ION EXCHANGE LETTERS

Ion Exchange Letters **2** (2009) 27-30

iel.vscht.cz

Core-shell microparticles based on acrylic ion exchange resin/polysaccharides as drug carriers

S. Vasiliu, I. Bunia, V. Neagu

"Petru Poni" Institute of Macromolecular Chemistry, Grigore Ghica Voda 41A, 700487, Iasi, Romania: vneagu@icmpp.ro

Received: 22.7.2009; Accepted 27.7.2009; Published 28.7.2009

ABSTRACT

Core-shell microparticles consisted of acrylic ion exchange resin as the core and two natural polymers (gellan or xanthan) as the shell are presented in this paper. These new polymeric materials were characterized by FT IR spectroscopy, optical microscopy and swelling degree in water. Taking into account the possibility of their use in the medical and pharmaceutical fields, the retention and release capacities of cefotaxime sodium salt were investigated.

Keywords: core-shell microparticles, acrylic ion exchange resin, gellan, xanthan, drug release

INTRODUCTION

Progress in polymer science and engineering led to the creation of new polymeric materials which represent one of the driving forces for the evolution of fundamental knowledge and development in various domains, especially in medical and pharmaceutical fields. In this context, ion exchange resins have received considerable attention for a broad spectrum of applications[1-3]. For the first time, the ion exchange resins were developed for applications in waste water purification[4-7] and later were used in isolation and purification of pharmaceutical active ingredients[8]. The utility of these materials as polymeric support in pharmaceutical formulations was suggested for the first time by Saunders and Chaudhary which used them in the manufacture of the sustained release system of charged drugs[9]. Also, the ion exchange resins were suggested for uses in control of gastric acidity[10], treatment of cardiac edema[11] or as taste-masking agents[12]. Sodium polystyrene sulfonate (Kayexalate, Kionex) a strongly acidic ion exchange resin has been reported as an adjuvant in the treatment of hyperkalemia[13]. Colestipole, a weakly basic ion exchange resin and cholestyramine, a strongly basic ion exchange resin are used to treat hypercholesterolemia[14], both of them being known as bile acid sequestrants. The use of ion exchange resins into drug delivery systems has been encouraged because of their properties, such as, uniform size, presence of functional groups leading to high loading capacity of the drugs, physico-chemical stability, controlled or sustained release profile of the drugs and reduction of the degradation of drug molecules in the gastrointestinal tract. Other advantages of the ion exchange resins are their insolubility in all solvents for all pH domains and also are not absorbed in gastrointestinal tract. Therefore they have not significant local and systemic side effects[15]. Sometimes the drug release can be very fast in the presence of an excess of ions and dose dumping can occur. This can be prevented by coating the surface of the ion exchange resin with a polymer layer for better control of drug release[16,17]. The objective of this study was to develop a new drug delivery system for sustained release in stomach by coating the surface of an acrylic weakly basic ion exchange resin based on the ethyl acrylate, acrylonitrile and divinylbenzene copolymer with two natural polymers: gellan gum (Gll) and xanthan gum (Xan). Natural polymers are two anionic polysaccharides produced by *Pseudomonas elodea* and *Xanthomonas campestris*, respectively[18-20]. The chemical structures of the polymers used are presented in Figure 1. The main advantage of core-shell type microparticles

is the possibility of both hydrophilic and hydrophobic drugs to be incorporated.

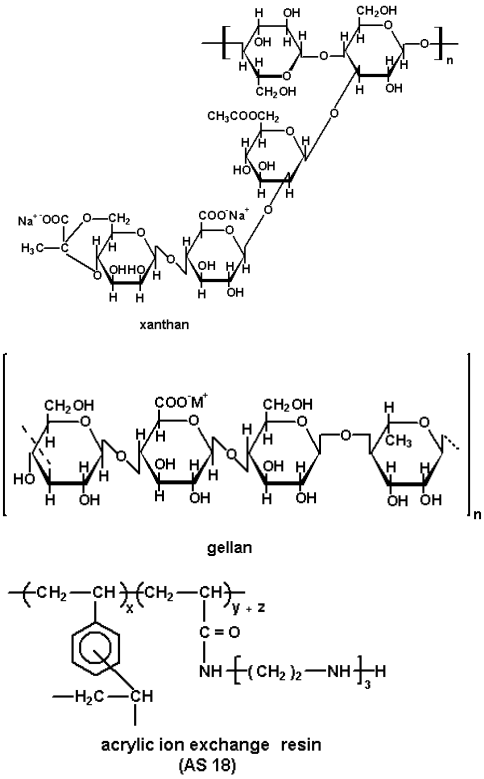


Figure 1 *Chemical structure of the xanthan, gellan and synthetic polymer*

EXPERIMENTAL

Materials

Acrylic ion exchange resin in the bead form was prepared by suspension polymerization technique, described elsewhere[21]. Gll and Xan were purchased from Fluka Chemical Company and were used as received. Cefotaxime sodium salt (CF) was also purchased from Fluka Chemical Company.

Methods

To convert the resin in Cl^- form, resin sample was equilibrated with 1M HCl solution for 24 h and then washed with deionized water to remove HCl in excess. This Cl^- form of resin was used for further studies.

To prepare the core-shell microparticles, 5 g of pre-formed resin microparticles were placed in 500 mL of 1% polysaccharides aqueous solutions at pH = 5 and 25^0C for 24 h with a permanent gentle stirring. After the specified time period, the beads were removed from the polysaccharides solutions by filtration and rinsed in distilled water, then centrifuged at 1000 rpm for 10 minute. The yields of core-shell preparation were 80% for R_1 microparticles and 85% for R_2 microparticles, respectively.

The FT IR spectra (Bruker Vertex 70 Spectrophotometer) of the resin and the core-shell microparticles in the range 5000-400 cm^{-1} were obtained using KBr pellet technique.

The optical microscope (Alpha STO5, Elektro-Optika Ltd. Hungary) was used to visualize the shape of beads.

The retention process was performed by batch method: each sample containing 50 mg resin or core-shell microparticles was contacted with 20 mL of aqueous drug solution of CF under gentle shake at 25^0C. After the specified times, the microparticles were removed quantitatively from aqueous solution of drug and centrifuged for 10 min. at 1000 rpm.

The release of CF from the resin and core-shell microparticles was carried out at 37^0C in hydrochloric acid-potassium chloride buffer solution at pH = 1.2. Thus, 100 mg of drug-loaded microparticles were suspended in 250 mL of buffer solution and a permanent gentle stirring was applied.

The retained and the release drug amounts were determined spectrophotometrically at 236 nm by means of UV-VIS SPEKOL 1300 spectrophotometer (Analytik Jena).

RESULTS AND DISCUSSION

Preparation of core-shell microparticles can take place following one-step process, based on the self-assembly of organic and inorganic components or two steps process by the deposition of the shell on a pre-formed core particles. In Figure 2 is presented the schematic representation of the preparation method for core-shell microparticles.

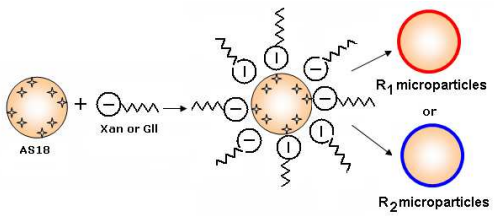


Figure 2 *Schematic representation of the preparation method for core-shell microparticles*

Figure 3 presents FT IR sprectra for AS18, gellan and core-shell microparticles based on gellan and AS18.

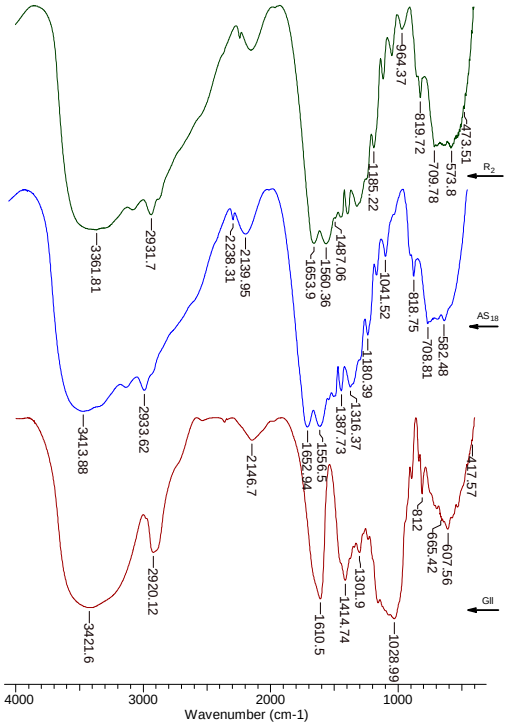
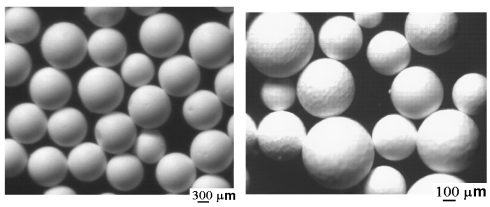


Figure 3 *FT IR spectra for: gellan, AS 18 and R_2.*

From Figure 3 it can be seen that gellan has interacted with acrylic ion exchange resin. This affirmation is sustained by the appearance of the new bands at 1487 cm^{-1}, 964 cm^{-1} and 473 cm^{-1} and by the displacement of some vibration bands in the spectra of the core-shell microparticles.
The optical micrographs presented in Figure 4 reveal a good spherical shape with diameter values in the range of 300 – 500 μm for AS 18 and R_2 microparticles.



(a) **(b)**

Figure 4 *Optical microscope images of AS 18 microparticles (a) and R_2 microparticles (b).*

The swelling measurements of the microparticles were carried out in water and in buffer solution at pH = 1.2 at room temperature. The water uptake coefficient (U_w) was calculated by using the following expression:

$$U_W = \frac{Ws - W_0}{W_0} \quad g/g \quad (1)$$

where: W_s and W_0 are the weights of the microparticles in swollen and in dry state, respectively. The values of U_W for the AS18, R_1 and R_2 microparticles were shown in Table I.

Table I *Water uptake coefficients for AS18, R_1 and R_2 microparticles*

Sample code	U_W (g/g)	
	pH = 1.2	pH = 5.5
AS18	7.126	6.541
R_1	5.850	7.869
R_2	5.367	7.123

The highest values of U_W in water of R_1 and R_2 microparticles can be explained by the presence of Xan and Gll, which are hydrophilic polymers and therefore, induced an increased water uptake.
For the efficient drug loading, it is important to know the time to reach equilibrium and how much drug will be loaded into microparticles, which depends on the microparticle-type and loading method. Generally, the loading with drugs can be achieved using batch and column methods. For this study the batch method was used. As the drug, cefotaxime sodium salt, which has the role to treat or prevent infections, was loaded on the microparticles. The chemical structure of CF is presented in Figure 5.

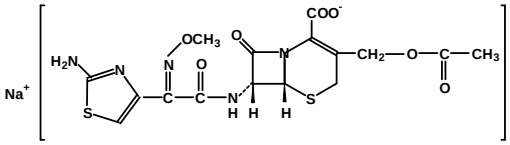


Figure 5 *Chemical structure of cefotaxime sodium salt.*

In Table II are presented the retained drug amounts as a function of the concentration of CF solution.
From Table II one can see that the R_1 and R_2 microparticles have a higher retention capacity of drug than ion exchange resin, due to their higher swelling capacity in aqueous solution.

Table II *Retained drug amounts as a function of the concentration of drug solution*

C_{CF}* (g/mL)	Q_R(mg CF/g dry beads)**		
	AS 18	**R_1**	**R_2**
$7x10^{-5}$	10.94	15.80	13.80
$7x10^{-4}$	135.56	296.12	173.79
$15x10^{-4}$	298.10	481.41	443.50
$30x10^{-4}$	436.24	590.67	534.56
$37.5x10^{-4}$	467.84	620.84	582.27

*C_{CF} = concentration of CF solution; ** Q_R= equilibrium retention capacity of drug

Figure 6 shows that the release rate of CF at pH = 1.2 is slower for R_1 and R_2 microparticles compared to AS 18 microparticles.

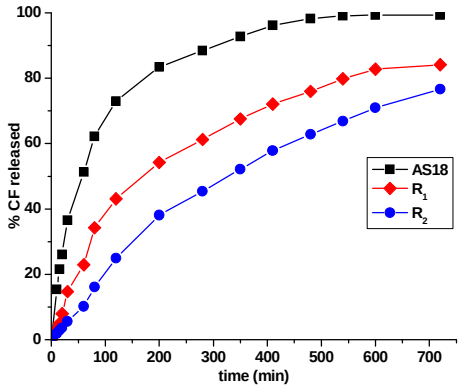


Figure 6 *In vitro release profile of CF from AS18, R_1 and R_2 microparticles*

CONCLUSIONS

Two types of core-shell microparticles based on the acrylic ion exchange resin and two polysaccharides are investigated. It was demonstrated the higher capacity of drug loading on the core-shell microparticles than the capacity of drug loading on the ion exchange microparticles. Based on the release profiles the core-shell microparticles could be considered suitable drug delivery systems in stomach for cefotaxime.

REFERENCES

1) Bunia I., Neagu V., Luca C., *React. Funct. Polym*. **66** (2206) 871-883
2) Blount C.W., Leyden D.E., Thomas T.L., Guill S.M., *Anal. Chem*. **45** (1973) 1045-1050
3) Vera E., Dornier M., Ruales J., Vaillant F., Reynes M., *J. Food. Eng*, **57** (2003) 199-207
4) Neagu V., Untea I., Tudorache E., Orbeci C., *J. Appl. Polym. Sci*. **93** (2004) 1957-1963
5) Luca C., Maruta C., Bunia I., Urmeny A.M., Sandu M., Rata D., *J. Appl. Polym. Sci.* **97** (2005) 930-938
6) Lin L.C., Juang R.S., *Chem. Eng. J*. **132** (2007) 205-213
7) Bennett A., *Filtr. Separat.* **44** (2007) 20-23
8) Belakhov V.V., Momot N.N., *Pharm. Chem. J.* **17** (1983) 369-371
9) Chaudhary N.C., Saunders L., *J. Pharm. Pharmacol.* **8** (1956) 975-986
10) Bass, B.H., *Br. Med. J*. **16** (1956) 1406-1407
11) Feinderg, A.W., Rosenberg B., *Am. Heart J*. **42** (1951) 698-709
12) Amita N., Garg S., *Ind. J. Pharm. Sci.* **64** (2002) 10-17
13) Yaseen H., Khalaf M., Dana A., Yaseen N., Darwich M., *Am. J. Perinatol.* **25** (2008) 193-197
14) Angelin B., Ernasson K., *Atherosclerosis* **38** (1981) 33-38
15) Kim C.J. Ion Exchange Resin Drug Delivery Systems, Technotronic Publishing Company, Lancaster / Pensylvania USA
16) Jeong S.H., Park K., *Int. J. Pharm.* **353** (2008) 195-204
17) Ichikawa H., Fujioka K., Adeyeye M.C., Fukumori Y., *Int. J. Pharm*. **216** (2001) 67-76
18) O'Neill, M.A., Selvendran R.R., Morris, V.J., *Carbohydr. Res.*, **124** (1983) 123-133
19) Jansson, P.E., Lindberg, B., Sandford, P.A., *Carbohydr. Res*., **124** (1983) 135-139
20) Casas, J.A., Santos, V.E., Garcia-Ochoa, F., *Enzyme Microb. Tech*., **26** (2000) 282-291
21) Maxim, S., Flondor, A., Bunia, I., Luca, C., *Eur. Polym. J*., **34** (1998) 1379-1385