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CHITOSAN-BASED POLYMER MEMBRANES FOR PARACETAMOL CONTROLLED-RELEASE SYSTEMS

BY

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Abstract. Polymer matrix systems were designed based on chitosan, surfactant and paracetamol, using the phase inversion process. There were investigated different membranes in which was varied either the concentration of the components or the type of the surfactant involved (a cationic or anionic one). These systems are good candidates for the controlled-release of the active substance (paracetamol) encapsulated in it, thus reducing the administration frequency and preventing the occurrence of side effects related to constant intake of conventional tablets. The drug release kinetics study performed in liquid models at a pH of 2, 5.2 or 9.3, by spectrophotometric analysis, shown a zero-order kinetics for a long period of time. It was found that the optimum combination for an efficient release of the drug from the membrane is by mixing 2% chitosan, 6 m*m* CTAB and 10 m*m* paracetamol.

Keywords: spectrophotometric analysis; dry phase inversion; biopolymer matrices; zero-order kinetics.

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1. Introduction

Chitosan has been used in various drug delivery systems. It has antimicrobial and other effects and can be used, for example, for kidney failure or to lower cholesterol. In the past decades it was employed in water purification plants to absorb greases, oils, metals and toxic substances. It can absorb four to six times its weight, and ascorbic acid can potentiate this action even further (Zoldners *et al*., 2005).

Chitosan's characteristic as a film-forming and protective polysaccharide suggests its potential use as a biomaterial. Its applications in this area have been investigated for many years. Among the various studies, safety and hemostatic potential have been evaluated, concluding low toxicity and tensile strength retention in many circumstances (Rao and Sharma, 1997).

Application of chitosan in the pharmaceutical industry is well documented. For example, its ability to mask bitter tastes in oral pharmaceuticals has been reported (Bora *et al*., 2008). There are reports employing chitosan in drug delivery systems of many types. Some of these reports include the following: peptide drug delivery enhancement using chitosan (Prego *et al*., 2006), colon-specific drug delivery of insulin using chitosan capsules (Tozaki *et al*., 1997), chitosan microcapsules to control insulin release (Finotelli *et al*., 2010), and diabetic drugs in chitosan matrix tablets (Önal and Zihniğlu, 2002).

One of the most used analgesic and antipyretic medication worldwide is paracetamol (acetaminophen) and its toxicity was initially indicated in the 1960s. From that moment, the poisoning incidence has increased, because paracetamol is the most common drug in self-administration. An adult person without illnesses that ingest a dose higher than 10 - 12 grams or a daily dose of 7.5 grams for a longer period can suffer a liver damage (Larson *et al*., 2005). Fatal fulminant damage is usually associated with ingestion of 25 g or more. It is important to mention that paracetamol intoxication has a critical evolution period of up to 72 hours, in which the first signs of cytolysis may or may not appear (process of destruction of cell integrity). Early manifestations of the intoxication include nausea, vomiting and abdominal pain, happening after 4 to 12 hours since ingestion. Renal failure and myocardial injury may also be present. As a consequence, studies are made to obtain various controlled drug delivery systems able to release a smaller quantity of the active substance for a longer time to avoid any possible toxic effects.

This study was focused on the preparation of membranes by using the dry phase inversion method of solutions containing chitosan and a small quantity of cationic or anionic surfactant. Afterward, paracetamol was also encapsulated in these membranes during the formation process to obtain a system with applications in controlled drug delivery.

2. Materials and Methods

As a biopolymer was used chitosan with an 80% deacetylation degree and 350,000 g/mol average molecular weight from Vanson Chemicals. The two surfactants utilized are cetyltrimethylammonium bromide (CTAB) (cationic, Chemapol) and sodium dodecyl sulfate (SDS) (anionic, Sigma-Aldrich). The active substance encapsulated was paracetamol, procured from Sigma-Aldrich (151.17 g/mol molecular weight). The acetic acid was purchased from Chemical Company (99.5% purity).

In a first step, solutions of 2% or 3% chitosan in 0.1% acetic acid and 2, 6 or 10 milli-molal (m*m*) CTAB/SDS surfactant were prepared and studied to find the optimal concentrations to be further used as matrices for drug encapsulation. Afterwards, solutions of 2% or 3% chitosan, 6 m*m* CTAB and 5, 7 or 10 m*m* paracetamol were prepared. All these solutions were stirred for 8 hours and centrifuged at 2000 rpm for 1 hour to remove any bubble formed during mixing. The final membranes were obtained dry phase inversion, which implies casting the solution into a mold and letting it in a thermostat chamber at 50°C/24 hours to evaporate.

The membranes surface energy was analyzed by measuring the contact angle of two liquids (water and diiodomethane) using the sessile drop method (Kwok *et al*., 1998). The drops had a volume of 1 μL and the images were obtained with a Bauch&Lomb microscope equipped with a Philips Pro II PCVC840 camera. The FTA32 software was used to calculate the surface energies. For this, two mathematical models were applied: Owens-Wendt-Rabe-Kaelble (Owens) – geometric mean and Wu – harmonic mean.

For kinetic studies, a NanoDrop-1000 spectrophotometer was used because it requires a small quantity of the sample (microliters) and the concentration of the eluent is considered unaffected. Moreover, the time for this assessment is noticeably short. Thus, the drug release from 2 and 3% chitosan membranes was studied at a temperature of 37°C in three different elution media: hydrochloric acid (pH = 2), phosphate buffer solution (pH = 5.2) and urea (pH = 9.3). For this, 20 mg of each membrane was immersed in 50 mL of different pH eluent and samples were taken at specific periods of times to assess the absorbance of the drug. The spectra were recorded in the UV range at the maximum wavelength (247 nm) obtained for the paracetamol spectrum. It is important to mention that the solvent or the polymer do not absorb UV light at this value.

3. Results and Discussions

The polymeric membranes obtained are semitransparent, mostly rigid and easy to break, since no cross – linker compound was used. Additionally, the chitosan membranes are dense as it took a long time to dry, the internal tensions

increasing with the thickness of membranes (Balau *et al*., 2004). When a surfactant is added, the internal tensions are locally distributed at the nanolevel, leading to a high degree of order as can be seen from the analysis below.

The surface energies of the obtained membranes are presented in Table 1 as a dependency of chitosan and surfactant concentration.

Table 1
Surface Energies for the Studied Chitosan Membranes

Chitosan (%)	Wu method				Owens method			
	CTAB (m*m*)	Surface energy (dyne/cm)	SDS (m*m*)	Surface energy (dyne/cm)	CTAB (m*m*)	Surface energy (dyne/cm)	SDS (m*m*)	Surface energy (dyne/cm)
2	2	61.92	2	43.76	2	57.12	2	38.01
	6	55.73	6	43.41	6	50.8	6	37.57
	10	65.73	10	38.06	10	62.16	10	34.2
3	2	56.83	2	37.89	2	50.93	2	32.66
	6	56.48	6	45.55	6	50.77	6	39.81
	10	60.13	10	49.86	10	55.24	10	45.32

The hydrophobicity of the membranes depends on the chitosan concentration and surfactant type used. It was observed that the membranes composed of chitosan and CTAB as a surfactant are more hydrophilic than the ones with SDS, which mean that they are better aspirants for drug release. The optimum results were obtained for chitosan in concentration of 2% or 3% and for CTAB in a concentration of 6 m*m*.

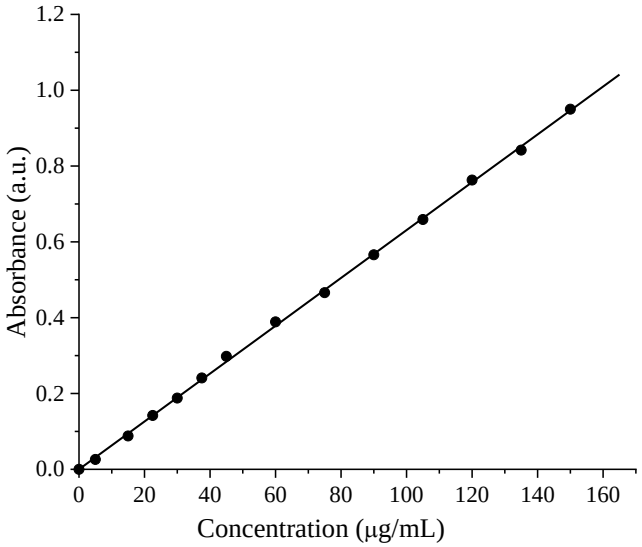


Fig. 1 − Calibration curve for paracetamol in water.

The kinetic study was accomplished by firstly recording the calibration curve (Fig. 1) of paracetamol in water (same values were obtained for hydrochloric acid and phosphate buffer).

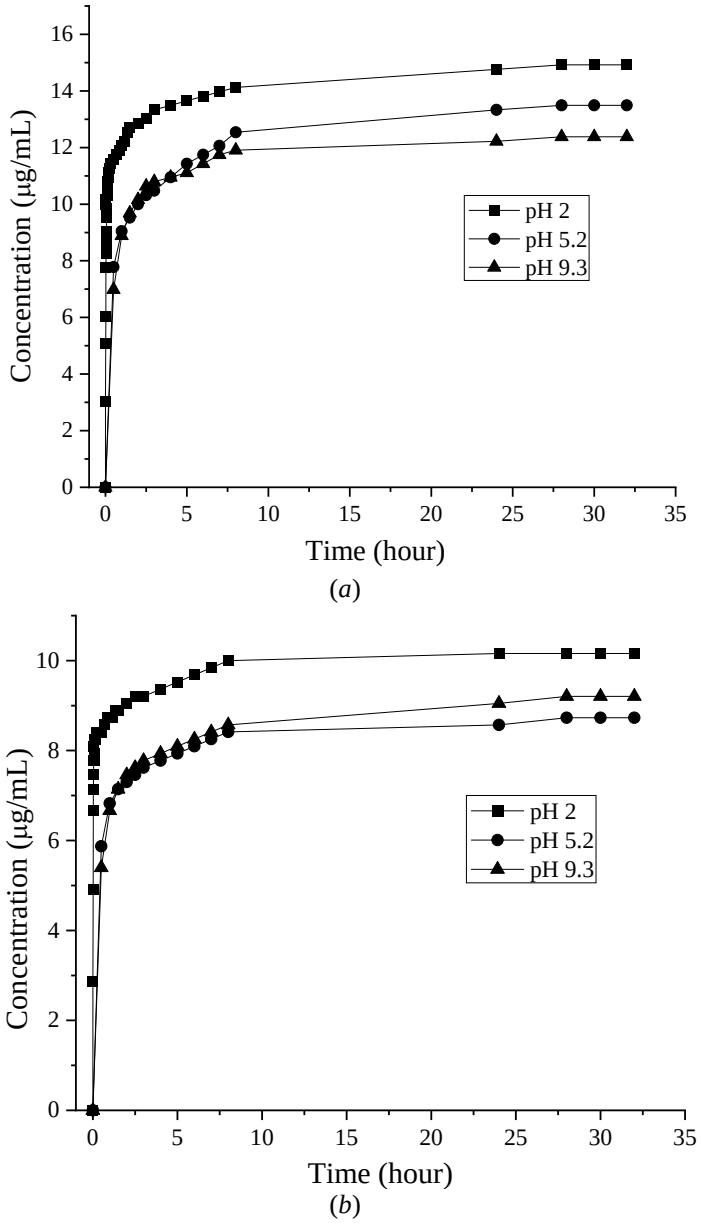
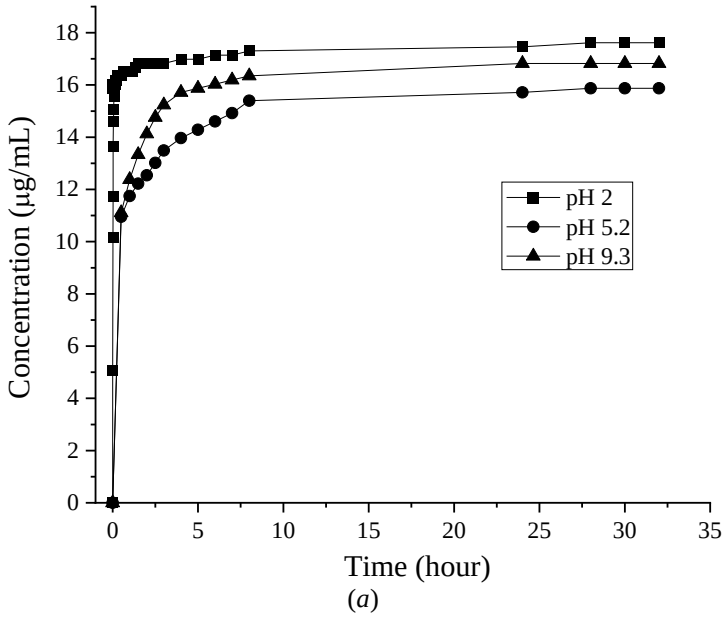
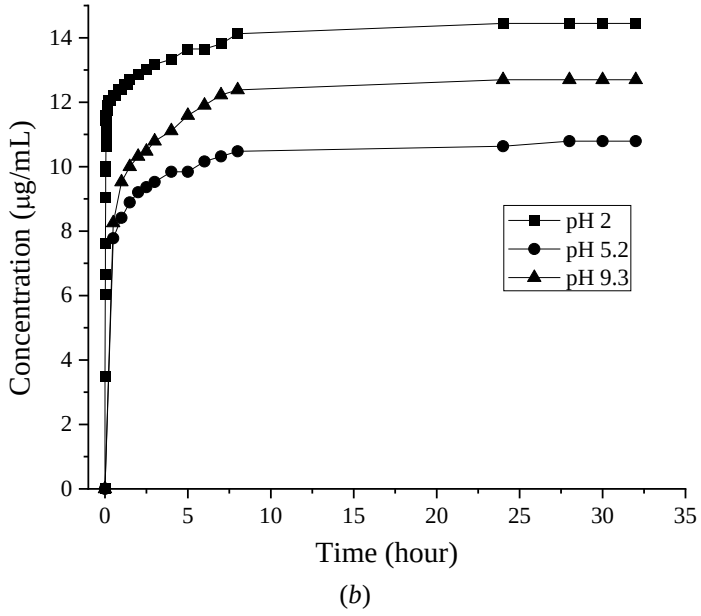


Fig. 2 − The kinetic curves for paracetamol release from the 2% (*a*) and 3% (*b*) chitosan membranes in combination with 6 m*m* CTAB and 5 m*m* paracetamol.

The drug release curves of the 2 and 3% chitosan matrices are shown in Figs. 2 - 4.

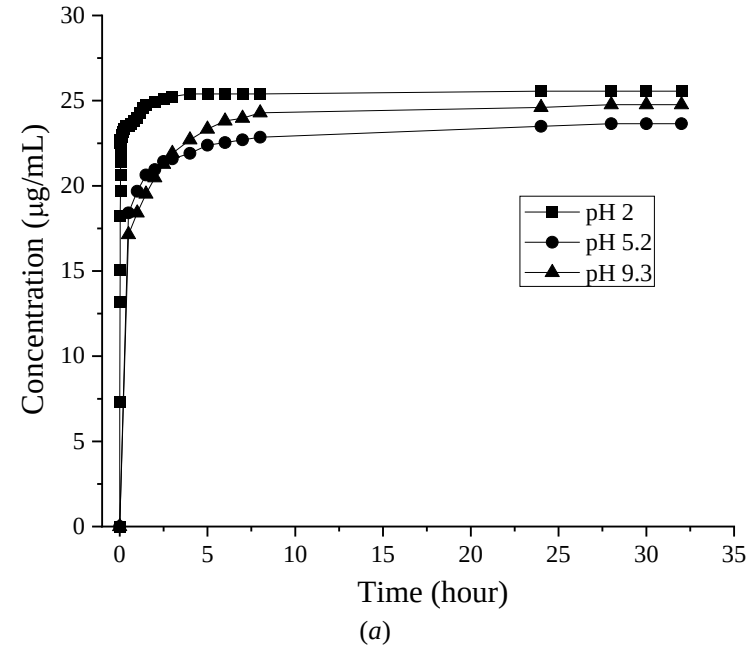


(*a*)

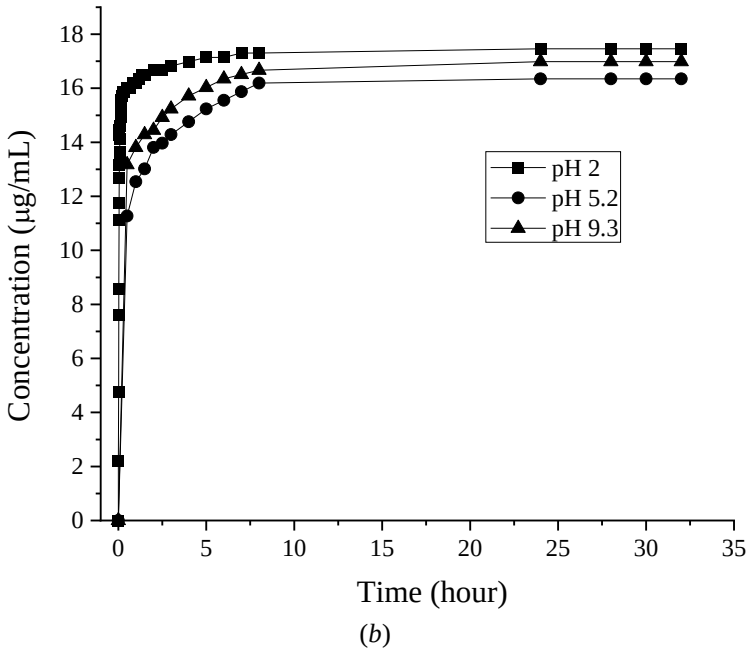


(*b*)

Fig. 3 – The kinetic curves for paracetamol release from the 2% (*a*) and 3% (*b*) chitosan membranes in combination with 6 m*m* CTAB and 7 m*m* paracetamol.



(*a*)



(*b*)

Fig. 4 – The kinetic curves for paracetamol release from the 2% (*a*) and 3% (*b*) chitosan membranes in combination with 6 m*m* CTAB and 10 m*m* paracetamol.

The amount of drug released from each type of membrane was determined spectrophotometrically. Thus, a sample quantity of 0.02 g was submerged in 50 mL of eluent solution and kept for 32 hours, the release being completed by that time. For each sample, the absorbance was measured and the concentration of released amount of paracetamol was assessed considering the values from the calibration curve.

Although the membranes immersed for 32 hours in solutions with a different pH have the same mass, they released the active substance differently. In hydrochloric acid the membranes were mostly degraded after 3 hours, while in phosphate buffer and urea remained partially degraded until the end of the experiment.

It was observed a complex process of two phenomena, namely erosion and diffusion, which are obviously much faster in the acid medium unlike the others. The kinetics is highly dependent on the erosion process, this being rate restrictive as it is slower than the diffusion.

The data show that in pH = 2 the kinetic profile is of zero order not long after the immersion, but in the other eluent solutions it takes around 7 hours. Therefore, this type of membranes is appropriate for use as a controlled drug release matrix in stomach and intestine, since the circadian rhythm allows enough time for releasing the active substance.

The best results were obtained for the sample composed of 2% chitosan, 6 m*m* CTAB and 10 m*m* paracetamol where the percentage of released paracetamol was: 50% in pH 2, 46% in pH 5.2 and 48% in pH 9.3.

For the sample of 3% chitosan, 6 m*m* CTAB and 10 m*m* paracetamol membrane the percentage was: 40% in pH 2, 36% in pH 5.2 and 38% in pH 9.3.

4. Conclusions

By the dry phase inversion method, membranes of chitosan, a cationic surfactant and paracetamol (as an active substance to be further released) were prepared in an easy manner and with a high degree of order, which is important for an effective controlled drug release.

Paracetamol is encapsulated in the polymer matrix and will be released in a controlled way as demonstrated by the kinetics study, after the membranes start to swell and occurs the erosion process that is complemented by diffusion. The optimum concentration of paracetamol to obtain a zero-order kinetics is 10 m*m*.

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REFERENCES

Balau L., Lisa G., Popa M.I., Tura V., Melnig V., *Physico-Chemical Properties of Chitosan Films*, Central European Journal of Chemistry, **2**, *4*, 638-647 (2004).

Bora D., Borude P., Bhise K., *Taste Masking by Spray-Drying Technique*, AAPS PharmSciTech., **9**, *4*, 1159-1164 (2008).

Finotelli P.V., Da Silva D., Sola-Penna M., Rossi A.M., Farina M., Andrade L.R., Takeuchi A.Y., Rocha-Leão M.H., *Microcapsules of Alginate/Chitosan Containing Magnetic Nanoparticles for Controlled Release of Insulin*, Colloids Surface B Biointerfaces, **81**, *1*, 206-11 (2010).

Kwok D.Y., Lam C.N.C., Li A., Leung A., Wu R., Mok E., Newmann A.W., *Measuring and Interpreting Contact Angles: A Complex Issue*, Colloids and Surfaces, **142**, 219-235 (1998).

Larson A.M., Polson J., Fontana R.J., Davern T.J., Lalani E., Hynan L.S., Reisch J.S., Schiodt F.V., Ostapowicz G., Shakil A.O., Lee,W.M., *Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study*, Hepatology, **42**, *6*, 1364-1372 (2005).

Önal S., Zihniğlu F., *Encapsulation of Insulin in Chitosan-Coated Alginate Beads: Oral Therapeutic Peptide Delivery*, Artificial Cells, Blood Substitutes, and Biotechnology, **30**, *3*, 229-237 (2002).

Prego C., Torres D., Fernandez-Megia E., Novoa-Carballal R., Quinoa E., Alonso M.J., *Chitosan-PEG Nanocapsules as New Carriers for Oral Peptide Delivery*, Journal of Controlled Release, **111**, 299-308 (2006).

Rao S.B., Sharma C.P., *Use of Chitosan as a Biomaterial: Studies on its Safety and Hemostatic Potential*, Journal of Biomedical Materials Research, **34**, *1*, 21-28 (1997).

Tozaki H., Komoike J., Tada C., Maruyama T., Terabe A., Suzuki T., Yamamoto A., Muranishi S., *Chitosan Capsules for Colon-Specific Drug Delivery: Improvement of Insulin Absorption from the Rat Colon*, Journal of Pharmaceutical Sciences, **86**, 1016-1021 (1997).

Woodward R.P., FTA200 Measurements Capabilities, www.firsttenangstroms.com.

Zoldners J., Kiseleva T., Kaiminsh I., *Influence of Ascorbic Acid on the Stability of Chitosan Solutions*, Carbohydrate Polymers, **60**, *2*, 215-218 (2005).

MEMBRANE POLIMERICE PE BAZĂ DE CHITOSAN PENTRU SISTEME DE ELIBERARE CONTROLATĂ A PARACETAMOLULUI

(Rezumat)

Sisteme sub formă de matrice polimerică au fost realizate pe bază de chitosan, surfactant și paracetamol, utilizând procesul de inversie de fază uscată. Au fost investigate diferite membrane în care a fost variată fie concentrația componentelor, fie tipul de surfactant folosit (cationic sau anionic). Aceste sisteme reprezintă modele

potrivite pentru eliberarea controlată a substanței active (paracetamol) încapsulată în interiorul lor, reducând astfel frecvența de administrare și prevenind apariția efectelor secundare legate de aportul constant de medicamente convenționale. Studiul cinetic de eliberare a medicamentului efectuat pe modele lichide la pH de 2, 5,2 sau 9,3, prin analiză spectrofotometrică, a arătat o cinetică de ordin zero pentru o perioadă lungă de timp. S-a constatat că, combinația optimă pentru o eliberare eficientă a medicamentului din membrană este obținută prin amestecarea compușilor în următoarea concentrație: chitosan 2%, CTAB 6 m*m* și paracetamol 10 m*m*.