Influence of the composition of hydroxypropyl cellulose/maleic acid-*alt*-styrene copolymer blends on their properties as matrix for drug release

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Abstract. Poly(carboxylic acid)-polysaccharide compositions have been found suitable for obtaining drug formulations with controlled release, most formulations being therapeutically efficacious, stable, and non-irritant. The influence of the characteristics of the aqueous solutions from which the polymer matrix is prepared (i.e. the total concentration of polymer in solutions and the mixing ratio between the partners, hydroxypropyl cellulose, HPC and maleic acid-*alternating*-styrene copolymer, MAc-*alt*-S) on the kinetics of some drugs release in acidic environment (pH = 2) has been followed by ‘*in vitro*’ dissolution tests. It has been established that the kinetics of procaine hydrochloride release from HPC/MAc-*alt*-S matrix depends on its composition; the diffusion exponent, n is close to 0.5 for matrices where one of the components is in large excess and $n \sim 0.02$ for middle composition range. The lower value of diffusion exponent for middle composition range could be caused by the so called ‘burst effect’, therefore the kinetic evaluation is difficult.

Keywords: biopolymers, interpolymeric association, maleic copolymer, drug release

1. Introduction

The design of interpolymeric complexes, which can be used for the immobilization of various drugs, hormones, enzymes, and proteins is of considerable interest because of the possibility of developing different controlled release systems.

Polysaccharides have several advantages as components in drug delivery systems. They are natural or semi-synthetic polymers showing a good biocompatibility with living cells. Blend of polysaccharides with synthetic water-soluble polymers lead to materials with improved physico-chemical and mechanical characteristics [1].

Several reports were devoted to the development of various drug dosage forms based on poly(car-

boxylic acid)-polysaccharide compositions indicating good results in the release of morphine sulfate [2], propranolol hydrochloride [3], carbamazepin [4], model peptide peroxidase [5], lidocaine [6] amoxillin and rifampicin, insulin [7], levomycetin [8, 9], proteins, lactate dehydrogenase [10], phenacetin [11], timolol maleate for ophthalmology application [12], antibacterial agent, ofloxacin [13] and many others. Most formulations were therapeutically efficacious, stable, and nonirritant [14]. The complexes based on poly(acrylic acid), PAA and methyl or hydroxypropyl methyl cellulose demonstrated very good ability to form capsules insoluble in acid media [15].

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Sato and co-workers [16] studied the bioadhesive properties of tablets consisting of hydroxypropyl cellulose (HPC) and carboxyvinyl polymer (CP) using mouse peritoneal membrane containing bleomycin hydrochloride, carboquone, and 5-fluorouracil and they found them favorable for the treatment of foci in the cervical canal.

In a previous work we showed that HPC and MAc-*alt*-S copolymer form interpolymeric complexes, IPC *via* hydrogen bonding interactions between the oxygen of the ether groups of HPC and the OH-groups of the carboxyl groups of MAc-*alt*-S [17, 18], IPC stabilized by hydrophobic interactions between the isopropyl side chain of HPC and the styrene groups of MAc-*alt*-S [19]. The stoichiometry of the interpolymeric complex was estimated to be HPC/MAc-*alt*-S = 40:60 [w/w] independent of the total polymer concentration in the system, c_{pol} . At $c_{pol} = 5 \text{ mg}\cdot\text{ml}^{-1}$, the mixtures with a content of HPC in the initial mixtures between 20 and 60 wt%, phase separate. At $c_{pol} = 10 \text{ mg}\cdot\text{ml}^{-1}$, depending on the mixing ratio between the partners, either a phase separation (in the mixtures with a prevailing content of one of the components) or a gelation (similar mixing ratio between components) occurs. The IR spectra indicated that there is a tendency of the MAc-*alt*-S, independent of the mixing ratio of the components, to accumulate in the gel until it reaches a concentration of around 60 wt%. The maximum concentration of the precipitate in the gel phase is also reached at a mixing ratio between HPC and MAc-*alt*-S of 40/60 that corresponds to the stoichiometry of the complex. At pH lower than 4.5 the HPC/MAc-*alt*-S, IPC becomes water-insoluble [18].

It is well known from membrane science that the morphology and therefore the permeability and transport characteristics highly depend on the way of preparation [20]. Also in mixtures that can form IPCs, it is expected that when one of the components is in large excess, the structure of the interpolymer associations to be different to the mixtures where the ratio between the components is close to the stoichiometry, therefore a different morphology and release profile of the drug is expected.

In this work, it is investigated the influence of the characteristics of the aqueous solutions from which the polymer matrix is prepared, i.e. the total concentration of polymer in solutions and the mixing ratio between the partners, hydroxypropyl cellulose

and maleic acid-*alternating*-styrene copolymer, on the kinetics of the various drugs released in acidic environment (pH = 2). Three drugs with different structure, molecular weight and solubility have been incorporated in the HPC/MAc-*alt*-S matrices, namely: procaine hydrochloride, vanillin and tannic acid.

Procaine hydrochloride, known also as novocaine, it is a local anaesthetic from the amino ester group, mainly used to reduce the pain of intramuscular infections, in stomatology, etc. It acts by constriction of blood vessels determining the bleeding reduction without generating a euphoric state or dependence. Procaine blocks the generation and transmission of the nervous impulses by lowering the membrane permeability to the ions, inhibiting the depolarization and so loosing of pain sensation. Procaine is also the main ingredient in the preparation of the Gerovital H3 known to slow down the aging effects. From theoretical point of view procaine is often used as model drug in many drug release experiments.

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is efficacious for the treatment of chronic hypoacidic gastritis and chronic non-acid gastritis. As well as this receptor inhibition, in the central nervous system, vanillin also influences the craving to consume food. In this context it is supposed that the vanillin is able to increase the concentration of the neurotransmitter serotonin in the brain [21]. Increased brain serotonin concentration, however, leads demonstratively to a reduced craving to consume food.

Tannic acid can be used for medical purposes such as: anti-diarrhoea, hemostats and anti-piles compounds, while together with other related compounds as those containing galic and elagic acids (epigalitaninuri) are inhibitors in HIV replications. It has anti-bacterial properties and is a very beneficial anti-oxidant. In high quantities it slows down the absorption of iron and possibly other trace minerals. The use of tannic acid as an adjuvant therapy for burn wounds has regained interest in present times. In particular, some preclinical and clinical studies indicate that highly purified tannic acids can provide a valuable tool to improve wound healing and to reduce scar tissue formation, it induces a durable, supple crust that did not obstruct the regular outgrowth of epithelium. The assumed hepatotoxicity of tannic acid is questioned [22].

2. Experimental

2.1. Materials

Hydroxypropyl cellulose LF, Klucel™, a food grade polymer, offered by courtesy of Aqualon Company, Hopewell, Virginia has been used. According to the producer specifications, HPC LF has a molecular mass of approximately 100 000 g·mol⁻¹ and a 3.4 moles of substitution [23]. The main chain of HPC consists of glucopyranosyl units linked in (1 → 4) β position. The side substituents are formed by short chains containing from one up to six hydroxypropyl units.

Maleic acid-*alternating*-styrene copolymer (MAc-*alt*-S) was prepared by the hydrolysis of maleic anhydride-*alternating*-styrene copolymer (MA-*alt*-S) in pure water, at 80°C for 4 h. MA-*alt*-S has been synthesized by free radical copolymerizations, in toluene, at 80°C (the detailed synthesis has been

described in ref. [24]). The molecular mass of the MAc-*alt*-S copolymer was calculated based on the molecular mass of the MA-*alt*-S copolymer as being 130 000 g·mol⁻¹, considering that there are no changes in chain length during hydrolysis. The MAc-*alt*-S copolymer is totally water-soluble.

Both samples (HPC and MAc-*alt*-S copolymer) were carefully purified before study by dialysis against water and then freeze dried.

The structure and the water solubility of the used drugs are summarized in Table 1.

Twice-distilled water was used as solvent for all measurements. The pH of the solutions was adjusted at value 2 with diluted HCl solution in twice-distilled water.

Procaine hydrochloride, vanillin and tannic acid were purchased from Sigma Aldrich and used as received.

Table 1. Characteristics of the used drugs

Drug	Structure	Water solubility [mg/l]
Procaine hydrochloride		9450 Easily soluble in cold water*
Vanillin		10000 Soluble in 125 parts water**
Tannic acid		Completely soluble: 1 g/0.35 ml water***

*Science Laboratories, http://www.sciencelab.com/xMSDS-Procaine_hydrochloride-9924715;

Mallinckrodt Baker Inc. Materials safety data sheet

**<http://www.jtbaker.com/msds/englishhtml/v2775.htm>

***<http://www.jtbaker.com/msds/englishhtml/t0065.htm>

2.2. Preparation of the IPC/drug systems

The drugs were incorporated in the polymeric matrix of HPC, MAc-*alt*-S or their mixtures at different mixing ratios, at a weight ratio between matrix and drug of 4 to 1. As MAc-*alt*-S forms a precipitate with procaine hydrochloride, the samples were prepared as followed: the corresponding amount of drug was previously dissolved in the aqueous solution of HPC and then the HPC-drug solution was mixed with the aqueous solution of the MAc-*alt*-S in different mixing ratios. The obtained samples were frozen at -50°C and freeze-dried.

The polymer matrix was prepared at the following weight mixing ratios between HPC and MAc-*alt*-S: 10/90, 40/60, 50/50, 80/20 at two different total polymer concentrations $c_{pol} = 5 \text{ mg/ml}$ and $c_{pol} = 10 \text{ mg/ml}$.

For comparison reasons the same preparation procedure was used to incorporate vanillin and tannic acid in the 40 wt% HPC/60 wt% MAc-*alt*-S matrix at $c_{pol} = 10 \text{ mg/ml}$.

2.3. Sample characterization

A Leitz Wetslar microscope, Germany was used to investigate the fluorescence behaviour of the samples at a magnification of 250 $\times$.

In vitro release studies have been conducted in a standard dissolution set-up. [25] Aliquots of the medium of 1 ml were withdrawn periodically at predetermined time intervals and analyzed using a Hewlett Packard 8540A spectrophotometer. In order to maintain the solution concentration the sample is reintroduced in the circuit after analyzing. The concentrations of the drug were calculated based on previously measured calibration curves for each drug at their specific maximum absorption wavelengths using solutions of known concentrations in the range of loaded drug. The maximum absorption wavelengths at pH = 2 are for procaine hydrochloride at $\lambda_{\max} = 292 \text{ nm}$, vanillin at $\lambda_{\max} = 229 \text{ nm}$ and tannic acid at $\lambda_{\max} = 212 \text{ nm}$.

A simple, semi-empirical equation using Higuchi model was used to analyze kinetically the data regarding the drug release from HPC/MAc-*alt*-S system at the initial stages (approximately 60% fractional release) [26–32] (Equation (1)):

$$\frac{M_t}{M_{\infty}} = k_H t^n \quad (1)$$

where M_t/M_{∞} is the fractional drug release; M_t and M_{∞} are the absolute cumulative amounts of drug released at time t and at infinite time (in this case maximum release amount in the experimental conditions used, at the plateau of the release curves), respectively; k_H is the Higuchi dissolution constant that incorporates the characteristics of the macromolecular network system and the drug, and n is the diffusional exponent, which is an indicative of the transport mechanism.

It has been established that for $n = 0.5$, the release mechanism follows the Fick's law diffusion. A value of $n = 1$, it means that the drug release is independent of time, while when n lies between 0.5 and 1 an anomalous transport is involved [27, 33].

3. Results and discussion

The matrices do not exhibit fluorescence or it is very weak for the MAc-*alt*-S copolymer. In fluorescence microscopy the colour depends on the drug type being brown-to-green for procaine hydrochloride (Figure 1a) transparent-to-light green for vanillin (Figure 1b) and dark-brown-to-dark blue (Figure 1c) for tannic acid and the aspect (Figures 1a to 1c) indicates a homogenous distribution of the drugs in the matrix.

3.1. Influence of the drug type

The release profile of the three drugs, procaine hydrochloride, vanillin, and tannic acid, with different solubility or size from a HPC/MAc-*alt*-S interpolymeric associations matrix was investigated at pH = 2 and $T = 37^{\circ}\text{C}$, an environment that simulate the physiological conditions in the stomach, Figure 2. The matrix has a composition of 40HPC/60MAc-*alt*-S and it was prepared from solutions with $c_{pol} = 5$ and 10 mg/ml. The maximum released quantity at pH = 2 is lower (~38%) when concentration was 5 wt% in respect with the case when concentration was 10% (~58%), while the release time decreased with increasing concentration. These values depend on the composition of HPC/MAc-*alt*-S. The kinetic values are evaluated for approximately 60% of drug released.

Figure 1. a) Microscopical aspects of the 40HPC/60MAc-*alt*-S/procaine hydrochloride system prepared from both a solution with a $c_{pol} = 5$ mg/ml and $c_{pol} = 10$ mg/ml in fluorescence light at various wavelengths of excitation: (I) white light, (II) 380 nm, (III) 410 nm and (IV) 440 nm. b) Microscopical aspects of the 40HPC/60MAc-*alt*-S/vanillin system prepared from a solution with a $c_{pol} = 10$ mg/ml in fluorescence light at various wavelengths of excitation: (I) white light, (II) 380 nm, (III) 410 nm and (IV) 440 nm. c) Microscopical aspects of the 40HPC/60MAc-*alt*-S/tannic acid system prepared from a solution with a $c_{pol} = 10$ mg/ml in fluorescence light at various wavelengths of excitation: (I) white light, (II) 380 nm, (III) 410 nm and (IV) 440 nm

One can notice that procaine hydrochloride is released the fastest from the matrix, while the vanillin was the slowest. The equilibrium values of the fractional release are reached after only 14 minutes for procaine hydrochloride while for tannic acid this value is reached after ca. 47 minutes, and vanillin needs about 190 minutes.

The kinetic data obtained by analysing the drug release profile according to Equation (1) are collected in Table 2.

Tannic acid and vanillin have similar release order, therefore similar transport mechanisms. The data for procaine hydrochloride are difficult to analyse,

Figure 2. Release profiles of procaine hydrochloride, tannic acid, and vanillin from a 40HPC/60MAc-*alt*-S matrix at pH = 2 and $T = 37^{\circ}\text{C}$

Table 2. Values of n and k_H for various drugs released from a 40HPC/60MAc-*alt*-S matrix at pH = 2 and $T = 37^{\circ}\text{C}$

Drug	n	k_H [min^{-n}]
Tannic acid	0.326 ± 0.008	0.384 ± 0.006
Procaine hydrochloride	0.018 ± 0.007	0.920 ± 0.020
Vanillin	0.351 ± 0.003	0.160 ± 0.001

as the release of the drug is very fast. It is characterized by a pronounced ‘burst effect’.

3.2. Influence of matrix composition on the release profile

The fractional release of procaine hydrochloride from matrices with different ratios between HPC and MAc-*alt*-S is shown in Figures 3a and 3b

The release profile of the drug depends both on the ratio between the HPC and MA-*alt*-S and on the total polymer concentration of the solutions used for the preparation of matrix. For example for the matrix containing 80HPC/20MAc-*alt*-S the release time decreases from 175 minutes when the system is prepared from a solution with $c_{pol} = 5$ mg/ml to 100 minutes when it is obtained from $c_{pol} = 10$ mg/ml, while for the matrix 50HPC/50MAc-*alt*-S, these values are 60 and 20 min, respectively. Procaine hydrochloride releases much faster from matrices with a composition close to the stoichiometry of the IPC than from matrices where one of the components are in excess. For example for the matrix containing 40HPC/60MAc-*alt*-S the plateau

Figure 3. Release profiles of procaine hydrochloride from HPC/Mac-alt-S matrix for various ratio between components and different total polymer concentration in the initial solution: (a) $c_{pol} = 5 \text{ mg/ml}$ and (b) $c_{pol} = 10 \text{ mg/ml}$

is reached after about 50 minutes while for 80HPC/20Mac-alt-S it takes about 175 minutes.

The similar values for the release time have been obtained by other authors from different non-covalent hydrogen bonding or polyionic interpolymeric complexes. For example using poly(vinyl alcohol)/poly(acrylic acid), PAA interpolymer complexes release time of mucosal drug delivery was max. 60 or 30 min [23], PAA/Chitosan (100 min) [34], Chitosan/polyethyleneoxide-maleic acid copolymer films (max. 50 min) [32]. In the last case for the polyelectrolyte complex films derived from polyethyleneoxide-maleic acid copolymer, Leong *et al.*, found a release time of ibuprofen of maximum 30 min [31]. When entering into intestine, where $\text{pH} \sim 7.4$ the H-bonding associations between polymer components and those between drug and polymer matrix are destroyed due to the basic pH and release rate and amount of the drug released will be faster and respectively higher [35–37].

The derivatives of the release profile curves, proportional with the rate of drug release, are shown in Figure 4. All show an exponential decrease with time up to 75 min then level off.

In the first 30 minutes, the release rate is very fast for all studied systems, they present the ‘burst effect’ and then a plateau value is reached for the entire investigated duration of the release study. One can notice that the slowest release rates is given by 10HPC/ 90Mac-alt-S matrix, when the mixture is prepared from a solution with a $c_{pol} = 5 \text{ mg/ml}$ and 80HPC/ 20Mac-alt-S matrix, respectively when this is prepared from a solution with a concentration of $c_{pol} = 10 \text{ mg/ml}$.

Figure 4. Derivative curves of the release profiles of procaine hydrochloride from HPC/Mac-alt-S matrix: a) $c_{pol} = 5 \text{ mg/ml}$ and b) $c_{pol} = 10 \text{ mg/ml}$

Kinetic analysis of our data is presented in Figures 5a and 5b and obtained values are given in Table 3.

The kinetics of procaine hydrochloride release from HPC/Mac-alt-S matrices depends on their composition; the diffusion exponent, n is close to

Figure 5. Graph for the evaluation of the release order: a) $c_{pol} = 5$ mg/ml and b) $c_{pol} = 10$ mg/ml

Table 3. Values of n and k_H for various studied cases

Sample	n	k_H [min ⁻ⁿ]
$c_{pol} = 5$ mg/ml		
MAc-alt-S	0.290 ± 0.010	0.177 ± 0.005
80HPC/20MAc-alt-S	0.430 ± 0.010	0.139 ± 0.006
50HPC/50MAc-alt-S	0.250 ± 0.030	0.400 ± 0.030
40HPC/60MAc-alt-S	0.113 ± 0.009	0.650 ± 0.010
10HPC/90MAc-alt-S	0.330 ± 0.050	0.370 ± 0.050
HPC	0.570 ± 0.010	0.100 ± 0.003
$c_{pol} = 10$ mg/ml		
MAc-alt-S	0.290 ± 0.010	0.177 ± 0.005
80HPC/20MAc-alt-S	0.560 ± 0.020	0.083 ± 0.004
50HPC/50MAc-alt-S	0.019 ± 0.006	0.920 ± 0.020
40HPC/60MAc-alt-S	0.018 ± 0.007	0.920 ± 0.020
10HPC/90MAc-alt-S	0.340 ± 0.010	0.250 ± 0.010
HPC	0.570 ± 0.010	0.100 ± 0.030

0.5 for matrix where one of the components is in large excess and $n \sim 0.02$ for middle composition range. An exception is the diffusional exponent for the release from pure MAc-alt-S. As it has been above mentioned, in this case the components form an insoluble complex.

4. Conclusions

The release profile of the drugs from a system that can form interpolymer association is influenced by the mixing ratio between the components and the total polymer concentration the matrix is prepared from. For compositions close to the stoichiometry of the IPC, the release drug rate is faster, while for pure MAc-alt-S it takes the longest to reach the plateau. The total polymer concentration of the HPC/MAc-alt-S solutions influences the procaine delivery release profile especially for mixture

where one of the components is in excess. The delivery rate slows down after around 30–40 minutes.

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