Desalination and Water Treatment
www.deswater.com

doi: 10.5004/dwt.2022.29096

279 (2022) 124–130
December

Optimisation of stability and stiffness of xanthan/polyacrylic acid/calcium-based hydrogels

Kaouther Ezzroug[a,b,*], Leila Chabane[c], Meriem Boudoukhani[a], Abdelkader HadjSadok[b], Moulai-Mostfa Nadji[a]

[a]*Materials and Environmental Laboratory (LME), University of Medea, Nouveau pôle urbain, 26000 Medea, Algeria, email: ezzerougkaouther@yahoo.fr*
[b]*Functional Analysis of Chemical Processes Laboratory, Chemical Engineering Department, Saad Dahlab University, BP 270, 09000, Blida, Algeria*
[c]*Laboratoire Eau Environnement et Développement Durable, Faculté de Technologie, Université Saad Dahlab-Blida1, BP270-09000, Algeria*

Received 29 June 2022; Accepted 28 September 2022

ABSTRACT

In this study, xanthan/polyacrylic acid hydrogels were prepared to improve their physical and physico-chemical properties with the aim of using them in different applications (food or pharmaceutical). The optimal concentration of crosslinking agent for which the hydrogel structure can be in its most stable form was also determined. The stability and stiffness of xanthan/polyacrylic acid/calcium based hydrogels were optimized by a centered face design response surface design. The hydrogels were characterized by studying the swelling profiles and the rheological properties. It was found that the stiffness of hydrogels depended mainly on the fraction of xanthan in the mixture. The physical cross-linking of hydrogels by calcium ions had a double impact on the hydrogels. At low calcium concentration, it behaved as a matrix stabilizer where the rigidity of the hydrogels increased with the increase in the concentration of xanthan, and the swelling rate reaches 78.9% without any erosion of the matrices. However, at high concentrations of calcium, it behaved as a destabilizer and caused phase separation at the microscopic scale. This, led to erosion of hydrogels at low concentrations of xanthan, and therefore their elastic limit was relatively low. The release of diclofenac from the optimal hydrogel composition was modeled by the Korsmeyer–Peppas model.

Keywords: Hydrogel; Gel physics; Xanthan; Polyacrylic acid; Calcium

1. Introduction

Hydrogels are pass-related 3-dimensional networks manufactured from natural resources or synthetic polymers which includes carbopol polyacrylic acid (PAA). They have high flexibility and biocompatibility. Hydrogels can absorb substantial amounts of water or body fluids. They are used in the pharmaceutical industry (drug shipping), the biomedical area (tissue engineering, wound dressing), and for environmental packages [1]. The hydrated polymeric networks show good electricity conductivity and elasticity [2,3] and are insoluble in water [4]. Polymeric hydrogels are responsive when their environments are altered, for example, pH, strain, solvent composition, and temperature [5–8]. Hydrogels hold their integrity because of physical and chemical cross-linking. The physical crosslinking involves non-covalent interactions which include chain entanglements or hydrogen bonding, Van Der Waals forces [9–11] while the chemical crosslinking occurs through covalent bonding [11]. Chemical crosslinking entails processes such as poly-purposeful pass-linking fabric of a hydrophilic

* Corresponding author.

Presented at the First International Congress of Energy and Industrial Process Engineering (ICEIPE'22) 23–25 May 2022, Algiers, Algeria

monomer or 3-dimensional polymerization, that is finished using direct crosslinking of water–soluble polymers. Polymerization is initiated via electronic beam radiations like UV, γ-radiation, or by way of the usage of loose radicals producing entities like persulfate, and peroxides [12].

Xanthan (xanthan) is high molecular weight and anionic extracellular polysaccharide with branched chains and acidic nature. Xanthan consists of d-glucosyl, d-mannosyl, and d-glucuronyl acid residues in a 2:2:1 molar ratio and variable proportions of o-acetyl and pyruvyl residues [13]. It is extensively used as a thickener in food, cosmetics, and pharmaceutical industries. It has the approval of the Food and Drug Administration (FDA) in the USA since 1969 [14]. Polyacrylic acid (PAA) is a pH sensitive polyelectrolyte polymer that can form ions while subjected to aqueous surroundings, resulting in swelling because of hydrogen bridge or covalent bond formation [14,15]. However, the excessive water solubility of poly (acrylic acid) has limited its utility as a drug delivery system [16].

The purpose of this study is to stabilise and optimize the stiffness of xanthan/polyacrylic acid/calcium-based hydrogels for pharmaceutical and biomedical applications. A centered face design (CCF) response surface design has been used. The hydrogels were characterized by assessing the swelling profiles and the rheological properties. As an application, the kinetics of the release of Diclofenac~® by the optimized hydrogel in gastric and intestinal medium was simulated by the Korsmeyer–Peppas model.

2. Materials and methods

2.1. Materials

Xanthan gum (XG) with a molecular weight (Mw) of 2.5×10^6 g/mol and 38% of acetylated group was purchased from Solvay (France). Polyacrylic acid (Carbopol 940) is kindly provided by Saidal (Medea, Algeria). The other analytical reagents (sodium hydroxide, hydrochloric acid and calcium chloride) were supplied by Merck (Switzerland).

2.2. Experimental

A design of experiments was adopted to minimize the number of tests and to ensure a better quality of the results using MODDE 6.0 software. After preliminary studies, the influence of $CaCl_2$ concentration on the rheological properties of xanthan in solution was assessed. The field of interest of the factors retained, which were in this case: the fraction of xanthan in mixture xanthan/PAA, the concentration of [$CaCl_2$], and the pH:

- X_1: xanthan: 0.1%–0.9%
- X_2: pH: 5–7
- X_3: [$CaCl_2$]: 0–0.2 M

The responses selected were the characteristics resulting from the rheological control as well as the rate of swelling.

- Y_1: storage modulus G' of the linear domain of viscoelasticity
- Y_2: the critical shear rate
- Y_3: the swelling rate

The matrix of experiments proposed by the MODDE 6.0 software was a centered face design (CCF) with three repetitions in the center, containing 17 trials (Table 1).

2.3. Preparation of hydrogels

For a mixture of 1 g of polymer dissolved in 7 mL in each concentration of $CaCl_2$, the pH of the hydrogels was fixed after homogenization by solutions of 0.1 N of HCl

Table 1
Matrix of experiments deduced from the plan adopted in this study

Exp. name	Fraction xanthan	pH	Con. Ca	Storage modulus	Swelling rate	Critical shear rate
N1	0.1	5	0	235	44	155
N2	0.9	5	0	825	56.8	345
N3	0.1	7	0	217	94.01	132
N4	0.9	7	0	344	54.6	162
N5	0.1	5	0.2	40.1	0	13.26
N6	0.9	5	0.2	1000	37.8	429
N7	0.1	7	0.2	74.2	0	27.28
N8	0.9	7	0.2	656	30.2	220.1
N9	0.1	6	0.1	127	45	89.86
N10	0.9	6	0.1	856	57.14	412
N11	0.5	5	0.1	686	56.77	323
N12	0.5	7	0.1	420	78.9	215
N13	0.5	6	0	497	82.2	228
N14	0.5	6	0.2	419	19.78	236
N15	0.5	6	0.1	455	58.2	245
N16	0.5	6	0.1	520	41.86	282.1
N17	0.5	6	0.1	448	55.6	233.1

and 0.1 N NaOH up to a volume of 10 mL to have a concentration of 10% in polymer.

2.4. Characterization of hydrogels

2.4.1. Rheological behaviour of hydrogels

The viscoelastic behavior of mixtures at 20°C was carried out using an MCR 302 Anton Paar Physica rheometer (Anton Paar, GmbH, Germany) with a plane-plane geometry (φ = 25 mm). The dynamic regime oscillating under a frequency of 1 Hz and under the application of an increasing deformation ramp, γ: from 0.01% to 100%. The domain of linear viscoelasticity, LVE, was then identified, from which were deduced the values of the two moduli of elasticity G' and loss G'' (G' characterizes the elastic behavior of the analyzed material; G'' characterizes the viscous behavior of the material).

2.4.2. Swelling kinetics

The gels were placed inside beakers and then immersed in distilled water. The gels (m_i) studied were weighed before their immersion in the dissolution media. At regular time intervals, the gel samples were removed from the medium, dried on filter paper to eliminate excess liquid, and then weighed (m_g).

The swelling rate was calculated according to Eq. (1).

$$\text{Swelling Ratio} = \frac{\left(m_g - m_i\right)}{m_i} \times 100 \quad (1)$$

2.4.3. Diclofenac release kinetics

The dissolution test of optimal hydrogels loaded with diclofenac sodium as a tracer was carried out under conditions like physiological gastrointestinal fluid. The dissolution media consisted of 0.1 N HCL and 0.5 M phosphate buffer n (PBS) at pH 6.8, which was prepared according to European Pharmacopoeia 8.0, with a slight modification. Samples were taken at different time intervals.

3. Results and discussion

The evolution of the two moduli G' and G'', as a function of the deformation, is given in Fig. 1. In the linear viscoelastic domain (LVE), in which case G' and G'' were constant (insensitive to deformation), it was noticed that $G' > G''$. Therefore, the mixtures exhibited the behavior of a viscoelastic solid. Outside the LVE domain, G' began to decrease and intercepted G'' at the freezing point ($G' = G''$). Beyond this point, a reversal of the rheological behavior was seen from a viscoelastic solid to a nonlinear viscoelastic liquid with a plastic character. In this case, the significant deformations were not totally recoverable. These results were like those obtained by Belhadji et al. [17].

Fig. 2 shows that the quality of the response surface model (RMS) of the responses (the percentage of the four indicators of modeling quality, R^2, Q^2, model validity and reproducibility) was acceptable, given the values of the prediction coefficients Q^2 (Table 2).

The storage modulus (G'), swelling rate (SR%), and critical shear rate (CSR) responses were modeled with the three factors of X_1, X_2, and X_3 using a polynomial model.

According to the correlated mathematical model, the storage modulus response depended mainly on the xanthan fraction (Fig. 3). The more the xanthan fraction increased, the more the hardness of the hydrogels increased. When the pH exceeded the value of 6 the mixture became less hard. This result was independent of the amount of salt in the medium.

Moreover, the swelling rate increased when the calcium concentration decreased and the pH increased. It records a maximum at pH equal to 7 and at [Ca++] greater than 0.1 M. When the pH came close to 5 and with a high calcium value, the mixture became soluble in the swelling medium. The same behaviour was observed at different concentrations of xanthan. The swelling ability of xanthan/PAA gel was better than that of xanthan/PAA/Ca++ gel. This can be explained by the formation of a more entangled and cross-linked polymeric network, making a better retention of the chains in the solvent, and therefore offering a better swelling capacity. This result indicated that more important interactions such as hydrogen bonding occur between xanthan and carbopol.

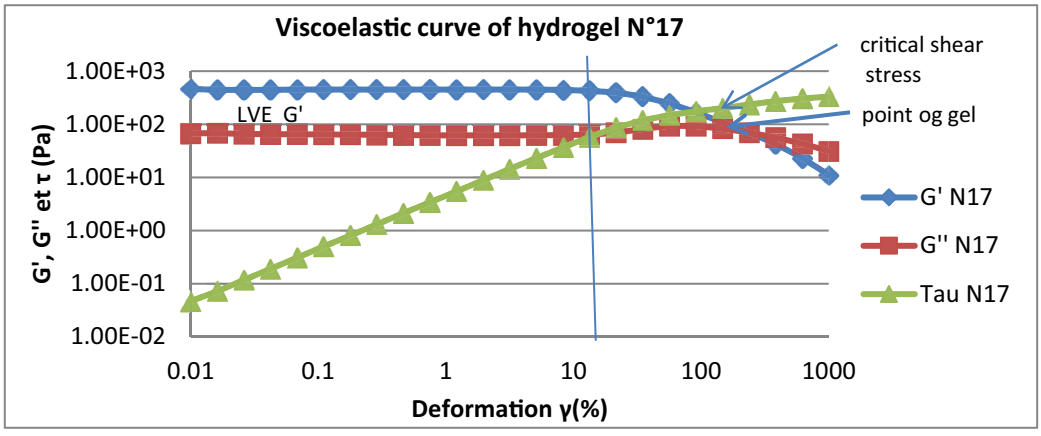

Fig. 1. Viscoelastic behavior of the hydrogel N17.

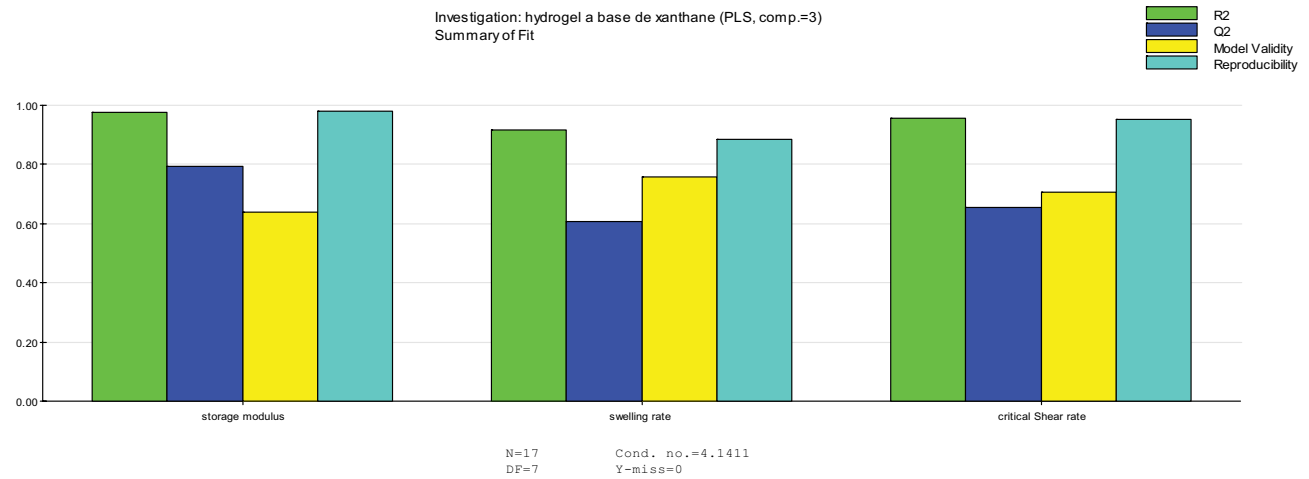

Fig. 2. Parameters indicative of the quality in the statistical sense of the models studied.

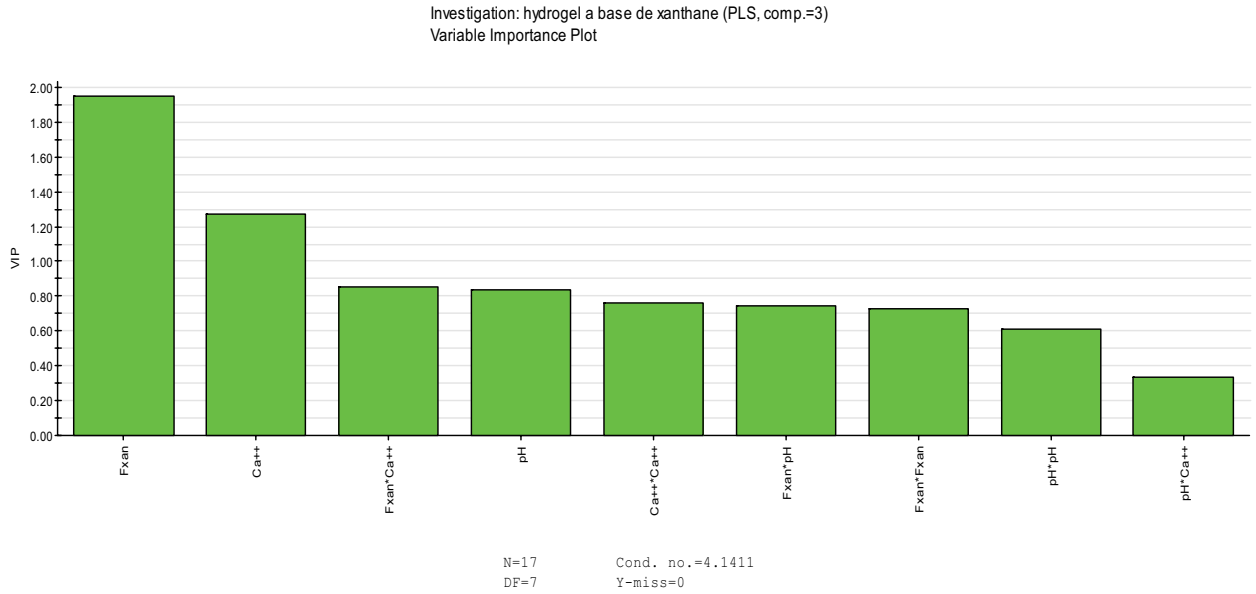

Fig. 1. Viscoelastic behavior of the hydrogel N17.

The response that corresponds to the critical shear rate depended mainly on the xanthan fraction (Fig. 4), while the effect of pH depended on the concentration of $CaCl_2$. At low [Ca++] the critical shear rate increased when the pH decreased for any xanthan fraction. But at high [Ca++] the effect of pH only appeared at a fixed value above 0.5%. It was noted that the consistency of the hydrogels increases when the concentration of xanthan increased. While the critical tau depended on the total composition of the mixture. The addition of PAA to the xanthan/$CaCl_2$ hydrogel gave the system additional hardness due to the presence of calcium ions which promote ionic cross-linking of the hydrogel [18].

Experimental validation of a simulation model is crucial. This validation requires experiments and will contribute to confirming the industrial interpretation of the simulation results. It is this experimental validation that will make it possible to compare the responses measured by experimentation with those provided by the model. A confidence interval around the predictions is defined (Table 3):

According to the results obtained, most of the results are included in the tolerance interval predicted by the model at the points considered, which proves that the mathematical model is valid for any point within the study area.

3.1. Kinetic study of drug release

In view of the dissolution profiles in Fig. 5, the levels of cumulative active principle released increased as a function of time according to a non-linear function which differed from one system to another. When the solvent entered the polymeric network in the vitreous state, the latter swelled. The polymer changed to the rubbery state (hydrogel) and a front separating the two states was thus created. After the relaxation of the macromolecules, the active ingredient

Table 2
Percentage of the four indicators of modeling quality

	R^2	R^2 Adj.	Q^2	Reproducibility
Storage modulus G'	0.974951	0.942745	0.792465	0.979639
Swelling rate	0.916522	0.809194	0.60732	0.883329
Critical shear stress	0.957307	0.902416	0.653745	0.953329

$$G' = 502.491 + 231.972X_1 - 93.9324X_2 + 3.4216X_3 - 17.9897X_1X_1 + 4.4377X_2X_2 - 31.638X_3X_3 - 67.8686X_1X_2 + 66.441X_1X_3 + 11.4101X_2X_3$$

$$SR\% = 57.6862 + 4.3341X_1 + 4.9851X_2 + 19.4953X_3 - 5.4665X_1X_1 + 0.5852X_2X_2 - 5.6065X_3X_3 - 4.7357X_1X_2 + 7.4861X_1X_3 - 4.3703X_2X_3$$

$$CSR = 266.832 + 93.6221X_1 + 35.3688X_2 + 7.2248X_3 - 17.8662X_1X_1 + 8.3693X_2X_2 - 23.0425X_3X_3 - 29.0289X_1X_2 + 29.6568X_1X_3 - 2.4897X_2X_3$$

Table 3
Values of the storage modulus G', swelling rate and critical shear stress of the validation experiments

Fraction xanthan	pH	Con. Ca++	Storage modulus (Pa) measured	Storage modulus (Pa) Min.	Storage modulus (Pa) Max.	Swelling rate (%) measured	Swelling rate (%) Min.	Swelling rate (%) Max.	Critical shear stress (Pa) measured	Critical shear stress (Pa) Min.	Critical shear stress (Pa) Max.
0.8999	**5**	**0.0997**	**956**	873.541	1,140.36	**54.12844**	33.7564	78.7547	**450**	362.327	510.429
0.9	**5**	**0.08**	**928**	800.038	1,055.94	88.76404	35.2358	78.3926	**425**	329.573	471.615
0.437	**6.9427**	**0.0003**	**302**	182.989	437.684	**95.66223**	67.2385	110.192	**224.5**	105.419	246.793
0.8999	**5.0008**	**0.1004**	860	878.335	1,144.69	**66.21621**	33.405	78.3245	**400**	363.976	511.82
0.888	**5**	**0.11**	**857**	842.117	1,100.93	**37.23849**	35.779	79.428	**430**	351.368	495.03
0.9	**5**	**0.08**	660	800.038	1,055.94	**51.14**	35.2358	78.3926	317.3	329.573	471.615
0.437	**6.9427**	**0.0003**	**242**	182.989	437.684	62.02531	67.2385	110.192	**142**	105.419	246.793
0.9	**5.0001**	**0.1002**	636	869.2	1,136.23	**40**	34.0431	79.077	331.1	360.754	508.974

The significant parameters in the models are mentioned in bold.

was then able to diffuse outwards. When the gel reached its maximum degree of swelling, a slowing down of the release of the active ingredient diclofenac was observed at the saturation time and therefore the rate of release tended to become constant.

The diffusion of the active ingredient diclofenac in the rubbery phase was of the Fickian type when the system had reached its swelling equilibrium. However, if this equilibrium was not reached, the diffusion was of anomalous type, or even zero-order kinetics. Dissolution profiles of all assays were fitted by the Korsmeyer–Peppas dissolution kinetics model. Its equation expressed the accumulated percentage of the active principle in solution. $Q(t)$ as a function of time t [Eq. (4)]:

$$Q(t) = Q_\infty \left(kt^n\right) \tag{4}$$

where Q_∞ represented the maximum dissolved percentage of the active principle for an infinite theoretical time, k is the constant relating to the phenomenon of diffusion while n is the exponent which depends on the mechanism of release and swelling. The results are grouped in Table 4.

The release mechanism exponents were less than 0.5 indicating that the diffusion of PA through the hydrogel matrix was of the Fickian type. The results showed that the amount of active ingredient released for 8 h in the intestinal medium was greater than that released in the gastric medium. This was due to the low dissolution of diclofenac at acid pH. According to the previous results, the rate of swelling of the hydrogels reached its maximum at pH close to 7 while at pH = 5 the hardness of the hydrogels which reached its maximum, which made diffusion through the macromolecular chains of the two polymers slow. Therefore, the value of the diffusion coefficients k of the gastric medium was very low in comparison with that of the intestinal medium.

Djekic et al. [18] targeted the components of hydrogels with the poorly soluble drug ibuprofen (5%). Hydrogels, formulated with xanthan gum 1% (HIB), sodium carboxymethylcellulose five% (CMCIB), poloxamer 407 16% (PIB), and

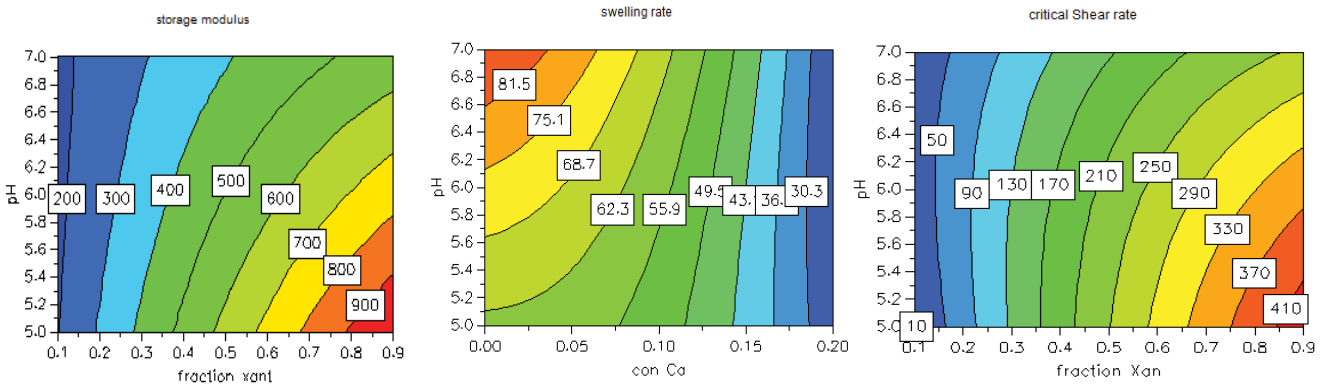

Fig. 4. Isocontours of the three responses, as a function of the variation of the xanthan fraction, concentration of Ca++ and the pH.

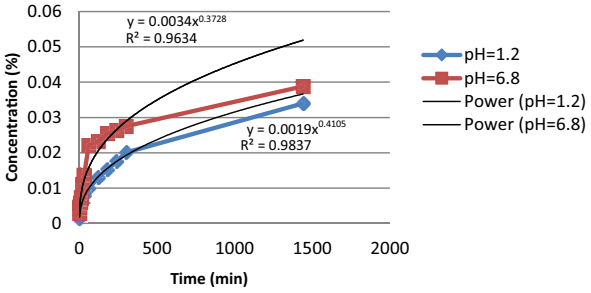

Fig. 5. Diclofenac release profile in gastric and intestinal media.

carbomer 1% (KiB), were smooth pseudo plastic semisolids with thixotropic and biocompatible pH. The drug launch in all investigated hydrogels changed into diffusion-controlled in accordance with the Higuchi version and sustained for 12 h, with the drug launch charge and the amount of drug released depending on the polymer.

4. Conclusions

In this study, xanthan/PAA hydrogels were prepared to improve their physical and physico-chemical properties with the aim of using them in different applications (food or pharmaceutical). A response surface design was used to find the optimal preparation conditions. The optimal concentration of crosslinking agent for which the hydrogel structure can be in its most stable form was also determined. The effect of pH on the chemical structures, swelling mechanism, and rheological behavior of hydrogels was studied. The formation of the xanthan/PAA hydrogel was based on the entanglement of its macromolecular chains which only occurred above a certain critical concentration. These hydrogels disintegrated in water due to weak hydrogen bonds. Their hardness increased significantly with increasing xanthan concentration. Strengthening the structure of xanthan gels prompted by using calcium, a most useful ratio among calcium and xanthan ions has been hooked up in phrases of elastic modulus (G'), an increase in gel hardness, and a coarsening of the network shape. The neutralization of the structure of the polysaccharide via an extra of divalent calcium ions was responsible for a marked aggregation of the polymer strands reminiscent of precipitation.

Table 4
Characteristics of the Korsmeyer–Peppas model in the gastric and intestinal domain

Release medium	Q∞ (%)	k	n	R^2
Gastric medium pH = 1.2	0.202	0.0094	0.4201	0.9837
Intestinal medium pH = 6.8	0.279	0.0121	0.3728	0.9634

The results obtained from this study look promising and can be used in different applications, such as wound care, drug delivery, agriculture, sanitary napkins as well as transdermal systems, dental materials, implants, injectable polymer systems, ophthalmic applications, hybrid type organs. It should be noted that this modest study is far from complete, and it would be interesting to complete it with other analyzes and the use of other polymers and polymer blends.

References

[1] R. Parhi, Cross-linked hydrogel for pharmaceutical applications: a review, Adv. Pharm. Bull., 7 (1017) 515–530.
[2] S. Ma, B. Yu, X. Pei, F. Zhou, Structural hydrogels, Polymer, 98 (2016) 516–535.
[3] C. Yang, Z. Suo, Hydrogel ionotronics, Nat. Rev. Mater., 3 (2018) 125–142.
[4] A.C. Daly, L. Riley, T. Segura, J.A. Burdick, Hydrogel microparticles for biomedical applications, Nat. Rev. Mater., 5 (2020) 20–43.
[5] X. Fan, L. Yang, T. Wang, T. Sun, S. Lu, pH-responsive cellulose-based dual drug-loaded hydrogel for wound dressing, Eur. Polym. J., 121 (2019) 109290, doi: 10.1016/j.eurpolymj.2019.109290.
[6] S. Aditya, S.G. Mark, L.T. Nancy, Wound dressings and comparative effectiveness data, Adv. Wound Care, 3 (2014) 511–529.
[7] J. Liu, S. Qu, Z. Suo, W. Yang, Functional hydrogel coatings, Nat. Sci. Rev., 8 (2021) 254, doi: 10.1093/nsr/nwaa254.
[8] T. Vermonden, B. Klumperman, The past, present and future of hydrogels, Eur. Polym. J., 72 (2015) 341–343.
[9] C. Echalier, L. Valot, J. Martinez, A. Mehdi, G. Subra, Chemical cross-linking methods for cell encapsulation in hydrogels, Mater. Today Commun., 20 (2019) 100536, doi: 10.1016/j.mtcomm.2019.05.012.

[10] E.M. Ahmed, Hydrogel: preparation, characterization, and applications: a review, J. Adv. Res., 6 (2015) 105–121.
[11] G. Muir, J.A. Burdick, Chemically modified biopolymers for the formation of biomedical hydrogels, Chem. Rev., 121 (2020) 10908–10949.
[12] S. Ahmad, M. Ahmad, K. Manzoor, R. Purwar, S. Ikram, A review on latest innovations in natural gums based hydrogels: preparations and applications, Int. J. Biol. Macromol., 136 (2019) 870–890.
[13] H. Cortes, I.H. Caballero-Florán, N. Mendoza-Muñoz, L. Escutia-Guadarrama, G. Figueroa-González, O.D. Reyes-Hernández, M. González-Del Carmen, M. Varela-Cardoso, M. González-Torres, B. Florán, M.L. Del Prado-Audelo, G. Leyva-Gómez, Xanthan gum in drug release, Cell. Mol. Biol., 66 (2020) 199–207.
[14] M.H.A. Elella, E.S. Goda, M.A. Gab-Allah, S.E. Hong, B. Pandit, S. Lee, H. Gamal, A. ur Rehman, K.R. Yoon, Xanthan gum-derived materials for applications in environment and eco-friendly materials: a review, J. Environ. Chem. Eng., 9 (2021) 104702, doi: 10.1016/j.jece.2020.104702.
[15] G. Jeong, J. Bak, B. Yoo, Physical and rheological properties of xanthan gum agglomerated in fluidized bed: effect of HPMC as a binder, Int. J. Biol. Macromol., 121 (2019) 424–428.
[16] M. Hajikhani, M.M. Khanghahi, M. Shahrousvand, J. Mohammadi-Rovshandeh, A. Babaei, S.M.H. Khademi, Intelligent superabsorbents based on a xanthan gum/poly (acrylic acid) semi-interpenetrating polymer network for application in drug delivery systems, Int. J. Biol. Macromol., 139 (2019) 509–520.
[17] L. Belhadji, Etude et mise au point de suspensions buvables médicamenteuses à libération prolongée par gélification in situ, Doctoral Thesis in Industrial Chemistry, University of Blida, Algeria, 2018.
[18] L. Djekic, M. Martinović, V. Dobričić, B. Čalija, Đ. Medarević, M. Primorac, Comparison of the effect of bioadhesive polymers on stability and drug release kinetics of biocompatible hydrogels for topical application of ibuprofen, J. Pharm. Sci., 108 (2019) 1326–1333.