ORIGINAL ARTICLE

RELEASE STUDIES OF CEFOTAXIME SODIUM SALT FROM COATED ION EXCHANGE RESIN MICROPARTICLES

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Abstract

Microparticles based on acrylic ion exchange resin and ion exchange resins coated with two microbial exopolysaccharides (xanthan and gellan) have been used as carriers for cefotaxime sodium salt delivery. The coated and uncoated ion exchange resin microparticles were loaded with the drug by a diffusion process. The release kinetics of the drug was studied by elution with solutions at different pH values. The analysis of the *in vitro* release data was performed using different mathematical models such as: Boyd, Higuchi, Korsmeyer-Peppas and Baker-Lonsdale models. The kinetic data of the release process indicates that the deliverance mechanism of cefotaxime from coated and uncoated ion exchange resin microparticles was controlled by swelling and diffusion processes. Also, the bactericidal potential of cefotaxime released from coated and uncoated microparticles was highlighted by antimicrobial tests.

Rezumat

Microparticulele pe bază de schimbători de ioni acrilici şi schimbători de ioni acoperiţi cu două exopolizaharide de origine microbiană (xantan şi gelan) au fost utilizate ca transportori ai cefotaximei sare de sodiu. Încărcarea medicamentului în microparticulele acoperite şi neacoperite s-a realizat printr-un proces de difuzie. Pentru eliberarea medicamentului s-au utilizat soluţii cu pH diferit. Analiza datelor obţinute la eliberarea *in vitro* a medicamentului s-a realizat cu ajutorul a diferite modele matematice, cum ar fi: modelele Boyd, Higuchi, Korsmeyer-Peppas şi Baker-Lonsdale. Datele cinetice ale procesului de eliberare au indicat faptul că mecanismul de eliberare a cefotaximei din microparticulele acoperite şi neacoperite a fost controlat prin procese de umflare şi difuzie. De asemenea, caracterul bactericid al cefotaximei eliberată din microparticulele acoperite şi neacoperite a fost evidenţiat prin teste antimicrobiene.

Keywords: drug delivery, ion exchangers, cefotaxime, polysaccharides

Introduction

Since the 1920 when the ion exchange principle was used for the first time in drug industry, the research in the ion exchange resins field has led to the discovery and creation of the modern systems that could be used to solve various problems in medicine and pharmacy [12]. It is known from literature that the complex formed between an ion exchange resin and the drug is called resinate. At present, two types of resinates are known in the pharmaceutical field: single resinate and multiple resinate products [16, 17].

Generally, ion exchange resins were used as macromolecular carriers in order to provide a controlled/ sustained release profile [1, 10, 20] as well as to improve some pharmaceutical properties of drugs like: bitter taste, systemic toxicity and stability [3, 4, 5, 6]. The main advantages of these systems consist of dose dumping avoidance, controlled/sustained release of drugs and flexibility of the administration route, by designing different types of dosage forms [11, 14, 19]. In our previous researches, we have carried out a study regarding the kinetics, equilibrium and thermodynamic parameters of the adsorption process of cefotaxime sodium salt (CF) onto coated and uncoated ion exchange resins [8, 21]. The present study is a continuation of the foregoing research, the main objective targeting the exploration of the release mechanism and highlights the preservation of the antimicrobial activity of the drug, subsequent its release from the coated and uncoated ion exchange resins.

Materials and Methods

Materials. Acrylic ion exchange resin was prepared by suspension polymerization method as described in literature [14]. Gellan gum (Gelzan^{TM}, M_w = 1 x 10^6 g/mol), xanthan gum (from *Xanthomonas Campestris*, M_w = 1.4 x 10^6 g/mol) and cefotaxime sodium salt (M_w = 477.45 g/mol) were purchased from Sigma-Aldrich Company and were used as received.

Methods

Characterization of the drug delivery systems. The surface morphology of coated and uncoated microparticles was observed with Environmental Scanning Electron Microscope type Quanta 200-FEI coupled with an energy dispersive X-ray system.

In vitro release of CF. The CF release process was investigated by immersing the uncoated and coated ion exchange resin microparticles in simulated gastric fluid (pH = 1.2) for 2 hours and then in phosphate buffer solution at pH = 7.4 for 12 hours. The release characteristics were performed by incubation of 20 mg coated and uncoated microparticles - CF systems in 10 mL of dissolution media, at 37ºC, in a water bath temperature-controlled shaker (Memmert M00/M01, Germany). A known volume (V_i, mL) of the supernatant was withdrawn at predetermined time intervals, being followed by replacement with an equal volume of the dissolution medium. The amount of CF released was determined by UV-VIS spectrophotometry (SPEKOL 1300 Spectrophotometer, Analytik Jena, Germany) at 236 nm, using a calibration curve. The cumulative CF release (Q %) was calculated by the following equation [22]:

$$Q\% = \frac{VxC_n + V_i x \sum_{i=1}^{n-1} C_i}{M} x100, \qquad (1)$$

where M is the total mass of CF absorbed into microparticles, C_n and C_i are CF content released from microparticles in dissolution media determined at different times, respectively.

Antimicrobial susceptibility tests. The antimicrobial susceptibility tests of coated and uncoated ion exchange resin-CF systems were performed on two microbial strains like *Escherichia coli* ATCC 25922 as Gram negative bacteria and *Staphylococcus aureus* ATCC 25923 as Gram positive bacteria, respectively. The reference strains were regenerated from storage media being verified in terms of metabolic and antigenic characteristics. All strains tested were pure and quantitatively suitable for use in the experiments. The antimicrobial activity of CF loaded on coated and uncoated ion exchange resins was evaluated using the Kirby-Bauer disk diffusion method [2]. The cultures were prepared according to the manufacture recommendations, using suspensions with concentration about 5.2 x 10^7 CFU/mL. The tests were carried out on Muller-Hinton agar and the Petri dishes were incubated for 24 h at 37ºC. The antibacterial activity was expressed as mean inhibition zone diameters (mm) and all experiments were realized in triplicate. The efficacy of CF loaded on coated and uncoated ion exchange resins was compared to that of commercially antibiotic tested alone on the same strains and by the same method. The antimicrobial susceptibility tests were performed according to the procedure of the National Committee for Clinical Laboratory Standards (2008).

Results and Discussion

The drug was loaded onto uncoated and coated ion exchange resins by the batch method. The amounts of CF loaded onto microparticles at T = 313 K and C_{CF} = 3750 mg/L are presented in Table I.

Table I

Several characteristics of A, T_1 and T_2 microparticles

Sample codes	Coat	Q_R (mg CF/g dry beads)	R (μm)	Zone of inhibition (mm)	
				E. coli	*S. aureus*
A	-	618.2	184	22	41
T_1	xanthan	783.62	189	16	35
T_2	gellan	720.83	187	19	38
CF	-	-	-	30	50

The SEM images (Figure 1) of drug loaded onto A, T_1 and T_2 microparticles (left side) point out the presence of drug molecules on the microparticles surface.

For A microparticles, a drug cluster on the microparticle's surface could be noticed, very probably due to the electrostatic interactions between NH_3^+ groups belonging to the ion exchange resin and the COO^- groups from the drug structure. The same behaviour was observed in case of CF loaded on the interpenetrating networks of poly(vinyl alcohol-g-acrylamide) and chitosan-g-polyacrylamide chains [18]. In case of T_1 and T_2 microparticles the drug is located on surface, but also in the pores of the complex shell situated on the surface of the microparticles. As shown in our previous study [21], the presence of xanthan and gellan in the structure of microparticles leads to higher values of the maximum adsorbed amount of CF.

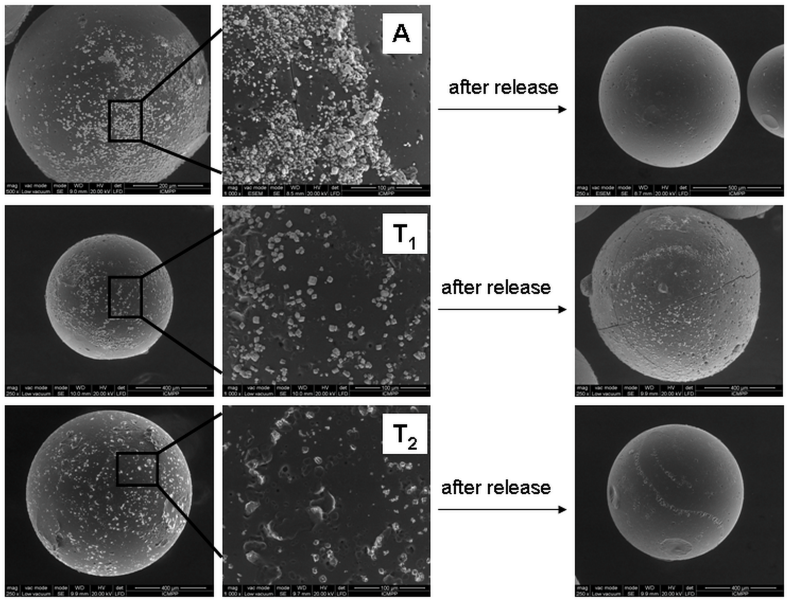

Figure 1.
SEM images of A, T_1 and T_2 microparticles after loading with CF (left side) and after CF release (right side)

Release studies

The release profiles are graphically presented in Figure 2.

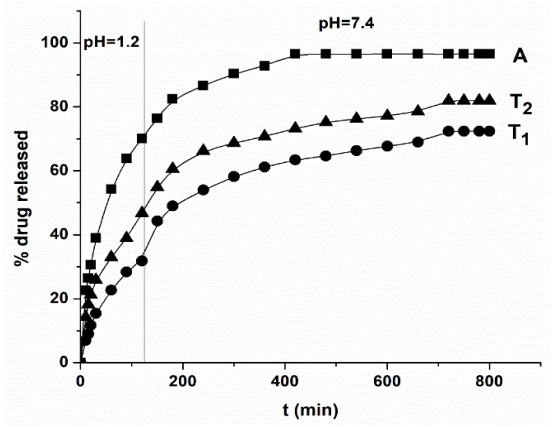

Figure 2.
In vitro cumulative release of CF from A, T_1 and T_2 microparticles

In the first 2 hours, the amount of CF released was lower for T_1 and T_2 microparticles (31.83 and 46.75 wt%, respectively), compared to A microparticles (70.16 wt%). In the case of A microparticles, the release of larger amount of cefotaxime may be attributed to the fact that drug is situated on the surface of the microparticles, as seen in Figure 1.

For T microparticles, the amount of discharged CF is lower, due to the presence of xanthan or gellan in the microparticle structures, probably due to the enhanced interactions between the drug and the polymer matrix, through H-bonding and ionic linkages.

In order to elucidate the kinetics and the mechanism of the release process from A, T_1 and T_2 microparticles, we applied four mathematichal models: Boyd, Higuchi, Korsemeyer-Peppas and Baker-Lonsdale (Table II).

Table II
Mathematical models of release process

Mathematical models	Equations		Ref.
Boyd	$F = \frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2Bt}}{n^2}$ $B = \frac{\pi^2 D}{r^2}$	M_t and M_∞ are the amounts of drug released after time t and after infinite time; r - radius of ion exchange resin, B - rate costant, D -diffusion coefficient.	[7]
Higuchi	$Q_t = k_H t^{\frac{1}{2}}$	Q_t - fraction of drug released at time t and k_H - Higuchi constant	[13]
Korsmeyer -Peppas	$F = k_r t^n$, $F = M_t/M_\infty$	k_r - release rate constant that is characteristic to drug-polymer interactions, n - diffusion coefficient that is characteristic to the release mechanism.	[15]
Baker-Lonsdale	$\frac{3}{2}\left[1-(1-F)^{\frac{2}{3}}\right] - F = k_{BL}t$	k_{BL} - release constant	[9]

The CF release profiles from the A and T microparticles are presented in Figure 3.

The values of the release parameters of CF from A, T_1 and T_2 microparticles are displayed in Table III.

The linearity obtained by film diffusion is lower (R^2 = 0.981 - 0.987) than that of particle diffusion (R^2 = 0.993 - 0.998), suggesting that the particle diffusion was the rate-controlling step. The release exponent "n" from Korsmeyer-Peppas equation is situated between 0.46 - 0.61. These values indicate that the delivery mechanism corresponds to anomalous (non-Fickian) diffusion. The values for R^2 (0.991 - 0.994), show that the Baker-Lonsdale model describes well the CF release from A, T_1 and T_2 microparticles.

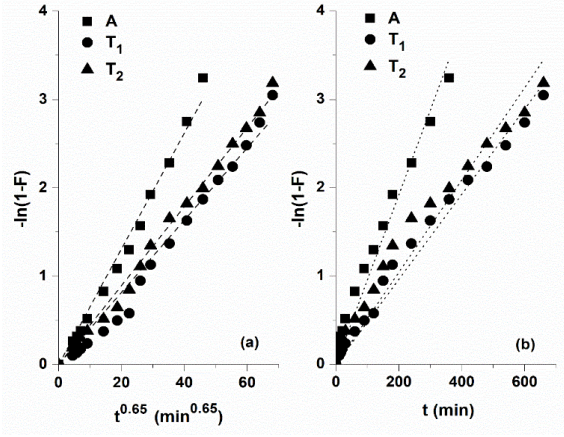

Figure 3.
The particle diffusion model (a) and the film diffusion model (b) for CF release from the A and T microparticles

Table III
Kinetic parameters of CF release process from A, T_1 and T_2 microparticles

Sample code	Boyd model		Higuchi model		Korsmeyer-Peppas model			Baker-Lonsdale model	
	D x 10^{14} (m^2/s)	R^2	k_H ($min^{-1/2}$)	R^2	k_r (min^{-n})	n	R^2	k_{BL} x 10^3 (min^{-1})	R^2
A	11.61	0.995	6.462	0.997	0.072	0.50	0.995	1.100	0.994
T_1	5.928	0.993	3.195	0.993	0.024	0.61	0.994	0.560	0.993
T_2	6.666	0.998	4.027	0.992	0.064	0.46	0.993	0.607	0.991

Antimicrobial activity

To assess the ability of the drug to preserve the antimicrobial activity when is released from coated and uncoated microparticles, the following steps were performed: (a) preparation of control Gram negative and Gram positive bacteria strains; (b) testing the susceptibility of bacterial strains to CF solution by diffusion method; (c) elution of the antibiotic from the drug-microparticle systems with further test of the microparticles as well as for the resulting drug solutions on the bacterial strains. The inhibition zone diameters are presented in Table I. As shown in Table I, the CF is highly effective against Gram positive bacteria. The antimicrobial activity of CF released from microparticles is illustrated in Figure 4. Also, it can be observed that the CF is released from A and T microparticles, retaining their bactericidal ability, as evidenced by the appearance of the inhibition zone around the microparticles. The inhibition zone, of A and T microparticles is lower compared to the free drug, as the amount of CF adsorbed is not completely released in 24 h.

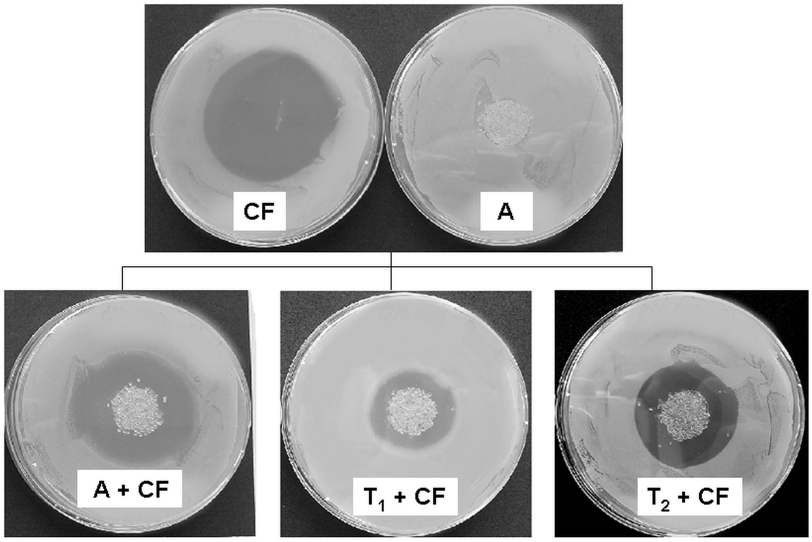

Figure 4.
Antibacterial activity of CF released from A, T_1 and T_2 microparticles against *S. aureus*

Conclusions

The study of the CF release mechanism from coated and uncoated ion exchange resins indicates that polysaccharides coated microparticles lead to the synthesis of the sustained drug release systems that can be used in the oral administration of CF. In addition, the antibiotic retains its bactericidal ability after it has been released from microparticles.

References

1. Atyabi F., Sharma H.L., Mohammad H.A.H., Fell J.T., Controlled drug release from coated floating ion exchange resin beads. *J. Control. Rel.*, 1996; 42(1): 25-28.
2. Bauer A.W., Kirby W.M.M., Sherris J.C., Turk M., Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Pathol.*, 1966; 45(4): 493-496.
3. Bercu E., Sandu I., Aldea H., Vasilache V., Toma V., Interaction of maleic acid copolymers with cationic dyes in aqueous solution. Influence of chemical structure of the partners. *Rev. Chim. (Bucharest)*, 2013; 64(10): 1121-1126.
4. Bercu E., Sandu I., Radu C.D., Vasilache V., Toma V., Interaction of maleic acid copolymers with methylene blue in the presence and absence of melana fibers. *Mat. Plast.*, 2013; 50(3): 215-219.
5. Bhise K., Shaikh S., Bora D., Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier. *AAPS Pharm. Sci. Tech.*, 2008; 9(2): 557-562.
6. Bilandi A., Mishra A.K., Pharmaceutical ion exchange resins - A review. *Int. J. Adv. Pharm.*, 2014; 4(2): 134-145.
7. Boyd G.E., Adamson A.W., Myers L.S., The exchange adsorption of ions from aqueous solutions by organic zeolites. II. *Kinetics. J. Am. Chem. Soc.*, 1947; 69(11): 2836-2848.
8. Burcea Dragomiroiu G.T.A., Popa D.E., Velescu B.Ș., Andrieș A., Ordeanu V., Nicolae A.C., Drăgoi C.M., Bârcă M., Ginghină O., Synthesis, characterization and microbiological activity evaluation of novel hard gelatine capsules with cefaclor and piroxicam. *Farmacia*, 2016; 64(6): 887-895.
9. Costa P., Sousa Lobo J.M., Modelling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.*, 2001; 13(2): 123-133.
10. Costuleanu M., Brailoiu E., Filipeanu C.M., Baltatu O., Slatineanu S., Saila L., Nechifor M., Branisteanu D.D., Effects of liposome-entrapped platelet-activating factor in the isolated rat trachea. *Eur. J. Pharm.*, 1995; 281(1): 89-92.
11. Diaconu D., Tatarciuc M., Vitalariu A., Stamatin O., Foia L., Checherita L., Researches on the influence of the resin cements micro-leakage to the resistance of the composite inlays. *Mat. Plast.*, 2014; 51(3): 271-274.
12. Folin O., A system of blood analysis: Supplement III. A new colorimetric method for the determination of the amino-acid nitrogen in blood. *J. Biol. Chem.*, 1922; 51(2): 377-391.
13. Higuchi W.I., Diffusional Models Useful in Biopharmaceutics: Drug Release Rate Processes. *J. Pharm. Sci.*, 1967; 56(3): 315-324.
14. Jeong S.H., Park H., Development of sustained release fast-disintegrating tablets using various polymer-coated ion exchange resin complexes. *Int. J. Pharm.*, 2008; 353(1-2): 195-204.
15. Korsmeyer R.W., Gurny R., Doelker E., Buri P., Peppas N.A., Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 1983; 15(1): 25-35.
16. Ngawhirunpat T., Goegebakan E., Duangjit S., Akkaramongkolporn P., Kumpugdee-Vollrath M., Controlled release of chlorpheniramine from resonates through surface coating with Eudragit RS 100. *Int. J. Pharm. Pharm.*, 2010; 2(2): 107-112.
17. Pongjanyakul T., Priprem A., Chitropas P., Puttipipatkhachorn S., Effect of polysulfonate resins and direct compression fillers on multiple unit sustained-release dextromethorphan resinate tablets. *AAPS Pharm. Sci. Tech.*, 2005; 30: E190-197.
18. Prabhakar S., Bajpai J., Bajpai A.K., Tiwari A., Cumulative release of cefotaxim from interpenetrating network of poly(vinyl alcohol-g-acrylamide) and chitosan-g-polyacrylamide chains. *Polym. Bull.*, 2014; 71(4): 977-988.
19. Sivaneswari S., Veena D., Sai Sumana P., Subhashree P., Ramya L., Rajalakshmi R., Chandana P.J., Karthikeyan E., Ion exchange resins as drug delivery carriers. *J. Chem. Pharm. Res.*, 2015; 7(4): 1436-1445.
20. Toderescu C.D., Dinu-Pîrvu C., Ghica M.V., Anuța V., Popa D.E., Vlaia L., Lupuliasa D., Influence of formulation variables on ketoprofen diffusion profiles from hidroalcoholic gels. *Farmacia*, 2016, 64(5):728-735.
21. Vasiliu S., Bunia I., Racovita S., Neagu V., Adsorption of cefotaxime sodium salt on polymer coated ion exchange resin microparticles: Kinetics, equilibrium and thermodynamic studies. *Carbohydr. Polym.*, 2011; 85(2): 376-387.
22. Zhu Y.F., Shi J.L., Li Y.S., Chen H.R., Shen W.H., Dong X.P., Storage and release of ibuprofen drug molecules in hollow mesoporous silica spheres with modified pore structure. *Micropor. Mesopor. Mat.*, 2005; 85(1-2): 75-81.