the salt form and the maximum swelling was obtained which accounted for similar swelling behaviors at alkaline pH. Swelling behavior of the CPR at different temperatures and pH 1.2 (*in vivo* body temperature; 37 ± 0.5 ^{0}C and 50 ± 0.5 ^{0}C) using dissolution apparatus was performed. As the temperature reaches to 37 ± 0.5 °C, the CPR swelled faster, and the equilibrium swelling ratio was enhanced accordingly. This was due to the disentanglement of interpenetrated swellable polymeric chains and destruction of hydrogen bonding between polymer molecules. At a higher temperature, the chain mobility was increased which helped the network expansion (Zhang *et al*., 2005). Such temperature responsiveness was also attributed to the high porosity of the CPR as the more pores would enhance the uptake of water during swelling in comparison with less porous hydrogels (figure 5).

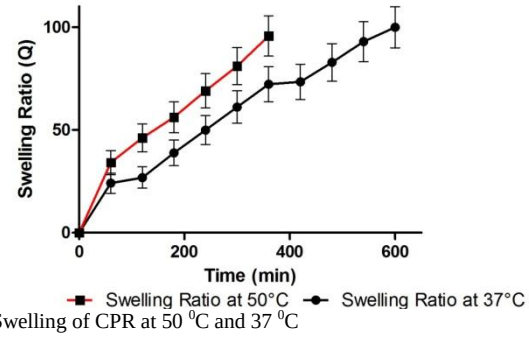

Fig. 5: Swelling of CPR at 50 ^{0}C and 37 ^{0}C

Effect of change in pH on CPR Swelling Kinetics

Lee *et al*., 1999 reported that the swelling of the polymer is described by the second order kinetics. For most of the pharmaceutical formulation for drug delivery and controlling the release of medicaments from the matrixes swelling of the polymer is the rate determining step (Lee *et al*., 1999). This second order kinetics is indicated by an equation

$dH/dt = k (Hu-H)^2$ … **(4)**

Where, k is swelling rate constant

By integrating the above second order equation, we get equation 5 and 6,

$t/H = 1/k_\infty + t/H_\infty$ … **(5)**

$k_\infty = kH^2$ … **(6)**

Where, k_∞ is the equilibrium swelling rate constant (table 2 and figure 6). When the swelling kinetics corresponds to a second order kinetics, Equation (4) is a linear relationship, and H_∞ and k corresponds to the slope and intercept of the line (Katime *et al*., 2004; Hanafi *et al*., 2000).

Table 2: Swelling rate constant (*k*)

Concentration of CPR (% weight)	Rate constant (k)	
	0.1 M HCl (pH 1.2)	6.8 pH phosphate buffer
0.5	0.030	0.039
5	0.045	0.050
10	0.085	0.098
15	0.120	0.134
20	0.190	0.234

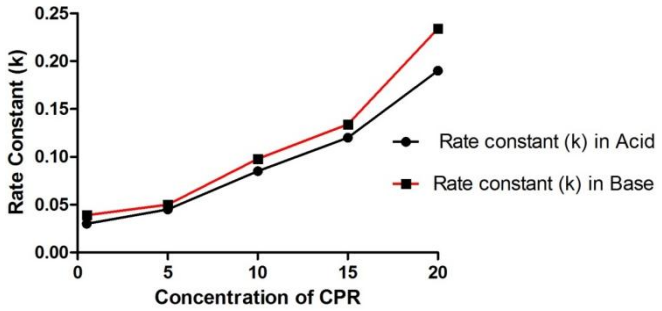

Fig. 6: Swelling rate constant (k) in acid; pH 1.2 and base; pH 6.8 (n=3, mean ± S.D)

Taking into the consideration that the swelling process is affected by specific relations between the molecules of the swelling medium and the polymer pendant groups' one can expect many kinds of polymer-swelling medium interactions, and probably a complex kinetics. The decrease in the swelling rate when the CPR concentration increases (k increases) suggests that specific interactions between the polymeric network loaded with CPR and the medium are weaker when compared to the interactions that occur with the polymeric network without CPR.

Water Holding Capacity (WHC) determination for formulations

Change in % WHC was used to illustrate the interaction potential of MS with CPR and along with the others auxiliary polymers like HMWCH and HPMC K15. CPR is dispersible in warm water (37 ^{0}C) to form viscous system alone and it's viscosity forming tendency increases when added with MS, HMWCH, and HPMC K15. MS when combines with CPR it forms the gel network type structure but its % WHC was not determined due to disruption of the structure after centrifugation. For efficient WHC, swelling of the polymer is the very rate-limiting step. HMWCH contains $–NH_2–$ groups bound by polymer chains. In the presence of acidic gelation medium, the polymer chains in HMWCH absorb dissolution medium and the binding of H^+ causes the polymer to swell ($NH3^+$). It was noted that the HBS capsule formulations prepared with MS and HMWCH, HPMC K15 and CPR alone have a different WHC profile (table 3 and figure 7). The poor % WHC could be attributed to the weak gel network formed due to the presence of highly soluble MS (192 mg/ml in 0.1M HCl at 37 ^{0}C). Thus, to increase the % WHC, the auxiliary polymers (HPMC K15 and HMWCH) were incorporated into HBS capsule formulations. These auxiliary polymers are expected to counter the rapid disruption of the gel layer, thereby preserving the unity of the swollen hydrogel.

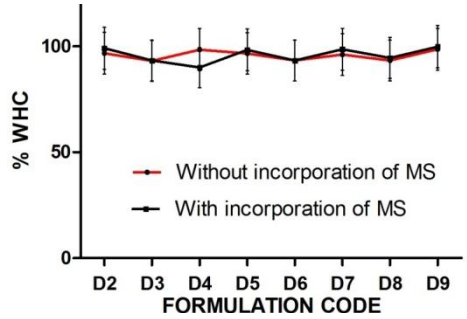

Fig. 7: WHC of formulations D1 – D9 (n=3, mean ± S.D)

All the formulations exhibited a better water holding capacity when MS was incorporated. It was noted that after the addition of auxiliary polymer % WHC increases. The addition of auxiliary polymer(s) resulted in improvement in swelling of the CPR which resulted in the increase in bulk volume. Without the incorporation of MS the % WHC decreases. This reason is attributed due to the MS being hydrophilic in nature, swelling of MS in acidic gelation medium will be a more entropy-favored process and as the number of ions within the hydrogel structure increases, more and more osmotic and electrostatic forces will be created within the hydrogel structure (Verma *et al*., 2017). This leads to increased dissolution medium (0.1M HCl) uptake and forces a typical hydrogel to behave thermodynamically like a liquid as it occupies more space. Moreover, MS being highly hydrophilic, this further dilutes the effectiveness of the aqueous gel layer due to high diffusion driving force and consequently increased erosion. As a result, this hydrogel lost its integrity and became distorted, leading to burst after centrifugation.

This above all the findings reveals that the all the formulations (D1-D9) remained buoyant during the drug release studies. This parameters are the rate limiting steps for the achieving the gastroretention.

Table 3: WHC determination of formulations D1-D9.

Formulation code	Experimental study time (Hours)	Without incorporation of MS		With incorporation of MS	
		Weight of mass before centrifugation (mg)	%WHC After centrifugation	Weight of mass before centrifugation (mg)	%WHC After centrifugation
D1	05	75	N.D	100	N.D
D2	06	150	96.78 ± 0.05	175	99.12 ± 1.13
D3	08	150	93.12 ± 1.11	175	93.33 ± 1.11
D4	09	150	98.48 ± 0.90	175	90.00 ± 2.09
D5	07	75	96.66 ± 1.12	100	98.33 ± 1.43
D6	07	75	93.33 ± 1.19	100	93.32 ± 1.54
D7	08	150	96.16 ± 1.87	200	98.65 ± 1.23
D8	08	150	93.33 ± 0.56	200	94.53 ± 1.98
D9	09	150	98.66 ± 1.45	200	99.89 ± 1.89

Table 4: Lag time, *in vitro* buoyancy studies and % Drug concentration determination

Formulation code	Floating lag time (Seconds)	Buoyancy time (Hours)	% Drug concentration uniformity*	Comments
D1	Nil	Buoyant for 05 hours	95.56 ± 1.10	Remained buoyant for 05 hr as a regular polymeric raft after the disruption of capsule shell. Initially remained unwetted throughout the period of buoyancy. Drug release was found to be erratic.
D2	Nil	Buoyant for 06 hours	97.89 ± 1.56	Remained buoyant for 06 hr. Acquired the shape of a cylindrical mass after the disruption of capsule shell (t = 0.5 hours). Drug release was retarded up to 06 hr.
D3	Nil	Buoyant for 08 hours	95.45 ± 1.62	Formulation sank after 08 hr. Acquired the shape of irregular gel matrix. Drug release was retarded up to 08 hr but irregular.
D4	Nil	Buoyant for 09 hours	98.10 ± 1.11	Formulation sank after 09hr. Acquired the shape of cylindrical gel matrix. Drug release was retarded up to 08 hr and release pattern was found to be smooth.
D5	Nil	Buoyant for 07 hours	96.48 ± 1.34	Remained buoyant up to 07 hr. Formulation acquired the shape of irregular gel matrix. Drug release was retarded up to 4hr and release pattern was found to be regular and system doesn't hold the drug for longer period of time. After 05 hours irregular gel matrix ruptures.
D6	Nil	Buoyant for 07 hours	68.45 ± 1.27	Remained buoyant up to 07 hr. Formulation acquired the shape of regular gel matrix. System does not hold the MS for longer period of time.
D7	Nil	Buoyant for 08 hours	97.89 ± 1.35	Remained buoyant up to 08 hr. Formulation acquired the shape of cylindrical gel matrix. Drug release was retarded up to 07 hr. Drug release was retarded and release pattern was found to be regular.
D8	Nil	Buoyant for 08 hours	95.56 ± 1.61	Remained buoyant up to 08 hr. Formulation acquired the shape of cylindrical gel matrix. Drug release was retarded up to 08 hr and release pattern was found to be regular.
D9	Nil	Buoyant for 09 hours	98.89 ± 1.01	Remained buoyant up to 09 hr. Formulation acquired the shape of cylindrical gel matrix. Drug release was retarded up to 09 hr and release pattern was found to be regular.

*****All determinations were carried out in triplicate, mean ± SD (n=3)

Drug Release Studies

The dissolution profile of the MS loaded formulations filled in hard gelatin colorless capsule shell size 1, was performed under experimental conditions (pH; 0.1 M HCl (pH 1.2), USP apparatus type II, temperature; 37±0.5 ^{0}C, rpm; 50) as shown in figure 8 and 9. In the present study, we have chosen the CPR, Chitosan, and HPMC because of its ability to release the loaded drug slowly in the stomach and they are biodegradable polymers. None of the work reported in the history of drug delivery technology using CPR as gastroretentive technique. Chitosan has received attention due to its excellent biocompatibility, biodegradability, and nontoxicity. Chitosan fulfills all the polymeric attributes that are pertinent to the high level of retention of applied and targeted sites via mucoadhesive bonds. The mucoadhesive property of Chitosan is due to an electrostatic interaction of the protonated amino group in Chitosan with negatively charged silicic acid residues in mucin (the glycoprotein that composes the mucus). This interaction takes place very near to the mucosal surface and thus possesses potential to confer significant gastroretention to the hydrogel. Additionally, the hydroxyl and amino groups may interact with mucus via hydrogen bonding. Along with CPR, auxiliary polymers, HPMC and HMWCH used alone and in combination both. When auxiliary polymers are used they are expected to delay the release of MS from the monolithic system by counteracting the rapid erosion process and maintaining the developed hydrogel structure. Formulation D1 shows the 68.89 % release of MS in the first three hours this is due to alone CPR is being hydrophilic polymer when it comes in contact with dissolution media it forms an hydrogel structure due to entropy favored process number of ions in hydrogel structure increases more and more osmotic and electrostatic forces created in the hydrogel structure. Being MS highly hydrophilic in nature, this reduces the aqueous gel layer due to high diffusion force and leads to erosion of a monolithic system. Due to this hydrogel lost its integrity and leading to burst release. In the formulation, D2 and D3 are combined CPR with CH and HPMC retardation time with MC increases in 06 and 08 hours and showing % drug release 97.89 and 94.45 respectively. This is attributed due to these polymers helps in interacting with CPR to form hydrogel type structure which helps in sustaining the MS for the longer period of time and also prevents the dilution of hydrogel structure.

Formulation D4 shows the significant ($p < 0.01$, D2 and D3) retardation when the equal proportion of HMWCH and HPMC was used only 35.67 % MS release was found in the first three hours of study. But when alone HMWCH and HPMC used with MS in formulations D5 and D6, after 04 hours and 03 hours, respectively hydrogel structure disrupted due to the development of osmotic and electrostatic forces. In formulation D7, D8 and D9 on increasing the concentration of MS the release profile significantly increased and also the retardation time (1-2 hours) as compared to formulations D1-D6. This type of behavior attributed due to the in increasing the concentration of MS leads to high a degree of ordering and crystal-like properties and have quite a compact structures development after exposure to dissolution medium. In this, there is a relatively quick gel formation due to association/dissociation/binding of ions with the polymer hydrogel structures (figure 10).

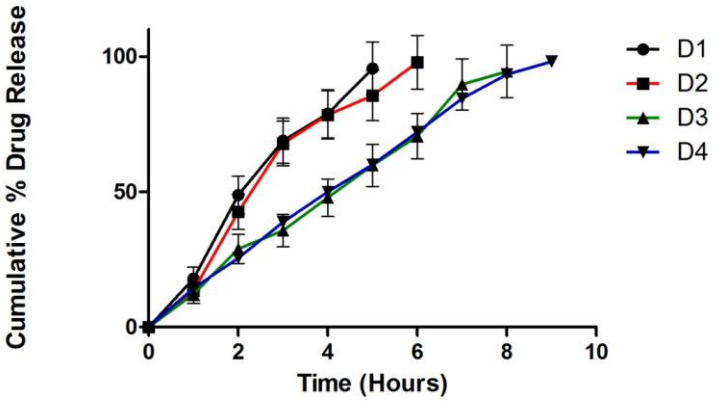

Fig 8: Cumulative % Drug Release of formulations D1 – D4 in 0.1 M HCl (pH 1.2) (n=3, mean ± S.D).

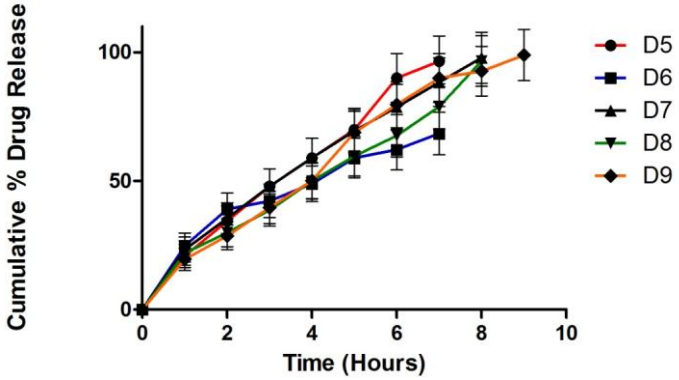

Fig. 9: Cumulative % Drug Release of formulations D5 – D9 in 0.1 M HCl (pH 1.2) (n=3, mean ± S.D).

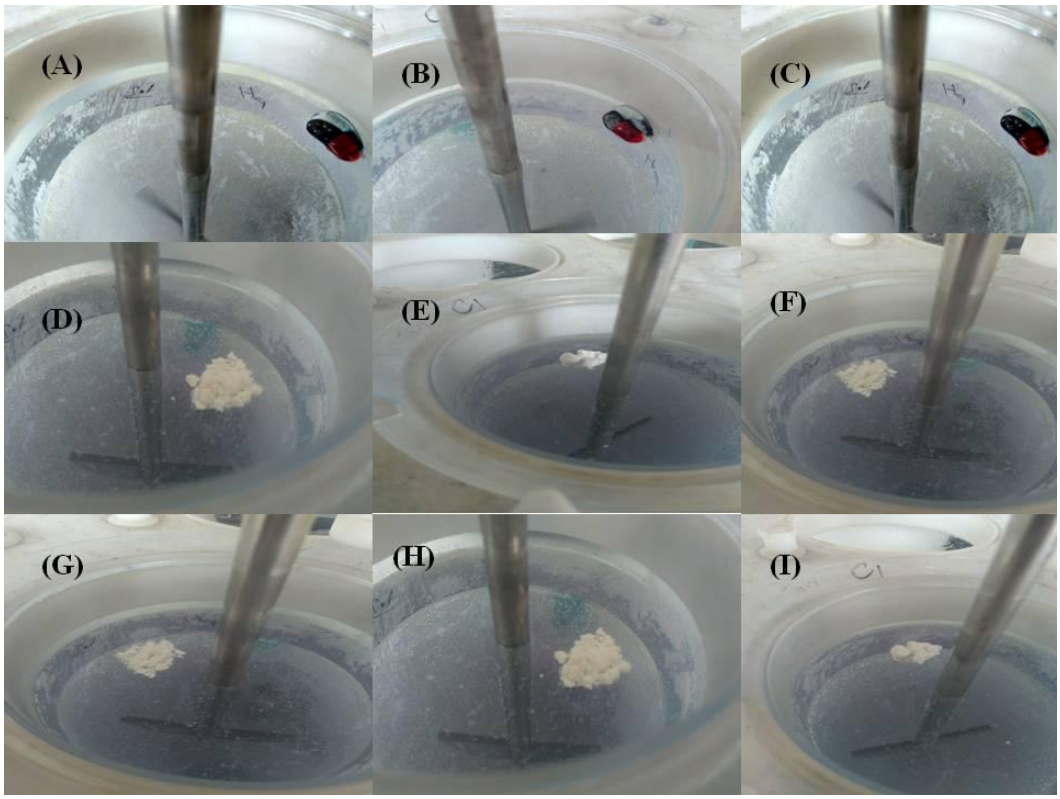

Fig. 10: Representing changes in the structure of HBS capsule system bearing MS after coming in contact with dissolution medium in 0.1 M HCl and remained buoyant for 09 hour; formulation D4 **(A)** after 15 minutes **(B)** after 30 minutes **(C)** after 45 minutes **(D)** after 01 hour **(E)** after 03 hour **(F)** after 05 hour **(G)** after 07 hour **(H)** after 08 hour **(I)** after 09 hour of study without sinking in the dissolution media

Table 5: Drug delivery kinetic and AIC value determination, determined for amount of drug which releases up to 60% (t 60 %).

Code	r^2				n -Value	AIC Value			Comments
	Zero Order	First Order	Higuchi model	Korsmeyer-Peppas		Zero Order	First Order	Higuchi model	
D1	0.9966	0.7104	0.9071	0.9430	0.45	41.76	53.23	45.90	Zero order model and Fickian diffusion
D2	0.9967	0.8768	0.7749	0.9530	0.40	39.56	60.12	69.45	Zero order model and Fickian diffusion
D3	0.9548	0.8760	0.8096	0.7886	0.44	56.32	88.12	61.51	Zero order model and Fickian diffusion
D4	0.9987	0.9670	0.8689	0.9731	0.43	58.89	97.65	65.98	Zero order model and Fickian diffusion
D5	0.9893	0.9751	0.9740	0.9523	0.42	43.56	64.12	89.87	Zero order model and Fickian diffusion
D6	0.9875	0.8604	0.7933	0.8974	0.43	58.89	96.78	89.90	Zero order model and Fickian diffusion
D7	0.9787	0.8764	0.8692	0.9764	0.45	44.43	87.78	49.67	Zero order model and Fickian diffusion
D8	0.9985	0.9127	0.8768	0.9122	0.44	52.98	88.23	66.01	Zero order model and Fickian diffusion
D9	0.9854	0.8967	0.9117	0.9014	0.43	65.98	82.23	56.56	Zero order model and Fickian diffusion

Drug Delivery kinetics and Akaike Information Criterion (AIC) value determination

Drug release rate depends on the water penetration rate, swelling properties of the polymer, diffusion of drug through the matrixes before and after erosion when it gets in contact with the dissolution media. From the data generated from release kinetics formulations D1-D9 zero order kinetics which is shown by its r^2 value. Zero-order kinetics refers the nearly uniform drug release rate, which is independent of its concentration of the drug; this type of system also shows minimum side effects. Zero-order kinetics r^2 value ranges from 0.9548 to 0.9987 and n value ranges from 0.40 to 0.45. Formulation D1- D9 follows the Fickian model. It means that the drug release from the monolithic barrier is controlled by drug diffusion through the gel barrier. When these formulations come in touch with the dissolution medium due to hydration it causes swelling which leads the development of façade viz: swelling façade, diffusion and erosion façade and all these facades are the governing parameters for the apparent motion of macromolecules from the matrix. Fickian diffusion release occurs by molecular diffusion of the drug due to a chemical potential gradient.

In addition to drug release kinetics, Akaike Information Criterion (AIC) was also determined and it is a measurement of goodness of fit. When compared with several models of data, the model related with the smallest AIC is considered as best fit model. AIC values determination reconfirms the formulations D1-D9 follows zero order kinetics (table 5).

CONCLUSION

The current experimental study was conducted to get insight into the suitability of CPR, HMWCH and HPMC K15 as a carrier for the single unit HBS capsule for stomach specific drug delivery for MS. HBS capsule formulations based on CPR shows excellent buoyancy imparting agent as well as drug retarding rate also significantly increases when used in combination with other auxiliary polymers. Since, CPR has been new in the field of drug delivery technology and also as a polymer for achieving gastroretention, its low density attracted us to use as an agent which promotes the buoyancy. HBS capsules based on CPR with different grades of HPMC K15 and HMWCH as carrier reflects excellent *in vitro* buoyancy and were found capable of sustaining the MS release in the upper part of the GI tract. Considering the experimental results of the current experimental investigation, it can be concluded that CPR alone and in combination with HPMC K15 and HMWCH can be used as a potential carrier material for the development of single-unit HBS system for stomach specific sustained release of hydrophilic drugs with absorption window in the upper GIT. However, CPR needs an exploration in future for drug delivery technology in different pH, different organ/tissue target, with combination with different polymers and alone itself.

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT

This research work supported by Sardar Bhagwan Singh PG Institute of Biomedical Sciences and Research, Dehradun, India. Authors are thankful to Indian Institute of Technology; IIT, Roorkee, India for characterization of samples. This paper is based, in part, on the work done for a Ph.D. degree of IFTM University, Moradabad, India by one of the author.

Conflict of Interests: There are no conflicts of interest.

REFERENCES

Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics, 2012; 81(3): 463-469. doi: doi.org/10.1016/j.ejpb.2012.04.007

Blomqvist I, Westergren G, Sandberg A, Jonsson UE, Lundborg P. Pharmacokinetics and pharmacodynamics of controlled-release metoprolol: a comparison with atenolol. European Journal of Clinical Pharmacology, 1988; 33(1): 519-524.

Boldhane S, Kuchekar B. Development and optimization of metoprolol succinate gastroretentive drug delivery system. Acta pharmaceutica, 2010; 60(4): 415-425.

Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Tropical Journal of Pharmaceutical Research, 2008; 7(3): 1055-1066. DOI: dx.doi.org/10.314/tjpr.v7i3.14691

Gupta NV, Shivakumar HG. Investigation of swelling behavior and mechanical properties of a pH-sensitive superporous hydrogel composite. Iranian journal of pharmaceutical research, 2012; 11(2): 481-489. PMCID: PMC3832170

Hanafi M, Amin S, Efrina D, Suwandi B. The Use of Shrimp Shell for Chitosan and Glucosamine. J. Kimia. Terapan, 2000; 10(1-2):17-21.

Huang CB, Jeng R, Sain M, Saville B, Hubbes M. Production, characterization, and mechanical properties of starch modified by Ophiostoma spp. Bioresources, 2007; 1(2): 257-269.

Huang Y, Tang J, Swanson BG, Rasco BA. Effect of calcium concentration on textural properties of high and low acyl mixed gellan gels. Carbohydrate Polymers, 2003; 54(4): 517-522.

Jobin G, Cortot A, Godbillon J, Duval M, Schoeller JP, Hirtz J, Bernier JJ. Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in stomach, duodenum, and jejunum, Br. J. Clin. Pharmacology, 1985; 19: 97–105.

Katime IA, Katime O, Katime D. Smart materials of this millenium: Macromolecular hydrogels. Servicio Editorial de la Universidad del Pais Vasco: Bilbao. 2004.

Kendall MJ, Maxwell SR, Sandberg A, Westergren G. Controlled release Metoprolol. Clinical pharmacokinetic and therapeutic implications. Clinical Pharmacokinetics, 1991; 21: 319–330. PMID: 1773547, DOI: 10.2165/00003088-199121050-00001

Kizil R, Irudayaraj J, Seetharaman K. Characterization of irradiated starches by using FT-Raman and FTIR spectroscopy. Journal of agricultural and food chemistry, 2002; 50(14): 3912-3918.

Lee JW, Kim SY, Kim SS, Lee YM, Lee KH, Kim SJ. Synthesis and characteristics of interpenetrating polymer network hydrogel composed of chitosan and poly (acrylic acid). Journal of Applied Polymer Science, 1999; 73: 113–120. DOI: 10.1002/(SICI)10974628(19990705)73:1<113::AIDAPP13>3.0.CO;2-D

Martinez-Ruvalcaba A, Sánchez-Díaz JC, Becerra F, Cruz-Barba LE, González-Álvarez A. Swelling characterization and drug delivery kinetics of polyacrylamide-co-itaconic acid/chitosan hydrogels. Express Polymer Letters, 2009; 3(1): 25-32. DOI: 10.3144/expresspolymlett.2009.5

Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing Metoprolol tartrate as a model drug for gastric retention. AAPS Pharm. Sci. Tech, 2006; 7, 23–29. DOI: 10.1208/pt070234.

Ravishankar H, Patil P, Samel A, Petereit HU, Lizio R, Iyer-Chavan J. Modulated release Metoprolol Succinate formulation based on ionic interactions: *in-vivo* proof of concept. J. Control. Rel, 2006; 111: 65–72.

Sandberg A, Blomqvist I, Jonsson UE, Lundborg P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. European journal of clinical pharmacology, 1988: 33; S9-S14.

Santha N, Sudha KG, Vijayakumari KP, Nayar VU, Moorthy SN. Raman and infrared spectra of starch samples of sweet potato and cassava. Journal of Chemical Sciences, 1990; 102(5): 705-12.

Sonaje K, Chuang EY, Lin KJ, Yen TC, Su FY, Tseng MT, Sung HW. Opening of epithelial tight junctions and enhancement of paracellular permeation by chitosan: microscopic, ultrastructural and computed-tomographic observations. Molecular pharmaceutics, 2012; 9(5):1271-79.

Soni S, Verma A, Ram V. Evaluation of Chitosan-Hydroxy Propyl Methyl Cellulose as a Single Unit Hydrodynamically Balanced Sustained Release Matrices for Stomach Specific Delivery of Piroxicam. MOJ Bioequivalence Availability, 2016; 1(3): 1-14. DOI: 10.15406/mojbb.2015.01.00014

Soni S, Verma N, Verma A, Pandit JK. Gelucire based floating emulsion gel beads: a potential carrier for sustained stomach specific drug delivery. FARMACIA, 2017; 65(1): 142-152.

Verma A, Bansal A, Ghosh A, Pandit, J. Low molecular mass chitosan as carrier for a hydrodynamically balanced system for sustained delivery of ciprofloxacin hydrochloride. Acta Pharmaceutica, 2012; 62(2): 237-250. DOI: doi.org/10.2478/v10007-012-0013-2

Verma A, Dubey J, Verma N, Nayak A. Chitosan-Hydroxypropyl Methylcellulose Matrices as Carriers for Hydrodynamically Balanced Capsules of Moxifloxacin HCl. Current drug delivery, 2017; 14(1): 83-90.

Verma A, Wahi AK, Pandit JK. Effect of crosslinking with Ca^{++} and Zn^{++} in the formation of gellan gum gels. Lat Am J Pharm, 2012; 31: 815-820.

Wikstrand J, Andersson B, Kendall MJ, Stanbrook H, Klibaner M. Pharmacokinetic considerations of formulation: extended-release metoprolol succinate in the treatment of heart failure. Journal of Cardiovascular Pharmacology, 2003; *41*(2): 151-157.

Wilson RH, Goodfellow BJ, Belton PS, Osborne BG, Oliver G, Russell PL. Comparison of Fourier transform mid infrared spectroscopy and near infrared reflectance spectroscopy with differential scanning calorimetry for the study of the staling of bread. Journal of the Science of Food and Agriculture, 1991; 54(3): 471-83.

Zhang JP, Li A, Wang AQ. Study on superabsorbent composite. V. Synthesis, swelling behaviors and application of poly (acrylic acid-co-acrylamide)/sodium humate/attapulgite superabsorbent composite. Polymers for advanced technologies, 2005; 16(11-12): 813-820

How to cite this article:

Soni S, Ram V, Verma A. Crushed Puffed Rice-HPMC-Chitosan based Single-Unit Hydro-dynamically Balanced System for the Sustained Stomach Specific Delivery of Metoprolol Succinate. J App Pharm Sci, 2017; 7 (12): 047-057.