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Research Article

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Fabrication of Colon Drug Delivery by Nanoparticle Drug Intended of Carboxymethyl Cellulose Sodium

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Abstract Double walled polymer with a Core of mixture of nanoparticle of carboxymethyl cellulose sodium salt and a model drug olsalazine [3,3´-azobis(6-hydroxy benzoic acid)] as an azo derivatives of 5-aminosalicylic acid and an external coat of cross-linked copolymers of N-vinyl-2-pyrrolidinone and methacrylic acid with various amounts of cross-linking agents. Cubane-1,4-dicarboxylic acid linked to two HEMA group is the cross-linking agent. The core nanocomposite was prepared by freeze drying method and then used as nuclei for subsequent sell copolymerization. The structure of core was characterized with scanning electron microscopy. The double walled hydrogels were characterized by differential scanning calorimetry and FT-IR. Equilibrium swelling studies were carried out in enzyme-free simulated gastric and intestinal fluids. The drug-release profiles indicated that the amount of drug released depend on the degree of swelling. The swelling was modulated by the amount of crosslinking in shell layer. Based on the great difference in hydrolysis rates at pH 1 and 7.4, these pH-sensitive hydrogels appear to be good candidates for colon-specific drug delivery.

Keywords Core-shell; pH-sensitive; Hydrogel; Oral drug delivery; Colon

1. Introduction

Various methods have been used to target biologically active molecules to the specific site and extend their lifetimes therapeutic inside the body [1,2]. The use of swellable materials for drug delivery applications has followed experimental and theoretical investigations of drug transport in polymeric delivery systems [3]. The controlled drug delivery occurs when the polymer, whether natural or synthetic is judiciously combined with a drug and then drug is released over a desired period into the appropriate biological environment [4]. The release of the active drug may be constant over a long period, cyclic over a long period or triggered by the environment or other external factors.

Advantages of controlled drug release devices thus possibly include delivery to the required site, delivery at required rate, fewer applications, reduced dangers of overdose and economic advantages by the virtue of more efficient dosage, at the expense of possibly more complicated fabrication [5].

Colon-specific drug delivery needs to protect the drug during transit through the stomach and small intestine before allowing rapid release on entry into the colon. Various approaches have been used for oral delivery of drug to the colon, which include time-dependent delivery, pH-dependent systems and delivery systems that use bacteria that colonize the colon or enzymes produced by these bacteria to affect drug release [6-8]. Attempts have also been made to develop a delivery system that uses multiple principles such as a pH-dependent system and enzymes produced bacteria residing at the colon [9-11]. To achieve successful colonic delivery, a drug needs to be protected from absorption of the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the

proximal colon; this is considered the optimum site for colon-targeted delivery of drugs. One strategy for targeting orally administered drugs to be colon includes coating drugs with pH-sensitive hydrogels.

Polymer bonded drugs (PBDs) usually contain one solid drug bound in the matrix of a solid polymeric binder. These can be produced by polymerizing specific monomers mixed with a particulate drug or mixing of drug with natural polymers. The limitation of a single polymer encapsulating drugs includes an initial burst caused by the release of the drug trapped on the surface during the encapsulation process and a progressively slower release rate. Therefore, devices made with a two-layered structure may have certain advantages over their counterparts made from single polymers.

In this article, the synthesis and hydrolytic behaviour double walled type matrix systems containing nanoparticle of olsalazine [3,3´-azobis(6hydroxybenzoicacid)] (OSZ) as an azo derivatives of 5-aminosalicylic acid (5ASA) as a model drug in the core is reported. The mixture carboxymethyl cellulose sodium (CMC) salt and (OSZ) were converted to nanoparticle by freeze-drying method. Free radical cross-linking copolymerization of N-vinyl-2-pyrrolidinone (NVP) and methacrylic acid (MAA) in two different molar ratios, with the various ratios cross-linking agent produced shell layer on the core by pH-sensitive properties. The polymer bonded drugs obtained were hydrolyzed in aqueous buffer solutions at physiological conditions. The influences of different factors, such as cross-linking and swelling, were studied.

2. Material and Methods

Cubane-1, 4-bis(methacryloyloxyethyl)carboxylate (CA) was prepared by the method described in the literature [12]. Carboxymethyl cellulose sodium (CMC) [viscosity 3000-6000 cps (1 % aqueous solution)] purchased from Aldrich Co. The solvents and reagents were obtained from Fluka. The IR spectra were recorded on a Shimadzu FT IR-408 spectrophotometer. The DSC curves were obtained on a TGA/SDTA 851 calorimeter at heating and cooling rates of 10ºC/min under nitrogen atmosphere. The amount of released drug was determined on a Philips PU 8620 UV spectrophotometer at the absorption maximum of the free drug in aqueous alkali (λ_{max} = 245 nm) using a 1 cm quartz cell. Enzyme-free stimulated gastric fluids (SGF) (pH 1) or stimulated intestinal fluids (SIF) (pH 7.4) were prepared according to the method described in the US Pharmacopeia [13]. The HPLC apparatus consisted of Brucker LC-21, equipped with a Brucker UV-vis detector model LC 313 I, Rheodyne loop injector and a C18 reverse-phase column of Spherisorb-CN (250 × 4.6 mm id, particle size 5 µm) and was from Bischoff (Germany). Freeze dryer from Christ Company: type: alpha 2-4 with ice condenser capacity: max. 4 Kg and ice condenser temperature: *ca*. -85ºC.

2.1. Preparation of nanoparticle core

A solution of 2 g CMC and 1 g OSZ was prepared in 20 mL deionized water, and then aqueous solution was sprayed into a liquid nitrogen bath cooled down to 77 K, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze-dryer. In the freeze-drying process, the products are dried by a sublimation of the water component in an iced solution.

2.2. Preparation of shell layer

Nanoparticle was coated with monomers as follows: 0.2 g of nanoparticle was mixed with monomers in 20 mL ether with a variable feed ratio as shown in table 1. Then the ether was removed by evaporation. The coated nanoparticles were allowed to soak in the liquid monomers for several hours at ambient temperature. Copolymerization was carried out at 60-70ºC in a thermostatic water bath. All experiments were carried out in pyrex glass ampoules sealed off under vacuum. After the desired time (24-48 h) the precipitated network polymer bonded drugs were collected, washed with ether and dried in vacuum (Fig. 1).

2.3. Characterization of hydrolysis of product

The composition (90 mg) was dispersed in 20 mL of pH 8 buffered solution. The reaction mixture was maintained at 37ºC. After 24 h, the solution was sampled and neutralized with 1 M HCl and the solvent was evaporated in vacuum. The resulting crude product was treated with 10 mL of solvent and heated. The suspension was then filtered and the solvent was evaporated under reduced pressure. Samples were measured using HPLC-UV. The column used was ODS (C18) and isocratic elution was performed using 50% methanol and 50% buffer containing

0.05 M NH_3. The flow-rate and injection volume were 1 mL/min and 100 µL, respectively. OSZ was detected at a retention time of 2.8 min.

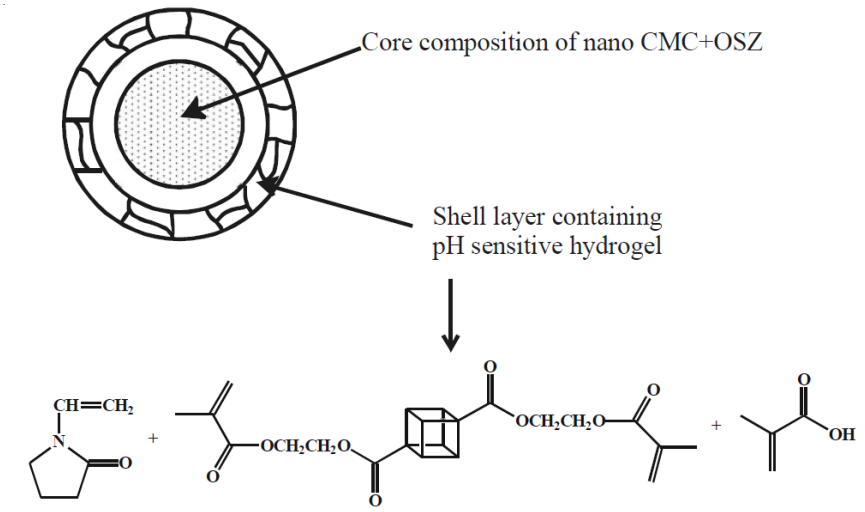

Figure 1: Schematic of double walled polymer

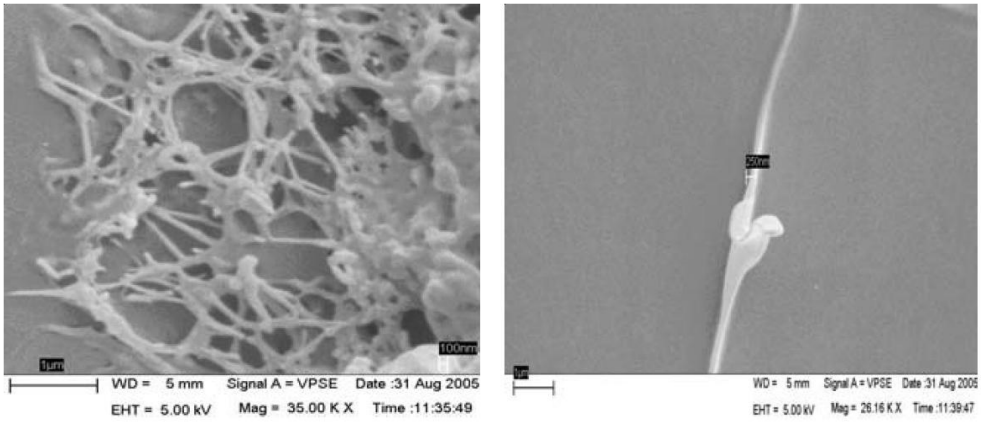

Figure 2: SEM of core: the composition of nano (CMC + olsalazine)

2.4. Measurement of swelling ratio

To measure the swelling, non-drug reweighed dry double-walled samples were immersed in various buffer solutions (pH 7.4 and pH 1) at 37ºC. Then excess water on the surface was removed by filter, the weight of the swollen samples was measured at various time intervals. The procedure was repeated until there was no further weight increase. The degree of swelling was calculated according the relation:

$$SW\ (\%) = [(W_s\text{-}W_d)/W_d] \times 100$$

where, W_s and W_d represent the weight of swollen and dry samples, respectively. Time-dependent swelling behaviour of cross-linked copolymers at pH 1 and pH 7.4 at 37ºC are plotted in Fig. 3.

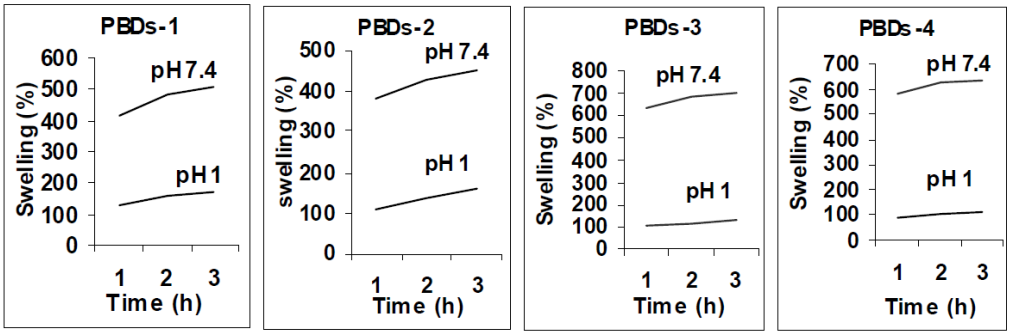

Figure 3: Swelling behaviour of double walled polymers as a function of time at 37 ºC

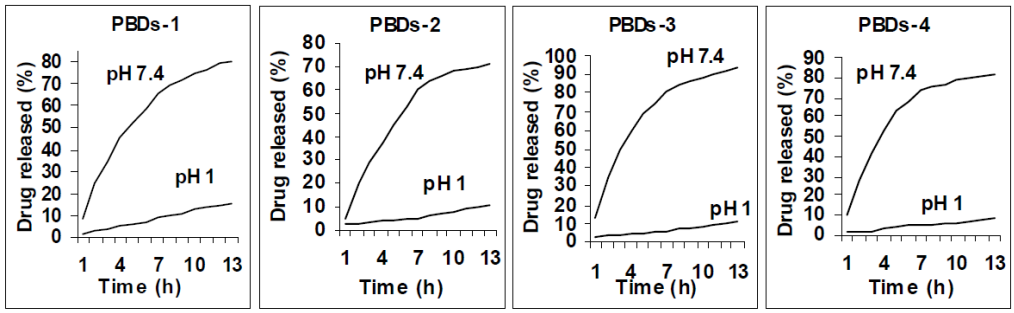

Figure 4: Release of nano OSZ from double walled polymers as a function of time at 37 ºC

2.5: In vitro release studies

Double walled polymers (50 mg) were poured into 3 mL of aqueous buffer solution (SGF: pH 1 or SIF: pH 7.4). The mixture was introduced into a cellophane membrane dialysis bag. The bag was closed and transferred to a flask containing 20 mL of the same solution maintained at 37°C. The external solution was continuously stirred and 3 mL samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. Triplicate samples were used. The hydrolyzed sample was analyzed by UV spectrophotometer and the quantity of OSZ as an azo derivative of 5-ASA was determined using a standard calibration curve obtained under the same conditions.

2.6. Thermal behavior

The thermal behaviour of a polymer is important in relation to its properties for controlling the release rate in order to have a suitable drug dosage form. Differential scanning calorimetry (DSC) and thermal gravimetry (TGA) for the hydrogels were evaluated. The glass transition temperature (Tg) was determined from the DSC thermograms.

3. Results and Discussion

Ionic hydrogels, containing acidic functional groups, have been reported to be sensitive to changes in different pH environment [13]. The present studies shows that the hydrolysis rate for hydrogels with higher concentration of NVP in SGF and SIF were similar, which clearly shows that NVP is not pH responsive. An increase in the MAA content in the shell layer resulted in less swelling in SGF but greater swelling in SIF. Because of increasing MAA, content in the hydrogels provides more hydrogen bonds at low pH and more electrostatic repulsion at high pH. In the low pH range of the stomach, the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes. The degree of swelling increases as the hydrogel passes down the gastrointestinal tract due to increased pH. In colon, the gels have reached a high degree of swelling that makes the drug is released from the gel. Increase in crosslinking density through addition of crosslinking agents are known to reduce the equilibrium swelling [14-18]. Reduced swelling is often marked with reduced diffusion coefficient.

Table 1: DSC data and composition of double walled polymers

Copolymer	Ratios of monomers in shell layer NVP: MAA	Cross linking agent (%)	Tg (ºC)
PBDs-1	1:3	5	89
PBDs-2	1:3	10	105
PBDs-3	1:5	5	110
PBDs-4	1:5	10	120

The Tg values of the polymers listed in Table-1. The higher Tg values probably related to the introduction of cross-links, which would decrease the flexibility of the chains and the ability of the chains to undergo segmental motion, which would increase the Tg values[12]. On the other hand the introduction of a strongly polar carboxylic acid group can increase the Tg value because of the formation of internal hydrogen bonds between the polymer chains [19-21].

Drug release by hydrolysis of polymer bonded drugs: In order to study potential application of PBDs containing azo derivatives of 5-aminosalicylic acid as a pharmaceutically active compound, we have studied the hydrolysis behavior of the polymers under physiological conditions. The degree of drug release of the network polymers containing OSZ as a function of time (Fig. 4). The concentration of OSZ released at selected time intervals was determined by UV spectrophotometry at 245 nm. It appears that the degree of hydrolysis double walled polymers depends on their degree of swelling and reticulated degree of shell layer. With increased cross-linking and an increase in the reticulated degree of the shell layer, diffusion of the hydrolyzing agents from shell is reduced and the hydrolysis rate is slower [22-27]. The order of hydrolysis in this series was significantly affected by polymer composition. As the content of MAA increased, hydrolysis rate decreased at pH 1 but increased at pH 7.4. This is due to higher MAA content in the shell layer led to higher carboxylate anion concentration at high pH. In other words, the existence of hydrogenbonding interactions between -COOH groups in the polymer matrix results in a complex structure within the network and so the movement of polymeric segments is restricted. This also accounts for minimum hydrolyzing of the gel in a medium of pH 1 [28-31]. However, when the sample is placed in a medium of pH 7.4, almost complete ionization of -COOH groups present within the polymer network not only increases the ion osmotic swelling pressure to a great extent but also enhances the relaxation of macromolecular chains because of repulsion among similarly charged -COO− groups. These two factors ultimately result in a greater increase in the water uptake. In pH 7.4 with completed ionization and an increase in the hydrophilicity of the polymer, diffusion of the hydrolyzing agents on polymer is increased and the hydrolysis rate increased.

4. Conclusions

Although, the drug delivery system (DDS) concept is not new, remarkable great progress has recently been made in the treatment of a variety of diseases. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of drug delivery system. To covey a sufficient dose of drug to the lesion, suitable carriers of drugs are needed. Nano and microparticle carriers have incredible abilities for administration of therapeutic molecules. The research in this area is being carried out all over the world at a great pace. Research areas cover novel properties that have been developed increased efficiency of drug delivery, improved release profiles and drug targeting. The double walled polymeric drug delivery system is able circumvent most of the limitations of traditional monolithic polymer systems. By using cross-linked copolymers of methacrylic acid as pH-sensitive hydrogels in shell layer, these materials are ideal for systems such as oral delivery, in which the drug is not released at low pH values in the stomach but rather at high pH values in the upper small intestine. The hydrolysis rate of the hydrogels in this study was slow at pH 1 but increased at pH 7.4 and with increasing amounts of methacrylic acid. Based on the great difference in hydrolysis rates at pH 1 and 7.4, these hydrogels appear to be potential candidates for colon-specific drug delivery.

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