Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Development and Evaluation of Superporous Hydrogels for Metoprolol Tartrate as a Gastro Retentive System

SHWETHA K, SWAMY NGN*

Department of pharmaceutics, Government College of Pharmacy, Bangalore–560027

ARTICLE DETAILS

Article history:
Received on 03 June 2012
Modified on 20 June 2012
Accepted on 25 June 2012

Keywords:
Gastro-retentive drug delivery,
Superporous hydrogels,
Chitosan,
Hydroxypropyl guar,
Metoprolol tartrate,
Swelling ratio

ABSTRACT

The aim of this work was to synthesize semi-Interpenetrating Polymer Network superporous hydrogels of hydroxypropyl guar and chitosan, by cross-linking chitosan with glyoxal and to study its swelling behavior for application as a gastro-retentive drug delivery system. Chitosan- hydroxypropyl guar superporous hydrogels of metoprolol tartrate were synthesized by gas blowing method. The effect of pH on the swelling ratio was determined. Swelling reversibility studies were also carried out. Fourier transform infrared spectroscopy analysis and scanning electron microscopy studies were undertaken to characterize the drug loaded super porous hydrogels, while dissolution studies were carried out to assess release characteristics. Swelling was highly dependent on the extent of cross-linking and the amount of the polymer present in formulation. The higher the amount of cross-linking agent, lower was the swelling ratio. The superporous hydrogels were highly sensitive to pH of swelling medium, and showed reversible swelling and de-swelling behaviour while still retaining their mechanical stability. Apparent density was dependent on the volume of the superporous hydrogels and decreased with increasing crosslink density. Degradation kinetics showed that chitosan superporous hydrogels had good water retention capability. Drug release was inversely related to the amount of cross-linking agent. The studies revealed that chitosan- hydroxypropyl guar superporous hydrogels can be used as a gastro-retentive drug delivery system in view of their swelling characteristics in acidic pH.

INTRODUCTION

The gastric retention device is designed to be suspended in the stomach for a long period of time to prolong the release of drugs, minimizing their loss while treating disease, particularly in the gastric environment[1]. several approaches are being designed and developed for increasing the residence time of dosage form in the GIT such as: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems, unfoldable, extendible, or swellable superporous hydrogel systems (SPH), magnetic systems etc[2]. Superporous hydrogels (SPHs) are a three-dimensional network of hydrophilic polymers that absorb a considerable amount of water in a very short period of time due to the presence of many pores with diameters ranging from micron to millimeter scale[3].

Author for Correspondence:
Email: ngnswami@yahoo.co.in

SPHs are hydrogels with numerous pores connected together to form open channel structures. Water is absorbed into the dried SPHs by capillary wetting rather than by diffusion. This makes swelling of dried hydrogels extremely fast (swelling in minutes). SPH composite swell to their equilibrium size in less than a few min regardless of the size of the dried form[4]. Several important properties of SPHs, such as fast swelling, large swelling ratio, and surface slipperiness, make them an excellent candidate to develop gastric retention devices[5]. Poly-electrolytes are ideally suited for the preparation of pH-sensitive hydrogels. Chitosan is a polyelectrolyte and is obtained from renewable resources. It is a linear, semi-rigid polysaccharide and is biodegradable, biocompatible and is of relatively low toxicity; it is a co-polymer of N-acetyl D-glucosamine and D-glucosamine. Because chitosan has abundant amine groups within its polymer chain, it dissolves in acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal.

In low pH solution, chitosan hydrogels swell due to the presence of positive charges in the network[6]. Metoprolol tartrate (MT) is a β_1-selective adrenergic blocking agent. When MT conventional tablets are administered with food rather than on an empty stomach, peak plasma concentrations are higher and the extent of absorption of the drug is increased. The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half-life of MT is ~3 to 4 h, 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 MT absorption in the duodenum and jejunum is directly proportional to the dose availability[7]. In the present work, an attempt has been made to formulate gastro-retentive drug delivery system (GRDDS) of MT using chitosan and hydroxyl propyl guar gum (HPG) of different concentrations in order to achieve the desired drug release in the stomach.

EXPERIMENTAL

Materials and methods

MT was obtained as a gift sample from Astra Zeneca India Pvt Ltd (Bangalore). Chitosan was obtained from Central Institute of Fisheries Technology, Kochi. HPG was generously donated by Encore Polymers, Ahmedabad. Glyoxal 40% aqueous solution used was from Sisco-research laboratories, Bangalore. Calcium chloride used was from Qaligens fine chemicals, Mumbai. Sodium bi-carbonate was gifted from Ce-Chem Pvt Ltd, Bangalore. Pluronic F127 of signet chemicals, Mumbai and Glacial acetic acid of Rankem (RFCL limited) Mumbai were used in the study.

Synthesis of SPHs containing semi-Interpenetrating polymer network

4 g of chitosan was dissolved in 100ml of 0.1M acetic acid solution to obtain the stock solution. An amount of the stock solution (3ml, 4ml, and 5ml) was placed in test tubes, and then 10% Glyoxal aqueous solution (0.15ml, 0.2ml and 0.25 ml respectively) was added to induce network structures. The pH of the solution was adjusted to 5 by adding 0.1M acetic acid. Sodium bicarbonate (50, 60, 70, 80, 90 mg) was added to the mixture and vigorously stirred for 10 to 30 s. Foaming ensured immediately after the addition of sodium bicarbonate and gelation was complete in the 30 to 60 s. Pluronic F127 was added as the foam stabilizer. The foamed SPHs were washed with 20ml of acetone 3 times. The SPHs obtained were allowed to stand overnight to complete the cross-linking reaction at room temperature.

Drug loading

The drug selected for the study was MT. The method of soaking or equilibrium was employed for drug loading. In this method, the amount of buffer necessary for complete swelling of SPHs was first determined. Thereafter, drug solution of required concentration was prepared and SPHs was placed in it and left until all the drug solution was sucked up. The completely swollen SPH loaded with the drug was dried at room temperature overnight[4,6].

Swelling studies

The dried SPH was allowed to hydrate in excess of swelling medium (25ml) at room temperature. At various time intervals, the hydrogel was removed from the solution and weighed after excess solution on the surface was blotted. The experiments were carried out three times for each sample, and the average was used to determine its swelling ratio. The swelling ratio (Q) was calculated by the following equation:

$$Q = (M_s - M_d) / M_d$$

Where,

M_s and M_d are the weight of the hydrogel in the swollen and dried states, respectively.

The swelling/de-swelling behaviors of the superporous hydrogels were examined by repeating the same experiments at two different pHs, pH 7.0 and pH 1.2[4,11].

Swelling reversibility studies

Pulsatile pH-dependent swelling of the superporous hydrogels was evaluated by alternation of the swelling medium between the 0.1N HCl solution (pH 1.2) and phosphate buffered solution (PBS, pH 7.4). The hydrogels were first swollen in pH 1.2 HCl solutions for 30 min. The swollen hydrogels in the HCl solution were weighed at each given time and transferred to the phosphate buffered solution. The same procedures were performed for swelling in PBS before transferring the swollen hydrogels back to the HCl solution. The hydrogels were transferred to the alternating solutions every 30 m[6].

Determination of gelation kinetics

As gelation (polymerization reaction) proceeded, the viscosity of the mixture continuously increased until the full network structure was established. Gelation time was defined as the

duration of gel formation and was measured with a simple tilting method after adjustment of pH to 5.0 with acetic acid. This parameter was taken as the time taken until the reactant mixture was no longer able to descend in the tilted tube position[4].

Evaluation of degradation kinetics

The degradation kinetics of the hydrogels was examined by measuring the swelling ratio as a function of water retention. The hydrogels were placed in pH 1.2 (0.1 N HCl) medium at 37°C for 12 h and the samples were periodically weighed at 6 h interval. Water retention capacity (WR_t) as a function of time was assessed according to the following equation;

$$WR_t = (W_p - W_d) / (W_s - W_d)$$

Where,

W_d is the weight of the dried hydrogel,

W_s the weight of the fully swollen hydrogel,

W_p the weight of the hydrogel at various exposure times[6].

Density of superporous hydrogel

The density (d) of the dried hydrogels was calculated by equation.

$$d = W/V$$

Where, W is the weight of dried hydrogel and V is its volume. The volume of the hydrogel was determined by the solvent displacement method using hexane as the displacement fluid. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it[5].

***In vitro* drug release studies**

The *in vitro* release of MT from the superporous hydrogels was carried out at 37 ± 0.5 °C in 900 ml of 0.1N HCl using USP XXIV Type 2 (paddle type). The medium was stirred at 100 rpm and 5 ml aliquots were withdrawn at specified time intervals; to maintain sink conditions; 5 ml of dissolution medium was immediately added after each sample was removed. MT was assayed spectrophotometrically[17].

RESULTS AND DISCUSSIONS

Swelling studies

The swelling ratios of all formulations in 0.1N HCl solution are represented in Fig 1. The swelling ratio of the prepared formulations in HCl solution was found to increase with time. Swelling was also found to be dependent on concentration of chitosan, glyoxal, HPG and sodium bicarbonate. The swelling ratios of superporous hydrogels decreased by increasing the cross-linking density, as much tighter networks were formed at higher concentration of cross-linking agents. Swelling ratios of superporous hydrogels decreased by increase in the concentration of HPG, as much tighter networks were formed because the pores are closed by HPG polymer, reducing the flexibility of polymeric chains retarding their swelling. The bicarbonate concentration was effective at certain optimum acid concentration on the foam volume. Increased resultant foam volume resulted in better swelling properties; increased bicarbonate or acid components generally result in increased foam volume, swelling capacity, capillary absorption and decreased resiliency, diffusional absorption and foam homogeneity.

Swelling reversibility studies

These studies show the swelling reversibility of the superporous hydrogel between pH 1.2 and pH 7.4 solutions. They were able absorb and de-absorb the swelling medium quickly upon the pH change from acidic to basic conditions quickly and vice versa. The time required for swelling was longer than that for deswelling of the hydrogels.

Gelation kinetics

The gelation kinetics give good information to determine the addition time of blowing agent (sodium bicarbonate). The foaming reaction took place only under the acidic condition (pH 5.0-5.5) and therefore the pH was adjusted to 5.0. The optimal pH for the gelation was around 7–8, where the polymerization proceeds rapidly and the gelling usually started within 0.5-1.0 m. Hence sodium bicarbonate was added 30s after the adjustment of pH to 5.0.

Degradation kinetics

As shown in Fig. 2, the weight loss of chitosan hydrogels occurred after 12h. Lower the concentration of the cross-linking agent, the faster was the loss of water from the superporous hydrogel. The superporous hydrogel consisting of higher amount of glyoxal had decreased polymer rigidity, thus improving the resiliency of the polymer in response to compression and prevention of the water loss efficiently. Hence, an increase in the amount of glyoxal decreased the rate of loss of water.

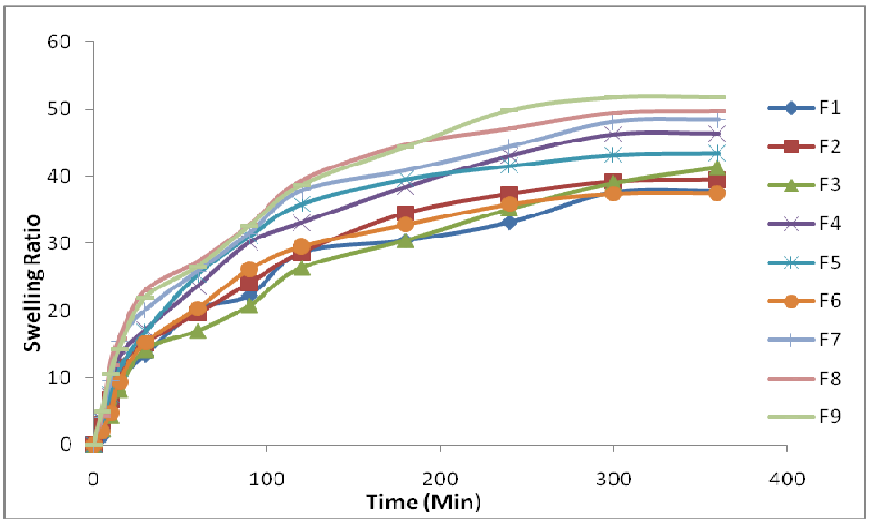

Figure 1: Swelling behaviours of chitosan hydrogels

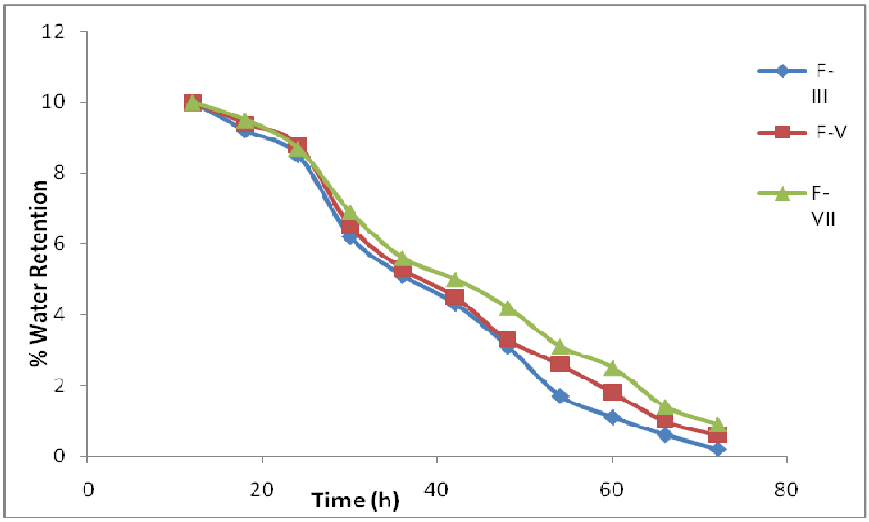

Figure 2: Water retention capacity of superporous hydrogels

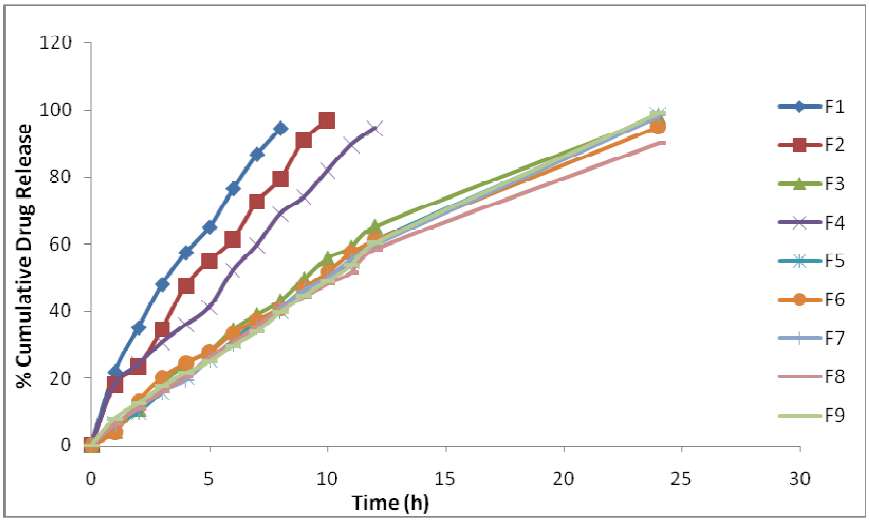

Figure 3: *In vitro* release of prepared metoprolol tartrate from superporous hydrogels

Density of the superporous hydrogels

The apparent densities of the various superporous hydrogels ranged between 0.786 and 0.871 g/cm^3. Since the hydrogels are very porous, the measured density is related to the porosity of the polymer and can be defined as apparent density. The actual density of the polymer is the same but when the polymer has fewer pores, the occupied volume will be less, thus resulting in high apparent density. Therefore, higher the concentration of the cross-linking agent, the greater is the apparent density.

***In-vitro* drug release studies from SPHs**

The *in-vitro* MT release data from the superporous hydrogels is depicted in Fig 3. The data obtained showed that increase in concentration of HPG and chitosan prolong the release of the drug. Complete drug release was observed within 10 hrs for formulations F-I and F-II, where as the formulation F-III , FV and F-VII completes the release in 24 h. Formulation F-VI, F-VIII, and F-IX showed sustained release beyond 24 h. At high crosslink density, the openings (pores) of the hydrogel are less in size and number, and hence drug release was lower.

The release mechanism was studied using Korsmeyer-Peppas equation. The parameters namely 'n' the time exponent and 'R' the regression coefficient were calculated. The n value, the time exponent calculated from the Korsmeyer-Peppas equation, was found to be greater than 0.66 in all the drug release profiles, hence the release mechanism is assumed to be super case-II transport, wherein, multiple release mechanisms exist.

Stability studies

The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity. The optimized formulations were subjected to stability studies according to ICH guidelines by storing at 5˚± 3ºC Ambient, 25º ± 2º C/60% ± 5% RH and 40º ± 2 º C/75% ±5% RH for 3 months. These samples were analyzed and checked for changes in physical appearance and drug content at 0, 1, 2 and 3 months. From the obtained data, it is clear that the formulation did not undergo any chemical changes/interaction during the study period**.**

CONCLUSION

In the presented study, Chitosan – HPG based superporous hydrogels were formulated by gas blowing method and characterized. From the results of the swelling studies, it was observed that with a decrease in pH from 7.4 to 1.2, a considerable increase in swelling was observed for all the formulations, which may be due to dissociation of the $-NH_2$ groups of chitosan, thereby increasing the osmotic pressure inside the hydrogels resulting in increased swelling. The findings indicated that the swelling behavior of the SPHs depends on the concentration of HPG, chitosan and of sodium bicarbonate. From the results of the de-swelling studies, it was observed that upon changing from acidic to basic medium, there is a decrease in swelling, confirming its pH sensitivity. Generally all formulations demonstrated their applicability *in-vitro* as a promising device for pH-dependent gastro retentive delivery of metoprolol tartrate. This study indicated that superporous hydrogels of chitosan and HPG can be successfully formulated as a gastro-retentive drug delivery device.

ACKNOWLEDGEMENTS

The authors wish to thank Messrs Astra Zeneca Pvt limited Bangalore, for sparing gift sample of metoprolol tartrate and Messrs Encore polymers, Ahmedabad for their generous gift sample of hydroxypropyl guar.

REFERENCES

[1] Park J, Kim D. Effect of polymer solution concentration on swelling and mechanical properties of glycol chitosan superporous hydrogels. J. Appl.Polym.Sci. 2010; 115: 3434-3441.

[2] Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review, Asian. J. Pharm. Clin. Res. 2010; 3(1): 2-10.

[3] Omidian H, Jose G. Rocca, Park K. Elastic Superporous Hydrogel Hybrids of Polyacrylamide and Sodium Alginate. Macromol. Biosci. 2006; 6: 703-710.

[4] Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. J. Control. Release. 2000; 64: 39-51.

[5] Chavda HV, Patel CN. Preparation and Characterization of Swellable Polymer-Based Superporous Hydrogel Composite of Poly (Acrylamide-co-Acrylic Acid). Trends. Biomater. Artif. Organs. 2010; 24(1): 83-89.

[6] Gupta NV, Shivakumar HG. Development of a Gastroretentive Drug Delivery System based on Superporous Hydrogel. Trop. J. Pharm. Res. 2010; 9(3): 257-264.
[7] Narendra C, Srinath MS, Ganesh Babu. Optimization of bilayer floating tablet containing Metopolol Tartrate as a model drug for gastric rentention. AAPS Pharm Sci Tech. 2006; 7(2): E1-E7.
[8] Tortora GJ, Derrickson B, Principles of anatomy and physiology. 11th edition.2006.
[9] Nagpal M, Singh SK, Mishra D. Superporous hydrogels as gastroretentive devices. Acta. Pharm. sci. 2011; 53: 7-24.
[10] Chen J, Park H, Park K. Synthesis of superporous hydrogels: hydrogels with fast swelling and superabsorbent properties. J. Biomed. Mater. Res. 1999; 44(1): 53-62.
[11] Gemeinhart RA, Chen J, Park H, Park K. pH-sensitivity of fast responsive superporous hydrogels. J. Biomater. sci. polymer. 2000; 11: 1371-1380.
[12] Farid A. Dorkoosh, Verhoef JC, Borchard G, Rafiee-Tehrani M, Hans E. Junginger. Development and characterization of a novel peroral peptide drug delivery system. J. control. Release. 2001; 71: 307-318.
[13] Qiuand Y, Park K. Superporous IPN Hydrogels Having Enhanced Mechanical Properties. AAPS Pharm.Sci.Tech.2003; 4(4): 406-412.
[14] Peppas NA, Simmons REP. Mechanistic analysis of protein delivery from porous poly (vinyl alcohol) systems. J. Drug. Del. Sci. Tech. 2004; 14(4): 285-289.
[15] Yin L, Ding J, LikunFei, Miao He, Cui F, Tang C et al. Beneficial properties for insulin absorption using superporous hydrogel containing interpenetrating polymer network as oral delivery vehicles. Int. J. Pharm. 2008; 350: 220-229.
[16] Hongyan He, Guan J, Lee L J, Hansford D. An Oral Delivery Device Based on Self-Folding Hydrogels. Biomedical Engineering Centre. The Ohio State University, Columbus. Ohio 43210.
[17] Kumar A, Pandey M, Koshy MK, Saraf S A. Synthesis of fast swelling superporous hydrogel: effect of concentration of crosslinker and Ac-Di-Sol on swelling ratio and mechanical strength. Int. J. Drug. Del. 2010; 2:135-140.
[18] Gemeinhart RA, Park H, Park K. Effect of compression on fast swelling of poly (acrylamide-co-acrylic acid) superporous hydrogels. J. Biomed Mater Res. 2001; 55: 54-62.
[19] Gupta NV, Shivakumar HG. pH-sensitive superporous hydrogels composed of methacrylic acid and acrylamide: preparation and properties. Acta. Pharm. Sci. 2010; 52: 239-246.
[20] Tang C, Yin C, Pei Y, Zhang M, Lifang W. New superporous hydrogels composites based on aqueous Carbopol solution (SPHCcs): synthesis, characterisation and *in vitro* bioadhesive force studies. Eur. Polym. J. 2005; 41: 557-562.
[21] Omidian H, Park K. Experimental design for the synthesis of polyacrylamide superporous hydrogels. J. Bioact. Compat. Pol. 2002; 17: 433-450.
[22] Demirtas TT, Karakecili AG, Gumusderelioglu M. Hydroyapatite containing superporous hydrogel composites: synthesis and *in vitro* characterization. J. Mater. Sci. Mater Med; 2008; 19: 729-735.
[23] Jia Kuang, Kun Young Yuk, Kang Moo Huh. Polysaccharide-based superporous hydrogels with fast swelling and superabsorbent properties. Carbohyd. Polym. 2011; 83: 284-290.
[24] Zhao S, Dong Ma, Zhang L. New semi-interpenetrating network hydrogels: synthesis, characterization and properties. Macromol. Biosci. 2006; 6: 445-451.
[25] Seo K, Kim D, Park K. Swelling properties of poly (AM-co-AA)/Chitosan pH sensitive superporous hydrogels. Ind. Eng. Chem. 2004; 10(5): 794-800.
[26] Bonina P, Petrova Ts, Manolova N. pH-sensitive hydrogels composed of chitosan and polyacrylamide-preparation and properties. J. Bioact. Compat. Pol. 2004; 19: 101-116.
[27] Park H, Park K, Kim D. Preparation and swelling behaviour of chitosan-based superporous hydrogels for gastric retention application. Inc. J Biomed Mater Res. 2006; 76A: 144-150.
[28] Park H, Kim D. Swelling and mechanical properties of glycol chitosan/poly (vinyl alcohol) IPN-type superporous hydrogels. Inc. J Biomed Mater Res, 2006; 78A: 662-667.
[29] Gemeinhart R A, Park H, Park K. Pore structure of superporous hydrogels. Poly. Adv. Technol. 2000; 11: 617-625.