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Development and bioadhesive properties of chitosan-ethylcellulose microspheres for nasal delivery

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Abstract

Loratadine-loaded microspheres were prepared by spray-drying of dispersions, emulsions and suspensions differing in polymeric composition and solvents used. Conventional microspheres were obtained by spray-drying of dispersions composed of chitosan (CM) as only polymer, while composed microspheres were obtained by spray-drying of two-phase systems composed of chitosan and ethylcellulose (EC). Microspheres differed in EC/CM weight ratio (0:1, 1:2 and 1:3) and in loratadine/polymers weight ratio (1:6 and 1:8).

The entrapment efficiencies were between 67.9 and 86.1%; less loratadine was entrapped as polymer/drug ratio decreased. In comparison to one-phase systems composed of CM as only polymer, spray-drying of two-phase systems composed of both, CM and EC resulted in improved loratadine entrapment (80.1–86.1%). All microspheres were positively charged, indicating the presence of chitosan at the surface, regardless of the drug content and the type of spray-dried system. The highest zeta-potential was measured for loratadine-free conventional microspheres, consisting of chitosan only (32.7 ± 1.3 mV). Tensile studies showed that both, EC/CM ratio and the type of spray-dried system influenced the bioadhesive properties of the microspheres in a way that the microspheres with higher chitosan content were more bioadhesive and microspheres prepared from suspensions were more bioadhesive than those prepared from emulsions, regardless of the same polymeric composition. The results suggested that the spray-drying method is useful to produce bioadhesive loratadine-loaded microspheres.

Keywords: Chitosan; Ethylcellulose; Microspheres; Nasal delivery; Bioadhesion; Drug delivery systems

1. Introduction

Microspheres, in general, are investigated for targeted and controlled release drug delivery. A polymeric device allows for slow, controlled, and predictable drug release over a period of time and hence reduces the overall amount of drug needed (Illum, 2003). In nasal

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drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa (Vasir et al., 2003).

The aim of this work was to develop bioadhesive microspheres for nasal delivery of lipophilic model drug loratadine. Loratadine is a second-generation antihistamine that is rapidly absorbed after oral administration and reaches peak plasma levels within 1–2 h. It undergoes extensive first-pass metabolism in the liver. Topical antihistamines are as effective as oral and may be more beneficial in relieving nasal obstruction. Although there is little difference with regard to speed of onset of clinical activity, unvanted effects are reduced and the preparations can be prescribed without risk of interactions with any concomitant medications (Trigg and Davies, 1996). Polymers used for the microsphere preparation were chitosan (CM) and ethylcellulose (EC).

Chitosan is a biocompatible and biodegradable polycationic polymer with low toxicity. The positive charges on the chitosan polymer can give rise to a strong electrostatic interaction with mucus or a negatively charged mucosal surface. This is to provide a longer contact time for drug transport across the nasal membrane, before the formulation is cleared by the mucociliary clearance mechanism (Singla and Chawla, 2001). Thus, investigation of the zeta-potential is an important part of the microsphere characterization, as the zeta-potential has a substantial influence on the adhesion of drug delivery systems onto biological surfaces (Berthold et al., 1996).

Microspheres were produced by spray-drying. The drug encapsulation efficiency, the size and morphology, the zeta-potential and bioadhesive properties were studied as a function of type of spray-dried system, polymeric composition and the drug content.

2. Materials and methods

2.1. Reagents and chemicals

The following materials were used as received: Chitosan of medium molecular weight, CM (M_r 400 000; deacetylation degree 83.5%, Fluka, Buchs, Switzerland), ethylcellulose, EC (Sigma, St. Louis, USA), loratadine (Pliva d.d., Zagreb, Croatia). Buffer substances and all other chemicals or solvents used were of analytical grade and purchased from Kemika (Croatia).

2.2. Preparation of microspheres

Drug-free and drug-loaded microspheres based on chitosan were prepared by spray-drying of simple dispersion, oil-in-water (O/W) emulsion and suspension, using a Büchi 190 mini spray drier (Flawil, Switzerland) with a standard 0.5 mm nozzle. The liquid was fed to the nozzle with peristaltic pump, atomised by the force of the compressed air and blown together with a hot air to the chamber where the solvent in the droplets was evaporated. The dry product was then collected in a collection bottle. The drying conditions were as follows: spray flow rate of 0.25 l h^{-1}, compressed air flow rate of 700 Nl h^{-1}, inlet air temperature of 135 °C and outlet air temperature of 85 °C.

For the simple dispersion system chitosan was solubilized in 0.5% acetic acid solution at 1% (w/v) concentration. Loratadine was dissolved at two different concentrations (1 and 0.75%, w/v) in 96% ethanol. These solutions were than mixed with chitosan solution in a 1:6 (v/v) ratio and subjected to spray-drying under process conditions described above. In that way, two different polymer/drug ratios (6:1 and 8:1, w/w) were obtained for the preparation of loratadine-loaded chitosan microspheres.

For the O/W emulsion system, the oil phase consisted of EC dissolved in ethyl acetate (4%, w/v), and chitosan solution (1%, w/v) in 0.5% (v/v) acetic acid represented water phase. Loratadine was dissolved in oil phase at the concentration of 2% (w/v), resulting in loratadine/EC ratio of 1:2 (w/w).

Emulsions were prepared by ultrasonic homogenisation (Cole-Parmer 4710 Series, USA; 2×30 s, at 60 μW, with 30 s intervals) of the oil phase and the part of the water phase, and were later diluted with the rest of the water phase. O/W emulsions prepared differed in volume oil/water phase ratios that were 1:8 and 1:12. Theoretical polymer/drug ratios were 6:1 and 8:1 (w/w), respectively.

Emulsions were stirred for 10 or 120 min using magnetic stirrer (900 rpm) and were then subjected to spray-

Table 1
The type and composition of spray-dried systems in the preparation of loratadine-loaded microspheres

	Type of spray-dried system					
	Dispersion		Emulsion		Suspension	
	LD1[a]	LD2[a]	LE1[a]	LE2[a]	LS1[a]	LS2[a]
Conc. CM (w/v, %)	1	1	1	1	1	1
Conc. EC (w/v, %)			4	4	4	4
EC/CM (w/w)	0/1	0/1	1/2	1/3	1/2	1/3
Polymers/loratadine (w/w)	6/1	8/1	6/1	8/1	6/1	8/1

[a] Sample.

drying under process conditions described above. By employing prolonged period of stirring (120 min) suspensions were formed, due to partial evaporation of ethyl acetate from the oil phase, and consequent partial precipitations of ethylcellulose.

Loratadine-free (empty) microspheres were prepared following the same procedure as for loratadine-loaded microspheres omitting loratadine.

Table 1 report the type and composition of spray-dried systems used for the preparation of loratadine-loaded microspheres.

2.3. Scanning electron microscopy (SEM)

The shape and surface characteristics of the microspheres were observed by scanning electron microscopy. The microspheres were sputter-coated with Au/Pd using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Philips 500, Eindhoven) at 10 kV accelerating voltage.

2.4. Particle size analysis

A microscopical image analysis technique for determination of microsphere size distribution was applied. The morphology and particle size distributions (based on the numbers of particles) were determined in an Olympus BH-2 microscope equipped with a camera (CCD Camera ICD-42E; Ikegami Tsushinki Co., Japan) and computer-controlled image analysis system (Optomax V, Cambridge). The microspheres were dispersed on a microscope slide. A microscopical field is scanned by video camera. The images of the scanned fields are digitalised and analysed by the software (Optomax V Software, Cambridge). In all measurements at least 3000 particles were examined.

2.5. Determination of the drug loading

Loratadine was extracted from the microspheres with mixture of 0.1 M HCl and 96% ethanol (3:2, v/v; 15 ml) under sonication in ultrasonic bath (Branson B1210E-DTH, Danbury, USA). The samples were filtered and the amount of loratadine was determined spectrophotometrically ($\lambda = 247$ nm; Ultrospec Plus, Pharmacia LKB). Preliminary studies showed that the presence of dissolved polymers did not interfere with loratadine absorbance at 247 nm.

2.6. Zeta-potential of the microspheres

Zeta-potential of the microspheres prepared was determined by photon-correlation spectroscopy (Zetasizer 3000 HSA, Malvern Instruments) in 10 mM NaCl solution (pH 6.7) at 25 °C.

2.7. Tensile studies

Sixty milligrams of drug-loaded microspheres as well as drug-free microspheres were compressed into 5 mm a diameter flat-faced test disc, which was attached to a precise torsion balance. A piece of porcine nasal mucosa (2 cm^2) was mounted on the glass dish and placed on a mobile platform. The discs and the mucosal surfaces were brought in contact in simulated nasal fluid (SNES; an aqueous solution containing 8.77 g NaCl, 2.98 g KCl and 0.59 g $CaCl_2$ per litre) pH 6.3 at 22 °C. The value for the force of detachment was measured as a function of displacement, by lowering the mobile platform at the constant rate of 2 mm min^{-1} until total separation of the components was achieved. The work of fracture, equivalent to the total work of bioadhesion (TWA)

was calculated as the area under the force/distance curve.

2.8. Statistical analysis

Statistical data analyses were performed using the Student's *t*-test with $P < 0.05$ as the minimal level of significance. Calculations were performed with the GraphPad Prism program (GraphPad Software, Inc., San Diego, USA; www.graphpad.com).

3. Results and discussion

3.1. Characterisation of microspheres

Six samples of loratadine-loaded, and corresponding loratadine-free microspheres were prepared by spray-drying of three different types of systems: simple dispersions, emulsions and suspensions. Suspensions were prepared out of emulsions, employing longer stirring time (120 min). Thus, partial extraction and evaporation of ethyl acetate from the inner oil phase was obtained, which resulted in partial ethylcellulose precipitation. The main characteristics of spray-dried systems and microspheres prepared are shown in Tables 2 and 3. Microspheres differed in EC/CM weight ratio (0:1, 1:2 and 1:3) and in case of loratadine-loaded microspheres, in loratadine/polymers weight ratio (1:6 and 1:8).

The yields of spray-dried microspheres were relatively high (30–54%), considering the preparation method employed. Similar yields were already reported for this method (Giunchedi et al., 2000). The loss of material during spray-drying process is mostly due to powder adhering to the cyclone walls (Pavanetto et al., 1992). In this work, low values of yields could also be attributed to the small amount of materials processed in each batch (1 g), as well as to the loss of the smallest and lightest particles through the exhaust of the spray-dryer apparatus as it is not equipped with a trap to recover the lighter and smaller particles (Giunchedi et al., 2002).

As shown in Table 2, the yields of spray-dried microspheres depended on their composition. Thus, higher yields were obtained for the conventional microspheres prepared by spray-drying of simple dispersions (samples LD1 and LD2), than for the composed microspheres prepared by emulsion and suspension spray-drying (samples LE1, LE2, LS1 and LS2). Emulsions

Table 2
The comparison of the main characteristics of loratadine-loaded and loratadine-free microspheres

Type of the spray-dried system	Polymer/drug ratio (w/w)							
	6:1 (EC:CM = 1:2)[a]				8:1 (EC:CM = 1:3)[a]			
	Sample	Yield (%)[b]	Zeta-potential (mV)[c]	Diameter (μm)	Sample	Yield (%)[b]	Zeta-potential (mV)[c]	Diameter (μm)
Dispersion	LD1[d]	40.3 ± 2.1 (54.0 ± 0.5)	27.3 ± 0.8** (32.7 ± 1.3)	3.23 ± 1.33 (2.93 ± 0.99)	LD2[d]	50.2 ± 1.9 (54.0 ± 0.5)	27.5 ± 1.3** (32.7 ± 1.3)	3.24 ± 1.46 (2.93 ± 0.99)
Emulsion	LE1	39.1 ± 2.0 (42.3 ± 1.2)	26.6 ± 1.4 (27.5 ± 1.7)*	3.32 ± 1.42 (3.20 ± 1.33)	LE2	41.6 ± 1.2 (47.1 ± 2.2)	27.5 ± 1.2 (29.1 ± 1.6)*	3.38 ± 1.33 (3.26 ± 1.24)
Suspension	LS1	37.7 ± 1.9 (40.3 ± 1.6)	27.2 ± 1.6 (27.0 ± 1.1)*	3.48 ± 1.48 (3.33 ± 1.28)	LS2	40.0 ± 1.5 (46.5 ± 1.3)	28.1 ± 2.0 (31.4 ± 1.9)	3.50 ± 1.53 (3.47 ± 1.51)

Values in brackets refer to loratadine-free microspheres. Values are mean ± S.D. ($n = 3$).
[a] EC:CM: weight ratio of EC dissolved in inner oil phase and chitosan dissolved in outer water phase of O/W emulsions.
[b] Product weight/total weight of starting components of the spay-dried system × 100.
[c] Zeta-potential was measured in 10 mM NaCl solution at 25 °C (pH 6.7).
[d] Samples with chitosan as the only polymer in composition.
* $P < 0.05$, compared to LD microspheres.
** $P < 0.05$, compared to loratadine-free microspheres.

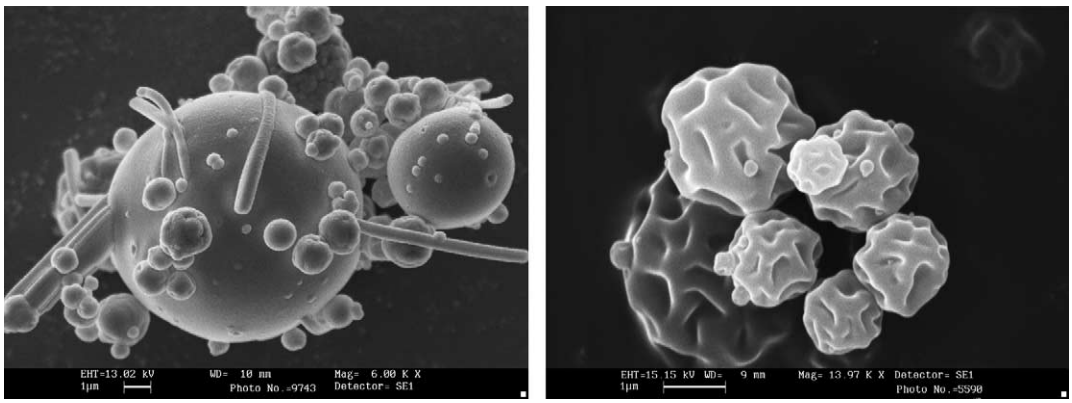

Fig. 1. SEM micrographs of loratadine-loaded (left) and loratadine-free (right) microspheres (LD2) prepared by spray-drying of simple dispersion.

and suspensions differed from simple dispersions in polymeric composition, as emulsions and suspensions were composed of chitosan and ethylcellulose, while simple dispersions were composed of chitosan only. It may be concluded that lower yields for the preparation of composed microspheres were due to EC inducement. Yields of the loratadine-free microspheres were 3–14% higher than yields of the corresponding loratadine-loaded microspheres, for all types of spray-dried systems. Such difference in yields between loratadine-free and loratadine-loaded microspheres could be described as insignificant, since the production yield was mostly determined by technological characteristics of the method employed, as described above (Giunchedi et al., 2002).

SEM analysis of the samples revealed that all microspheres prepared were spherical in shape. Fig. 1 presents morphology of conventional loratadine-loaded microspheres (sample LD2), with crystals of loratadine visible at the surface.

SEM images of the composed, loratadine-loaded and loratadine-free microspheres, prepared by spray-drying of two-phase systems (emulsions and suspensions) are shown in Fig. 2. The pores at the surface are suspected to be the result of rapid evaporation of ethyl acetate, when compared to the water evaporation. During the solvent evaporation process, crust that is first formed on the surface of the droplets prevents the evaporation of the solvent causing the building up of the vapour pressure. As a result, small eruption openings—pores are formed (Wang and Wang, 2002). Surface indentations could be attributed to the subsequent shrinking of the microspheres after solid crust is formed. This effect is even more evident for loratadine-free (empty) microspheres prepared from simple dispersions (Fig. 1). Comparing loratadine-loaded and loratadine-free composed microspheres (Fig. 2) it could be concluded that loratadine incorporation in such systems had no influence on surface or morphological characteristics of microspheres prepared. From SEM images of microspheres it could be concluded that two-phase system spray-drying resulted in microspheres with better loratadine entrapment than spray-drying of simple dispersions. It could be ascribed to the presence of lipophilic ethylcellulose in two-phase systems.

Particle size analysis indicated narrow logarithmic-normal distribution for all samples with about 90% particles having spherical diameter up to 5 μm and only 5% particles less than 2 μm, with mean diameters ranging between 3.32 ± 1.42 and 3.50 ± 1.53 μm (Table 2).

The type of spray-dried colloidal system influenced particle size characteristics. Thus, spray-drying of dispersions produced smaller microspheres than spray-drying of two-phase systems. Similar observation was already reported in the literature (He et al., 1999). There was no significant difference in mean diameters among the microspheres prepared by two-phase system spray-drying, showing that the polymeric composition, polymer/drug ratio and duration of stirring of emulsions did not influence particle size characteristics.

The entrapment efficiencies were always very high, between 67.9 and 86.1% (Table 3). In the case of simple dispersion spray-drying, the microspheres

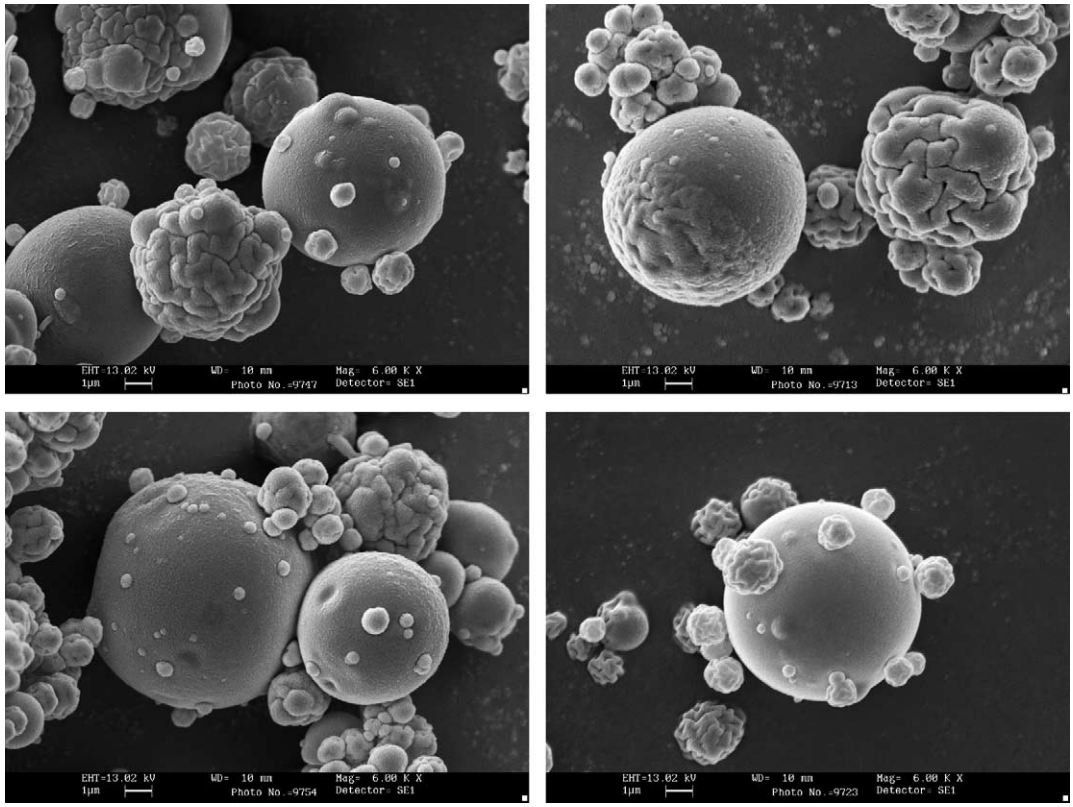

Fig. 2. SEM micrographs of drug-loaded (left) and drug-free (right) microspheres prepared by spray-drying of emulsions (up; LE2) and suspensions (down; LS2) with EC/CM weight ratio of 1:3.

prepared with theoretical polymer/drug ratio 8:1 showed higher loratadine entrapment (72.0%; sample LD2) than the microspheres prepared with the theoretical polymer/drug ratio 6:1 (67.9%; sample LD1), indicating that less loratadine was entrapped as polymer/drug ratio decreased. In comparison to these systems composed of chitosan as only polymer, spray-drying of two-phase systems composed of both, chi-

Table 3
Preparation and characteristics of chitosan microspheres with loratadine

Type of spray-dried system	Polymer/drug ratio (w/w)					
	6:1 (EC:CM = 1:2)[a]			8:1 (EC:CM = 1:3)[a]		
	Sample	Drug loading (%)[b]	EE (%)[c]	Sample	Drug loading (%)[b]	EE (%)[c]
Dispersion	LD1[d]	9.7 ± 0.9	67.9 ± 6.1	LD2[d]	8.0 ± 0.6	72.0 ± 5.6
Emulsion	LE1	12.3 ± 0.7	86.1 ± 4.9*	LE2	9.3 ± 0.4	83.7 ± 3.9*
Suspension	LS1	11.7 ± 0.7	82.6 ± 5.0*	LS2	7.3 ± 0.3	80.1 ± 4.1

Values are mean ± S.D. ($n = 3$).
[a] EC:CM: weight ratio of EC dissolved in inner oil phase and chitosan dissolved in outer water phase of O/W emulsions.
[b] Actual drug content/examined quantity of microspheres × 100.
[c] Entrapment efficiency (EE): drug loading/theoretical drug loading × 100.
[d] Samples with chitosan as the only polymer in composition.
* $P < 0.05$, compared to LD microspheres.

tosan and ethylcellulose resulted in significantly improved ($P < 0.05$) loratadine entrapment (80.1–86.1%). It is in agreement to previous conclusions drawn from SEM micrographs of the microspheres (Figs. 1 and 2).

3.2. Zeta-potential of the microspheres

The zeta-potential of the loratadine-loaded and loratadine-free microspheres was measured in 10 mM NaCl solution at 25 °C (pH 6.7). The results obtained are presented in Table 2. Also, as the control, the zeta-potential of EC microparticles was measured in the same medium and was -17.8 ± 1.6 mV. The negative zeta-potential for EC microparticles in medias such as acetate buffer (1 mM; pH 4) and phosphate buffer (0.1 mM; pH 7) was already reported (He et al., 1998).

All microspheres prepared were positively charged, indicating the presence of chitosan at the surface of all microspheres formed, regardless of the drug content and the type of spray-dried system. The highest zeta-potential was measured for loratadine-free conventional microspheres, consisting of chitosan only (32.7 ± 1.3 mV; loratadine-free samples LD1 and LD2), which was expected since chitosan free amino groups are responsible for the measured positive zeta-potential (Berthold et al., 1996).

Zeta-potential of loratadine-free composed microspheres, ranging between 27 ± 1.1 and 31.4 ± 1.9 mV, was significantly ($P < 0.05$) lower than the zeta-potential of loratadine-free conventional microspheres. It can be explained by the inducement of EC in two-phase systems and partial presence of EC at the surface of the composed microspheres. As shown in Table 2, in case of loratadine-free composed microspheres, zeta-potential of the microspheres with EC/CM ratio 1:2, w/w was lower than the zeta-potential of the microspheres with EC/CM ratio 1:3, w/w, regardless of the type of spray-dried system (emulsion or suspension). It may be concluded that a better chitosan coating of EC cores was obtained when higher chitosan content (EC/CM 1:3) was employed. Also, microspheres prepared from suspensions with higher chitosan content were higher positively charged, than microspheres prepared from emulsions of the same polymeric composition. It seems like that in case of suspensions, partial evaporation of ethyl acetate and consequent partial precipitation of EC prior to spray-drying, led to formation of more compact chitosan layer around EC cores of microspheres obtained.

Zeta-potential of loratadine-loaded microspheres ranged between 26.6 ± 1.4 and 28.1 ± 2.0 mV and was always lower than zeta-potential of corresponding loratadine-free microspheres. Influence of the drug entrapped on the zeta-potential of the microspheres was already reported in the literature (Huang et al., 2003). It was noted that zeta-potential decreased with the increase of the drug content in the preparation. Reduction of zeta-potential caused by loratadine was much more evident for the conventional microspheres, prepared from the simple dispersions (27.5 and 32.7 mV, loaded and free, respectively), than for the composed microspheres, prepared from the emulsions (27.5 and 29.1 mV, loaded and free, respectively), or suspensions (28.1 and 31.4 mV, loaded and free, respectively).

Stronger effect of loratadine on surface characteristic such as zeta-potential in case of the conventional microspheres composed of chitosan only than in the case of composed microspheres consisted of both, EC and CM, is in agreement to SEM micrographs (Figs. 1 and 2) that revealed that loratadine was more present at the surface of conventional than composed microspheres.

Recently, it was reported (Škapin and Matijević, 2004) that introduction of non-solvent (water) into ethanol solution of loratadine and its subsequent evaporation could produce spherical particles which on ageing of their aqueous dispersions containing a small amount of ethanol transforms into fibrils. Such particles showed negative zeta-potential at pH 6 (about -40 mV, 0.001 mol l^{-1} KCl solution).

In the dispersions from which the conventional microspheres were prepared loratadine was dissolved in water/ethanol mixture. It could be speculated that evaporation of ethanol during spray-drying process resulted in similar structures, which affected the surface characteristics of microspheres as well as zeta-potential.

It is important to conclude that the zeta-potential of all microspheres prepared was positive, indicating the presence of chitosan at the surface of the microspheres. That observation is of great importance, since positive charge originating from chitosan is necessary for the interaction with negatively charged mucus, and consequently, bioadhesion (He et al., 1998).

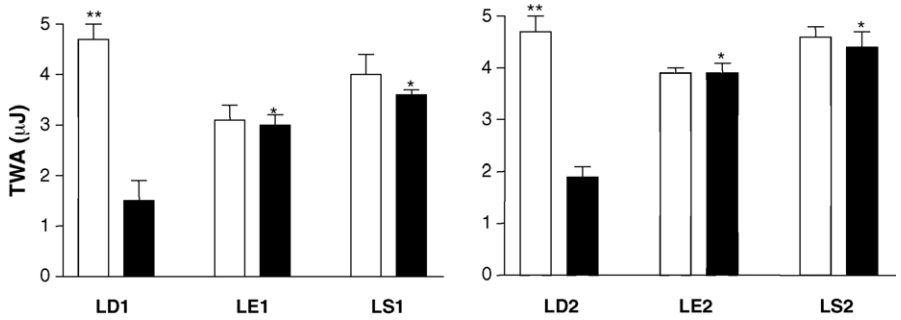

Fig. 3. The comparison of bioadhesive properties of loratadine-free (□) and loratadine-loaded (■) microspheres prepared by spray-drying of simple dispersions (LD), emulsions (LE) and suspensions (LS) with polymer/drug ratio of 6:1 (LD1, LE1, LS1) and 8:1 (LD2, LE2, LS2). Bioadhesive properties were evaluated by tensile studies and are expressed as the TWA. Indicated values are means of at least three experiments ±S.D. * Differs from LD loratadine-loaded microspheres ($P < 0.05$); ** differs from other microspheres ($P < 0.05$).

3.3. Bioadhesion studies

Results of tensile studies with loratadine-loaded and loratadine-free chitosan microspheres are shown in Fig. 3.

The highest total work of adhesion was measured for loratadine-free conventional microspheres, consisting of chitosan only (4.7 ± 0.3 μJ; loratadine-free samples LD1 and LD2), which was expected since chitosan free amino groups are responsible for the interaction with mucin. This result is in agreement with the highest zeta-potential measured for this sample.

Tensile studies performed with composed loratadine-free microspheres showed that both, EC/CM ratio and the type of spray-dried system (emulsion or suspension) influenced the bioadhesive properties of the microspheres obtained (Fig. 3).

Thus, the microspheres with higher chitosan content (EC/CM 1:3, w/w; samples LE2 and LS2) were more bioadhesive than the microspheres with lower chitosan content (EC:CM 1:2, w/w; samples LE1 and LS1). Also, microspheres prepared from suspensions (samples LS1 and LS2) were more bioadhesive than microspheres prepared from emulsions (samples LE1 and LE2), regardless of the same polymeric composition. It can be explained by already mentioned better separation and formation of EC cores and chitosan coating, when suspensions were spray-dried and when higher content of chitosan is employed in the preparation.

The lowest bioadhesion was observed with loratadine-loaded conventional microspheres (1.5 ± 0.4 and 1.9 ± 0.2 μJ; samples LD1 and LD2), with a clear correlation between the amount of drug in preparation and the decrease in bioadhesion: the total work of adhesion for the microspheres with chitosan/loratadine ratio 8:1 (sample LD2) and 6:1, w/w (sample LD1), decreased 2.5-fold and 3.1-fold, respectively, compared to the control (loratadine-free microspheres; Fig. 3). This is most likely due to the presence of loratadine at the surface of the microspheres, which reduced the chitosan-mucin interaction and consequently the bioadhesion. In addition, loratadine seemed to cause the reduction in zeta-potential of the microspheres, which also reduced their mucoadhesive properties. At the same time, there was no significant difference in bioadhesion between loratadine-loaded and loratadine-free composed microspheres (Fig. 3),

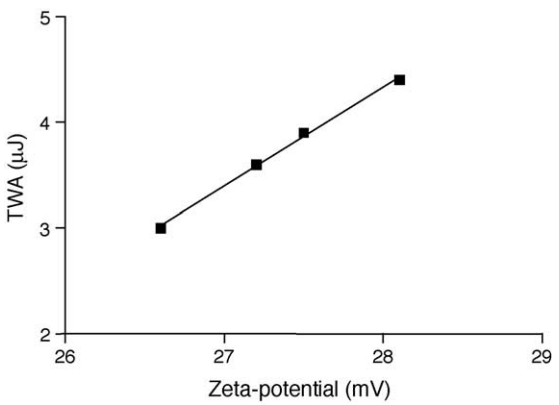

Fig. 4. Correlation between zeta-potential and bioadhesion of loratadine-loaded microspheres prepared by spray-drying of two-phase systems.

indicating insignificant influence of loratadine on surface properties in composed systems that consisted of both, chitosan and ethylcellulose, which was responsible for improved loratadine encapsulation.

For all two-phase systems the clear correlation between bioadhesion and zeta-potential could be drawn as presented in Fig. 4. Similarly, He and co-workers (1998) evaluated the mucoadhesive properties of chitosan and chitosan microspheres by measuring mucin adsorption on the microspheres, and concluded that the adsorption was proportional to the absolute values of the positive zeta-potential of chitosan microspheres and negative zeta-potential of mucus glycoprotein.

4. Conclusions

It may be concluded that due to the presence of ethylcellulose, the composed microspheres were characterised by improved loratadine entrapment efficiency in comparison to conventional chitosan microspheres. Thus, composed microspheres should ensure longer retention of the drug delivery system at the site of deposition, as loratadine was significantly less present at their surface, and consequently had less influence on bioadhesion. Higher chitosan content (EC/CM 1:3) ensured more compact coating of EC cores of microspheres, improving their bioadhesive properties.

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