STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLVI, 1-2, 2001

A CHITOSAN/CARBOXYMETHYLCELLULOSE COMPLEX USED FOR THE pH-CONTROLLED DELIVERY OF CEFTRIAXONE

N. AELENEI, M. CHIRITA*, I.M. POPA, DELIA AELENEI*, DANIELA ANDREI, GABRIELA CARJA

"Gh. Asachi" Technical University Iasi, Physical Chemistry Department, r/6600 Iasi
"Gr. T. Popa" University of Medicine and Pharmacy, Medical Bioengineering University, Iasi, 6600

ABSTRACT. Ceftriaxone is a parenteral third generation cephalosporin antibiotic owing a typical "zwitterion" molecule, containing both basic and acidic radicals. Due to the specific structure this drug forms stable complexes with both polyanionic macromolecular compounds - as carboxymethylcellulose (CMC) and polycationic macromolecular compounds - as chitosan. Consequently, a chitosan/CMC/ceftriaxone complex can be obtained and used for the controlled release of the drug, the release rate being strongly influenced on the pH.. The optimal chitosan/CMC combination ratio was determined spectrophotomrtrically. An insoluble chitosan/CMC/Ceftriaxone complex, containing 17% ceftriaxone, was prepared. The kinetic of ceftriaxone release was analyzed as a function of the elution medium pH. The experimental data point out that the maximum quantities of the released ceftriaxone are obtained after 200 min at pH=1.95 and pH=11.75, and after 1600 min at pH=4.68, pH=5.74, pH=6.54 and pH=7.34. The maximum quantity of drug released from the complex is strongly dependent on the pH, being closed by 100% in strong acidic and basic solutions, while it becomes only approximately 5% at pH = 6.54. This behaviour was explained by the intricate structure of the complex.

KEY WORDS: chitosan/carboxymethylcellulose/ceftriaxone complex, controlled-release

INTRODUCTION

Controlled-release drug delivery combines reproductible dosage from design with clinical pharmacology, particularly steady-state pharmacology. Controlled release drug delivery currently involves control of either the time course or location of drug delivery. Control of time course of drug is the more classical approach, while site specific or targeted delivery – which involves drug delivery to a specific organ, a class of cells or a physiological compartment – is mostly in the research stage.

Delivery rates from temporal controlled systems may be characterized in terms of their kinetics and physical processes. Of particular interest are zero-order systems - for which the released drug quantity is constant with time. These systems can allow foe selection of precise efficacious plasmatic levels after titration for inter-individual variation or its may be important to select plasma levels that avoid adverse drug reactions [1]. A second potential advantage of zero-order dosage forms is improved efficiency of delivery of the drug; steady-state delivery of the drug may be more efficient when the distribution of the drug into the receptor compartment is much slower than elimination from the receptor compartment.

The variety routes available for drug delivery corresponds to the biological membranes in human body: oral, nasal or vaginal mucous, gastrointestinal tract, eye or skin. Oral drug delivery is the most common route, the drug being absorbed through the various membranes along the gastrointestinal tract and the controlled release device traverses a whole domain of pH, from 1...2 in stomach, 4 ... 5.5 in duodenum and 5.5 ... 7.5 in jejunum. Transit through the ileum is more regular (pH = 7...7.5) and entrance in the colon may be accompanied by a 0.5 to 1.0 units increase in pH [2], [3]. The total gastrointestinal transit time is highly variable, varying from less than a day to several days [3], [4]. Oral delivery of drugs seems to offer a combination of advantages of transdermal and oral delivery. A bucal device is both a sublingual tablet and a sub-gingival pellet - used in periodontal treatments. The sub-lingual device has the advantage of a very easy application and removal, and permitting to obtain a rapid increase in the local concentration of the drug, for a long period of time. However, a very limited domain of pH, comprised between 5.5 and 7.5 restricts the bucal administration, this fact entails the choice of an adequate delivery device, with very high delivery rate - in sublingual administration and with very slow release rate in sub-gingival application.

Ceftriaxone is a parenteral third generation cephalosporin antibiotic owing a typical “zwitterion” molecule, containing both basic and acid radicals (Fig. 1,a).

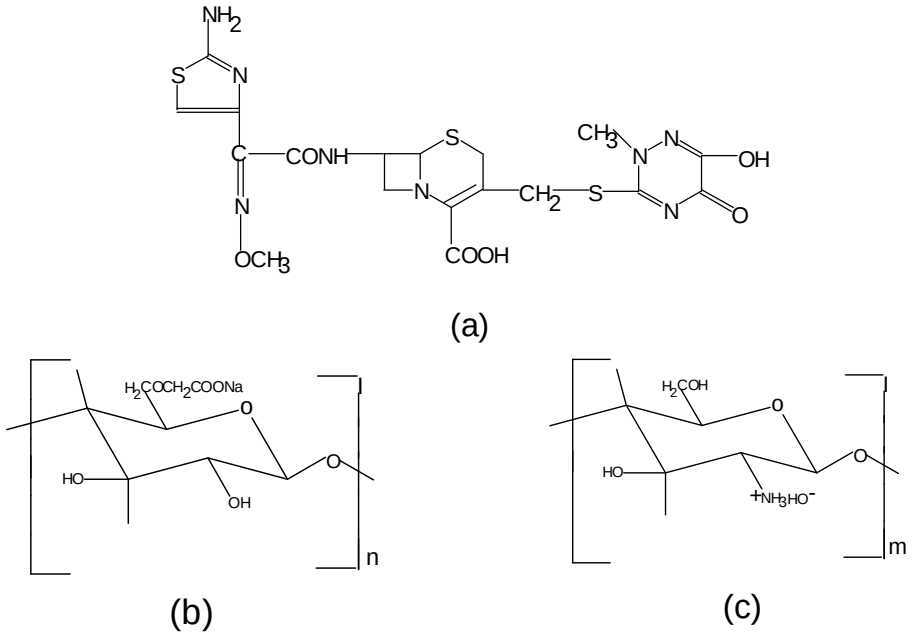

Fig. 1 – Structure of ceftriaxone (a), Carboxymethylcellulose (b) and Chitosan (c)

In vitro, this antibiotic exerts a pronounced activity against a wide range of gram negative and gram positive microorganisms. Dou to the specific structure this drug is able to form stable complexes with both polyanionic macromolecular compounds - as carboxymethylcellulose (CMC) (Fig.1,b) and polycationic macromolecular compounds /- as Chitosan (Fig. 1,c).

Simultaneous complexation of ceftriaxone with CMC and chitosan leads to a very pH-sensitive complex, which can be used for controlled delivery of ceftriaxone.

EXPERIMENTAL

Chitosan sample, having a molecular weight of 150,000 g mol^{-1} and a 12% acetylation degree was obtained from the Genetical Chemical Department of Sherbrooke University, Canada. Carboxymethylcellulose was supplied by Austranal Co. and has an esterification degree of 81 %.

The optimal Chitosan/CMC was determined spectrophometrically, measuring the absorbency of the supernatant phase separated from a series of dilute solutions with various CMC/chitosan ratios (Fig. 2.). From these data, the optimal gravimetric ratio was found to be m (CMC)/ m (Chitosan)= 1.2.

The quantitative determinations of ceftriaxone, both for analysis and kinetically studies, were performed by spectrophotometric measurement [5] using an UV-VIS spectrophotometer of VSU-2P type.

The Chitosan/CMC/Ceftriaxone complex was obtained, at ordinary temperature, solving an excess of ceftriaxone into a 0.4 % CMC solution (pH = 5.8) and pouring this solution, drop by drop, under energetically stirring for three hours, into 0.4 % Chitosan solution (pH = 5.8). The gravimetric ratios between the three components in the final mixture was m (Chitosan)/ m (CMC)/ m (Ceftriaxone)= 1:1.5:1.45.

The insoluble complex was separated through centrifugation at 3500 rpm, for 15 min, washed with water and acetone and dried in vacuum at room temperature. This complex contain 17.3 % Ceftriaxone.

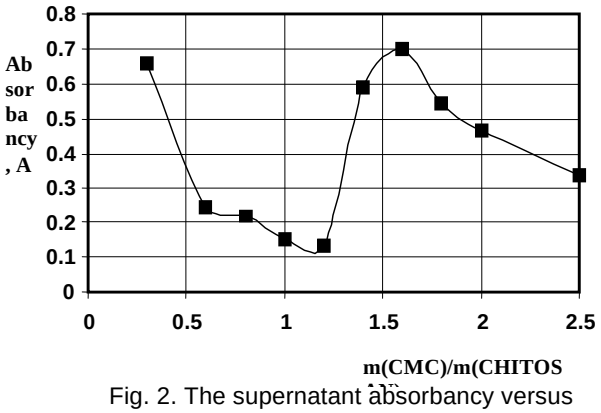

Fig. 2. The supernatant absorbancy versus CMC/CHITOSAN ratio

For kinetic studies the dry complex was compressed, at 5 kg/cm^2 for three minutes, in platelike cylindrical form of 13 mm diameter and 1.1 ... 1.4 mm thickness.

The weights of the complex samples were comprised between 0.13 and 0.2 g for an eluent volume of 100 cm^3.

The study of Ceftriaxone release from the complex was carried out by an elution technique in aqueous medium

of different pH values, at 37 ^{o}C, The solution samples of 1mL were extracted at different time intervals and analyzed spectrophotometrically, determining the quantity of released ceftriaxone (m_t).

The maximum quantities of ceftriaxone present in the solid samples, m_f, were determined by measuring the solution absorbency 72 hours after the initiation of the release.

RESULTS AND DISCUSSIONS

The kinetic curves obtained by elution in different buffer solutions are presented in Fig. 3.

From these curves it can be see that in very strong acid solutions (pH=1.95) or in very basic solutions (pH=11.73) the release rate is very great achieving maximum release after eight hours of elution, but the drug shows a weak; the degradation rate being of 0.7 % in acidic media and 0.4 % in basic media.

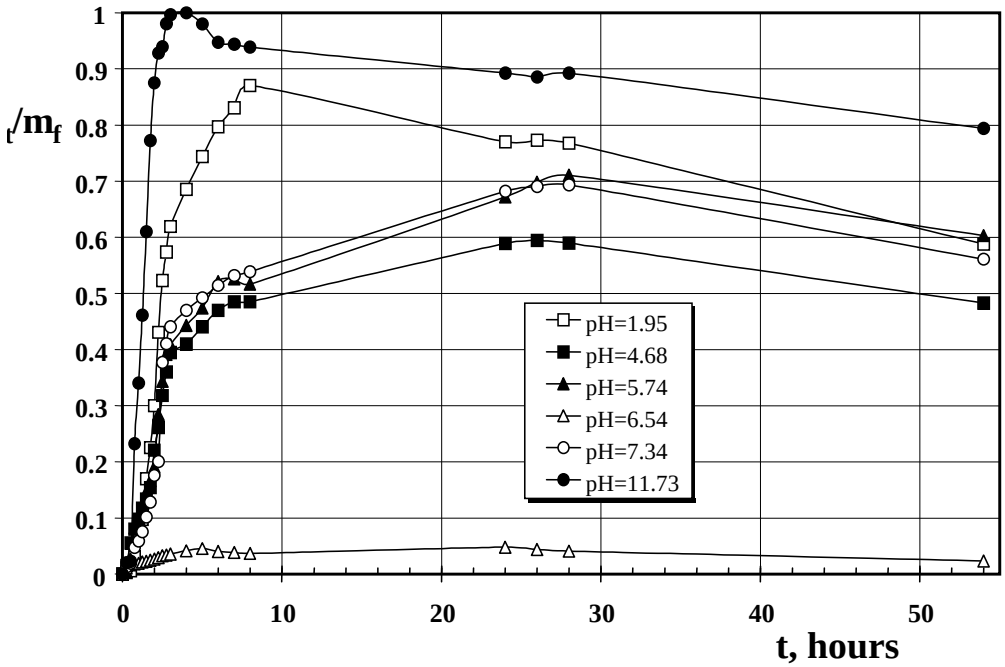

Fig. 3 - Ceftriaxon release from the CHITOSAN/CMC/CEFTRIAXON complex , as of pH and time

At moderate pH values (pH = 4.69; 5.74 and 7.34) the release rate is also moderate and degradation process is at the same time present, excepting for pH = 5.74.

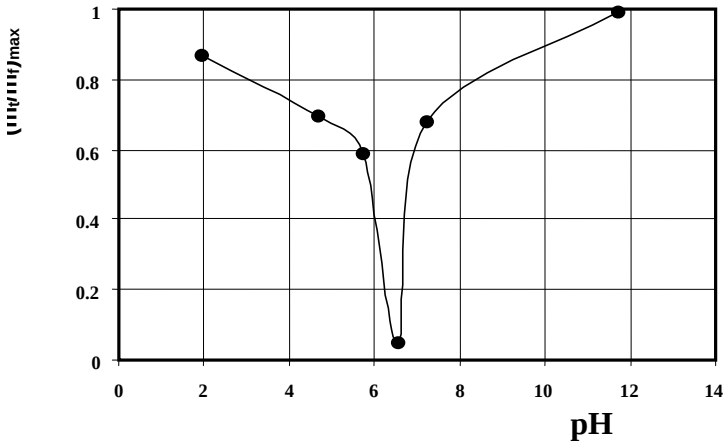

Fig. 4 Dependence on pH of the maximum
relative quantity released after 50 hours of elution

The sample mentained in water (pH = 6.54) through was scattered like a powder after 90 min, release a very small quantity of drug (~ 5 %) and the degradation process is very reduced.

The maximum quantity of the released drug from complex is strongly dependent on pH; being closed by 100 % in strong acidic and basic solutions and becoming equal with only 5 % at pH = 6.54. This behaviour is due to the intricate structure of the studied complex, which presents an isoelectric point in the weak acidic domain, and to "zwitterion" structure of the drug, this being characterized by pK_a=3 for COO^-, pK_b= 3.2 for NH_3^+ and pK_{OH} (enolic) = 4.1

CONCLUSIONS

The Ceftriaxone, a parenteral third generation cephalosporine antibiotic, can be used as long-time local application in treatment of some severe periodontal infections. This utilization is assigned by the very lower rate of ceftriaxone release from the Chitosan/CMC/Ceftriaxone complex in the neutral pH media (pH=6.54 – which is in the same time the isoelectric point of the drug.

The higher release rates obtained in both strongly acid and strongly basic media is due to the increasing solubility of the drug as a result of the ionization of the acidic or basic groups.

REFERENCES

1. Berner B., Dinh S. "Fundamental concepts in controlled Release", in Treatise on Controlled Drug Delivery, A. Kydonieus Ed., Marcel Dekker Inc., N.Y, 1989
2. R. J. Mrsny, Controlled Drug Delivery – Challenges and Strategies, Kinam Park, Ed., ACS Professional Refference Book, Whasington, 1997.

3. L. Long, A.S. Hoffman & P. Sadurny, Ph Sensitive Hydrogels, Based on Thermally Reverseble Gels for Enteric Drug Delivery, Proc. Int. Symp. Control. Rel. Bioact. Mater, 1989, p. 95.
4. H. W. Davenport, "Phy Biology of Digestivo Tract", Year Book Medical Publishers, Chicago, 1982.
5. N. Aelenei, I. M. Popa, D. Andrei, Delia Aelenei, A. Mărculescu. *Farmacia*, vol. XLVII, nr. 6, 2000, p. 43 – 49