RHEOLOGICAL CHARACTERIZATION OF SOME CELLULOSE DERIVATIVES-BASED HYDROGELS

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Cellulose derivatives serve as a feasible alternative to the insoluble natural cellulose considering their high solubility in the most frequent organic solvents and particularly in water. Alongside this advantageous physical property, cellulose derivatives exhibit proper biocompatibility, biodegradability, thermo-gelling nature, and mechanical characteristics. Due to their high hydrophilicity, these biopolymers possess a great capacity to absorb large amounts of water into their structural chains, forming hydrogels with multiple biomedical applications, such as wound healing. Therefore, the main objective of this present work was to assess the rheological properties of some cellulose derivatives-based hydrogels. For this purpose, different commercial varieties of methylcellulose and hydroxyethylcellulose, two of the most used cellulose derivatives, were dispersed in water and stirred continuously until a clear and transparent hydrogel was formed. Depending on the quantities used of each biopolymer, hydrogels of different concentrations were obtained, from 3 to 20%. The topical semisolid systems were rheologically investigated at 23°C using a rotational viscometer and the rheograms of the experimental data were drawn. The hydrogels showed a non-newtonian pseudoplastic behaviour, which represents a requested requirement for topical semisolid systems, both in terms of conditioning, but also of spreading on the skin surface, improving the topical administration.

Keywords: cellulose derivatives, hydrogels, rheological evaluation

INTRODUCTION

Cellulose is the most plentiful biopolymer, a crystalline and rigid molecule, insoluble in water (Popa *et al*., 2022), which due to its chemical structure can suffer several changes at hydroxyl groups, resulting cellulose derivatives (Fekete *et al*., 2014). The most regularly used cellulose derivatives are cellulose ethers (methylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose,) (Tudoroiu *et al*., 2021) because they exhibit high water solubility (Lee and Yoo, 2021).

Due to their excellent availability, biocompatibility, renewability, non-toxicity, immunogenicity, thermo-gelling capacity, mechanical and rheological properties, stability, low cost, and antibacterial efficacy (He *et al*., 2021; Ho and Leo, 2021), cellulose derivatives are appealing polymers for vast applications in pharmaceutical, biomedical, and bioanalysis fields (wound dressings, drug delivery systems, tissue engineering, biosensors, or smart materials) (Abdelhak, 2019; Oprea and Voicu, 2020).

In this present work, the focus is on cellulose-based hydrogels, water-soluble bases, with high water content, cooling effect, washability, transparency, safety, porosity,

https://doi.org/10.24264/icams-2022.II.26

tolerability, and adherence to the skin. The main physical properties of these hydrogels are transitional and rheological properties that are essential in the process of their formulation (Kabir *et al*., 2018). Therefore, the purpose of this paper was to evaluate the rheological properties of some cellulose derivatives-based hydrogels, using different commercial varieties of methylcellulose and hydroxyethyl cellulose in order to select the suitable sorts to prepare hydrogels for further application as wound dressing.

MATERIALS AND METHODS

Materials

In this work, six commercial varieties of methylcellulose (MC), differing in composition and viscosity were used. They were divided into two series, each one containing three sorts. Series I includes: first sort coded as Sort MC 1, viscosity of 4000 cPs at 2% in H_2O (Janssen Chimica, Belgium), second sort coded as Sort MC 2, viscosity of 1500 cPs at 2% in H_2O (ICN Biomedicals Inc., USA), and third sort coded as Sort MC 3 (Methocel® MC), high viscosity, 27.5-32% methoxyl content, 3000-5000 mPa.s at 2% in H_2O, 20°C (Sigma-Aldrich, USA). Series II contains: first sort coded as Sort MC 1, viscosity of 15 cPs at 2% in H_2O (Janssen Chimica, Belgium), second sort coded as Sort MC 2 (Methocel® MC) with 27.5-32% methoxyl content and 10-25 mPa.s at 2% in H_2O, 20°C (Sigma-Aldrich, USA), and third sort coded as Sort MC 3, viscosity of 25 cPs at 2% in H_2O (ICN Biomedicals Inc., USA). Regarding the hydroxyethyl cellulose (HEC), three commercial varieties differing in viscosity were used. First sort coded as Sort HEC 1 with ~ 92% cellulose ether (Merck Schuchardt, Germany), second sort coded as Sort HEC 2, viscosity of 145 mPa.s at 1% in H_2O, 20°C (Loba Chemie Pvt. Ltd., India), and third sort coded as Sort HEC 3, viscosity of 4000 cPs (Sigma-Aldrich, Germany). Distilled water was used throughout the study.

Preparation of Methylcellulose Hydrogels

MC hydrogels were prepared in various concentrations according to the viscosity of the commercial sorts. For Series I, hydrogels of 3 and 4% concentration were prepared and for Series II, hydrogels of 8 and 10% were prepared. The MC powder was added slowly over half of the amount of distilled water required for preparation (heated at 80°C), gently stirring with a glass rod until the entire amount of powder was dispersed. The rest of the amount of distilled water (cold water) was added to the obtained mixture, continuously stirring. To jellify, mixtures were left to rest, continuing mixing.

Preparation of Hydroxyethyl Cellulose Hydrogels

HEC hydrogels were prepared in different concentrations according to the viscosity of the commercial varieties. Therefore, for Sort HEC 1 and Sort HEC 3, hydrogels of 4% concentration were prepared. For Sort HEC 2, hydrogel of 20% concentration was prepared. HEC hydrogels were prepared in the same way as MC hydrogels, the only difference being the use of distilled water at room temperature.

https://doi.org/10.24264/icams-2022.II.26

Analysis of Rheological Properties

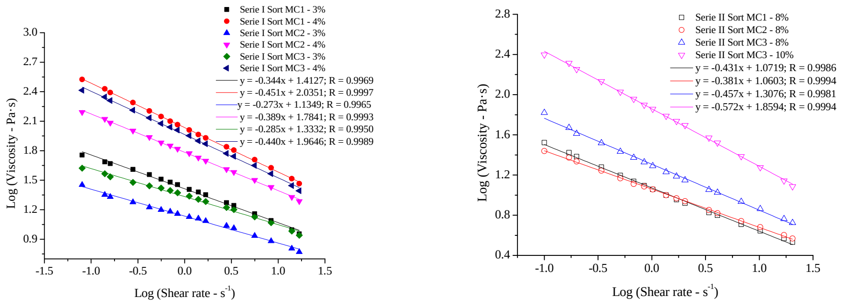
Rheological determinations of all cellulose derivatives-based hydrogels were performed with a rotational viscometer (Fungilab), using standard spindles, TR 9 and TR 10. All analyses were conducted at 23°C. The operational conditions were formerly described (Albu *et al.*, 2009; Ghica *et al.*, 2012).

RESULTS AND DISCUSSION

To quantify the pseudoplastic behaviour of the tested hydrogels, the Power law model was used, which indicates the relation between viscosity and shear rate (eq. 1):

$$\eta = m \cdot \dot{\gamma}^{-n} \tag{1}$$

where m parameter corresponds to the viscosity resulted for the shear rate of $1 \cdot s^{-1}$ and n represents the flow behaviour index (Dănilă et al., 2019). They are evaluated by the linearization of eq. (1) through double logarithmic method (Figure 1).



a) b)

Figure 1. Log-log plots of viscosity versus shear rate for MC hydrogels, analyzed at 23°C: a) Series I; b) Series II

Interpreting Figure 1, the viscosity of MC hydrogels from both series decreases with increase of shear rate, indicating a non-newtonian pseudoplastic behaviour at 23°C, which is a mandatory condition for topical systems, promoting the hydrogels flow and corresponding to a suitable application on the skin surface. The values for m and n parameters and correlation coefficient R specific for Power law model and the thixotropic descriptors for MC hydrogels, analyzed at 23°C are presented in Table 1 (Series I) and Table 2 (Series II).

Table 1. Values for m and n parameters and correlation coefficient R specific for Power law model, and the thixotropic descriptors analyzed at 23°C (Series I)

Gels Series I	m	n	R	S_{asc} (Pa· s^{-1})	S_{thix} (Pa· s^{-1})	T_{hyst} (%)
Sort MC 1 - 3%	25.864	0.34	0.9969	1616.187	93.197	5.76
Sort MC 1 - 4%	108.417	0.45	0.9997	5527.273	526.205	9.52
Sort MC 2 - 3%	13.642	0.27	0.9965	1009.651	62.184	6.16
Sort MC 2 - 4%	60.827	0.39	0.9993	3514.012	256.994	7.31
Sort MC 3 - 3%	21.537	0.29	0.9950	1534.456	83.833	5.46
Sort MC 3 - 4%	92.172	0.44	0.9989	4752.580	385.180	8.10

https://doi.org/10.24264/icams-2022.II.26

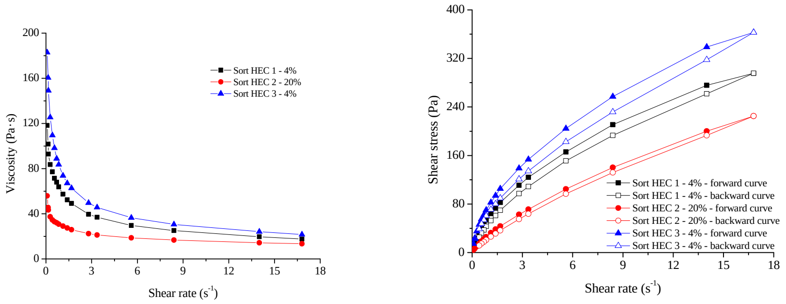
For all analyzed hydrogels from Series I, values of the correlation coefficient R higher than 0.9900 (between 0.9950 and 0.9997) are recorded, which means that the experimental data fitted the Power law model properly. The rheological parameter m for Sort MC 1 - 3% and Sort MC 3 - 3% has close values due to similar viscosities for the two commercial sorts (~4000 cP). Contrary, for Sort MC 2 - 3%, the m value is less than the other two, because it has a lower viscosity (1500 cP). It can be easily noticed that for all three sorts, but at 4% concentration, the m values are considerably higher than the same parameter at 3% concentration. Thus, m value is about 4.2 times higher for Sort MC 1 - 4% than for Sort MC 1 - 3%, 4.45 times higher for Sort MC 2 - 4% than for Sort MC.2 - 3%, and 4.3 times higher for Sort MC.3 - 4% than for Sort MC.3 - 3%. According to the m parameter previously detailed, Sort MC 1 - 3% and Sort MC 3 - 3% have close values of the thixotropy area (S_{thix}), while for Sort MC 2 - 3%, this thixotropic descriptor is less than the other two, because of their difference in viscosity. For all three sorts, but at 4% concentration, the S_{thix} values are significantly higher than the same descriptor at 3% concentration. Thus, S_{thix} is about 5.64 times higher for Sort MC 1 - 4% than for Sort MC 1 - 3%, 4.13 times higher for Sort MC 2 - 4% than for Sort MC.2 - 3%, and 4.6 times higher for Sort MC.3 - 4% than for Sort MC.3 - 3%. For a system to be thixotropic, the value of the thixotropy index ($T_{hyst\%}$) must be higher than 5% (Dănilă et al., 2019). It can also be noticed that the $T_{hist\%}$ for Sort MC 2 - 3% is higher than 5% compared to other sorts at the same concentration. The thixotropic behaviour is much more obvious at 4% concentration for all sorts analyzed at 23°C.

Table 2. Values for m and n parameters and correlation coefficient R specific for Power law model, and the thixotropic descriptors analyzed at 23°C (Series II)

Gels Series II	m	n	R	S_{asc} (Pa· s^{-1})	S_{thix} (Pa· s^{-1})	$T_{hyst\%}$ (%)
Sort MC 1 - 8%	11.800	0.43	0.9986	874.317	34.823	3.98
Sort MC 2 - 8%	11.489	0.38	0.9994	943.821	34.051	3.61
Sort MC 3 - 8%	20.305	0.46	0.9981	1415.572	80.017	5.65
Sort MC 3 - 10%	72.343	0.58	0.9994	3684.886	282.851	7.68

For all tested hydrogels from Series II, values of the correlation coefficient R higher than 0.9900 (between 0.9981 and 0.9994) are recorded, showing that the experimental data best fitted the Power law model. Table 2 shows that for Sort MC 1 and Sort MC 2, the rheological parameters m has very close values, while for Sort MC 3, this parameter is only about 1.74 times higher, at a concentration of 8%. This aspect can be explained by the fact that these three commercial sorts have similar viscosities (~10-25 cP). On the other hand, there is a significant increase of the m parameter for Sort MC 3 at a concentration of 10%, which is about 3.56 times higher compared to the value recorded at 8%. Sort MC 1 - 8% and Sort MC 2 - 8% have very close values of S_{thix}, while this thixotropic descriptor is about 2.30 times higher for Sort MC 3 - 8%. It can be noticed that for Sort MC 3, but in a concentration of 10%, S_{thix} increases considerably, being about 3.53 times higher than S_{thix} value at 8%. Thus, S_{thix} can be correlated with the previously determined rheological parameter m, because both descriptors have similar increases when comparing the two concentration (8 and 10%) of Sort MC 3. Regarding the thixotropic behaviour, Sort MC 1 - 8% and Sort MC 2 - 8% are not thixotropic, because $T_{hist\%}$ values are less than 5%. For Sort MC 3 - 8%, a low degree of thixotropy is observed, but at 10%, $T_{hyst\%}$ value is much higher than 5%, which indicates that this hydrogel is thixotropic at 23°C. It can also be remarked that for all sorts from Series II, a high concentration of polymers is required to gelation, which could raise problems for their lyophilization.

The results of the rheological experiments conducted at 23°C for HEC hydrogels led to rheograms - viscosity as a function of shear rate - illustrated for exemplification in Figure 2a. The Power law model, previously detailed, was used to quantify the flow behaviour of HEC hydrogels. To evaluate the thixotropic behaviour of HEC hydrogels, the rheological profiles corresponding to forward and backward curves – shear stress as a function of shear rate - obtained at 23°C are presented in Figure 2b.



a) b)

Figure 2. a) Cumulative rheograms viscosity as a function of shear rate corresponding to HEC hydrogels, analyzed at 23°C; b) Forward and backward curves shear stress as a function of shear rate corresponding to HEC hydrogels, analyzed at 23°C

Analyzing Figure 2a, the viscosity of HEC hydrogels decreases with increase of shear rate, indicating a non-newtonian pseudoplastic character at 23°C. Figure 2b shows the thixotropic character of HEC hydrogels because the backward curve is placed under the forward curve, which means that at the same shear rate, the shear stress for the backward curve is lower.

Table 3. Values for m and n parameters and correlation coefficient R specific for Power law model, and the thixotropic descriptors analyzed at 23°C

Gels	m	n	R	S_{asc} (Pa· s^{-1})	S_{thix} (Pa· s^{-1})	T_{hyst} (%)
Sort HEC 1 - 4%	54.701	0.35	0.9897	3271.555	230.350	7.04
Sort HEC 2 - 20%	28.595	0.25	0.9966	2227.234	115.505	5.19
Sort HEC 3 - 4%	73.994	0.40	0.9970	4025.635	328.835	8.17

For Sort HEC 2 - 20% and Sort HEC 3 - 4%, values of the correlation coefficient R higher than 0.9900 are recorded, which means that the experimental data fitted the Power law model properly. For Sort HEC 1, this value is less than 0.9900. According to the Table 3, the values of the rheological parameters m are well correlated with the viscosity of the commercial sorts; thus, the highest value is registered for Sort HEC 3 - 4%, which has the highest viscosity (4000 cP), and the lowest value is registered for Sort HEC 2 - 20%, which has the lowest viscosity (145 cP). In accordance with the previously mentioned, S_{thix} has a similar variation of its values. The highest value is recorded for Sort HEC 3 - 4%, which is 2.85 times higher than the one recorded for Sort HEC 2 - 20%. It can also be observed that the lowest values of $T_{hyst\%}$ was obtained for

https://doi.org/10.24264/icams-2022.II.26

Sort HEC 2 - 20%, which presents a slightly thixotropy at 23°C. Sort HEC 1 - 4% and Sort HEC 3 - 4%, are thixotropic at 23°C because their value are higher than 5%.

CONCLUSIONS

Cellulose derivatives-based hydrogels showed a non-newtonian pseudoplastic behaviour, which represents a preferable property for the semisolid systems because this feature improves their conditioning and spreadability on the skin surface, promoting the topical administration. Considering the experimental data recorded for the flow and thixotropic parameters, Sort MC 2 and Sort HEC 3 could be selected in a concentration between 3 and 3.5% for further applications in wound healing domain.

Acknowledgement

This work was financially supported by “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania, through Contract no. 33PFE/30.12.2021 funded by the Ministry of Research and Innovation within PNCDI III, Program 1—Development of the National RD system, Subprogram 1.2—Institutional Performance—RDI excellence funding projects.

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