POLYSACCHARIDE-BASED MATRIX DOPED WITH PLANT EXTRACT FOR MEDICAL AND COSMETIC APPLICATIONS

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Herein, we present a new biomaterial based on xanthan, chitosan and lignin, which served as a matrix for the incorporation of flavonoids extracted from *Agropyron repens* L. rhizomes. The simultaneous presence of lignin and xanthan esterified with acrylic acid leads to better retention of the active principles in the polymer matrix, which is reflected in their slow release into the environment. A more compact structure resulting from the incorporation of lignin into the chitosan/xanthan matrix contributed to a three times higher value of diametral tensile strength. The release kinetics of flavonoids through the matrix components was described by the Korsmeyer-Peppas model, indicating Fickian diffusion. The presence of bioactive principles extracted from *Agropyron repens* L. (couch grass) imparts an antioxidant capacity to biomaterials, on average 30% higher compared to that of the base matrix. Considering the mucoadhesiveness, bioadhesiveness, release kinetics and antioxidant capacity of all the formulations developed in this study, it can be concluded that they have potential for health and cosmetic applications.

Keywords: *Agropyron repens*, xanthan, lignin, chitosan, antiradical activity

INTRODUCTION

Wastes resulted by petroleum-based products generate environmental and ecological problems because of their intrinsic feature of non-biodegradability. This has led to the appearance of biodegradable polymers, which are biocompatible and, in most cases, easily degradable under environmental conditions, thus relieving pollution. However, bio-based materials do not meet certain properties, such as flexibility, mechanical strength, water and gas vapor barrier properties, *etc*. These deficiencies may be solved by the development of new formulations comprising polymeric matrices by mixing reinforcing polysaccharides, such as cellulose or chitosan, with other ones presenting characteristics of elasticity, swelling capacity, bioadhesiveness, *etc*. Such formulations can constitute the basis for obtaining bio-composite materials that function as delayed release systems for bioactive, natural or synthetic principles, with medicinal and cosmetic applications.

Medicinal plants play a very important role in the development of alternative drugs, without the adverse effects of synthetic drugs. A phytocomplex extracted from various plant materials is a multicomponent system and can vary for the same extracted plant material, depending on the extraction procedure applied, the ratio between the drug and the extract obtained, *etc*. Depending on the groups of bioactive substances, they have different composition, several mechanisms of action that complement each other, enhance each other, the result often exceeding a simple summation of effects.

The use of plant extracts in the therapeutic practice is not new, especially considering that it is part of the human history, but their incorporation into supporting biomaterials to ensure the controlled transfer of active ingredients is a somewhat recent trend. The present study considered the design of a new polymer platform based on xanthan, chitosan and lignin to serve as a support for the release, under optimal conditions, of a phytocomplex extracted from the rhizomes of couch grass.

Couch grass (*Agropyron repens* L.) is a perennial plant with recognized medicinal value,[1] due to its antimicrobial, antiviral, hypolipidemic, anti-inflammatory[2] and diuretic activity.[3,4] The

literature data also stipulate a certain antibiotic effect that would be due to the presence of agropyrene in the composition of the natural extract, a fact that has been under debate until now.[5] Another use of this herbal product is based on its diuretic properties, being indicated in the therapy of inflammatory kidney diseases, as well as in the prevention of the formation of kidney stones.[6,7] Moreover, the couch grass extract has attracted the attention of major cosmetic brands, as a component in creams or cosmetic masks intended for facial reshaping and lifting, which has brought, in this way, considerable added value to a common herb.

Chitosan is a natural polysaccharide, cationic by its nature, derived from chitin. It is insoluble in almost all common solvents, but it is soluble in acid solutions, its solubility depending on the degree of deacetylation, the distribution of acetyl groups along the main chain, and the molecular weight. Due to its cationic charge, it is prone to establishing electrostatic interactions with some anionically charged polysaccharides, such as xanthan. This opens up new possibilities for the design of polysaccharides based composite architectures that can function as retarding systems for the release of bioactive principles.[8] In this regard, Bilanovic *et al*. reported the preparation of some biocomposites based on chitosan and xanthan, which, by combining the swelling capacity of xanthan and the mechanical strength of chitosan, proved to be effective for the retention or release of drugs or other chemicals.[9] Moreover, Liu and Huang[10] used a soybean protein coated with genipin-crosslinked chitosan and *Bletilla striata* extract as a wound dressing material, for which the histological evaluation showed the reconstruction of skin upon the slow release of the phytocomplex from the polymeric matrix. The inclusion of plant extracts into polymeric matrices based on natural polysaccharides has been shown to change not only the morphology, mechanical and thermal properties of the materials in question, but also the antimicrobial profile, as shown in a recent article by Kasai *et al*., who doped a biomaterial based on chitosan and polyvinyl alcohol with an extract of *Syzygium cumini* leaves.[11] Thus, chitosan and its derivatives are good candidate biomaterials for applications in cosmetics, medicine, biotechnology and food industry,[12-14] being non-toxic, biodegradable and biocompatible polysaccharides.[15]

Lignin, the most widespread aromatic polymer of vegetable nature, has important antioxidant properties, which make it attractive for potential use in food packaging, medicinal or cosmetic applications.[16-20] The antioxidant properties of lignin come from the hydroxy and methoxy phenolic groups, along with the double bond between the outermost carbon atoms in the side chain of the phenylpropanic moiety. Due to their ability to scavenge free radicals, phenolic hydroxyl groups have been extensively reported as descriptors for the antioxidant capacity of this natural product.

Xanthan (produced, on an industrial scale, by the fermentation of simple sugars under the action of the bacterium *Xanthomonas campestris*) has found medical applications in scaffolds for tissue engineering,[21] implants,[22-24] topical applications[25-29] or drug release systems.[30-33] Although xanthan has found wide applications in various fields that interfere with the biological environment, its low intrinsic mechanical strength does not recommend it as such for the manufacture of medical devices that require mechanical strength. For this reason, its fine chemical modification, as well as the presence of reinforcing materials, can overcome this impediment, highlighting its attractive bioadhesive and swelling properties. Moreover, because of its hydrophilicity, which makes it likely to lose its structural edifice in a humid environment, the introduction of functional groups to establish hydrophobic bonds between the polysaccharide chains is desirable.[34-39]

It has been reported by Raschip *et al*.[40] that xanthan-lignin films showed high antibacterial activity against *Salmonella typhymurium*, *E. coli* and *Listeria monocytogenes* bacteria. Thus, the aim of this paper has been to design and investigate xanthan-based composites modified with acrylic acid to serve as a support matrix for the controlled release of a phytocomplex with antioxidant properties extracted from couch grass. To ensure the mechanical strength of the modified xanthan, the basic formulation involved the introduction of chitosan and lignin, the latter being used as a binder and plasticizer for the components of the base matrix. The combination of the extreme ability of xanthan to swell, the intrinsic mechanical resistance of chitosan potentiated by the presence of lignin, and the regenerative properties of the couch grass extract can form a new basis for potential applications, especially in the cosmetic field.

EXPERIMENTAL

Materials and methods

Xanthan (Mw = 2.5×10^6 Da) from *Xanthomonas campestris*, 4-toluenesulfonyl chloride (TsCl), pyridine (Py), methylene chloride, poly(vinylpolypyrrolidone)–PVPP, vanillin, rutin (quercetin 3-rutinoside), tricin (4',5,7-trihydroxy-3',5-dimethoxyflavone), baicalein (5,6,7-trihydroxy flavone) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich (USA); acrylic acid was obtained from Merck & Co. (USA). Chitosan (Mw = 1.2×10^6 Da, degree of acetylation 34%) was received from the University of Sherbrooke, Canada. *Agropyron repens* L. roots were collected from a local area in Iasi, Romania. The plant was identified and authenticated at the Iasi Botanical Garden, Romania.

Plant extract

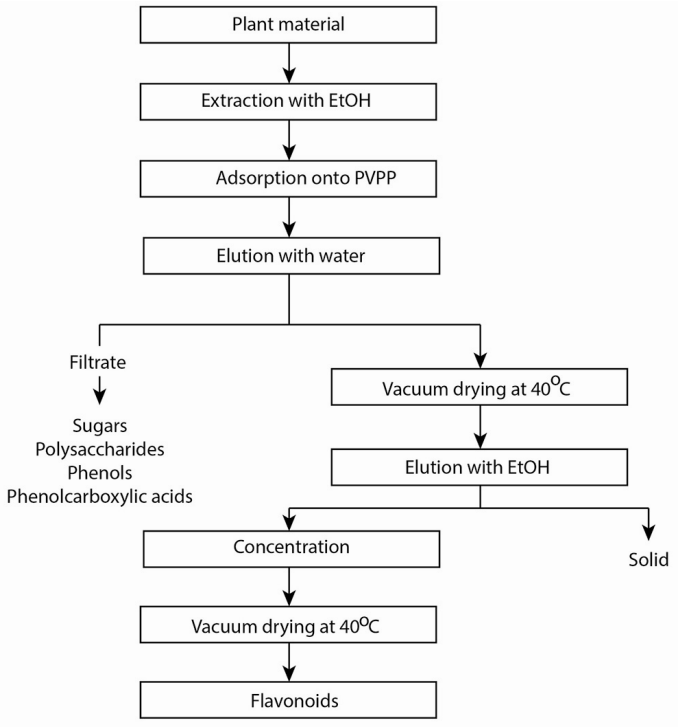
An amount of 200 g of couch grass roots was cut into pieces and extracted with 400 mL of ethanol at room temperature, in the dark. The extract was concentrated under vacuum and adsorbed on 50 g poly(vinylpolypyrrolidone). The solid was washed with distilled water to remove polysaccharides, sugars, phenols and simple phenolcarboxilic acids and dried under vacuum at 40 °C. Then, flavonoid phytocomplex was recovered by extraction of the solid with ethanol, concentration and drying under vacuum at 40 °C (Scheme 1). The yield was 1.86 g.

HPLC (High Performance Liquid Chromatography) analysis of couch grass extract

A Shimadzu Prominence HPLC system, equipped with an Alltech Econosil C18 column (4.6 × 250 mm, 5 µm), was used for HPLC analysis. Gradient elution was performed (solvent A (water with 1% AcOH), solvent B (methanol), gradient 100% A 2 min, 0-100% B 40 min, 100% B 10 min, 100-0% B 5 min, rebalancing 100% A 15 min). Detection was performed at 360 nm, with a flow rate of 1 mL/min, temperature of 25 °C and injection volume of 20 µL (concentration 1 mg extract/mL). Vanillin, rutin, tricin and baicalein were used as internal standards.

Total flavonoid content of *Agropyron repens* L. extract

The determination of total flavonoids of the couch grass roots extract was performed spectrophotometrically at 415 nm, by the formation of a chromofore between flavonoids and aluminium chloride according to a method described by Hayt *et al.*[36] Thus, the flavonoid content of the plant extract was 1.82% expressed as rutin, using a calibration curve.



Scheme 1: Workflow for the extraction and purification procedure of flavonoids from A*gropyron repens* L. rhizomes

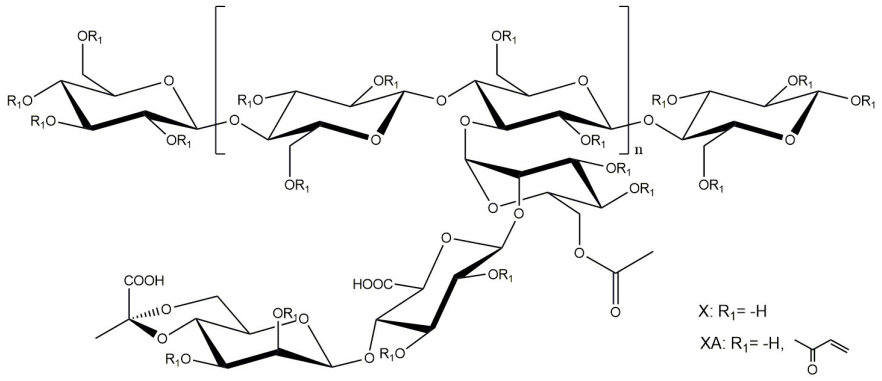
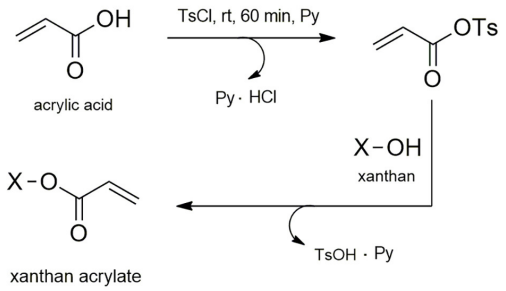


Figure 1: Chemical structure of xanthan (X) and xanthan acrylate (XA)



Scheme 2: Synthetic route for esterification of xanthan with acrylic acid

Chemical modification of xanthan

Esterification of xanthan with acrylic acid (Fig. 1, Scheme 2), in order to introduce double bonds capable of establishing hydrophobic interactions, was performed by a method presented elsewhere.[37] In short, TsCl (2.55 g, 0.0133 mol), pyridine (3 mL, 0.077 mol) and acrylic acid (0.95 mL, 0.0133 mol) in 50 mL methylene chloride, were placed in a round bottom flask, equipped with a magnetic stirrer. The mixture was kept under stirring at room temperature for 60 min. Xanthan (5 g, 0.053 mol) was added to the filtrate thus obtained and the mixture was stirred for 24 h at room temperature. The reaction product was separated by filtration and washed on the filter with methylene chloride and ethanol, and dried at room temperature. The yield obtained was 4.95 g.

The esterification process proceeds selectively at the primary hydroxyl groups, not excluding the participation of a certain proportion of the secondary alcohol groups present in the structure of xanthan.

Preparation of biocomposites

The reference materials CXE (Chitosan/Xanthan/Extract) and CXAE (Chitosan/Xanthan Acrylate/Extract) were obtained by dissolution (under stirring, at room temperature, for 60 min) of 400 mg chitosan and 100 mg xanthan or xanthan acrylate in 50 mL of acidified distilled water (0.1% HCl), along with 100 mg of plant extract. The solvent was evaporated under vacuum at 40 °C and the solid was powdered in a mortar. Other biomaterials named CXLE (Chitosan/Xanthan/Lignin/Extract) and CXALE (Chitosan/Xanthan Acrylate/Lignin/Extract) were prepared in the same way, with the difference that they also contain 100 mg of lignin. From each material, aliquotes of 300 mg were compressed in a Carver Hydraulic Laboratory Press Model C, at a ram pressure of 6 tons for 2 min to obtain capsules with 13 mm diameter and 2 mm thickness.

Mucoadhesion tests

The adhesive and mucoadhesive behavior of all the systems was evaluated by measuring the adhesion force (maximum detachment force) and total work of adhesion, as described in a previous paper,[41] using a TA.XT plus® analyzer from Stable Micro Systems (UK). Mucoadhesion tests were performed on biological porcine stomach tissue (stomach mucosa) in PBS (Phosphate Buffer Saline) at 37 °C, pH = 6.2, while the bioadhesion test was performed onto a hydrated dialysis tubing membrane (cellulose, Visking DTV14000), in the same environment at pH 7.4 and 37 °C. The reported values are the result of five determinations.

***In vitro* release studies**

Release studies were carried out at 37 ± 0.5 °C and pH value of 7.2. Aliquots of the medium withdrawn at predetermined time intervals were analyzed at λ_{max} value of 360 nm. The bioactive compounds release kinetics was evaluated using the semi-empirical equation proposed by Korsmeyer and Peppas (1):[42]

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ represents the fraction of the drug released at time t, M_t and M_∞ are the absolute cumulative amount of drug released at time t and the maximum amount released under the experimental conditions used, at the plateau of the release curves, k is a constant incorporating the characteristics of the macromolecular drug loaded system and n is the release exponent, which is indicative of the release mechanism.

Dynamic vapor sorption (DVS)

To evaluate the water sorption at atmospheric pressure, IGAsorp equipment (Hiden Analytical, Warrington – UK) was used. The studies were performed at humidity between 0 and 95%, in the temperature range from 5 °C to 85 °C, with an accuracy of ±1% for 0–90% RH (Relative Humidity) and ± 2% for 90–95% RH.

Radical scavenging assay

The antiradical activity was evaluated using a DPPH solution, as presented in our previous paper.[43]

Diametral tensile measurements

After being taken out of the moulds, the specimens were incubated at 37 °C in 100% humidity for 1 day. The diametral tensile strength (DTS) testing was performed on an EZ–Test machine (Shimadzu, Kyoto, Japan), at a loading rate of 0.5 mm × min^{-1}. The DTS value was calculated according to Equation (2):

$$DTS = \frac{2 \times P}{\pi \times D \times T} \quad (2)$$

where P is the peak load (Newtons), D is the diameter (mm) and T is the thickness (mm) of the specimen. The maximal compression load at failure was obtained from the recorded load-deflection curves. The reported value is the average of 5 measurements.

RESULTS AND DISCUSSION

In order to separate and purify the flavonoid fraction from the rhizomes of *Agropyron repens*, the crude alcoholic extract was first absorbed on PVPP and then eluted with water to remove most of sugars, polysaccharides, simple phenols, polyphenolcarboxylic acids, *etc*. Subsequent elution with ethyl alcohol led to a fraction enriched in flavonoids, which, after concentration and drying *in vacuo*, gave a brown solid with a yield of 1.86 g. According to the quantitative analysis described in the experimental part, the total flavonoid content was 1.32%.

HPLC analysis

The HPLC chromatogram shown in Figure 2 indicates the presence of vanillin, rutin, tricin and baicalein in the flavonoid-enriched extract of *Agropyron repens* – a combination of polyphenols characteristic of the plant in question. These bioactive principles are responsible for its antioxidant properties.

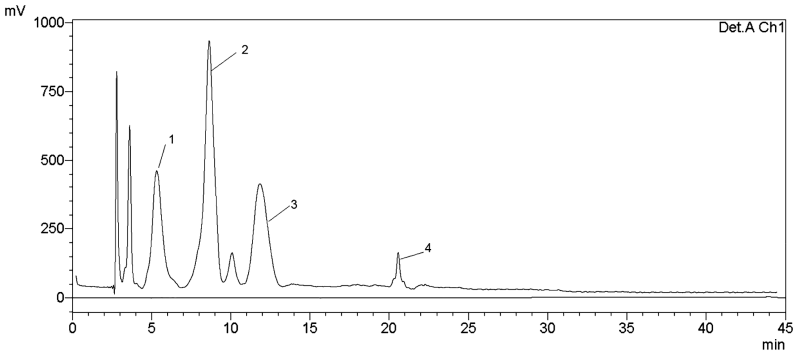


Figure 2: HPLC chromatogram for *Agropyron repens* L. flavonoid-enriched extract: 1 – vanillin, 2 – rutin, 3 – tricin, 4 – baicalein

Table 1
Adhesive properties of the studied materials

Sample	Mucoadhesion		Bioadhesion	
	Force of detachment (g)	Work of adhesion (N×s)	Force of detachment (g)	Work of adhesion (N×s)
CXE	15.7	0.0141	7.7	0.0082
CXAE	10.4	0.0240	9.9	0.0100
CXLE	17.9	0.0225	8.2	0.0061
CXALE	9.9	0.0080	8.2	0.0109

Bio/mucoadhesivity

The adhesion of pharmaceutical formulations to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and, in combination with controlled release of the drug, also improves patient compliance by reducing the frequency of administration.

By comparing the adhesion parameters of the materials (Table 1), in the presence and in the absence of mucin, it is clear that they are higher in the presence of mucin, suggesting good interaction between the material and mucins, which is in accordance with the data reported by other authors.[44] As expected, the presence of lignin, a hydrophobic material, leads to a slight decrease in mucoadhesive properties, the more pronounced the more syringyl or guaiacyl phenylpropane units are involved in hydrophobic bonds with modified xanthan (*e.g.* the force of detachment for CXALE is much lower than that for CXAE). The total work of adhesion values are in good agreement with those of adhesive forces.

Dynamic vapour sorption (DVS)

According to DVS data (Table 2, Fig. 3), xanthan modification reduced the sorption capacity. Thus, the sorption capacity of CXAE was reduced with 1.83%, as compared to that of CXE. When lignin was added, the sorption capacity decreased further, the most pronounced decrease being between CXAE and CXALE, of about 13.8%. The lignin addition into the polymeric matrix resulted in a significant increase in BET area (Brunauer–Emmett–Teller theory aims to explain the physical adsorption molecules on a solid surface and serves as the basis for an important analysis technique for the measurement of the specific surface area of materials). As may be seen below, the BET area and pore size vary depending on the material formulation and play an important role in releasing the bioactive principles from the polymeric matrix.

Diametral tensile strength

The compaction of the composites was evaluated by assessing the diametral tensile strength (DTS). As compared to the polysaccharide matrix (CX), all the biocomposites presented an increase in DTS. All the formulations presented sufficient mechanical strength (Fig. 4). No significant effect on this parameter was found when the *Agropyron* extract was added into the chitosan/xanthan matrix, while the xanthan modification increased DTS by 66.85%. A more compact structure has resulted after the incorporation of lignin into the chitosan/xanthan matrix, which raised three times the DTS value due to high intermolecular hydrogen bonding between the components, as well as the van der Waals forces. Both make possible good adhesion between the polysaccharides and lignin.[45] The use of the modified xanthan also had a positive effect, probably due to strong hydrophobic interactions that reduce the macromolecular mobility of polysaccharide chains. This avoids the sliding of chains over the others and a reinforcement effect occurs.[46]

***In vitro* release of *Agropyron repens* extract**

The *in vitro* release profiles of the formulations were observed and, according to Figure 5, the best model describing the *in vitro* release kinetics of the couch grass extract was the Korsmeyer-Peppas model. The correlation coefficient R^2 varied between 0.9948 and 0.9954.

According to data from Table 3, the value of n is lower than 0.5 for all the systems, suggesting a diffusion-controlled release of the bioactive principles from the matrix, as has been also established for other systems based on polysaccharides.[43]

Table 2
Relevant BET data related to the studied materials

Sample	Sorption capacity (% d.b.)	Average pore size (nm)	BET data	
			Area ($m^2 \times g^{-1}$)	Monolayer ($g \times g^{-1}$)
CXALE	23.1	2.41	192	0.0549
CXLE	27.4	2.36	233	0.0665
CXE	27.3	3.83	143	0.0401
CXAE	26.8	6.98	77	0.0225

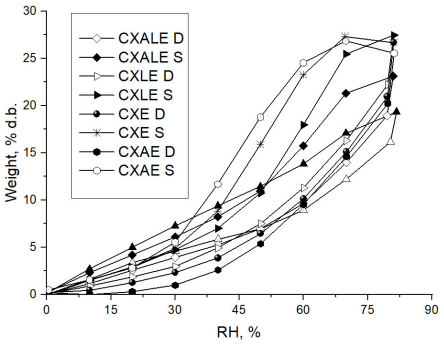


Figure 3: Influence of lignin and modified xanthan on water uptake properties of the studied materials (S – sorption; D – desorption)

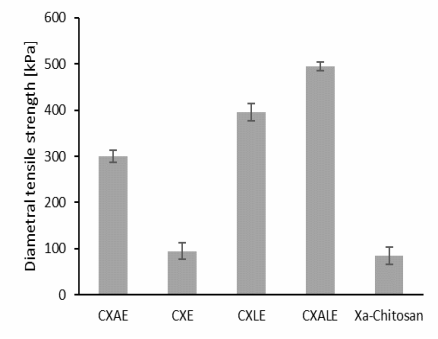


Figure 4: Diametral tensile strength of the analyzed materials

The faster release mechanism of active principles from samples CXE and CXAE, as compared to samples CXLE and CXALE, could be due to diffusion through swelling of the polymer matrix and also due to porosity (see DVS data). CXE and CXAE present large pores on the surfac and increased water absorption capacity enables the active principles to diffuse with a higher speed and quantity than in the case of samples containing lignin. The presence of lignin in the polymer matrix determines not only a structuring of the material, as highlighted by the decrease in the average pore diameter (Table 2), but also a decrease in the water absorption capacity, which leads to a lower release rate of bioactive principles into the medium. Thus, the difference between the release rates of CXE and CXLE is of 92.4%. The presence of xanthan acrylate slows down, through hydrophobic interactions, even more the speed of diffusion of the drug in the external environment, on average by 93% (CXAE *vs* CXALE). The polymeric matrix may form loose channels within the network, due to the hydrophilic nature of polysaccharides. Hydrophilic polysaccharides readily absorb water molecules and will swell, resulting in the formation of large pores that influence the release rate. A slight decrease in the release rate of the bioactive principles was registered for the formulation comprising modified xanthan, probably owing to the increased chain length of xanthan and low swellability.[47]

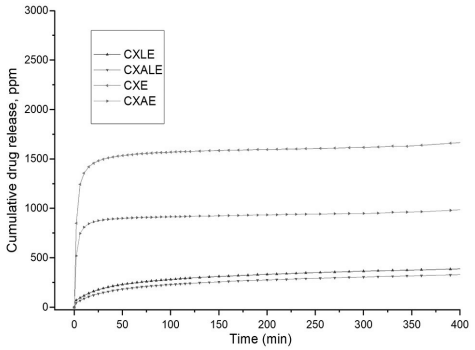


Figure 5: Release profiles of bioactive principles from the investigated samples

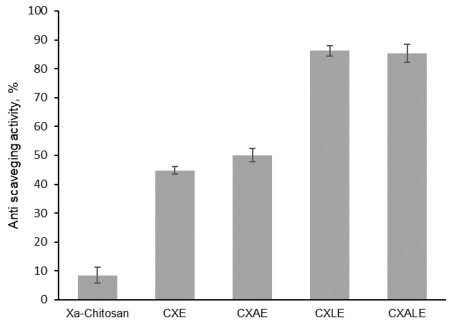


Figure 6: Antiradical activity of the tested materials

Table 3
Kinetic parameters of drug release from the investigated samples

Samples	n	R^2_n	k (min $^{-n}$)	R^2_k
CXE	0.2989	0.9616	6.9818	0.9951
CXAE	0.2846	0.9602	4.3057	0.9954
CXLE	0.3680	0.9938	0.5308	0.9954
CXALE	0.4258	0.9955	0.3314	0.9948

Free radical (DPPH) scavenging activity

It is well known that higher percentage of DPPH radical scavenging activity is correlated with higher antioxidant activity.[48] The antioxidant activity was measured against radical species generated in their action system, such as DPPH radicals. Our results showed that the percentage of radical scavenging activities produced by CXE and CXAE formulations is significantly different from that of the xanthan-chitosan matrix (Fig. 6). The presence of lignin highly increased the DPPH scavenging activity of formulations CXLE and CXALE, on average by about 47%, compared with CXE and CXAE. These results confirm the antioxidant properties of lignin. Future studies are necessary to evaluate its antimicrobial effects.

CONCLUSION

Capsules comprising chitosan and xanthan/modified xanthan as matrix and *Agropyron repens* extract were obtained. The phytocomplex was characterized by HPLC in terms of qualitative composition. The total flavonoid content, responsible for the antioxidant properties, was assessed. The biocomposite materials were analyzed in terms of mechanical and bioadhesion properties, water adsorption (which also play an important role in the diffusion mechanism of drugs), as well as antioxidant and delayed release properties of the active principles incorporated in the polymer matrix. It was found that the prepared capsules presented different properties, as a function of their composition. When lignin was added, a high antiscaveging activity and a slow release rate of *Agropyron repe*ns extract were recorded. Compressive strengths were between 0.09–0.49 MPa, being influenced by sample composition (an increase of approximately 500% was registered in the case of CXALE, compared to the xanthan-chitosan matrix due to strong hydrophobic interactions that reduce the macromolecular mobility and increase the mechanical strength). The release kinetics of bioactive principles through the matrix components fitted the Korsmeyer-Peppas model, indicating Fickian diffusion. The presence of lignin and acrylate xanthan in the prepared biomaterials leads to a decrease in the rate of release of bioactive principles into the environment, by an average of 92%, compared to the samples containing only chemically unmodified xanthan. However, after about 100 minutes, all the formulations show a plateau in terms of the release of bioactive substances from the basic matrix. How much drug is released in a given time, through the fine tuning of the component ratio, will be the subject of a stochastic study based on neural networks. All the formulations developed in this study present significant antiradical activity and have potential in health and cosmetic applications.

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