Artículo original

Effect of surfactant on hydration and stress-strain of hypromellose film formation

Efecto del surfactante en hidratación y tensión-deformación en la formación de película de hipromelosa

Sidhartha Sankar Hota[1] https://orcid.org/0000-0002-0198-8677
Souvik Nandi[1] https://orcid.org/0000-0002-6606-1223
Subrata Mallick[1*] https://orcid.org/0000-0002-6606-1223

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University). Odisha, India.

[*]Correspondence to: profsmallick@gmail.com; subratamallick@soa.ac.in

ABSTRACT

Introduction: Surfactant in general has got significant influence on swelling and mechanical properties of hydrogel forming film, particularly used for drug delivery purposes.

Objective: The effect of surfactants on hydration and swelling, and physicomechanical behavior of the hypromellose film formulations has been studied.

Methods: Hydrogel forming films were prepared with hypromellose and different surfactants and cosurfactant systems (Croduret 40, Kolliphor HS 15, Soluplus, Transcutol HP, Captex 355, Dimethyl Sulfoxide and/or Benzalkonium chloride) using macitentan as model drug by solvent casting technique. Swelling at regular interval of time and erosion after hydration of the film formulation were estimated followed by mechanical properties such as, tensile strength, toughness etc.

Results: The highest swelling and least erosion were found in the film containing transcutol and captex (1860 and 17.43% respectively) while the film containing no surfactants/co-surfactants showed 1335 and 41.87% swelling and erosion respectively. Folding endurance of 138 and a high toughness (5.78) was found in film without surfactant where the film formulations containing surfactant/co-surfactants showed a better folding endurance and lower toughness. Elongation at break was found to be 21,30 in the case of MH where 13.80%

was observed in the film containing transcutol. Tensile strength of 39.28 and 36.80 was found of the film containing transcutol and without surfactant respectively.

Conclusions: Exhibited swelling and mechanical properties were found to be the most acceptable in the Hydroxypropyl Methylcellulose film formulation containing transcutol which may be very much suitable for mucoadhesive type ocular drug delivery.

Keywords: Surfactants and co surfactant; hypromellose film; Stress-strain behavior; Swelling and erosion.

RESUMEN

Introducción: El surfactante en general tiene una influencia significativa en las propiedades mecánicas y de hinchamiento de la película formadora de hidrogel, particularmente utilizada para fines de administración de fármacos.

Objetivo: Estudiar el efecto de los surfactantes sobre la hidratación y el hinchamiento, y el comportamiento físico-mecánico de las formulaciones de películas de hipromelosa.

Métodos: Se prepararon películas formadoras de hidrogel con hipromelosa y diferentes sistemas de surfactantes y cosurfactantes (Croduret 40, Kolliphor HS 15, Soluplus, Transcutol HP, Captex 355, Dimetilsulfóxido y/o cloruro de benzalconio) usando macitentan como fármaco modelo mediante la técnica de colada en solvente. Se estimó el hinchamiento a intervalos regulares de tiempo y la erosión después de la hidratación de la formulación de la película, seguido de propiedades mecánicas tales como resistencia a la tracción, tenacidad, etc.

Resultados: El mayor hinchamiento y la menor erosión se encontraron en el film que contenía transcutol y captex (1860 y 17, 43 %, respectivamente) mientras que el film sin surfactantes/co-surfactantes presentó 1335 y 41, 87 % de hinchamiento y erosión respectivamente. Se encontró una resistencia al plegado de 138 y una dureza alta (5, 78) en la película sin tensioactivo donde las formulaciones de película que contenían tensioactivo/co-tensioactivos mostraron una mejor resistencia al pliegue y menor dureza. Se encontró que el alargamiento a la rotura era 21,30 en el caso de MH donde se observó 13,80 % en la película que contenía transcutol. Se encontró una resistencia a la tracción de 39,28 y 36,80 de la película que contenía transcutol y sin surfactante respectivamente.

Conclusiones: Se encontró que las propiedades mecánicas y de hinchazón exhibidas son las más aceptables en la formulación de película de hidroxipropilmetilcelulosa que contiene transcutol, que puede ser muy adecuada para la administración ocular de fármacos de tipo mucoadhesivo.

Palabras clave: tensioactivos; cotensioactivos; película de hipromelosa; comportamiento tensión-deformación; hinchazón y erosión.

Received: 26/02/2022

Accepted: 22/07/2022

Introduction

With strong functional properties hydroxypropyl methylcellulose (HPMC) seems to be the most relevant film-forming drug delivery agent.(1,2,3) The three-dimensional cross-linked polymeric hydrogels are formed with substantial water retention capability. HPMC solution in presence of surfactants in advancing and receding contact angles makes it more hydrophilic.(4)

Surfactants greatly influence the water sensitivity and water uptake capabilities of polymeric films.(5,6) The variant and quantity of surfactant alone or in combination in hydrogel films can alter the mechanical, disintegration and dissolution properties to a great extent.(7) The HPMC polymeric films with PEG (polyethylene glycol) were found with good gloss and free from key defects like cracking, orange peel and picking.(8) Structural design of hydrogels gets altered a lot in presence of surfactants with a promising shelf life.(9) The hydrogen bonds of hydrocolloid and polar groups interact in surfactants and thereby reduce the existing number of polar groups to interact with water molecules. A critical ratio of surfactant in the HPMC film was effective to control the water permeance and moisture level possibly because of the plasticization of hydrocolloid matrix.(10,11) As the mechanical presentation of hydrogels is vital, it has been under focus of investigators for continuous improvement.(12,13,14,15) Hydrogen bonding and hydrophobic association form new physical crosslinkers in hydrogels leading to a great improvement of mechanical properties.(16)

Surfactant when added to hydrogel shows an increased elastic behavior, Maxwellian fluid behavior also significantly lowers the gel-sol transition temperature.(17) Surfactants aid the capability in hydrogels to withstand the catastrophic damage caused by the transmission of destructive force between the crystals and greatly enhance the mechanical properties like tensile strength.(18,19) Surfactants in polymeric hydrogels markedly enhance the general mechanical prevalence of the film like folding endurance, tensile strength, percent elongation and Young's modulus.[20] Encouraging mechanical characteristics of biopolymer hydrogels with surfactants are often used in biomedical devices as their porous network effortlessly transport fluids, and ease its degradation in body fluids.[21] Softness and high water content of polymeric hydrogels resemble living tissues are biocompatible and can resist stress due to physiological conditions actively with surfactants. These can take up the structural shape of application area exhibiting sufficient.[22] Surfactants in HPMC hydrogel effectively decrease the temperature of gelation and thus make it compatible with body temperature and a choice of combination for an optimized formulation.[23]

The current work was undertaken to study the effect of surfactants on swelling and physicomechnical aspects of HPMC hydrogel film formulations containing macitentan as a model drug prepared by solvent cast technique.

Methods

Materials: Macitentan and HPMC K100M were received as gift samples from Aurobindo Pharma, India. Polyoxyl 40 hydrogenated castor oil (Croduret 40) was obtained from Croda Inc. U.S., as a gift sample. Polyoxyl 15 hydroxystearate (Kolliphor HS 15) and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus) were received as gift samples from BASF India. Diethylene glycol monoethyl ether (Transcutol HP) and glycerol caprylate caprate (Captex 355) were gifts acquired from Gattefosse, France and Abitec Corp., U.S. respectively. PEG 600 was bought from Merck India and Dimethyl Sulfoxide (DMSO) along with Benzalkonium chloride (BKC) were procured from Gattefosse, France.

Film Preparation: Ophthalmic mucoadhesive films were made using a solvent casting and evaporation process. HPMC (800 mg each) was distributed in 10-20 mL of water and refrigerated for 36-40 hours at about 4 to 8 °C. For 18 hours, the swelled HPMC was agitated at 20 rpm on a magnetic stirrer in room temperature. Surfactants (Captex/soluplus/Kolliphor) and transcutol/PEG/DMSO were combined together and added to the hydrogel drop wise while stirring. Macitentan as a model drug (100 mg each) was dissolved in ethanol and added into the clear HPMC-surfactant-cosurfactant mixture, which was stirred for another 6 hours. The resulting transparent gel was cast into a Petri dish (diameter: 90 mm, Tarsons) and spread evenly before being dried at 40 °C for 24 hours.

Swelling and erosion study: Hydration extent and matrix erosion of the film (≈1 cm×1cm) was evaluated in 40 mL of simulated tear fluid on a Petri dish (eq. 1). The swelling index was determined at regular interval of time from the weight gain by the film. Hydrated films were dried to constant weight in the desiccators over silica gel at 60 °C for matrix erosion study (eq. 2). The swelling rate (Ks) was determined from the slope of the linear profile of percent swelling index vs. time plot.

$$\text{Dynamic hydration}(\%) = \frac{(\text{Weight after hydration} - \text{Initial dry weight})}{\text{Hydrated weight}} \times 100 \text{ (eq. 1)}$$

$$\text{Matrix erosion} = \frac{\text{Initial dry weight} - \text{Dried Swelled film weight}}{\text{Initial dry weight}} \times 100 \text{ (eq. 2)}$$

Mechanical properties of the film: The films were cut into dog bone shape with uniform dimensions.[24] Then the thickness of the films on an average was calculated. The mechanical aspects of the films were determined by Instron 8801(Norwood, MA, USA). The dog bone shaped film was held in between the jaws of light weight screw vise grips with cyanoacrylate adhesive tapes. Tensile load was applied on the films to break the dog bone strips. Breakage at the center of the film was accepted for further data analysis. The data generated by the Instron Bluehill 2 (version 2.6) systems for load and displacement data were recorded till the point of split. Mechanical behavior of the films like tensile strength, strain at break, percent elongation, Young's modulus (elastic modulus), and the ratio of tensile strength to Young's modulus were calculated.

FTIR: Fourier transform infrared spectroscopy of the prepared film formulations has studied. The scan was commenced in the range of 500-4000 cm^{-1} to study API and excipients compatibility.

The scanning was done by placing the sample on the diamond crystal in ATR Pro One [JASCO] present in JASCO FT/IR-4600. The resulting FTIR spectra was an average of 30 scans.

Results

The measured surface pH of the films varied from pH 6.90 to 7.12 (Table 1).

Table 1 - Effect of surfactant and cosurfactant on swelling and erosion of HPMC film formulation containing macitentan as a model drug

FILMS	Surafctants/cosurfactant	*Moisture content (%) w/w mean±SD (n=3)	**Swelling (%) mean±SD (n=3)	Swelling rate (Ks; h^{-1}) mean±SD (n=3)	**Erosion (%) mean±SD (n=3)
MH	---	12.87±0.12	1335±45	1.99±0.03	41.87±2.50
MHSB	BKC. Soluplus	11.67±0.14	1374±38	2.68±0.02	36.20±3.27
MHSD	DMSO. Soluplus	11.50±0.08	1250±45	2.06±0.07	22.77±3.52
MHEmP	PEG. Captex. Kolliphor. Croduret	12.06±0.08	1730±66	3.58±0.13	18.73±2.17
MHEmT	Transcutol. Captex. Kolliphor. Croduret	12.17±0.13	1860±37	3.86±0.03	17.43±2.14

*Laboratory ambient condition (25 °C Relative humidity 50-60 % RH)
**At 6 h. BKC=Benzalkonium Chloride, DMSO=Dimethyl Sulfoxide, PEG=Polyethylene Glycol.

Film thickness was found to be: MH: 99.6±1.1, MHSB: 98.3±1.1, MHSD: 113±1.0, MHEmP: 143.6±1,5, MHEmT: 141.6±0.5. MH showed a folding endurance of ~138 where other films showed >200 (Table 2). Surface pH study has also revealed the pH range to be within 6.90 and 7.12. MH has shown 1335% of swelling where the surfactant containing films has shown swelling profile of 1250-1860%. The swelling rate and erosion were observed to be 1.99 and 41.87 respectively for MH. Other film formulations showed swelling rate in the range of 2.06 to 3.86 h^{-1} and erosion in the range of 17.43 to 36.20% (Table 1). Very good swelling behavior has been observed with all the films (Fig. 1A, B).

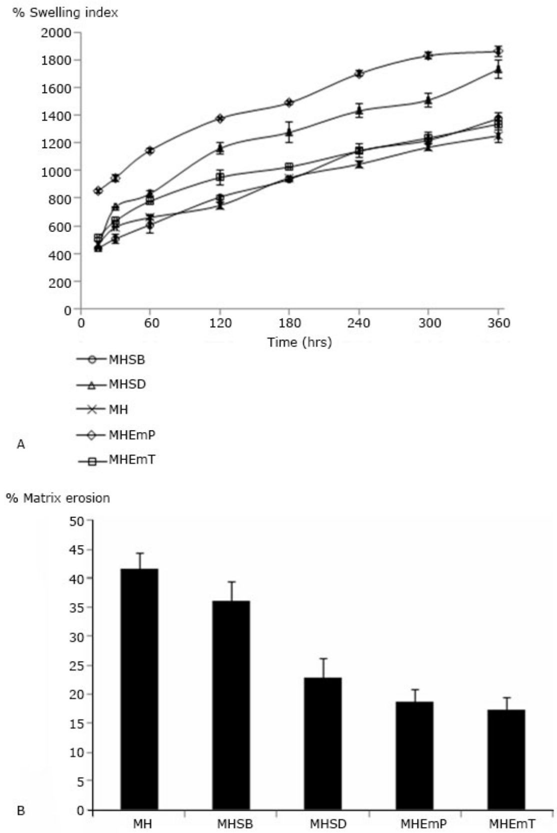

Fig. 1 - A has now been corrected the unit of time is changed to minute. (A) Swelling index of film. (B) Matrix erosion of film.

FTIR: The FTIR spectra (Fig. 2) of MCT has given significant peaks at 1383, 1160, 2963, 1560, 1312, 1160 and 929 cm^{-1}. The prepared formulations have not shown any significant change in drug peak intensity or positioning.

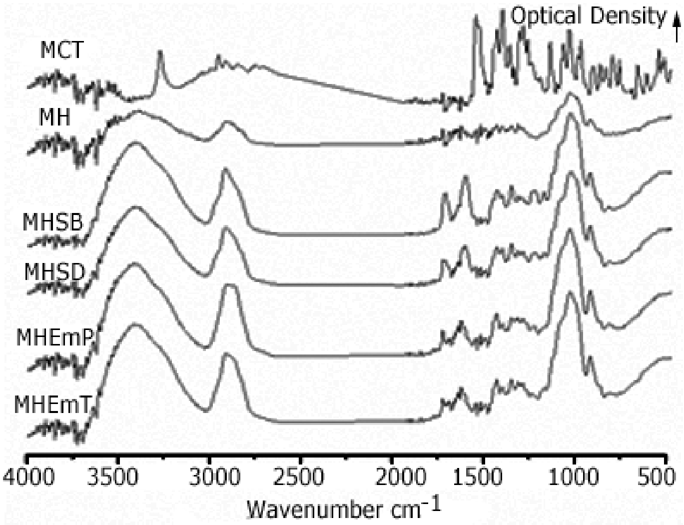

Fig. 2 - FTIR spectra of the prepared film formulations.

Mechanical and solid-state properties of the film: Tensile strength study has revealed 36.80 MPa for MH where the other formulations have shown 24.28 to 39.28 MPa. Elongation at break, elastic modulus, surface energy and toughness was found to be 21.30%, 69.80 MJ.m-3, 0.527 and 5,78 MPa respectively for MH.

Stress-strain curve from the tensile experiments indicated the mechanical behavior of solvent cast film (Fig. 3).

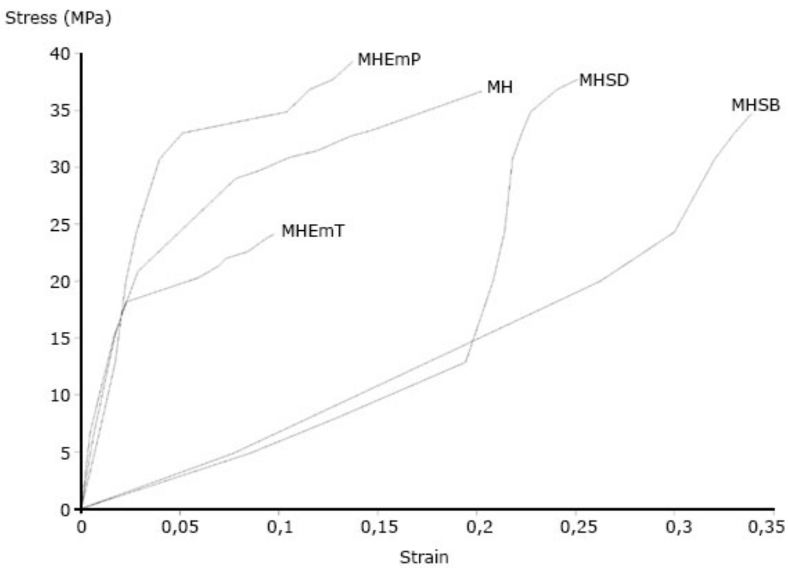

Fig. 3 - Mechanical strength (Stress-strain plot) by Instron.

Table 2 - Effect of surfactant on Mechanical properties of HPMC film formulation

FILM	Tensile strength (MPa)	Elongation at break (%)	Elastic modulus ($MJ.m^{-3}$)	Surface energy	Toughness (MPa)	Folding endurance
MH	36.80	21.30	69.80	0.527	5.78	138
MHSB	34.80	36.36	80.97	0.430	4.51	> 200
MHSD	37.71	25.10	66.03	0.571	2.80	> 200
MHEmP	24.28	10.56	87.05	0.279	1.82	> 200
MHEmT	39.28	13.80	74.00	0.531	4.03	> 200

Discussion

All prepared film thickness was found to be well within predetermined limits.[25] A very good folding endurance value of surfactant containing films (more than 200 folds) ensures that the films are not brittle and having sufficient plasticity. The presence of liquid excipients (surfactant/co-surfactant) and the moisture content (11.5 to 12.9 %) facilitated the improved plasticity and flexibility of the films to meet good patient compliance. Presence of moisture in this range also protects from getting dried and brittle. The measured surface pH of the films varied from pH 6.90 to 7.12 which is indicative of non-irritant and highly biocompatible for mucosal application (Table 1).

Swelling and erosion behavior: Very good swelling behavior has been observed with all the films (Fig. 1A, B). Highest extent of swelling (1860 %), least erosion (17.43 %) and highest swelling rate (3.86) of MHEmT may be due to presence of Transcutol as hydrophilic surfactant in the film compared to 1730%, 18.73% and 3.58 h^{-1} respectively of MHEmP containing PEG 600 as surfactant. Other films (MH, MHSB and MHSD) swelling index was found to be in the lower level (1250 – 1374%), higher erosion level in the range of 22.77 to 41.87% and Ks level in the range of 1,99-2,68 h^{-1}. Such hydrogel formulation when comes in contact with water it swells with erosion leading to degradation of film due to presence of HPMC.

FTIR: The FTIR spectra (Fig. 2) of MCT has given significant peaks at 1383, 1160 cm-1 indicating the presence of sulfonyl radicals in the structure of macitentan. Peaks at 2963, 1560 and 1312 cm^{-1} was observed due to CH_2 stretching, C=N stretching and C-O stretching respectively. Peaks at 1160 and 929 cm^{-1} was evident caused by asymmetrical and symmetrical stretching of SO_2 and S-N respectively.[26] The prepared formulations have not shown any significant change in drug peak intensity or positioning from which it can be concluded that there are incompatibilities between MCT and the excipients.

Mechanical and solid-state properties of the film: The profiles of the mechanical and solid-state properties of the film formulations are presented in Table 2. For characterization of mechanical properties, uniform dog bone shaped film strips were used. The raw data of load and extension resulted from the experiment were recorded and analyzed. The maximum tensile strength of a film is the largest emphasis for the film to be stretched before necking or rupture. Stress-strain curve from the tensile experiments indicated the mechanical behavior of solvent cast film (Fig. 3). Tensile strength was calculated from the load per unit area ($N*mm^{-2}$) and percentage elongation from the strain at break. Presence of transcutol in the film (MHEmT) as co-surfactant increased the tensile strength to the highest extent (39.28); on the contrary MHEmP has shown least value of 24.28 $N*mm^{-2}$ may be due to the presence of PEG 600. Other films have exhibited moderate tensile strength in the range of 34.80 – 37.71 $N*mm^{-2}$. Elongation at break (%) in the range of 10.56 – 36.36; the highest value belongs to the film MHSB and least to MHEmP. Young's modulus was calculated from the slope of the stress strain curve on the initial linear section before the film undergoes elastic deformation (66.03 – 87.05 MPa). MHSB film has shown smallest modulus of elasticity as low as 66.03 and highest value of 87.05 MPa was shown by MHEmP. Different values of tensile strength, elongation at break and modulus of elasticity to some extent formulation wise could be comparable with commercial products in a recent report and suggested to be well acceptable for mucosal drug delivery.[26] The surface energy of a film is the ratio of tensile strength to Young's modulus (TS/Ym) considered as resistance to the initiation of cracking process and a useful parameter to predict the initiation of necking.[27] All the formulations showed almost a similar pattern of tensile strength, surface energy, elongation at break and Young's modulus which implies such different values still can produce acceptable bio-films. The prepared biofilms can be applied as ocular drug delivery system.[28] MHEmP shows a good tensile strength of 24.28 MPa, and 10.56 % elongation at break satisfying the requisites. Flexibility of all the films except MH is sufficient on the addition of the plasticizer to meet the good patient compliance. Transcutol, DMSO, PEG, and Soluplusin the film formulation exhibited good plasticizing properties besides being surfactant/co-surfactant and penetration enhancer.[29,30,31] A lower folding endurance and higher toughness of MH (138 and 5.78 respectively) may be an indication of stiff film formulation which can lead to reduced patient compliance. Presence of surfactant contributed to higher folding endurance and lower toughness than MH may be because of the breakage of interpolymeric hydrogen bonds leading to better flexibility.

It is concluded that the effect of surfactants on swelling and stress-strain behaviour of hypromellose hydrogel film formulations containing macitentan as a model drug has been studied successfully. FTIR study revealed no drug excipient incompatibilities. Presence of surfactant increased swelling and decreased erosion rather than its absence in the film. Transcutol containing film exhibited highest swelling and least erosion (1860 and 17.47% respectively) among the others. Transcutol containing film also showed overall good mechanical behavior and fexibility very much suitable for drug delivery purposes particularly mucoadhesive type ocular drug delivery with much acceptable patience compliance.

Acknowledgement

The authors are grateful to the Department of Science & Technology, Ministry of Science & Technology, New Delhi, India, for providing INSPIRE fellowship to Souvik Nandi (IF 180534).

The authors are grateful to the Honorable Prof. Manojranjan Nayak, President, Siksha 'O' Anusandhan (Deemed to be University) for facilitating and encouraging the research. The authors are also thankful to Dr. (Ms) Barsha Dash, Senior Scientist, CSIR-Institute of Minerals and Materials Technology, Bhubaneswar, for facilitating the other analytical facilities for the research.

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Conflict of interests

The authors report no conflict of interest

Author Contributions

Conceptualization: Subrata Mallick.

Data curation: Sidhartha Sankar Hota.

Software: Souvik Nandi.

Supervision: Subrata Mallick.

Writing - original draft: Sidhartha Sankar Hota.

Writing - review & editing: Souvik Nandi.