New co-polymer zwitterionic matrices for sustained release of verapamil hydrochloride

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Stable co-polymer [vinyl acetate-co-3-dimethyl(methacryloyloxyethyl)ammonium propane sulfonate, p(VA-co-DMAPS)] latex of different compositions has been synthesized for the first time by emulsifier-free emulsion copolymerization. The unusual »overshooting« behavior of the co-polymer tablets has been explained by the formation of specific clusters from the opposite oriented dipoles-zwitterionic species. The change of their concentration with the DMAPS unit fraction (m_{DMAPS}), pH and ionic strength has been considered responsible for the differences observed in the swelling kinetics. The results obtained prove that m_{DMAPS} and ionic strength could be used to control the swelling degree of the p(VA-co-DMAPS) matrices and their sustained drug delivery. In this way, p(VA-co-DMAPS) matrices could be effectively used to control the sustained release of drugs with basic properties like verapamil hydrochloride from model tablets.

Keywords: co-polymer [vinyl acetate-co-3-dimethyl(methacryloyloxyethyl)ammonium propane sulfonate, emulsifier-free emulsion copolymerization, polyzwitterion, dipole-dipole clusters, swelling degree, matrix tablets, drug delivery

One of the most effective and widely used methods for preparation of modified release systems is the production of matrix tablets, composed of the drug and polymeric carrier, enabling sustained drug release (1). The development of modified release dosage forms for weakly basic drugs is an important technological challenge. Basic drugs are characterized by pH-dependent solubility, which could significantly influence their release in the gastro-intestinal (GI) tract (2, 3). The drug pK_a value defines its ability to be deprotonated in intestinal fluids, as well as its solubility and release rate (4). This is why it is crucial to provide pH-independent release of such drugs (5, 6). Various approaches have been applied: (*i*) addition of organic acids (2, 5); (*ii*) using a combination of a hydrophilic and an enterosolvent polymer (4, 5, 7); (*iii*) polymer, whose swelling behavior depends on pH and the ionic strength of the medium. Polyzwitterions (PZIs) are poly-

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mers whose swelling depends strongly on ionic strength. There are some studies (8, 9) on the synthesis and properties of PZIs as matrices for drug delivery. PZI's self-association determines their interactions with low-molecular zwitterions (10) and surfactants (11) as their physico-mechanical properties (12). Their self-association in an aqueous solution is due to the dipole-dipole interactions, leading to the formation of dipole-dipole clusters (DDC) (the left hand side in Fig. 1) (13–18). These DDCs are destroyed in the presence of a low-molecular-mass salt (LMS) and the PZI macromolecules swell (Fig. 1). This is the essence of the antipolyelectrolyte effect (APE) (11, 15, 16). Upon swelling of the PZI macromolecules, the hydrophobic fragments are associated in hydrophobic cores, coated with a hydrophilic shell, consisting of co-ions and their atmosphere (the right hand side in Fig. 1) (16, 19, 20).

Fig. 1. Reversible destruction of the zwitterionic dipole-dipole clusters (junction points) to single self-neutralizing ionic parts by increasing the ionic strength, and self-association of the PZI macromolecules as amphiphilic structures with a hydrophobic core and a hydrophilic shell after the addition of LMS into aqueous solutions.
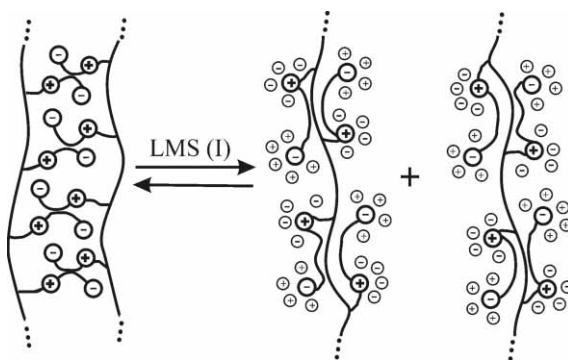
The aim of this study was to evaluate the feasibility of the newly synthesized PZIs latex based on vinyl acetate (VA)-co-3-dimethyl(methacryloyloxyethyl)ammonium propane sulfonate (DMAPS) [p(VA-co-DMAPS)s] as a matrix carrier for verapamil hydrochloride. Thus far, no data about the preparation and application of p(VA-co-DMAPS) as a matrix for drug delivery could be found. Verapamil hydrochloride is an L-type calcium channel blocker with a class IV antiarrythmic activity (21).

EXPERIMENTAL

Materials

Vinyl acetate (VA) (Merck, Germany) was purified by vacuum distillation. 3-Dimethyl(methacryloyloxyethyl)ammonium propane sulfonate (DMAPS) (Merck, Germany) was used as obtained. The initiator potassium peroxide disulfate (KPS, Fluka, Switzerland) was purified by recrystallization from water. Verapamil hydrochloride was supplied by Knoll AG, Germany. Kollidon® SR (polyvinylacetate-polyvinylpyrrolidone, BASF AG, Germany) was used as polymer matrix. Magnesium stearate was used as lubricant (Herwe Chemisch-technische Erzeugnisse, Germany) and silica colloidal dioxide as glidant (Aerosil 200) (Degusa, Germany).

Methods

Emulsifier-free emulsion co-polymerization of VA and DMAPS. – Emulsifier-free emulsion copolymerization (EFC) of VA and DMAPS was performed in water using the method described in our previous paper (22). The VA/DMAPS mole ratios in the monomer feed were 90/10 (co-polymer 1), 85/15 (co-polymer 2), 80/20 (co-polymer 3) and 70/30 (co-polymer 4). p(VA-co-DMAPS)s were obtained as white porous powders, insoluble in water and in most organic solvents.

Elemental analysis. – The co-polymer composition was determined by nitrogen analysis using a Vario EL III elemental analyzer (Elementar Analysensysteme GmbH, Germany).

Swelling kinetics of p(VA-co-DMAPS). – The lyophilized co-polymers 1–4 were molded into tablets of 7 mm diameter and 2 mm height. The swelling degree (Q) of the co-polymer samples was determined in an aqueous solution (pH 1.2 – 0.1 mol L^{-1} HCl) and in a phosphate buffer solution (PBS) (pH 6.8 – $Na_2HPO_4 \times 2H_2O + KH_2PO_4$) at 37 °C. The ionic strength at pH 1.2 was 0.100 mol L^{-1} and 0.136 mol L^{-1} in PBS. The mass of dry samples was determined after drying in a vacuum oven (60 °C) to constant mass. The dried co-polymer tablets were placed into 20-mL aqueous solution (pH 1.2) and in PBS (pH 6.8). The mass of wet samples was determined after removal of surface water by blotting with filter paper. For each co-polymer, the average value of Q was calculated from three tablets.

Preparation of matrix tablets. – Sustained release (SR) tablets were prepared using polymer carriers: (*i*) p(VA-co-DMAPS); (*ii*) Kollidon® SR. All tablets contained 120 mg verapamil hydrochloride, 125 mg co-polymers 1 to 4 or Kollidon® SR, 1% (*m/m*) magnesium stearate and 1% (*m/m*) silica colloidal dioxide. The Kollidon® SR matrix tablets were prepared by the method of direct compression, and p(VA-co-DMAPS) matrix tablets were prepared by wet granulation.

Preparation of direct compression matrix tablets. – Direct compression matrix tablets were prepared using the polymer carrier Kollidon® SR with verapamil hydrochloride as follows: verapamil hydrochloride and Kollidon® SR were dry mixed in a HLSH2-6 high shear mixing granulator (Bamtri, China) for 25 min at 300 rpm. Magnesium stearate and silica colloidal dioxide (Aerosil 200) were added and mixed for another 5 min. The blend obtained was tableted to 250 mg using a set of 9 mm-diameter standard concave punches and a single punch tablet press (EK 0, Korsch, Germany).

Preparation of wet granulation matrix tablets. – Wet granulated tablets with verapamil hydrochloride and p(VA-co-DMAPS) were prepared by dry mixing of both compounds using a HLSH2-6 high shear mixing granulator (Bamtri, China) for 25 min at 300 rpm. Isopropanol was added as a wetting agent dropwise under stirring at 500 rpm. The mixture obtained was granulated and passed through a 1500-μm sieve. The granules obtained were spread evenly on a tray and dried for 8 h at 40 °C. Each granule formulation was passed through an 800-μm sieve and dry-blended with magnesium stearate and silica colloidal dioxide (Aerosil 200) for 5 min. The resultant blend was tableted as stated for direct compression matrix tablets.

In vitro *drug dissolution studies*. – Drug release profiles were evaluated using a dissolution test apparatus (Erweka DT 600, Germany). The USP paddle method was applied (23). The test was carried out at a paddle rotation speed of 50 rpm, in 900 mL dissolution medium maintained at 37 ± 0.5 °C at three different pH values: (*i*) pH 1.2; (*ii*) pH 6.8; (*iii*) throughout the release experiments, pH was changed in order to evaluate the effect of pH (ionic strength) modification. For this purpose, the tablets were first immersed in 0.1 mol L^{-1} HCl solution (pH 1.2) for 2 h and were then transferred into PBS solution (pH 6.8) for 6 h. Five mL aliquots of dissolution media were withdrawn at selected intervals up to 8 h. Each sample was filtered through a 0.45-μm membrane filter (Sartorius cellulose acetate filter, Germany). The quantity of the drug in the sample solution was determined by UV spectroscopy (absorbance at 278 ± 2 nm) using a Hewlett-Packard 8452 A Diode Array spectrophotometer (USA). The cumulative percentage of drug release was calculated and the average of six determinations was used in the data analysis.

RESULTS AND DISCUSSION

Characterization of the p(VA-co-DMAPS) co-polymers

A new p(VA-co-DMAPS) latex with different compositions has been synthesized by EFC. The preliminary screening of p(VA-co-DMAPS) matrices suggested that only four co-polymer compositions (1–4) exhibit the desired verapamil hydrochloride release. Their characteristics are given in Table I. The results show that the co-polymers are enriched in DMAPS units. One of the most significant results obtained is that although no emulsifier was used, the obtained microspheres were of small average diameter (200 nm). This is especially important for the performance of these co-polymers as sustained drug delivery matrices. This effect could be related to the favourable co-monomer hydrophobic-hydrophilic ratio in the copolymerization mixture.

Swelling behavior of p(VA-co-DMAPS) matrices

In general, *Q* is related to the osmotic pressure, cross-linking density and co-polymer affinity to adsorb water (24). Being a zwitterionic monomer, DMAPS has a zero total

Table I. *Characteristics of the synthesized co-polymers*[a]

Co-polymer No.	Monomer feed (VA, mol %)	Elemental analysis N (%)	Co-polymer composition (VA, mol %)
1	90	1.73	86.03
2	85	2.30	80.00
3	80	2.74	73.00
4	70	2.92	67.99

[a] Total monomer concentration: 7.5 x 10^{-2} mol L^{-1}; [KPS]: 1% (*m/m*); solvent: distilled water; temperature: 49 ± 1 °C; VA – vinylacetate.

monomer charge, so the main effect on Q is the affinity to water. The ability of the p(VA-co-DMAPS) matrix to swell in aqueous solutions depends on the mole fraction of DMAPS units in the co-polymer (m_{DMAPS}), pH (ionic strength). It could be assumed that by varying m_{DMAPS} and ionic strength, it should be possible not only to change the swelling degree of p(VA-co-DMAPS)s, but also to control the rate of drug release in the GI tract.

The Q values of p(VA-co-DMAPS) matrices as a function of time at pH 1.2 and 6.8 at 37 °C are shown in Figs. 2a and b. As it is seen in Figs. 2a and b, Q values increase rapidly and then decrease. This process is more clearly pronounced at pH 1.2. This phenomenon is known as »overshooting« and is attributed to the slow macromolecular relaxation (24). From the dependencies in Figs. 2a and b, it can be clearly seen that the »overshooting« phenomenon has been observed by all co-polymers. At a high diffusion rate of both water and LMS molecules in the co-polymer matrix, the large macromolecules have not enough time to rearrange to the equilibrium structural organization, specific to each co-polymer. Large numbers of intermolecular bonds are destroyed during this fast diffusion and their recovery to reach the above mentioned equilibrium structural organization leads to a decrease in the Q value. The DDC (the left hand side in Fig. 1) represents the physical nodes between different fragments of the co-polymer macromolecule or between different macromolecules. The relationship between these junctions, which could be reversibly destroyed to single self-neutralizing ionic pairs (IPs) (Fig. 1), and the »overshooting« phenomenon is quite interesting.

At the beginning (before immersion of the co-polymer tablets 1–4 into an aqueous solution), most of the zwitterionic units (ZIs) in the co-polymer tablets 1–4 are in IPs form, while the small number of DDC act as physical nodes. When the co-polymer tablets are immersed into an aqueous solution, IPs are first hydrated, since they are more evenly distributed and more accessible. The VA units are hydrophobic and not hydrated. Water molecules diffuse at a higher rate because of the high initial concentration gradient. The hydrated IPs form a phase (hydrophilic phase) separated from the total mass of VA hydrophobic units. The process of two-phase formation, hydrophobic (VA units) and
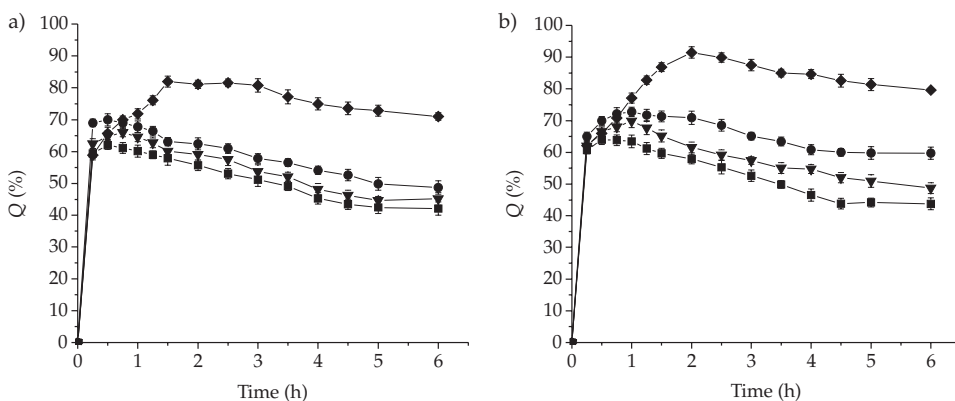

Fig. 2. Swelling kinetics of p(VA-co-DMAPS) matrices at pH: a) 1.2 and b) pH 6.8 (37 °C); (■) co-polymer 1; (▼) co-polymer 2; (●) co-polymer 3; (♦) co-polymer 4 (mean ± SD, n = 3).

hydrophilic (hydrated IPs) is hindered by DDC-physical nodes. Therefore, the effect of both ionic strength and m_{DMAPS} on the DDC destruction to IPs (Fig. 1) also affects the »overshooting« phenomenon.

The dependencies in Figs. 2a and b and the data from Table II show that at pH 1.2 the Q_{max} values for all co-polymers are lower than at pH 6.8. The higher ionic strength at pH 6.8 (ionic strength = 0.136 mol L^{-1}) contributes to easier destruction of DDC to IPs (Fig. 1), resulting in higher swelling of the p(VA-co-DMAPS) matrices.

Table II. Q_{max} and relaxation time (t_{max}) values of p(VA-co-DMAPS) matrices[a]

Co-polymer No.	Q_{max} at pH 1.2 (%)	Q_{max} at pH 6.8 (%)	t_{max} at pH 1.2 (h)	t_{max} at pH 6.8 (h)
1	62.05	64.01	0.50	0.5
2	65.98	69.88	0.45	1.0
3	69.95	72.78	0.50	1.0
4	81.97	91.46	1.50	2.0

[a] Temperature: 37 °C

Despite the relatively narrow limits of m_{DMAPS}, the changes of its values affect the swelling kinetics of the p(VA-co-DMAPS) matrices. From Figs. 2a and b, it can be seen that with increasing m_{DMAPS} in co-polymers 1–4, the Q_{max} values also increase at both pH values. The plot for co-polymer 4 at both pH values is quite different from the plots obtained for co-polymers 1 to 3. The action of m_{DMAPS} is twofold: (*i*) it enhances the hydrophilicity of the co-polymer matrix (especially for co-polymer 4, exhibiting the highest m_{DMAPS} value); (*ii*) increases DDC density, size and precision in the co-polymer matrices 2, 3 and 4. For co-polymer 4 (highest m_{DMAPS}), a markedly extended relaxation time (t_{max}) was observed at both pH 1.2 and 6.8 (Table II). This could be attributed to the higher DDC concentration (in co-polymer 4), their slower destruction and probably slower relaxation.

The Q_{max} value is reached after the microphase separation into hydrophobic and hydrophilic parts has taken place. In the hydrophilic (swollen) part of the co-polymer matrix, the IPs concentration increases, which helps the equilibrium shift to the left (Fig. 1), leading to the formation of new physical nodes in the aqueous (swollen) phase, contributing to its shrinkage – the Q value decreases. Furthermore, the lower the ionic strength, the higher the probability of physical nodes creation; the p(VA-co-DMAPS) matrices shrink more and the Q value decrease is more strongly pronounces. These results were obtained at pH 1.2 (ionic strength = 0.100 mol L^{-1}) (Fig. 2a).

The dependencies in Figs. 2a and b, showing the swelling behavior of p(VA-co-DMAPS) matrices, could be explained as follows. The swelling kinetics of p(VA-co-DMAPS) matrices shows a close relation between the »overshooting« phenomenon and DDC formation, typical of co-polymers with zwitterionic units. Perhaps, the influence of the DDC reversible destruction (Fig. 1) on the specific »overshooting« phenomenon is the-

Table III. p(VA-co-DMAPS) and Kollidon® SR tablet composition

Co-polymer No.	Verapamil hydro-chloride mass (mg)	Co-polymer mass (mg)	Silica colloidal dioxide (%, *m/m*)	Magnesium stearate (%, *m/m*)
1	120	125	1	1
2	120	125	1	1
3	120	125	1	1
4	120	125	1	1
Kollidon® SR	120	125	1	1

reby explained for the first time. The above discussed results reveal that m_{DMAPS} and ionic strength (LMS) affect the reversible equilibrium between DDC and IPs (Fig. 1), defining the Q value.

Release of verapamil hydrochloride from tablets with p(VA-co-DMAPS) matrices

Verapamil hydrochloride, characterized by pK_a = 8.6 (25), was chosen as a model drug. It is soluble in water (82 mg mL^{-1} at pH 2.32, 11 mg mL^{-1} at pH 6.76 (26), and practically insoluble in basic solutions (27).

The composition of the p(VA-co-DMAPS)-based tablet formulations studied is shown in Table III. Kollidon® SR-based model formulations were used as reference.

The release profiles of verapamil hydrochloride from the model p(VA-co-DMAPS) tablets at pH 1.2 and pH 6.8 are presented in Figs. 3a and b. The dependencies show the influence of the m_{DMAPS} values on the release profiles after 6 h. The amount of drug released from co-polymer 4-based formulation at pH 1.2 reached 73.4% after 8 h. This result suggests that the high solubility of verapamil hydrochloride at pH 1.2 leads to a higher release rate despite the lower swelling degree of the p(VA-co-DMAPS) matrices at this pH.

At pH 6.8 (Fig. 3b), the release rate could be expected to be markedly lower. However, the results obtained (Fig. 3b) do not confirm this assumption – after 8 h the amount of drug released from co-polymer 4-based matrices reached 51.7%. This result could be explained by the effect of APE (the presence of LMS and higher ionic strength at pH 6.8) on the swelling degree of p(VA-co-DMAPS) matrices. This high swelling degree compensates for the very low solubility of verapamil hydrochloride at this pH.

The drug release profiles from the four model p(VA-co-DMAPS) matrices and the matrix based on Kollidon® SR were investigated under varying pH values as well (Fig. 4). First, both p(VA-co-DMAPS) and Kollidon® SR tablets were put for 2 h in dissolution media with pH 1.2, then for 6 h at pH 6.8. The results obtained (Fig. 4), show that with increasing m_{DMAPS} in the p(VA-co-DMAPS) matrices, the verapamil hydrochloride release rate was also increased. The difference between the release rates for co-polymers 1 and 4 after 8 h is about 6.5%. The m_{DMAPS} increase in p(VA-co-DMAPS) tablets results in enhanced possibility of DDC destruction as well as a higher swelling rate. The equilibrium in Fig. 1 is shifted to IPs, which permits faster diffusion of verapamil hydrochlo-
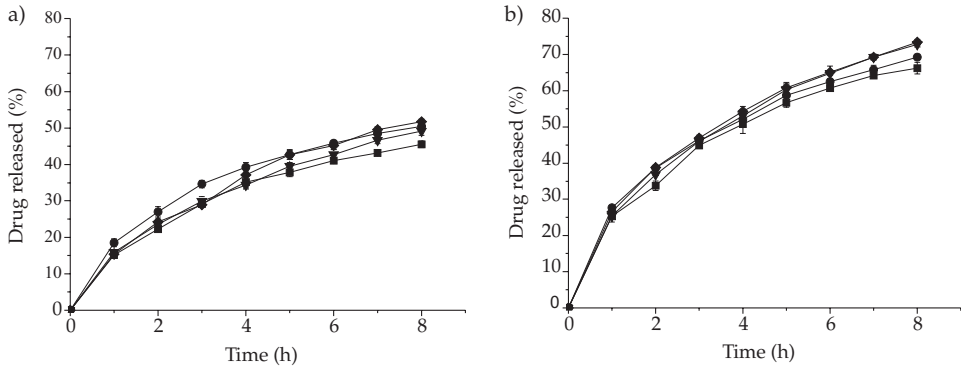
a)

b)

Fig. 3. Release kinetics of verapamil hydrochloride from model p(VA-co-DMAPS) tablets at pH: a) 1.2 and b) pH 6.8 (37 °C); (■) co-polymer 1; (▼) co-polymer 2; (●) co-polymer 3; (♦) co-polymer 4 (mean ± SD, n = 6).

ride from the gel structure. Hence, the release profile of verapamil hydrochloride can be modified just by varying m_{DMAPS} in p(VA-co-DMAPS)s.

The results presented in Fig. 4 clearly indicate that all p(VA-co-DMAPS) matrices release verapamil hydrochloride at higher rates compared to Kollidon® SR. After 8 h, matrices based on p(VA-co-DMAPS) released 49.8% to 56.1% verapamil hydrochloride, while the amount of released drug from Kollidon® SR matrix was only 39.5%. The difference in the amount of released verapamil hydrochloride after 8 h from Kollidon® SR matrix and co-polymer 4 (higher m_{DMAPS}) is more than 16% while in case of co-polymer 1, this difference is only 10%. These values could be attributed mainly to the PZI character of the p(VA-co-DMAPS) matrix. In the case of Kollidon® SR matrix [a physical mixture of poly(VA) and poly(*N*-vinyl pyrrolidone) poly(NVP)], the swelling behavior is pH-independent. However, this behavior of the Kollidon® SR matrix (without addition of subsidiary materials like enterosolvent polymers and organic acids) is not favorable in the case of verapamil hydrochloride and this is the reason for its low release rate. The pre-
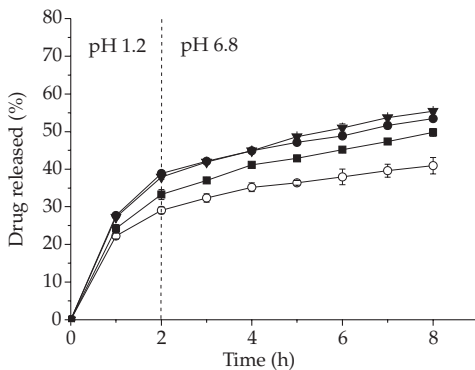

Fig. 4. Release kinetics of verapamil hydrochloride from model p(VA-co-DMAPS) tablets and from Kollidon® SR at pH 1.2 (the first 2 hours) and at pH 6.8 (after the second hour) (37 °C); (■) co-polymer 1; (▼) co-polymer 2; (●) co-polymer 3; (♦) co-polymer 4; (O) Kollidon® SR (mean ± SD, n = 6).

sented results demonstrate the advantages of the newly synthesized p(VA-co-DMAPS) matrices. Due to their specific zwitterionic structure, higher drug release in the GI tract could be achieved.

According to Streubel *et al.* (5) ethyl cellulose polymer matrices released 34% verapamil hydrochloride after 8 h at pH 6.8. The same authors explained that formulations based on the intensively swelling HPMC in 1:1 ratio (*m/m*) to lactose in these conditions released only 17% of the drug after 8 h. The comparison of these release profiles with our results shows that p(VA-co-DMAPS)s, especially those with higher m_{DMAPS} (co-polymers 3 and 4), are effective and suitable matrices for incorporation of verapamil hydrochloride and possibly of other drugs with similar physicochemical properties.

CONCLUSIONS

It has been established that the newly synthesized p(VA-co-DMAPS)s are promising candidates for matrix carriers of verapamil hydrochloride and possibly of other drugs with basic properties. Specific structure organization of a p(VA-co-DMAPS)s permits to solve the problems associated with the release behavior and makes them advantageous over other polymer matrices.

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S A Ž E T A K

Novi kopolimerni zwitterionski matriksi za polagano oslobađanje verapamil hidroklorida

BISTRA KOSTOVA i DIMITAR RACHEV

Metodom emulzijske polimerizacije sintetiziran je novi stabilni kopolimer [vinil acetat-ko-3-dimetil(metakriloiloksietill)amonijev propan sulfonat, p(VA-co-DMAPS)] lateks promjenjivog sastava. Neobično »pretjerano« ponašanje tableta pripravljenih iz tog kopolimera objašnjava se stvaranjem specifičnih klastera suprotno orijentiranih dipola – zwitterionskih specija. Proučavan je utjecaj njihovih koncentracija s udjelom DMAPS jedinica (m_{DMAPS}), pH i ionskom jakosti na kinetiku bubrenja. Dobiveni rezultati dokazuju da se promjenom m_{DMAPS} i ionske jakosti može kontrolirati stupanj bubrenja p(VA-co-DMAPS) matriksa i oslobađanje verapamil hidroklorida iz tableta pa se ti matriksi mogu upotrijebiti za polagano oslobađanje bazičnih lijekova srodnih verapamilu.

Ključne riječi: kopolimer [vinil acetat-ko-3-dimetil(metakriloiloksietill)amonijev propan sulfonat, emulzijska kopolimerizacija bez emulgatora, polizwitterion, dipol-dipol klasteri, bubrenje, matriksne tablete, isporuka lijekova

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