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Effect of PVA on the gel temperature of MC and release kinetics of KT from MC based ophthalmic formulations

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ABSTRACT

The effect of molecular weight of poly(vinyl alcohol) (PVA) and sodium chloride on the gelation temperature of methylcellulose (MC) was studied with the objective to develop a MC based formulation for sustained delivery of ketorolac tromethamine a model ophthalmic drug. Pure MC showed sol–gel transition at 61.2 °C. In order to reduce the gelation temperature of MC and to increase the drug release time, PVA was used. Different techniques such as test tube tilting method, UV–vis spectroscopy, viscometry and rheometry were used to measure gelation temperature of all the binary combinations of MC and PVA. It was observed that the gelation temperature of MC was reduced with the addition of 4% PVA and also the extent of reduction of the gelation temperature of MC was dependent on the molecular weight of PVA. The strong interactions between MC and PVA molecules were established using Fourier transform infrared spectroscopy. To study the *in vitro* drug release properties of the MC–PVA binary combinations, 6% sodium chloride was used to reduce the gelation temperature further up to physiological temperature. It was observed that the drug release time increased from 5 to 8 h with the increase of molecular weight of PVA from 9×10^3 to 1.3×10^5 and this was due to the higher viscosity, better gel strength and greater interactions between the drug and PVA molecules in case of PVA (1.3×10^5) compared to PVA (9×10^3). In order to have an idea about the nature of interactions between the functional moieties of the drug and the polymer unit of PVA, a theoretical study was carried out.

1. Introduction

Hydrogels are hydrophilic polymer networks, which absorb enough quantity of water [1–3]. Hydrogels can be prepared by physical or chemical crosslinking of polymers. Physically crosslinked hydrogels may show thermoreversible gelation behavior as polymer entanglement or secondary force including ionic, H-bonding or hydrophobic forces are being responsible for gelation. Physically crosslinked hydrogels are increasingly being used in biomedical applications due to its hydrophilicity and reversibility [4,5].

In recent years, the stimuli-responsive hydrogels have received great attention [6,7]. Temperature is one of the familiar external stimuli for sol–gel transition. Recently, thermoresponsible hydrogels have been used for various applications such as drug delivery, tissue engineering, chemical separations, sensors, catalysis, and enzyme immobilization [8,9]. Some natural and synthetic polymers exhibit *in situ* gelling characteristics and therefore they are used as injectable candidates for controlled delivery of drugs [10,11].

In polymer solution, the polymer–solvent interactions are stronger than the polymer–polymer interactions. During heating at a certain temperature, the polymer–polymer interactions become stronger than the polymer–solvent interactions and then gelation takes place. The characteristic temperature is called gelation temperature [3].

Many polymers show the thermoreversible gelation behavior [12–25]. Heymann first investigated the thermoreversibility of gelation of methylcellulose (MC) [12]. MC is a derivative of cellulose and is soluble in water. MC molecules are linked to the water molecules by intermolecular hydrogen bonds forming a cage like structure. The gel strength depends on the degree of substitution and the molecular weight [13,14]. Recently, the effect of molecular weight of PEG on the gelation temperature of MC has been studied [3]. MC undergoes swelling and erosion *in vivo*, so it is not

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necessary to remove the gel after complete release of drug [15]. MC is approved by the Food and Drug Administration, USA, and it has multidisciplinary applications [15]. MC is highly biocompatible [16–18] and is used to prepare ophthalmic formulations. MC is used for maximum precorneal residence time of ofloxacine [19]. Haddad and Loucas patented the use of a MC based formulation for dry eye syndromes [20]. Smith advocated the use of MC in ophthalmic compositions of carbonic anhydrase inhibitors [21]. MC with carbopol is used to increase the viscosity of the formulation and used as an ophthalmic drug delivery system [22,23]. Deardorff et al. stated that MC does not create any eye irritation or damage and they used 1% MC to develop ophthalmic formulation [24,25].

Haehnel and Herrmann have first synthesized poly(vinyl alcohol) (PVA) [26]. The intermolecular hydrogen bonds between hydroxyl groups belonging to monomer units of PVA with water molecules assist the dissolution of PVA in water [27]. PVA is increasingly being used in the field of biomedical applications due to its biocompatibility [28–31]. The sol–gel transition temperature of PVA is 120 °C [32,33]. PVA of molecular weights 9×10^3 and 1.3×10^5 Da are used to see the effect of molecular weight of PVA on the gelation behavior of MC as well as on the drug release profile of ketorolac tromethamine (KT).

The MC–PVA combinations show lower gelation temperatures compared to the individual gelation temperatures of MC and PVA. But as the gelation temperature of MC–PVA combinations is far away from the physiological temperature, NaCl has been used to reduce the gelation temperature further for drug delivery at physiological temperature [3,34]. The addition of a salt will affect the structure of water, which is mainly due to the interactions between ions and water molecules [35]. NaCl, which is categorized as a salt-out salt, tends to compete with MC chains for the water molecules, and they succeed in attracting more water molecules surrounding them due to their stronger hydration abilities. This competition causes the decrease of MC solubility in water. As a result, at the same temperature, there are more hydrophobic aggregates of MC in a salted MC solution than in a non-salt MC solution. Thus, upon heating it will be easier for a salted MC solution to meet the requirement for the critical number of hydrophobic aggregates to form a gel, so that the sol–gel transition occurs at a lower temperature, or it is better to say that the salt accelerates the formation of a MC gel.

The objective of the present research work is to see the effect of the molecular weight of PVA on the gelation temperature of MC and also on the drug release kinetics of ketorolac tromethamine from different MC–PVA–NaCl combinations.

2. Experimental

2.1. Materials

Methylcellulose (MC, MetoloseSM-4000) was obtained from Shinetsu Chemical Co., Japan. The methoxyl content of MC was 29.6%. The sample was vacuum dried at 50 °C for 7 h before use and kept in vacuum desiccators. Sodium chloride, sodium bicarbonate, calcium chloride dihydrate, and PVA of weight average molecular weight (M_w) of 9×10^3 and 1.3×10^5 Da were purchased from Sigma–Aldrich, USA. Ketorolac tromethamine (KT) was a gift sample from Sun Pharma, Baroda, Gujarat, India. The dialysis membrane (LA390, average flat width-25.27 mm, average diameter around 15.9 mm and capacity 1.99 mL/cm) was purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India.

2.2. Sample preparation for measurement of gelation temperature and drug release kinetics

Methylcellulose (MC) solution (1%) was prepared by dispersing the MC in water with continuous stirring until homogenous dispersion and kept in a refrigerator for 48 h to obtain a transparent solution [36,37]. The solution of PVA was prepared by dissolving 4% PVA (w/v) in double distilled water by vigorously stirring at 60–70 °C using a magnetic stirrer. After total dissolution of PVA, 1% MC (w/v) was added in the hot PVA solution. The whole solution was stirred vigorously until total dispersion of the MC. The solution was kept in the refrigerator for 24 h to get complete transparent binary solution of MC–PVA. The binary and ternary *in situ* gelling systems with and without PVA were developed by incorporation of 6% NaCl with continuous stirring with MC and MC–PVA solutions. Then all the solutions were kept in refrigerator at about 10–15 °C for 1 day. 0.5 wt% of KT was used to prepare the stock solution for drug delivery application. Deionized double distilled water was used to prepare all solutions. Throughout the experiment, 1% MC solution was used as a stock solution. 4% PVA was kept constant because this is the maximum percentage that can be tolerated by human eye [38].

2.3. Measurement of gelation temperature

The reversible sol–gel transition temperature was measured by test tube tilting method (TTM). To measure the gelation temperature by this process, the solution was sealed in a 20 mL glass tube and placed in a controlled temperature bath. The temperature of the bath was increased at a very slow rate. At a certain temperature the solution was completely converted into gel. The gel became turbid and did not flow with the tilting of the test tube. This characteristic temperature is called the gelation temperature. The same process has been repeated 2–3 times to get the accurate value. The gelation temperature was also confirmed by measurement of viscosity, UV–vis spectroscopy, and rheological studies.

3. Characterization

3.1. Fourier transform infrared (FTIR) spectroscopy

The samples were analyzed by attenuated total reflectance (ATR) method of FTIR spectrometry (Bruker, Germany, Model Alpha-E). A total of 36 scans at resolution of 4 cm^{-1} were collected to get average spectra.

3.2. UV–vis spectrophotometer

UV–vis spectrophotometer (Agilent 8453 Spectrophotometer) equipped with a temperature controller was used for the turbidity measurement. The sample was placed in the cell and covered with a plastic cap to prevent evaporation of solvent. Deionized double distilled water was used as the reference. The absorbance was measured at a wavelength of 500 nm through a thermal cycle of 20–70 °C at a scanning rate of 1 °C/min. The absorbance was converted to transmittance according to Lambert–Beer's Law [39,40].

3.3. Measurement of viscosity

The viscosity and gelation temperature of the solutions was measured with viscotester (HAAKE, V-550) equipped with a temperature controller. The sample was placed in the sample container and kept idle for 5 min so that it reached the constant temperature. The viscosity of the solutions was measured at 10 shear rate.

3.4. Rheological measurement

Rheological characterization of the MC–PVA gels was done using an Advanced Rheometer (TA Instrument, model AR 2000). The experiment was performed by using cone and plate geometry on the peltier plate. The cone diameter was 4 cm (4°) cone and 60 cm