Controlled Release of Drug to the Intestine from pH-responsive Chitosan-Poly (vinyl alcohol) Interpenetrating Network Hydrogels

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Introduction

Hydrogels are polymeric networks with three-dimensional configuration capable of imbibing high amounts of water or biological fluids. Hydrogels work well in the body because they mimic the natural structure of the body's cellular makeup. As a result of this, the area of hydrogel research has expanded dramatically in the recent past, primarily because hydrogels perform well for biomedical applications [1]. Recent advances in the use of hydrogels have led to the potential to design artificial organs, deliver drugs to specific sites in the body in a controlled fashion and fabricate the extended wear contact lenses [2-4].

A truly amazing class of hydrogels that has found potential use for a wide variety of applications is the class of "smart" or "intelligent" hydrogels. The uniqueness of this class is due to the unusual volume changes that these polymers exhibit under the application of very specific stimuli. Smart hydrogels exhibit significant volume changes in response to stimuli such as changes in pH, temperature, electric field, ionic strength and light *etc*. Research efforts on the design of smart hydrogels for drug delivery application have increased significantly over the past few years [5-6]; the idea behind this approach is that smart hydrogels will both expand and contract, forming a hydrogel "switch" that releases drug or protein in a controlled fashion. The developments in this area of research have been extensively reviewed periodically by various scientists [2-6].

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract, vagina and blood vessels, and these can provide a suitable base for pH-responsive drug release. Most commonly studied ionic polymers for pH-responsive behaviour include chitosan, poly (acrylamide) (PAAm), poly (acrylic acid) (PAA), poly (methacrylic acid) (PMAA), poly (diethylaminoethyl methacrylate) (PDEAEMA) and poly (dimethylaminoethyl methacrylate) (PDMAEMA) [7-8].

Chitosan, α (1→4) 2-amino-2-deoxy-β-D glucan, is a polycationic bioplomer generally obtained by alkaline deacetylation of chitin, which is the main component of the exoskeleton of crustaceans such as shrimps [9]. Chitosan has received a great deal of attention in the fabrication of pH-responsive hydrogels due to its biocompatibility, low toxicity, degradability by human enzymes, membrane permeation enhancing effect, mucoadhesive, antimicrobial as well as wound healing properties [10]. Chitosan hydrogels have been greatly employed for targeted drug delivery applications and have also been utilized for gene and protein delivery purposes [11]. The interest in chitosan as intestinal drug delivery carriers arises from the fact that it is degraded by the microflora of the colon and is not digested in the upper gastrointestinal tract. Moreover, it has the special feature of adhering to mucosal surfaces which makes it highly useful for mucosal drug delivery applications. Chitosan hydrogels, however, suffer from certain limitations such as poor mechanical strength, high porosity and tendency to absorb moisture [12]. The high porous nature of chitosan hydrogels lead to extensive swelling which eventually leads to faster dissolution of the hydrogel before the drug has even been delivered. Thus the applicability of pure chitosan hydrogels in drug delivery is hindered. A number of strategies have been developed in this context to alleviate these problems. One of the most common methods is to incorporate chitosan into another polymeric network by the formation of an interpenetrating network (IPN). It has been conjugated with other polymers such as poly (vinyl alcohol) (PVA), poly (ethylene glycol) (PEG), poly (N-isopropylacrylamide) (PNIPAAm) or PAA. Such composite hydrogels possess improved mechanical properties over individual polymers. PVA is widely used in the fields of pharmaceutics. It is cheap, bio-compatible, non-toxic and a water soluble polymer. Because of the ease of film formation, long-term temperature and pH stability, it is widely considered in the class of biomaterials, hydrogels in particular. PVA is commonly used in contact lenses, artificial muscles and burn wound dressing material among other biomedical

applications [13]. Block copolymers of chitosan and PVA have emerged as one of the most promising biodegradable materials due to their highly controllable chemical and physical properties [14].

In the past few decades, pharmaceutical formulations that target specific areas and control the rate and period of drug delivery (*i.e.* timed-release medications) have gained much impulse. Conventional drug dosage forms which include pills, tablets, capsules, injections, ointments, creams *etc.* release the drug instantaneously in a bolus form; which calls for frequent dosing and increase patient non-compliances. Controlled release of drugs reduces the dosing frequency, enhances activity of duration of short half-life drugs, eliminates side-effects and drug wastage, optimizes therapy and improves patient compliances [15].

Cyclodextrins are of special interest in this context given their hydrophilic exterior, which is useful for maintaining the bulk hydrophilicity and swelling state of the hydrogel, and their hydrophobic interior, which can facilitate the entrapment and controlled release of variety of hydrophobic drugs. Cyclodextrins have the potential to reduce the release rate of drug from hydrogels even without any covalent linking to the matrixes, for they diffuse in the gel much slower than small molecule drugs probably due to their higher excluded volumes, low water-solubility, and the hydrogen bonding [16]. Efforts are still being made to incorporate cyclodextrins into various polymer matrices in order to explore and modify current drug release systems. Incorporation of cyclodextrin to polymer matrix is often carried out by copolymerization of functionalized cyclodextrin with the polymer of interest. Copolymerisation of cyclodextrins with other polymers involves extensive synthesis work and most often needs the surface modification of simple cyclodextrins. In order to avoid the important drawbacks of the chemical modification of cyclodextrins, a simple and easy strategy for incorporating cyclodextrin to hydrogel matrix is to load drug-cyclodextrin complexes directly into the hydrogel after or during the gel cross-linking.

Objective

To synthesize pH-responsive chitosan-PVA interpenetrating network hydrogels for controlled delivery of drug to the intestine.

Work Plan:

I. Synthesis of pH-responsive chitosan-PVA interpenetrating network hydrogels using glutaraldehyde as crosslinker. Characterisation of these hydrogels by FTIR, XRD and SEM techniques. Evaluation of pH-responsive swelling characteristics of the hydrogels in phosphate buffer solutions. Antibacterial assay of the synthesized hydrogels using *E. coli* (gram negative) by the disc diffusion method.

II. Investigation of drug inclusion in cyclodextrin. Preparation of solid inclusion complexes of drug in β-cyclodextrin (CD). Characterization of the inclusion complexes by various spectroscopic methods such as FTIR, XRD, DSC, SEM, NMR, UV-Vis spectrophotometry and Fluorescence spectroscopy.

III. Study of drug releasing properties of the hydrogels *in vitro* by UV-Vis spectrophotometry. Preliminary kinetic analyses and determination of probable mechanism of drug release from the hydrogels using four basic empirical mathematical models; Zero order, Higuchi, Ritger-Peppas and Peppas-Sahlin models.

Work done so far:

- A detailed literature appraisal is being carried out on chitosan and PVA hydrogels and their applications in biomedical and pharmaceutical industries and more importantly as drug delivery agents.
- Hydrogels composed of chitosan and PVA in different feed ratios were synthesized using glutaraldehyde as crosslinker. The compositions of the hydrogels are listed in Table I.

Table I. Compositions of synthesized hydrogels

Sample	CS: PVA (wt%)	CS/PVA
1	1:0	CS
2	1:1	HG11
3	1:3	HG13
4	1:5	HG15

- The representative FTIR spectra of the hydrogels are shown in Figure 1.

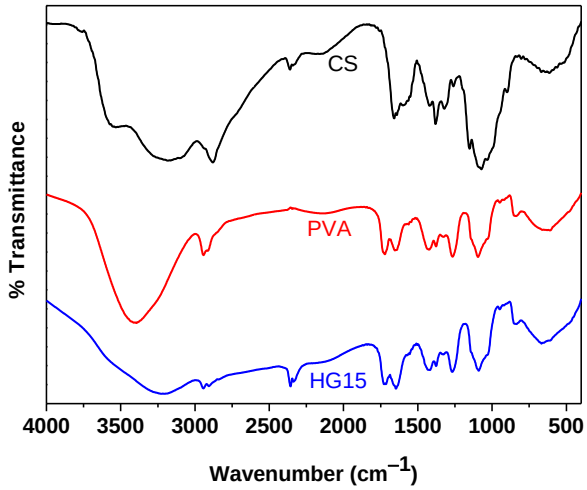

Figure 1. FTIR spectra of pure Chitosan, pure PVA and HG15 hydrogel

As observed from the FTIR spectra, the characteristics peaks of CS and PVA are seen in the spectrum of HG15 hydrogel with certain modifications in the absorption frequencies. The amide peak at 1510 cm^{-1} which is a characteristic of CS, is present. Moreover, the peaks at 893 cm^{-1} and 1155 cm^{-1} due to the pyranose ring and saccharin structure confirm the presence of chitosan in the HG15 hydrogel. The broad band at 3400 - 3250 cm^{-1} in is due to O-H stretching of PVA. Alkyl group C-H stretching is also observed in the IPN sample at 3000 cm^{-1}.

- The X-ray diffraction profiles of the hydrogels are shown in Figure 2.

Pure chitosan shows a broad and weak diffraction at around 10° and a relatively sharp diffraction at 19.5°. PVA shows a sharp peak centred on diffraction angle of 19.64°

associated with the crystalline nature of PVA. The diffraction profile of HG15 hydrogel exhibits a strong reflection at an angle of around 19°. The diffraction peak has been somewhat shifted and broadened in nature, probably due to interpolymer interaction between chitosan and PVA.

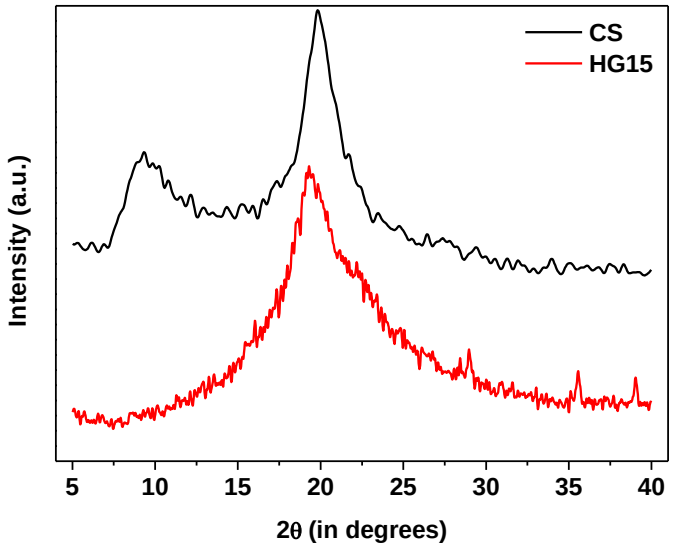

Figure 2. XRD profiles of Chitosan and HG15 hydrogel

- The morphology of the hydrogels was investigated by Scanning Electron Microscopy (SEM). The hydrogels were initially swollen in buffer solutions till equilibrium swelling was attained. They were then frozen at −20°C for 6 h and then lyophilized for 48 h. SEM was performed on freeze-dried hydrogels to know the bulk morphology of the hydrogels. The SEM micrographs are depicted in Figure 3.

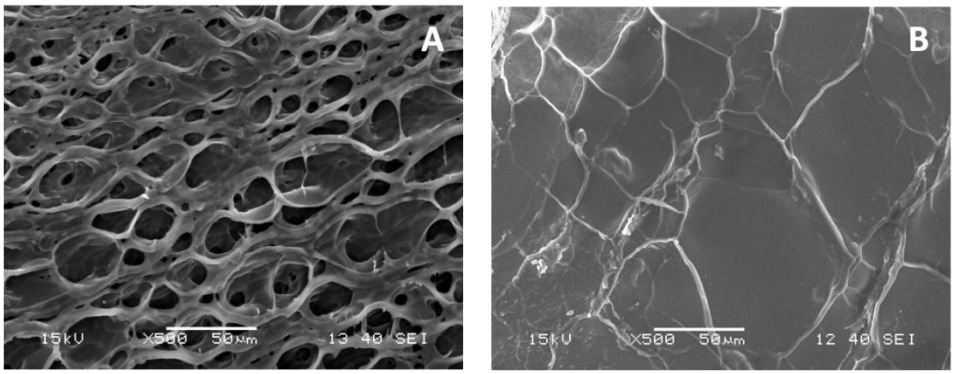

Figure 3. SEM micrographs of (A) pure chitosan and (B) HG15 hydrogel

Pure chitosan exhibits a highly porous matrix while HG15 hydrogel is compact in nature. This shows that porosity decreases with addition of PVA in the hydrogel which might be due to entanglement between chitosan and PVA chains.

- The pH-responsive swelling behaviour of HG15 hydrogel was studied at pH 1.2 and pH 7.4. The swelling curve is indicated in Figure 4.

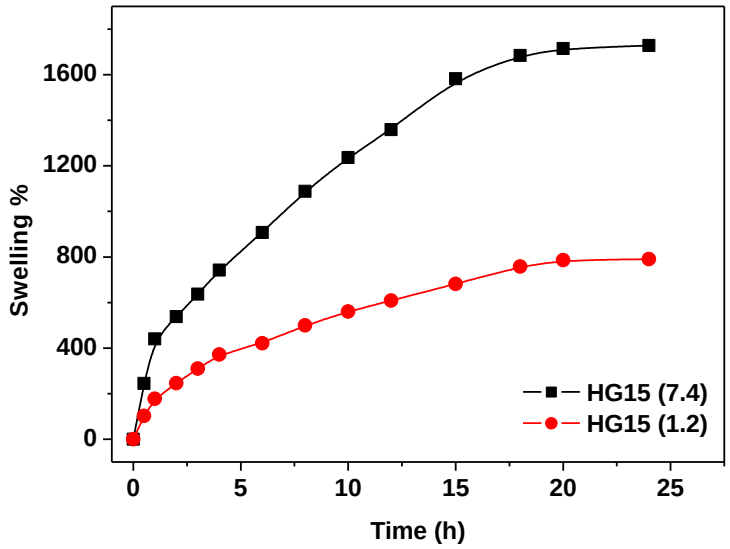

Figure 4. pH-responsive swelling behaviour of HG15 hydrogel

The HG15 hydrogel displayed pH-sensitive swelling with maximum swelling at pH 7. 4 than at acidic pH 1.2. Due to protonation of the amino group of chitosan at lower pH, strong electrostatic repulsion occurs between the polymer chains. The flow of counterions takes place to make the overall static potential neutral. Thus there is an increased osmotic pressure inside the matrix which reduces the swellability. At neutral pH, de-protonation of the amino group occurs and thus more water enters the hydrogel.

Conclusion

- pH-sensitive IPN hydrogels composed of chitosan and PVA were synthesized using glutaraldehyde as crosslinker.

- The characterization of the hydrogels suggested the proper blending of the individual polymers with each other.
- The swelling properties of the hydrogels indicated maximum swelling at neutral pH and lower swelling at acidic pH.
- The pH-sensitivity of these hydrogels could be utilized for controlled delivery of drug to the intestine.

Future work

- Preparation of drug-CD inclusion complex by different methods.
- Detailed analysis of the inclusion complexes by various spectroscopic methods.
- Synthesis and characterization of hydrogels containing the drug-CD complexes.
- Antibacterial activity of the hydrogels.
- Cytotoxicity evaluation of the hydrogels by MTT colorimetric technique.
- Drug release from hydrogels in simulated gastric and intestinal fluids.
- Kinetic analysis of drug release process.

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