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Cellulose Derivatives as Thermoresponsive Polymer: An Overview

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ABSTRACT

Cellulose is a linear homopolymer polysaccharide having water insoluble property. Various cellulose derivative prepared by etherification gains water solubility and shows thermoresponsive gelation. Thermoresponsive polymers are sensitive to thermal environment surrounding them and in response to it they show change in their property. Thermogelation behaviour of cellulose derivatives varies with degree and type of substitution. The main aim behind presenting this article is to summarize the thermosensitive property and application of various cellulose derivatives. This review stresses mainly on cellulose derivatives, methyl cellulose, hydroxypropyl methylcellulose and ethyl (hydroxyethyl) cellulose.

INTRODUCTION

Hydrogels can swell in the presence of water or physiological fluids. In some cases, they show swelling behaviour dependent on the external environment. These polymers are physiologically-responsive hydrogels, where polymer complexes can be broken or the network can be swollen as a result of the changing external environment. Some of the factors affecting the swelling of physiologically-responsive hydrogels include pH, ionic strength, temperature and electromagnetic radiation (Peppas, 1996 & 1986). Temperature-sensitive hydrogels have gained considerable attention in the pharmaceutical field due to the ability of the hydrogels to swell or de-swell as a result of changing the temperature of the surrounding fluid. Hydrogels have been used for various purposes, such as on-off drug release regulations, biosensors and intelligent cell culture dishes (Kikuchi, 1998). The sensitivity to the thermal environment is useful as no other requirement for chemical or environmental treatment and stimulus for their gelation can be produced by simply administering into the body, when temperature is increased from ambient to physiological (Klouda e*t al.*, 2008).

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The phenomenon of transition from a solution to a gel is commonly referred to as sol–gel transition. Thermoresponsive hydrogels exhibit a phase separation from solution and solidification above a certain temperature. This threshold temperature is defined as the lower critical solution temperature (LCST). On the basis of this, thermosensitive hydrogels can be classified as positive or negative temperature-sensitive systems. Negative temperature-sensitive hydrogels have a LCST. These hydrogels contract upon heating above the LCST i.e., below the LCST, the polymers are soluble and above the LCSTs they become increasingly hydrophobic and insoluble, leading to gel formation. In contrast, positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST). Such hydrogels contract upon cooling below the UCST (Peppas *et al.*, 2000). The phase separation in hydrogels is generally viewed as a phenomenon governed by the balance of hydrophilic and hydrophobic moieties on the polymer chain and the free energy of mixing (Taylor *et al.* 1975; Heskins *et al.* 1968). The free energy of association varies with enthalpy, entropy and temperature ($\Delta G = \Delta H - T\Delta S$). As the positive enthalpy term (ΔH) is smaller than the entropy term (ΔS); an increase in temperature results in a larger ($T\Delta S$) making ΔG negative and favouring polymer chain association. The temperature dependence of certain molecular interactions, such as hydrogen bonds and hydrophobic effects, contribute to phase separation.

At the LCST, compared to polymer–polymer and water–water interactions, hydrogen bonding between the polymer and water becomes unfavourable, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure (Schild, 1992; Hoffman, 1997). Alternatively, some amphiphilic polymers that self-assemble in solution, show micelle packing and gel formation because of polymer–polymer interactions when temperature is increased (Mortensen *et al*, 1993). The determination of the boundary between the sol and gel phases depends on the experimental method. A simple test-tube inverting method was employed to roughly determine the phase boundary (Jeong *et al*, 1999). When a test tube containing a solution is tilted, and if the solution deforms by flow it is the sol phase and if there is no flow it will be defined as gel phase. The flow is a function of time, tilting rate, amount of solution, and the diameter of the test tube. Considering the time-temperature superposition principle in polymer deformation, the test parameters should be fixed before determining the sol–gel boundary. The falling ball method is another simple way to determine the sol–gel transition condition. When a small heavy ball resting on top of a solution (gel phase) begins to penetrate into the gel under specific conditions, it can be regarded as a gel–sol transition, again being dependent on the relative ball density compared to the gel strength (Yoshida *et al*, 1998). When gelation is induced by temperature, the endothermic peak during heating obtained from differential scanning calorimetry (DSC) determines the transition temperature as well as the enthalpy of gelation (Yoshida *et al*, 1998; Wanka *et al.*1990) & Dynamic mechanical analysis has been used to determine the sol–gel transition in a more reproducible manner (Jeong, 2001). An abrupt change in the storage modulus or viscosity reflects the sol–gel transition. Many of the natural polymers have been reported to show thermoreversible gelation. Examples include gelatin, polysaccharides such as agarose, amylase, amylopectin, cellulose derivatives, carrageenans and gellan (Karim *et al.*, 2008; Arnott *et al.*, 1974; Rees *et al.*, 1977; Rozier *et al.*, 1989; Li *et al.*, 2002). This article reviews the properties and work done on thermosensitive gels based on cellulose derivatives.

CELLULOSE DERIVATIVES

Cellulose is a linear homopolymer polysaccharide consisting of D-anhydroglucopyranose units joined together by β-1, 4-glycosidic bonds. Extensive intramolecular and intermolecular hydrogen bonding present in cellulose renders it insoluble in water. Various cellulose ethers (CEs) have been prepared by etherification of the three hydroxyl groups on anhydroglucose units of cellulose producing water-soluble derivatives resulting in the production of CEs such as methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) (now termed hypromellose), hydroxylethyl cellulose (HEC) and ethylhydroxyethyl cellulose (EHEC), etc. (Clasen *et al.*, 2001) (Fig. 1, Table 1). Pharmaceutical application of CEs include matrices in controlled-release drug delivery systems using matrices, binding agents during granulation, film formation during tablet coating, suspending agents for suspensions, steric stabilisers for colloids and thickening agents for creams and ointments, and hydrogels (Guo *et al.*, 1998).

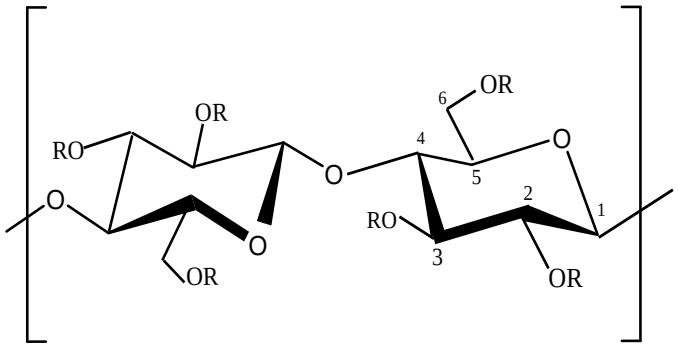

Fig. 1: Structure of cellulose derivatives. (Where R=H or R= substituent from table 1) [20]

Table. 1: Structural formulas of various cellulose ethers.

Cellulose ether derivatives	R
Methyl cellulose	$-CH_3$
Hydroxypropyl cellulose	$-CH_2CH_2CH_2OH$
Hydroxypropylmethyl cellulose	$-CH_3$ or $-CH_2CH(OH)CH_3$
Hydroxylethyl cellulose	$-CH_2CH_2OH$
Ethylhydroxyethyl cellulose	$-C_2H_5$ or $-CH_2CH_2OH$

Most natural polymers form a gel phase on lowering the temperature. However, aqueous solutions of some cellulose derivatives exhibit reverse thermogelation (gelation at elevated temperatures) (Klouda *et al.*, 2008). When cellulose derivatives have an optimum balance of hydrophilic and hydrophobic moieties, they undergo a sol-to-gel transition in water and this transition actually depends on substitution at the hydroxy group (Franz, 1986).Water becomes a poorer solvent with increasing temperature and polymer–polymer interactions become dominant at higher temperatures, resulting in a gel (Bekturov *et al.*, 1981).

METHYL CELLULOSE

MC is a cellulose derivative that has been extensively investigated for biomedical applications. It has thermoreversible gelation properties in aqueous solutions, gelling at temperatures in the range of 60–80 °C and turning into a solution upon cooling (Li *et al.*, 2002; Takahashi *et al.*, 2001). MC is long-chain substituted cellulose consisting approximately 27–32% of the hydroxyl groups in the methyl ether form. The degree of polymerization for various grades of MC lays in the range of 50–1000 Da, and molecular weights (number average) in the range 10,000–220,000 Da. The physical properties of MC, such as its solubility are affected by the degree of substitution. MC is known under various synonyms such as Methocel, Metolose, etc. (Rowe *et al.*, 2009). MC can be prepared using two different routes, one giving a uniform and the other a random distribution of substituent along the chains (Ibbett *et al.*, 1992; Kobayashi *et al.*, 1999). On commercial basis, MC is produced by a reaction in which cellulose is exposed to aqueous sodium hydroxide and methyl chloride under mechanical mixing,

with the methylation occurring more rapidly in NaOH-rich and/or higher temperature regions, which leads to inhomogeneous distribution of methyl groups along the chain. MC prepared in a more homogeneous manner, i.e., the reaction carried out in solution, was reported not to undergo gelation for the same average degree of substitution (DS) (Ibbett RN *et al*., 1992). The number of substituted hydroxyl groups per anhydro-glucose unit is the DS; it may vary from 0 to 3. Commercial MC is a heterogeneous polymer consisting of highly substituted zones called "hydrophobic zones" and less substituted ones called "hydrophilic zones (Arisz *et al.*, 1995). The uniformly substituted MC does not gelate at the DS needed for providing water solubility. Therefore, only the heterogeneous type, which is water soluble when the DS is between 1.3 and 2.6, is used commercially (Schupper *et al.*, 2008). Although a large number of studies have been performed regarding gelation procedure for MC (Haque *et al*., 1993; Hirrien *et al.*, 1993) but all studies favour a two stage procedure. The first stage was attributed to hydrophobic association leading to cluster formation, whereas the second stage corresponded to phase separation accompanied by gelation; the crossover temperature between the two stages depended on concentration but was in the vicinity of 50°C. Very dilute solutions showed no evidence of hydrophobic association but did exhibit aggregation above 50°C. This interpretation was supported by studies performed by Lodge and workers, using a combination of scattering techniques (Kobayashi *et al.*, 1999).

Effect of molecular weight on thermogelation

Li et al. measured gelation properties and the gel elasticity as a function of polymer concentration by means of micro differential scanning calorimetry and rheology, respectively. The experimental results prove that the aqueous solutions of MC are completely thermoreversible and the thermoreversibility of MC is independent of either polymer concentration or molecular weight. Aqueous solutions of two methylcellulose (MC) polymers with different molecular weights (Mw=100,000 and 400,000) have been studied. They measured quasi-equilibrium modulus Ge as a function of concentration c. It was found that at the same concentration of MC, with increasing molecular weight, Ge increases while the heat absorbed during the sol–gel transition remains constant (Wang *et al*.,2005). In another study, it was shown that the rate of gelation and gel strength is marginally dependent on molecular weight (Sarkar *et al.*, 1995). However, in the study conducted by Hatakeyama et al., gelation of MC and chemically cross-linked MC via urethane linkage with various molecular weights was investigated in a concentration range from 0.1 to 4.0 wt %. The temperature where the turbid solution changed into a homogeneous gel was defined as sol–gel transition temperature (Tsg). The gel samples with high molecular weights were stable and gel shape was maintained even when they were inverted. However, the gel samples with low molecular weights were fractured. In the cases of concentrated and high molecular mass samples, the whole solution was completely converted into the gel at Tsg (Hatakeyama *et al.*, 2007).

Application of methyl cellulose

MC is used widely in food and pharmaceutical industries because of its properties like, excellent film-forming ability, lipid barrier function, and low oxygen as well as moisture vapour transmission rate (Debeaufort *et al.*, 1998; Liang *et al.*, 2004). Besides this it has some additional property as thickener, protective glue, auxiliary emulsification agent, binder or film-coating/forming agent for different dosage forms which accounts for its widespread utility in pharmaceutical fields (Liang *et al.*, 2004; Kokubo *et al.*, 1998). Another important property of sol-gel transformation has been exploited to design various in situ gelling systems. The applicability of water-soluble cellulose ether (Metolose®) as a thermoresponsive base of the liquid suppository has been studied by investigators previously (Pasztor *et al*., 2007; Pasztor *et al.*, 2011) Metolose® can be used as gel and film-forming agent. Metolose® is available in three forms: SM type has methyl groups, SH type Metolose® has hydroxypropyl and methyl groups, and SE type has cellulose with hydroxyethyl and methyl groups (Pasztor *et al*., 2011). The study was conducted to shift the thermal gelation temperature (Tt) of Metolose® SM-4000 (methylcellulose) of 68°C (2% solution) to body temperature for in situ gelling of the liquid suppository (Pasztor *et al.*, 2007). In an another study, in situ gelling liquid suppository of piroxicam was prepared using Metolose® SM-4000 (methylcellulose) to study different factors affecting gelation temperature (Pasztor *et al*., 2011). Bain et al. developed ophthalmic formulations by using an ion sensitive polymer MC and polyethylene glycol as a viscosity-modifying agent. Two different salts such as sodium tartrate and sodium citrate were used to reduce the gelation temperature close to physiological temperature. The release of drug was extended from 6 h to 9 h on incorporation of polymeric excipients such as polyethylene glycol and more profoundly due to sodium citrate. This increase in drug release time was probably due to the change in morphology of gel structure from hollow fibrous to interconnected microporous structure. The developed formulation also promised to reduce the frequency of drug administration, thus improving patient compliance (Baina *et al*., 2013). A thermoreversible double gel was prepared by incorporating κ-carrageenan and MC mixtures in water. With this combination they were able to achieve double thermal gel-sol-gel transition. This specific thermal behaviour provides a liquid state of the system between the low-temperature and high-temperature, providing a scope for various colloidal particles as an entrapment medium (Tomsic *et al*., 2008). Kim et al. prepared MC-based thermo-reversible gel/pluronic micelle combination system for local and sustained delivery of docetaxel. The combination system was found to release docetaxel for more than 30 days thus enhancing the anticancer effect and prolonging it in comparison to free drug (Kim *et al.*, 2012). MC has been grafted with the synthetic N-isopropylacrylamide (NIPAAm), combining the thermogelling properties of both materials. It was possible to prepare fast reversibly thermogelling hydrogels by adjusting the ratios of the two components. They reported that a low percentage of MC decreases the LCST as compared to pNIPAAm, but with a

high MC ratio the LCST increases. They also found that addition of MC to NIPAAm polymers enhances the mechanical strength of the hydrogel with no syneresis (Liu *et al.,* 2004). Tate et al. for the first time developed MC as a tissue engineering scaffold in the treatment of injured brain. They found this neutral polymer to gel intracerebrally and also biocompatible both in the presence of cultured cells and in the injured brain. In another study performed in rat's brain MC was found to be present even after two weeks post-injection (Tate *et al.*, 2001). Stabenfeldt et al. prepared thermosensitive polymer-based scaffolds where MC was functionalized with laminin to form hydrogel with an aim to deliver cells and therapeutics to the injured CNS. It was found that functionalization with laminin increased survival and primary cortical neuron attachment when compared with unfunctionalized supports (Stabenfeldt *et al.,* 2006).

HYDROXYPROPYL METHYLCELLULOSE

HPMC is a partly O-methylated and O-(2-hydroxypropylated) cellulose (Rowe *et al.*, 2009). The presence of methoxy residues of HPMC are responsible for gelation, like in MC and the hydroxypropyl residues have been reported to significantly alter the gelation characteristics in a temperature-dependent manner (Haque *et al.*, 1993; Sarkar, 1995). HPMC is also characterised by the DS, i.e. the average number of substituted hydroxyl groups, the maximum being 3. In addition, the number of hydroxypropyl groups attached is given by the degree of reaction, also known as molar substitution (MS), i.e. the average number of molecules of reagent (propylene oxide) reacted with each anhydroglucose unit, which can exceed 3 (Doelker, 1993). Gelation of HPMC is considered to be due to increase in hydrophobic interactions and exclusion of water (syneresis) from heavily methoxylated regions of the polymer (Ford JL 1999). Various methods have been used to monitor thermal gelation processes in HPMC solutions. The results obtained from the attenuated total reflectance Fourier transform infrared spectroscopy were in good agreement with that obtained using two separate methods; differential scanning calorimetry and oscillatory rheometry indicating the removal of weakly hydrogen bonded water species from between the polymer layers during gelation (Sammon *et al.*,2006). HPMC (Metolose 60SH) has been used as a thermoresponsive and bioadhesive material, because it shows thermal gelation and has excellent bioadhesive features (Choi *et al.*,1998; Baloglu *et al.,* 2010). In one of the study performed by Mako et al., bioadhesive cellulose derivative (Metolose 60SH) was used as a thermoresponsive material. The thermal gelation temperature (T2) of Metolose 60SH 2%w/w solution is above body temperature (65-66°C), but by using water-soluble salts and changing the concentration of Metolose 60SH solution between 2 and 3 %w/w the thermal gelation point could be decreased (Mako *et al.,* 2009). Similarily, G. Sandri et al. prepared thermosensitive and mucoadhesive eyedrops containing platelet lysate for the treatment of corneal lesions by employing HPMC associated with chondroitin-6-sulphate sodium (CS). Association of CS with HPMC lowered the gelation temperature of HPMC by means of salting-out mechanisms and showed a sol-gel transition at 32-35°C. This was also supported by the good mucoadhesion behaviour (Sandri *et al.,* 2012).

ETHYL (HYDROXYETHYL) CELLULOSE

Ethyl(hydroxyethyl)cellulose (EHEC) is a non-ionic amphiphilic polymer containing ethylene oxide (EO) groups, having mixed hydrophobic (low amount) and hydrophilic structural units. EHEC shows macroscopic phase separation when the temperature is raised above the LCST, as the result of the intermolecular aggregation of hydrophobic domains. The presence of hydrophilic segments in more amounts in relation to hydrophobic units renders EHEC water-soluble (Lindell *et al.,* 1998; Kjoniksen *et al.,* 2005) Semi-dilute aqueous solutions of a certain, rather hydrophobic type of the nonionic cellulose derivative EHEC have been shown to exhibit thermogelling properties in the presence of ionic surfactants (Carlsson *et al.,* 1990; Carlsson *et al.,*1990). The sol-gel transition may occur at temperatures around 35°C, making the system interesting from a drug delivery point of view (Lindman *et al.,* 1991; Lindman *et al.,* 1993). In one of the study, it was found that on addition of surfactants, the aqueous solution of EHEC become more viscous with increase in temperature, forming stiff gels below cloud point. Here, surfactant was proposed to act as efficient crosslinker of polymer (Goldszal *et al.,* 1996). The interactions between polymer chains and ionic surfactant give rise to the formation of micellar-like clusters involving substituent from one or more EHEC chains, causing the network to swell due to charge repulsion (Kjoniksen *et al.,* 2005; Calejo *et al.,* 2012). In the presence of ionic surfactants, the surfactant is assumed to bind to the polymer, giving an apparent polyelectrolyte character to the originally non-ionic EHEC. The binding of an ionic surfactant (such as sodium dodecyl sulfate (SDS) or cetyltrimethylammonium bromide (CTAB)) to EHEC increases the cloud point temperature (CP) because of improved thermodynamic conditions of the systems (Kjoniksen *et al.,* 2005). However, these surfactants show poor biocompatibility; therefore in the last decade surfactants consisting of an amino acid as the polar headgroup have been given more importance. Lysine based surfactants have been used to in the production of a thermoresponsive EHEC gel for pharmaceutical and medical applications (Calejo *et al.,* 2012). In one of the work, their cytotoxicity were evaluated and it was found that toxicity increases with increase in chain-length of surfactant but it is partly compensated by its superior gel forming efficiency (Calejo *et al.,*2013). In another work, arginine-based surfactants were explored considering the production of a low toxicity EHEC thermoresponsive hydrogel (Calejo *et al.,* 2012). Scherlund et al. and Scherlund *et al.,* (2000) evaluated the EHEC/surfactant system for the local delivery of anesthetic agents to the periodontal pocket. They incorporated small amounts of lidocaine and prilocaine into the solution without affecting gelation behavior.

The tested formulations showed drug release over a minimum of 60 min, making them interesting for short-term pain control. They used cationic myristoylcholine bromide surfactant because of the dual role played by it of being antibacterial and readily biodegradable. The effects of addition of the photosensitizer riboflavin (RF) to semidilute solutions of the systems ethyl(hydroxyethyl)cellulose (EHEC)–surfactant system was studied by investigators. The rheological features of all systems were found to be affected by the presence of RF at lower temperatures, whereas temperatures close to the CP were less affected. Effect was more pronounced for the EHEC/SDS system which was found to be due to light irradiation of RF in the EHEC/SDS/RF system causing fragmentation of the network and a higher temperature was required to re-form the incipient gel network (Bu *et al.,* 2004).

CONCLUSION

In the past few years, number of thermosensitive polymers has been reported in the literature. Various derivatives of cellulose were reported to show thermosensitive behaviour depending upon the substitution on the three hydroxyl groups on anhydroglucose units of cellulose. MC shows gelling at temperatures in the range of 60–80 °C. In some studies it was found that the rate of gelation and gel strength for MC are dependent on molecular weight. Gelation procedure for MC involves two stage procedures. In first stage there was hydrophobic association followed by phase separation which is accompanied by gelation. In HPMC, the hydroxypropyl residues alter the gelation characteristics in a temperature-dependent manner. The effect of surfactant on HPMC and EHEC was found to decrease the gelation temperature thus bringing it nearer to body temperature.

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