CHITOSAN/MONTMORILLONITE COMPOSITES AS MATRICES FOR PROLONGED DELIVERY OF SOME NOVEL NITRIC OXIDE DONOR COMPOUNDS BASED ON THEOPHYLLINE AND PARACETAMOL

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Received January 21, 2011

Chitosan-montmorillonite nanocomposite hydrogels were prepared by crosslinking chitosan nanocomposites with glutaraldehyde. The following types of clays have been used: Cloisite 15A, Cloisite 93A, Dellite HPS and Dellite 67G. The swelling behaviour of the crosslinked hydrogels containing nanoparticles was followed in acidic media with pH = 2.2. These hydrogels have been loaded with paracetamol, theophylline, two xanthine derivatives 7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-R-1,3-dimethyl-xanthine derivatives (with R=H and NO_2 for D_1 and respectively D_2) and two corresponding new nitric oxide donors (NO-donors) as 7-[2-nitroxyacethyl-oxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-R-1,3-dimethyl-xanthine compounds (R=H, NO_2 for 65 and respectively 77 compounds), their controlled release being also evaluated in an acidic solution (pH = 2.2) simulating gastric fluid. The swelling and release kinetics was studied. It has been established that almost all releases involve a non-Fickian or an anomalous transport mechanism.

***Keywords**:* chitosan, montmorillonite, NO-donor drugs, paracetamol, theophylline, drug release, kinetics

INTRODUCTION

Polymer/layered silicate nanocomposites are of particular interest due to the demonstrated significant enhancement – relative to an unmodified polymer resin – of their numerous physical properties, including barrier properties, flammability resistance, thermal and environmental stability, solvent uptake and biodegradability rate of biodegradable polymers.[1,2]

Chitosan (CS)-montmorillonite (MMT) nanocomposites have a great potential for the biomedical field. For combining the advantages of the biopolymer with clay in a drug delivery system, the hot intercalation technique was used for the preparation of quaternized chitosan-montmorillonite (HTCC-MMT) nanocomposites. Transmission electron microscopy (TEM), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR) results revealed that the HTCC chains entered the MMT interlayer, causing their interaction, which represents the basis of an advantageous combination. Further on, the HTCC-MMT nanocomposites were modified to prepare nanoparticles, whose controlled drug release behaviours were evaluated. The results suggest that, compared to pure HTCC nanoparticles, certain montmorillonite loadings on quaternized chitosan enhanced the drug encapsulation efficiency of the nanoparticles and slowed down the drug release from nanocomposites.[3] Nanocomposite hydrogels (nanohydrogels) composed of chitosan (CS) and montmorillonite (MMT) were prepared and systematically studied as to their drug release behaviour, following electrostimulation. The deterioration of responsiveness and the reversibility of CS upon repeated on-off electrostimulation switching operations are major

limitations for clinical applications, because of its high structural instability, which prevents a precise control of the drug release upon cyclic electrostimulation. To overcome these limitations, an inorganic phase, MMT, was incorporated into the CS matrix, to enhance the anti-fatigue property and the corresponding long-term stable release kinetics. X-ray diffraction analysis and time-dependent optical absorbance showed that the MMT incorporated into the nanohydrogel exhibited an exfoliated nanostructure. The exfoliated silica nanosheets are able to act as crosslinkers to form a network structure between CS and MMT, this difference in crosslinking density strongly affecting the release of vitamin B(12) under electrostimulation. At a lower MMT concentration (1 wt%), the release kinetics of vitamin B(12) from the nanohydrogel shows a pseudo-zero-order release, the release mechanism being changed from a diffusion-controlled to a swelling-controlled mode, under electrostimulation. Further increase of the MMT content reduced both the diffusion and the responsiveness of the nanohydrogel to electrostimulation.[4] Other CS-nanocomposites may be prepared from CS and rectorite. The CS-organic rectorite (CS-OREC) nanocomposite films provide promising applications as antimicrobial agents, water-barrier compounds, anti-ultraviolet compounds and controlled release drug carriers in antimicrobial food packaging and drug-delivery systems. *In vitro* controlled drug release studies showed a slower and more continuous release for nanocomposite films, in comparison with pure CS films, while the drug-delivery cumulative release was proportional to the amount and interlayer distance of OREC.[5]

In recent years, drug molecules intercalated into smectite clays have attracted great interest, as these clays come to exhibit novel physical and chemical properties. Zheng *et al*.[6] have investigated the intercalation of ibuprofen into MMT as a sustained release drug carrier, while Lin *et al*.[7] studied the intercalation of 5-fluorouracyl with MMT as a drug carrier. Fejer *et al*.[8] reported the intercalation and release behaviour of promethazine chloride and buformin hydrochloride from MMT. Nunes *et al*.[9] studied the loading and delivery of sertraline using MMT K10. Dong and Feng[10] synthesized poly(d,l-lactide-co-glycolide)-MMT nanoparticles by the emulsion/solvent evaporation method for oral delivery of paclitaxel.[11] Some nanocomposites, based on organically modified layered silicates (OLS), such as Closite 15A and poly(urethane urea)s (used in a variety of blood-contacting applications in biomedical devices), exhibit increased modulus with increasing OLS content, while maintaining polymer strength and ductility.[12]

Paracetamol and theophylline have been used as parent drugs for the synthesis of new nitric oxid donor compounds, known as especially important for improving the pharmacological profile, in terms of increased therapeutical efficiency and reduced side effects. Paracetamol is a common analgesic and antipyretic drug, having also a weak anti-inflammatory activity.[13-17] Theophylline is a drug used for the treatment of asthma, due to its bronchodilatatory, anti-inflammatory and immunomodulatory effects.[18-20] The controlled release of all studied drugs is important for patients' confort and also for reducing the side effects.

Considering the advantages provided by the incorporation of nanoparticles in various matrices, the chitosan-based ones included, the present study evaluates the effect of the montmorilonite type on the swelling and release behaviour of some CS/MMT matrices.

EXPERIMENTAL

Materials

CS samples (with average molecular weight – MCS, Mn = 400 000 kDa, $\eta \sim 200$ MPas in 1 wt% of 1% acid acetic, Brookfield) and the glutaraldehyde (GA) aqueous (50% concentrated) solution were purchased from Fluka and Sigma Aldrich. All other chemicals and solvents were of analytical grade and were used without further purification.

Nanoclays, such as Cloisite 15A, Cloisite 93A, obtained from Southern Clay Products, Inc., and Dellite HPS and Dellite 67G, from Laviosa Chimica Mineraria S.P.A., were also employed.

Cloisite 15A is a natural montmorillonite modified with quaternary ammonium salt, containing organic modifier, dimethyl dehydrogenated tallow [2M2HT], where HT is hydrogenated tallow with an approximate composition[21] of 65% C18, 30% C16, 5% C14. The specific gravity of Cloisite 15A is of 1.66 g/cm^3 and bulk density – 172.84 kg/m^3.[22] Particle size distribution shows that 90% of them are less than 13 microns, 50% are less than 6 microns and 10%, respectively, less than 2 microns.

Cloisite® 93A is a natural montmorillonite modified with a ternary ammonium salt (methyl, dehydrogenated tallow ammonium), with the specific gravity of 1.88 g/cm^3, and with typical dry particle sizes from 2 to 13 μm (microns, by volume).

Dellite HPS (hydrated aluminium silicate) is chemically stable and insoluble.

Dellite 67G (ditallowdimethylammonium ion with montmorillonite) is insoluble in water.

Theophylline and *paracetamol* were purchased from Fluka.

The synthesis of *7-[2-hydroxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-R-1,3-dimethyl-xanthine* derivatives (where R is H or NO_2 for D1, or D2 respectively) and of *7-[2-nitroxyacethyl-oxy-3-(4-acethyl-amino-phenoxy)-propyl]-8-R-1,3-dimethyl-xanthine* (where R is H or NO_2 for 65 and 77, respectively) novel NO-donor compounds, together with their chemical and pharmacological characterization, have been previously reported.[23,24] The newly synthesized xanthine derivatives and NO-donor compounds, occurring as white powders, soluble in acidic solutions, are less toxic than paracetamol and theophyline, and exhibit bronchodilatatory and anti-inflammatory effects. The structure of the two xanthine derivatives and that of the NO-donor compounds are presented in Scheme 1.

CS-nanocomposite synthesis

CS-nanocomposites crosslinked with glutaraldehyde (GA) have been prepared in two steps: 1) CS-MMT synthesis, and 2) CS-MMT crosslinking with GA. CS was dissolved in a 1% aqueous acetic acid solution, at room temperature, and left overnight with continuous mechanical stirring, to obtain a 1% (w/v) solution. In a separate stage, clays were dispersed in a 1% aqueous acetic acid solution, which gave a 5% clay solution (also at room temperature, and left overnight under continuous mechanical stirring). The two prepared solutions were then mixed for 4 h. The 5% (w/v) aqueous GA solution (in a 1:0.3 ratio) was added to the CS-MMT solution, under stirring at room temperature. After 1 h, the viscous solution was poured into Petri dishes and dried at room temperature overnight, to form the hydrogel. Crosslinking took place at room temperature in a dark space, to protect the system against oxidative/photodegradation of GA, for 4 h.[25] The hydrogels obtained were extensively washed with twice-distilled water to remove the excess of crosslinking agent (GA being easily water-soluble), then freeze-dried by means of a Labconco FreeZone device and stored until further use.

Swelling tests

The chitosan-MMT compositions were swollen in an acid solution (pH = 2.2) and then weighed at predetermined periods of time. The equilibrium swelling degree was calculated according to Eq. (1):

$$Q_{max}\ (\%) = (W_{eq} - W_d) / W_d\ 100 \qquad (1)$$

where W_{eq} is the weight of the swollen sample when thermodynamic equilibrium was reached, and W_d is the dry weight of the sample.

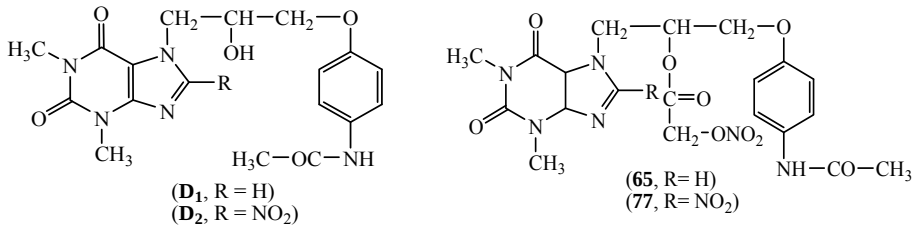
The dried hydrogels were loaded at 37 °C, by immersion in drug solutions with concentrations of 18 mg/mL, (the amount of solution being evaluated from the maximum swelling degree) for 2 h, inside encapped containers, while the drugs penetrated and/or were attached to the matrices. Finally, the loaded hydrogels were dried by freezing-drying at low temperature and pressure, with a Labconco FreeZone device, for 2 h. Each experiment was repeated three times.

To determine the kinetics of solvent diffusion into the hydrogels, the following equation was used:

$$F_t = \frac{W_t}{W_{eq}} = k_{sw} t^{n_{sw}} \qquad (2)$$

where W_t and W_{eq} represent the amount of water absorbed by the hydrogel at time t and at equilibrium, respectively, k_{sw} is the swelling constant characteristic of the system, and n_{sw} is the power law diffusion exponent that considers the type of solvent transport. Eq. 2 applies to the initial states of swelling and linearity is observed when log Ft as a function of log t is represented with a high correlation factor, R.

The release experiments of the drug-loaded hydrogels were carried out at 37 °C, in an acidic solution (pH = 2.2). Aliquots of about 1 mL were periodically withdrawn at predetermined time intervals and analyzed with a Hewlett Packard 8540A spectrophotometer. To maintain the solution concentration, the sample was carrefully reintroduced into the circuit after analysis.



Scheme 1: Structures of xanthine derivatives (D_1, D_2) and of two new NO-donor compounds (65, 77)

Drug concentration was calculated on the basis of the previously measured calibration curves for each drug, at their specific maximum absorption wavelengths, using solutions of known concentrations in the range of the loaded drug, at different wavelengths, as depending on the drug used, namely: λ = 240 nm for paracetamol, and λ = 271 nm for theophylline, xanthine derivatives D_1, D_2, and for NO-donor compounds 65 and 77, respectively.

A simple, semi-empirical equation was used to analyze kinetically the data on the drug release from crosslinked CS matrices in the initial stages (approximately 60% fractional release):[26-32]

$$M_t/M_\infty = k_r\, t^{nr} \quad (3)$$

or

$$\mathrm{Ln}(M_t/M_0) = \mathrm{Ln}(k_r) + n_r\,\mathrm{Ln}(t) \quad (4)$$

where M_t and M_∞ are the cumulative amounts of drug released at time t and infinite time, respectively; k_r is a constant incorporating the structural and geometric characteristics of the drug dosage form, and n_r is the release exponent, indicative of the mechanism of drug release. Drug release data were employed for determinining the release exponent and release rate constants.

RESULTS AND DISCUSSION

Swelling kinetics

The swelling kinetic curves of the CS-MMT crosslinked with GA are plotted in Figure 1. The swelling of all hydrogels occurs very fast in the first 3 min (see insert), after which the swelling degree remains approximately constant for 400-600 min.

The effect of clay incorporation is significant, leading to the decrease of the maximum swelling degree (Q_{max}) from 3240 to 1692%. CS-GA had the highest swelling degree comparatively with CS-MMT:GA.

The most important decrease is obtained in the case of incorporating Cloisite 15A and Dellite 67G, both of them being organically modified, therefore it can be concluded that they are especially suitable to tailor the properties of CS-MMT hydrogels (Fig. 2 and Table 1).

Table 1
Swelling kinetic parameters for CS crosslinked with GA

Composition	Q_{max}%	n_{sw}	R^2	k_{sw} (min^{-n})	R^2
CS	3240.43	0.190	0.95	38.43	0.99
CS-15A	1692.59	0.040	0.89	17.98	0.99
CS-93A	2390.90	0.009	0.96	20.90	0.99
CS-DelHPS	2462.31	0.004	0.94	23.52	0.99
CS-Del 67G	2322.70	0.020	0.98	21.87	0.99

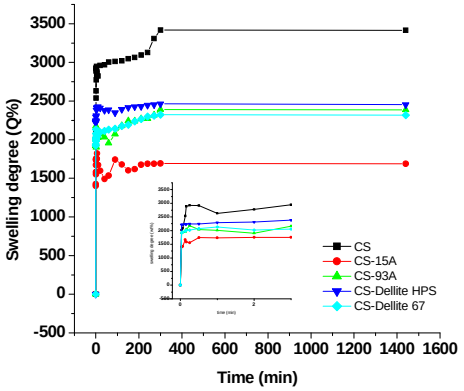


Figure 1: Swelling kinetic curves of CS-MMT crosslinked with GA

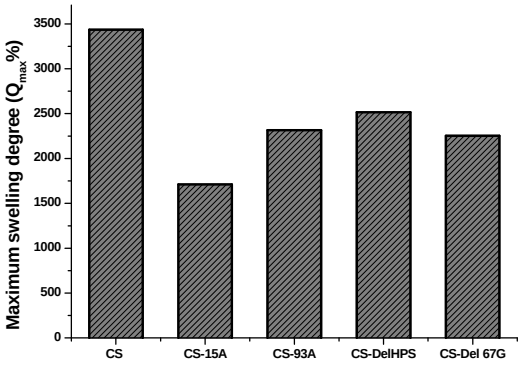


Figure 2: Maximum swelling degree *vs*. clay type

Table 1 summarizes the swelling kinetic parameters n_{sw} and k_{sw} and the maximum swelling degree for CS-MMT crosslinked with GA in a 1:0.3 ratio. The swelling kinetic parameters n_{sw} and k_{sw} are higher for CS:GA without MMT (n_{sw} = 0.19; k_{sw} = 38.43 $min^{-0.19}$). The swelling kinetic parameter k_{sw} is lower for CS-15A:GA (k_{sw} = 17.98 $min^{-0.04}$).

As known, the swelling kinetics of hydrogels can be classified as diffusion-controlled (Fickian) or relaxation-controlled (non-Fickian).[43] The type of transport is judged by the n values. When

diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is said to be diffusion-controlled. When exponent *n* takes a limiting value of 0.5, it is the case of diffusion-controlled drug release (Fickian release). In the case of relaxation-controlled delivery (zero-order), the exponent *n* is close to unity for drug release from the cylinders. When *n* lies between 0.5 and 1, an anomalous transport is involved.[33-37]

The non-Fickian kinetics is regarded as coupled diffusion/polymer relaxation.[38-42] As all n_{sw} values are close to zero, one may conclude that it corresponds to an anomalous mechanism of swelling, which is influenced by clay incorporation.

Drug release from CS nanocomposite hydrogels

Figures 3-8 plot the release profiles of paracetamol, theophylline, xanthine derivatives D_1 and D_2, and of the two NO-donor compounds (65 and 77) studied.

All these nanocomposite hydrogels have the same crosslinking degree of CS with GA at the ratio of 1:0.3. The highest amount of all these drugs was released from CS-Del HPS:GA at the ratio of 1:0.3 (Table 2). A lower amount of drug was released from CS crosslinked with GA without any clay in the composition. The CS-MMT:GA nanocomposite hydrogels with 5% clay solution presented an increased quantity of released drug.

The maximum drug release may vary from 46 to 73 wt%, as depending on the type of clay from the CS-nanocomposite hydrogels. Paracetamol has been released from CS hydrogel at 63.06 wt%, the maximum amount of paracetamol released (73.86 wt%) being provided by CS-Del HPS. The maximum release of theophylline has been registered for CS-Del HPS (70.55 wt%). All mentioned drugs (except D_2) have been released in smaller amounts from CS crosslinked with GA at a 1:0.3 ratio, comparatively with the CS-MMT nanocomposite hydrogels. At this concentration of nanoclays in hydrogels, no slowing down of the release was expected, as also shown by other authors. Gorrasi *et al.*[44] obtained an appreciable slowing down of the release only with organically modified clays at concentrations higher than 5 wt%.

The results of the present investigation show that the most efficient in this respect should be Cloisite 15A.

Table 2
Maximum drug release from nanocomposite hydrogels

	Paracetamol	Theophylline	Xanthine derivative D_1	Xanthine derivative D_2	NO-donor compound 65	NO-donor compound 77
	Drug released (%)					
CS:GA	63.06	56.34	53.31	61.66	51.78	46.84
CS-15A	64.28	56.63	57.29	54.04	56.38	47.81
CS-93A	68.64	65.21	62.88	57.56	56.72	50.14
CS-Del 67G	65.47	60.06	65.00	58.25	56.89	54.06
CS-Del HPS	73.86	70.55	69.93	70.56	58.14	53.60

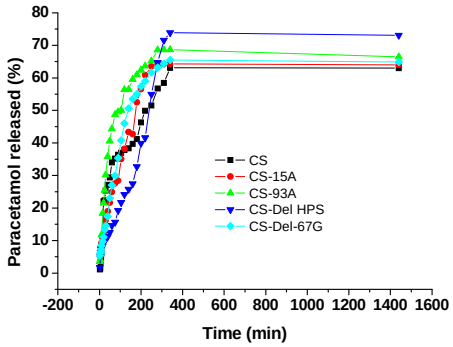


Figure 3: *In vitro* cumulative release profiles of paracetamol from CS and CS-MMT nanocomposite hydrogels

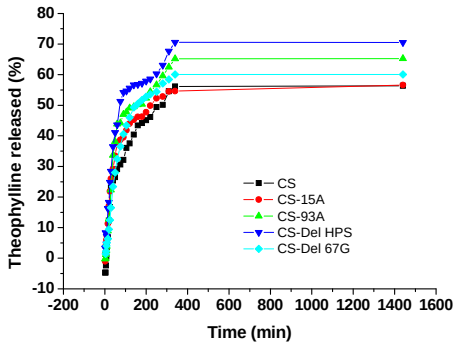


Figure 4: *In vitro* cumulative release profiles of teophylline from CS:GA and CS-MMT:GA nanocomposite hydrogels

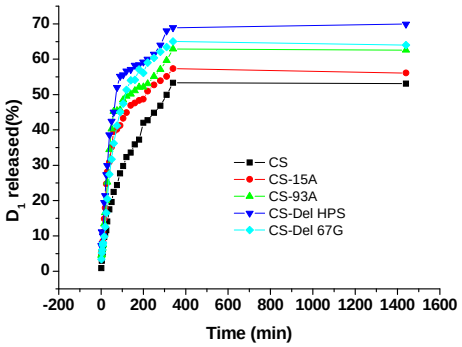


Figure 5: *In vitro* cumulative release profiles of D_1 xanthine derivative from CS:GA and CS-MMT:GA nanocomposite hydrogels

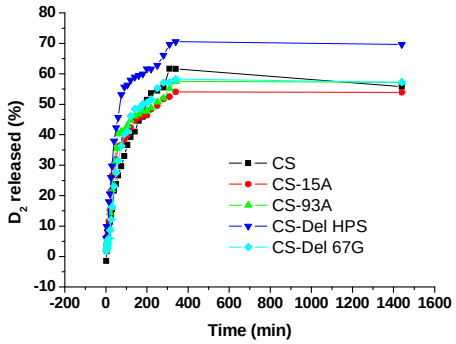


Figure 6: *In vitro* cumulative release profiles of D_2 xanthine derivative from CS:GA and CS-MMT:GA nanocomposite hydrogels

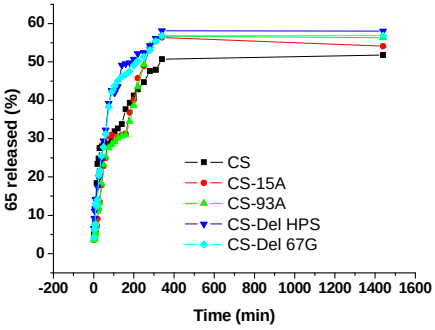


Figure 7: *In vitro* cumulative release profiles of NO-donor drug 65 from CS:GA and CS-MMT:GA nanocomposite hydrogels

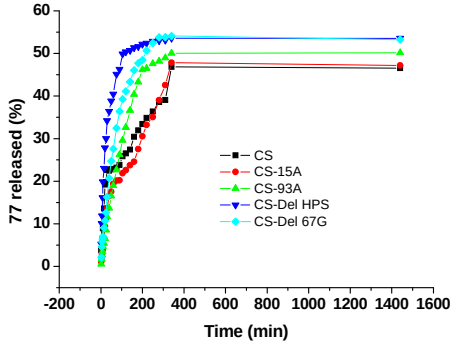


Figure 8: *In vitro* cumulative release profiles of NO-donor drug 77 from CS:GA and CS-MMT:GA nanocomposite hydrogels

The increase of its concentration is necessary for attaining such results, which will be the topic of a future paper.

Some dependence of the amount of drug release on drug properties should be mentioned, namely the decrease in the amount of drug released with the increase in drug molecular weight and with the decrease in solubility (Figs. 9 and 10). The relationship is not influenced by the presence of clays.

Table 3 summarizes the kinetic parameters of drug release (diffusion exponent n_r and kinetic release constant k_r) from CS and CS-MMT hydrogels both crosslinked with GA in a 1:0.3 ratio.

The kinetic diffusion exponent, n, for paracetamol, theophylline, xanthine derivatives D_1, D_2, and for the NO-donor compound 77 has registered values between 0.5 and 1, which indicates a non-Fickian release or an anomalous transport, with the exception of the NO-donor compound 77 release from CS-Del HPS (n = 0.39) and from CS (n = 0.46), which indicates a Fickian release (case I). A Fickian release was also observed for the release of NO-donor compound 65 from CS and CS-Del HPS (n = 0.44).

The three most common kinetic profiles, namely, zero-order, first-order and Higuchi, are expressed mathematically as follows:[45]

Zero-order: $D_t = D_0 + k_0 t$

First-order: $\ln D_t = \ln D_0 + k_1 t$

Higuchi: $D_t = D_0 = k_H t^{1/2}$

where D_t is the amount of drug released at time t, D_0 is the initial amount of drug released, as a result of an initial rapid release, k_0 is the zero-order release constant, k_1 is the first-order release constant, and k_H is the Higuchi release constant.

The delivery of most drugs is accomplished by oral administration or by injection, following a first-order kinetics. The ideal release profile for most drugs would follow a steady release rate, so that the drug levels in the body remain constant during drug administration.

Table 3
Kinetic drug release parameters for CS and CS-MMT crosslinked with GA in 1:0.3 ratio

Composition		n_r	R^2	k_r	R^2
CS	P	0.74	0.94	0.009	0.94
	T	0.83	0.86	0.01	0.96
	D_1	0.69	0.97	0.01	0.98
	65	0.44	0.95	0.04	0.97
	D_2	0.71	0.98	0.01	0.98
	77	0.46	0.95	0.03	0.96
Composition					
CS-15A	P	0.54	0.99	0.028	0.99
	T	0.87	0.96	0.013	0.98
	D_1	0.51	0.97	0.03	0.95
	65	0.59	0.98	0.01	0.98
	D_2	0.53	0.94	0.02	0.95
	77	0.67	0.98	0.009	0.98
Composition					
CS-93A	P	0.7	0.97	0.02	0.96
	T	0.86	0.92	0.01	0.99
	D_1	0.59	0.96	0.02	0.93
	65	0.59	0.98	0.01	0.98
	D_2	0.67	0.96	0.01	0.92
	77	0.82	0.98	0.006	0.99
Composition					
CS-Del HPS	P	0.55	0.96	0.01	0.97
	T	0.68	0.94	0.02	0.98
	D_1	0.54	0.95	0.03	0.95
	65	0.44	0.99	0.04	0.98
	D_2	0.62	0.95	0.02	0.96
	77	0.39	0.95	0.06	0.94
Composition					
CS-Del 67 G	P	0.59	0.98	0.02	0.99
	T	0.88	0.97	0.008	0.98
	D_1	0.66	0.99	0.01	0.97
	65	0.52	0.98	0.03	0.97
	D_2	0.73	0.98	0.01	0.95
	77	0.63	0.98	0.01	0.97

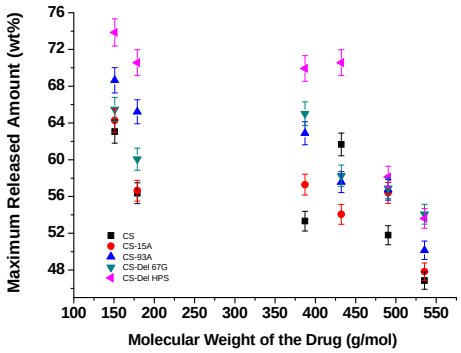


Figure 9: Maximum released amount of various drugs from different types of matrices of crosslinked CS and CS nanocomposite hydrogels, *vs.* their molecular weight

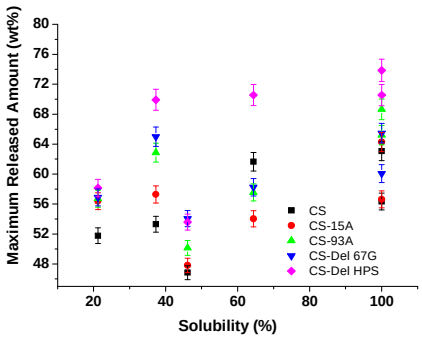


Figure 10: Maximum released amount of various drugs from different types of matrices of crosslinked CS and CS-MMT hydrogels, *vs.* their solubility in a medium with pH = 2.2

More recently described transdermal drug delivery mechanisms follow the Higuchi model.[46] In our case, most of the drugs have been released through a Higuchi kinetic model, except theophylline, which had been released after a first-order kinetic model only from CS-Del HPS.

CONCLUSIONS

All CS-MMT nanocomposites studied have been crosslinked with GA in the same ratio (1:0.3). The swelling degrees and the drug released from the CS hydrogel without MMT and from CS-MMT nanocomposite hydrogels were compared for a series of drugs, such as paracetamol, theophylline, xanthine derivatives (D_1, D_2) and NO-donor compounds (65, 77).

The CS hydrogel had the highest swelling degree, comparatively with CS-MMT nanocomposite hydrogels, nanocomposites with MMT had a lower swelling ability. The swelling kinetic parameters n_{sw} and k_{sw} were higher for the CS hydrogel without MMT (n_{sw} = 0.19; k_{sw} = 38.43 $min^{-0.19}$), while the swelling kinetic parameter k_{sw} was lower for CS-15A (k_{sw} = 17.98 $min^{-0.04}$).

As all n_{sw} values were close to zero, one may conclude that both the CS and the CS-MMT hydrogels correspond to an anomalous mechanism of swelling.

The highest amount of all these drugs was released from CS-Del HPS. A lower amount of drug was released from CS crosslinked with GA without any clay in composition. The CS-MMT nanocomposite hydrogel with a 5% clay solution had no significant influence on drug release, as the drugs have to be released slowly, over a long period of time, in the case here considered, drug release being faster from CS-MMT than from CS.

Slowing down of the release is obtained only with organically modified clays, at concentrations higher than 5 wt%. The present results show that the most efficient in this respect should be Cloisite 15A.

The kinetic diffusion exponent n_r for paracetamol, theophylline, xanthine derivatives D_1, D_2, and for the NO-donor compound 77 registered values between 0.5 and 1, which indicates a non-Fickian release or an anomalous transport, except the NO-donor compound 77 release from CS-Del HPS (n_r = 0.39) and from CS (n_r = 0.46), which indicates a Fickian release (case I). A Fickian release was also observed for the NO-donor compound 65 release from CS hydrogel and CS-Del HPS (n_r = 0.44).

All mentioned drugs (except the xanthine derivative D_2) have been released in smaller amounts from CS crosslinked with GA in a 1:0.3 ratio, than from CS-MMT nanocomposites. Most of them have been released by a Higuchi kinetic model, except theophylline, released according to a first-order kinetic model only from CS-Del HPS:GA.

ACKNOWLEDGEMENTS: A. Cojocariu acknowledges the support offered by the Department of Physical Chemistry of Polymers, "Petru Poni" Institute of Macromolecular Chemistry of Iasi, as well as by the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania.

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