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ORIGINAL CONTRIBUTION

Methyl Cellulose Based Thermoreversible In-Situ hydrogel Systems For Controlled Drug Delivery

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ABSTRACT

Thermoreversible in-situ hydrogels have recently received particular interest as drug delivery vehicle because of the easy instillation and sustained drug release capacity. In this review, we have focused on the thermoreversible gelation behavior of methyl cellulose and application of methyl cellulose as in situ gelling systems in controlled drug delivery. A lot of research work is going on in this area to prove the effectiveness of methyl cellulose based in-situ hydrogel forming drug delivery system and it is demonstrated that this drug carrier systems have several advantages over traditional strategies because they improve the drug delivery efficiency by controlling the release profile.

KEY WORDS: Ophthalmic In-situ gel, Methyl cellulose, Gelation temperature, sustained release of drug.

1. INTRODUCTION

Research of designing polymeric drug delivery systems has been carried out extensively. During the last few years, there has been a lot of emphasis on the evolution of in situ gel systems. [1]. The features of in situ forming polymeric delivery systems, including as simplicity of application, lower rate of medication, greater patient compliance, and comfort, have sparked attention. [2].

In situ gel system comprising of a mixture of drug and polymeric material and undergo in situ phase transition on the instillation side into the body. For the fabrication of in situ gelling drug delivery formulations, different natural as well as synthetic polymers are utilized [3]. In the course of recent years in situ forming gelling systems exhibit numerous potentials for several biomedical uses like delivery of drug, injectable implantation, tissue healing etc [4-8]. These delivery systems can be introduced into the body as injectable liquid with minimum invasiveness and undergo solidification or gel formation inside the intended organ, tissue or spaces of body. In situ gelling systems is more preferable for use over the traditional preshaped implant. For example, to implant any injectable materials surgery is no more necessary and different medicinal agents can be conveniently integrated by simply mixing them together. Their fluid behavior allows them to conform nicely when utilized to plug a hole or an imperfection. In situ gelling system is vastly used to draw out release rate and extend release period of drug. The development of in situ implants can be attributed to either physical modification or chemical modification of the system. There is a few potential system which prompts development of implants. The in situ gelling systems which do not need organic solvent or copolymerizing agents have attracted much interest. These are in the liquid state before instillation but in a physiological circumstance transformed to gel. In situ Gelation can takes place due to one or more stimuli like presence of certain ions [9-11] or pH change [12-13] or temperature change.

Ion-sensitive hydrogels are capable of experiencing sol-gel interconversion when exposed to certain ions like Na^+, K^+ etc. Several polysaccharides have ion-sensitive gelation property [14-15]. Such as kappa-carrageenan

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forms gel in presence of K+ whereas i-carrageenan shapes elastic gel ideally with Ca^{2+}. Ca^{2+}, Mg^{2+}, K^{+} and Na^{+} encourage gelation of Gellan gum. Gelation of low methoxy pectins generally takes place in presence of Ca^{2+}whereas alginic acid forms gel matrices in exposure to divalent and monovalent cations e.g. Ca^{2+} .

Stimuli reactive hydrogel system which form gel in a particular pH value is known as pH responsive hydrogel [16-17]. Polymeric systems which show pH sensitive gelation property are poly acrylic acid (PAA), poly (N, N-diethylamino ethylmethacrylate) (PDEMA) etc.

Thermoreversible in-situ hydrogel system undergoes sol-gel transition when surrounding fluid temperature is modified [18]. Mechanical behavior as well as release features of drug of this hydrogel change because of the variation of temperature of external environment [19-20]. Different polymers such as poloxamer 407, tetronics, methyl cellulose and other cellulose derivatives show thermoreversible gelation behavior and are widely used in drug delivery area [21-23]. These polymer solutions show liquid like flow behavior at room temperature but can form gel at physiological temperature. Xyloglucan is a natural polymer that also has thermoreversible gelation property [24].

This review briefly demonstrates the thermoreversible gelation behavior of methyl cellulose (MC), diverse parameters which affect the gelation behavior of methyl cellulose and use of methyl cellulose in controlled drug delivery.

2. Thermoresponsive behavior of methylcellulose:

Naturally occurring cellulose are water insoluble however it may be made water soluble by replacing part of the hydroxyl groups with hydrophobic methyl groups or hydroxylpropyl groups. Actually in cellulose, there are strong intermolecular hydrogen bonding which make it water insoluble. But when the hydrophilic part is replaced with hydrophobic methyl group or hydroxylpropyl group, then fraction of hydrogen bonding are wiped out and cellulose get soluble in water. The resultant derivatives are called hydrophobically modified cellulose or water soluble cellulose [25-27]. But if all the hydroxyl groups of cellulose are substituted by hydrophobic group then the resultant cellulose derivative become water insoluble [27]. Therefore for proper water solubility an optimum degree of substitution which is in between 1.4 to 2 is required.

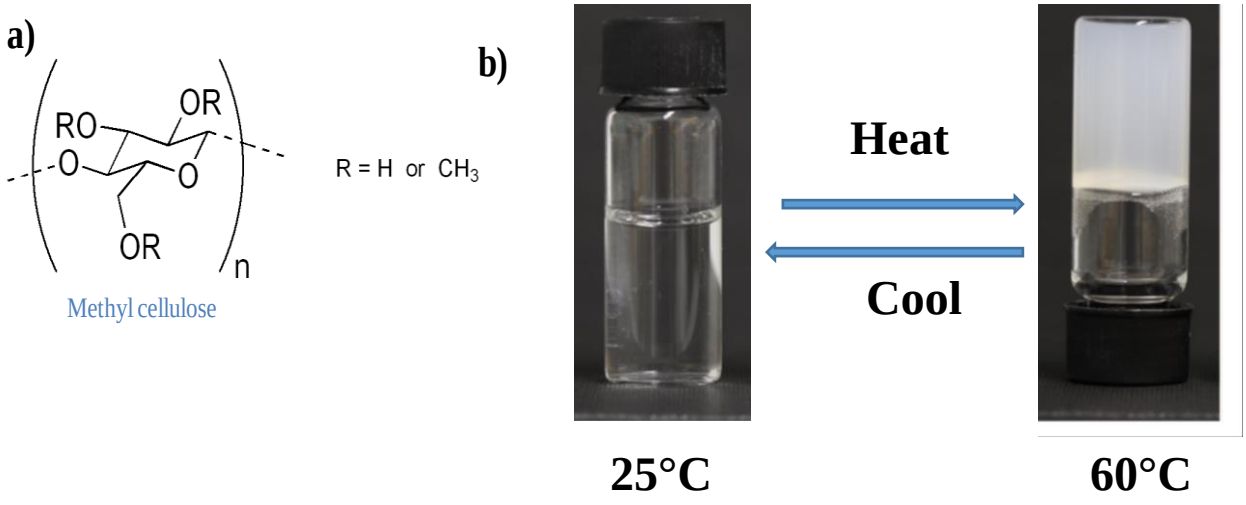


Fig. 1: (a) Chemical structure of methylcellulose repeating unit. (b) Photographs of 1% MC (SM 4000 grade) aqueous solution at 25 °C and 60 °C. MC exhibit lower critical solution (LCST) bellow which it remains as a single phase solution and above which turns into a turbid gel [28]

Methyl cellulose is formed when the –OH group of cellulose is replaced by the –OMe group. Appropriately substituted methyl cellulose exhibits thermally reversible gelation behavior and at temperatures ranging from around 50°C to 70°C it endures a sol-gel phase transition. At elevated temperature methyl cellulose become dehydrated and hydrophobic association become pronounced which make the polymer to become gel [29-34].Thermal gelation of methyl cellulose may also happen because of separation of liquid phase by heating [32]. The associated agglomerates or junctions which are formed at higher temperature can revert to liquid form when hydrophobic interaction is dissociated on cooling. This makes the polymer a thermoreversible one.

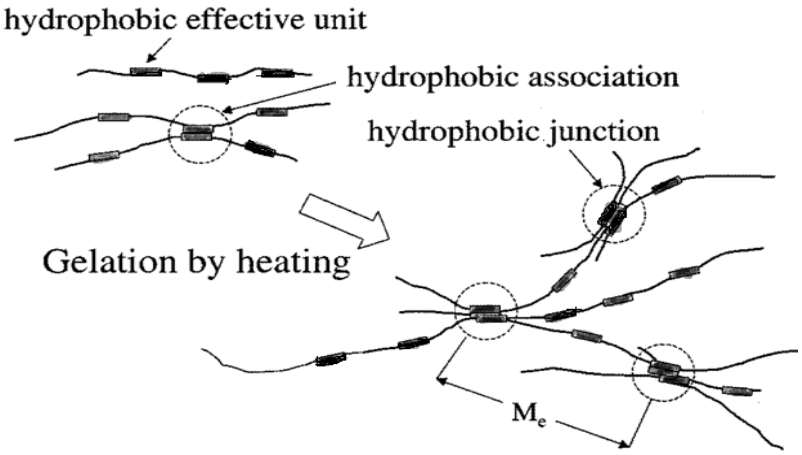


Fig. 2: The gelation process was mediated by the hydrophobic effective units of methyl cellulose, as seen in this diagram [35]. According to Li et al. [35] at reduced temperature, the hydrophobic effective units cause association of hydrophobic part. During heating, when the temperature is raised above 42.5°C, the hydrophobic junctions which are made up of such hydrophobic effective units are responsible to create the gel and two hydrophobic junctions remain at unaltered mean length (M_e).

Heymann first investigated the thermoreversible gelation behavior of methyl cellulose [36]. When methyl cellulose solution is heated, the hydrogen bonding between water molecule and methyl cellulose is ruptured leading to an entropy rise that allow the hydrophobic region of methyl cellulose to associate, causing agglomeration and gelation [37-38]. The dissolved bundles of partially methylated chains in methyl cellulose solution are interconnected by residual cellulose crystallites and by hydrophobic association of highly substituted areas in the cellulose chain. In the temperature region between 30°C to 55°C, these hydrophobic zones become solvated, shaping a cage-like framework encircling the polymer chain. At higher temperature melting of this cage like solvated framework takes place and gelation of methyl cellulose initiated as a result of hydrophobic interaction.

3. Effect of degree of substitution on thermogelation property of methyl cellulose

When hydroxyl group of cellulose is substituted by methoxyl group, this modification is expressed as degree of substitution (DS). It is expressed as the ratio of methyl group per repeating entity of methyl cellulose. Methyl cellulose with too low or too high DS is immiscible with water. As a result, marketed materials typically have an optimal DS of around 1.7-2.0. The water solubility of methyl cellulose is determined by its DS as well as by the

distribution of methyl group inside the entity [39-42].

Hirrien et al. synthesized water soluble methyl cellulose by utilizing CH_3 as the alkylating agent, a dimsyl sodium solution as the activating agent and DMAc/LiCl as the solvent. They have observed the behavior of a water soluble polymer without intermolecular interaction at 20°C. Intermolecular interaction is observed with DS > 1.5 and T > 45°C, while there is no evidence for further association with DS < 1.5. Therefore, they have concluded that the MC structure and particularly the DS value have significant impact on its physical characteristics in aqueous polymer solution also at lower concentration [43].

4. Effect of methyl cellulose molecular weight on thermo gelation property:

Li et al. [44] investigated the influence of methyl cellulose molecular weight on sol-gel transition temperature. They employed two distinct molecular weights (Mw = 100,000 and 400,000) of methyl cellulose to study their thermogelation behavior and proved that two solution of different molecular weight of methyl cellulose are thermoreversible and their thermoreversibility is independent of molecular weight.

Funami et al. [45] have investigated the thermal aggregation of methyl cellulose of various molecular weights in an aqueous system. He has proved that thermogelation property of methyl cellulose is molecular weight dependant. He has also demonstrated that raising the molecular weight of methyl cellulose promotes thermal aggregation and network structure creation.

Nishinari et al. [46] have also shown that gelation temperature of methyl cellulose and elastic modulus of methyl cellulose gel directly reliants on the molecular weight of methyl cellulose. As molecular weight increases, sol-gel transition temperature has been shifted to lower side.

Neely and Khun et al. [41, 47] observed that low molecular weight methyl cellulose has lower cloud point than the higher molecular weight and they have concluded that the aggregation of low molecular weight is comparatively easier via parallel aggregates due to its rod like structure than the high molecular weight where methyl cellulose molecules are in the form of random coil configuration.

5. Use of methyl cellulose as controlled drug delivery vehicle:

The Food and Drug Administration (FDA) in the United States has authorized methyl cellulose, and it has a wide range of uses. [48]. It shows extreme biocompatibility [49-51] and is utilized to make ocular formulations to sustain drug release rate due to its thermoreversible in-situ gelation characteristic. Methyl cellulose is employed for optimum precorneal retention period of Ofloxacine. [52].

The application of a methyl cellulose based formulation for dysfunctional tear syndromes was patented by Haddad and Loucas [53]. Smith proposed for the use of methyl cellulose in carbonic anhydrase inhibitor ophthalmic formulations [54]. To improve the viscosity of the formulation, methyl cellulose with carbopol is employed as an ocular drug delivery vehicle [55-56]. According to Deardorff et al., methyl cellulose induces no irritation or injury to the eyes, and they developed an ophthalmic formulation with 1% methyl cellulose [57-58].

Muller et al. [59] have studied methyl cellulose based formulations and determine its effectiveness as ophthalmic vehicles for Homatropine Hydrobromide eye drop. They proved that Homatropine Hydrobromide instilled in 1% methyl cellulose induced greater cycloplegia and myndriaasis at almost all doses. Methyl cellulose reduced reflex lacrymation and caused no eye irritation or damage.

Bain et al. [55, 60-62] have developed a series of methyl cellulose based ophthalmic formulations of Ketorolac Tromethamine by using salt mixture and different polymer as additives. They

proved that methyl cellulose is an efficient polymer for in-situ gel formulation to reduce drug release rate.

Similarly, Bhowmick et al. [63] has used methylcellulose as in situ gelling vehicle to develop an ophthalmic formulation of a model drug named pilocarpine hydrochloride. According to in vitro and in vivo investigations of their ophthalmic formulations the current approach may be a better replacement for traditional eye drops.

Dewan et al. [64] used different molecular weight (Mw) of methyl cellulose to investigate their impact on the thermoreversible gelation properties of poloxamer 407 and in vitro Ketorolac Tromethamine (KT) release from several ocular formulations. They have proved that KT release rate was highly affected by the molecular weight of methyl cellulose and greater molecular weight of methyl cellulose have better ability to maintain drug release rate.

Boonrat et al. [65] have studied the release pattern of Doxycycline hyclate; a model antibacterial drug for periodontitis, from a pluronics F 127/methyl cellulose based in situ gel formulation. These findings have indicated that the pluronics F 127/methyl cellulose mixtures hold promise as efficient drug delivery systems for periodontitis.

Itoh et al. [66] have upgraded the rheological property and release behavior of thermorevrsible methyl cellulose solution by blending it with pectin having ion sensitive gelation behavior with the goal of developing an in situ gelling vehicle for oral sustained drug administration to dysphagic patients. They have proved that this in situ gelling formulation improved sustained release characteristics.

Nagai et.al [67] has developed a methylcellulose and tranilast solid nanoparticles based ocular in situ gelling strategies which has prolonged ocular bioavailability leading to higher percentage of drug absorption by the cornea and conjunctiva.

Gupta et al. [68] have developed hyaluronan – methylcellulose based fast-gelling intrathecal injection, for targeted delivery to the wounded spinal cord. Their finding implies that gel made of hyaluronan and methylcellulose might be useful for targeted delivery of therapeutic medicines to the effected spinal cord.

Sharma et al. [69] have designed an In-situ quick gelling methyl cellulose based formulation for controlled delivery of paracetamol through oral route to dysphagic patients. In vitro tests revealed that paracetamol was released from the gels in a diffusion-controlled manner. The paracetamol release behavior from the in-situ gel formulation entered into the stomach of rabbit was more extended when compared to the marketed Calpol® solution having a similar dosage of paracetamol.

Nasir et al. [70] have designed and assessed thermoreversible subcutaneous diclofenac sodium drug delivery system. To develop the delivery system, poloxamer 407, hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), and polyethylene glycol (PG) were utilised separately and in combined form of varied ratios. According to the drug delivery data, the investigated polymers poloxamer, MC, and PG are suitable candidates for extending drug release due to their thermoreversible feature.

Nasir et al. [71] also constructed and evaluated an in-situ gelling drug delivery strategie for insulin using pluronic F 127 and methylcellulose having temperature sensitive gelation property. According to the data based on in-vitro and in-vivo study the formulation made of 15% (w/v) pluronic F-127 and 3% (w/v) methylcellulose was the most persistent and efficient formulation for prolonging the drug release and sustaining the level of basal plasma insulin between 10 and 40 mU/ml for 240 h (10 d).

Payne et al. [72] have developed a temperature sensitive in-situ gelling vehicle of methylcellulose and collagen to stimulate encapsulated stem cell viability and proliferation in vitro. Their findings point to the gel's prospective as a therapeutically applicable in vivo delivery strategy for stem cells and therapeutic agents.

6. Conclusion:

From this review it has been shown that methyl cellulose show thermoreversible in situ gelation behavior. The physical characteristics of methyl cellulose in aqueous solution are greatly influenced by the degree of substitution value. Thermal aggregation and network structure formation of methyl cellulose is enhanced as the molecular weight increase. The aggregation of low molecular weight is comparatively easier via parallel aggregates due to its rod like structure than the high molecular weight where methyl cellulose molecules are in the form of random coil configuration. Methyl cellulose based in situ gels represent potential vehicles for sustain drug release.

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