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The effects of bivalent inorganic salts on the mucoadhesive performance of a polymethylmethacrylate sodium salt

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Abstract

The effects of bivalent inorganic salts, namely $CaCl_2$, $MgCl_2$, $MgSO_4$, $ZnCl_2$ and $ZnSO_4$, on the mucoadhesive performance of a polymethylmethacrylate sodium salt (EuSNa) were investigated. The swelling properties and mucoadhesion of ten different blends made of EuSNa and 5 or 10% (m/m) inorganic salts were evaluated. Only the addition of Zn salts caused a significant reduction of mucoadhesive properties and an increase of swelling. Swelling and mucoadhesive properties of the linear polymethylmethacrylate salt were affected by a physical cross-linking due to bivalent cations. The extent of such interaction may be mainly ascribed to the different electronegativity of the bivalent cations. Attenuated total reflectance infrared spectroscopy (ATR-FTIR) and texture analysis supported this hypothesis.

Adding magnesium and calcium salts, the intrinsic dissolution rate of EuSNa decreased of at least 25%. Mucoadhesive tablets were prepared with the most suitable blends and tested on human healthy volunteers. The addition of the magnesium and calcium increased the in vivo permanence time without affecting the mucoadhesive performances. The lack of swelling, mucosal irritation and unpleasant sensation allow the use of such blends in the preparation of mucoadhesive tablets.

Keywords: Polymethylmethacrylate sodium salt; Buccal tablets; Mucoadhesion; ATR-FTIR spectroscopy

1. Introduction

Buccal cavity provides an attractive alternative route of drug administration in the treatment of topical diseases and systemic pathologies. Problems such as first-pass metabolism and drug degradation in the gastrointestinal tract can be circumvented by direct absorption via oral mucosa. Additionally, the route provides easy accessibility; patient compliance and the dosage form can be removed at any time (De Vries et al., 1991; Miyazaki et al., 1994). Nevertheless, the buccal mucosa is considerably less permeable than the sublingual area and thus, it is not able to provide rapid drug absorption. The bioavailability of drugs administered via the buccal mucosae is affected by their removal from the oral cavity following the swal-

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lowing (Shojaei, 1998; Machida and Nagai, 1999; Weatherell et al., 1996). As a result, drug mucoadhesive delivery systems have been designed to prolong the permanence time of dosage forms and/or localize drug release on the site of absorption. The bioadhesive components commonly used in buccoadhesive tablets are polyacrylic acids and cellulose derivatives (Ponchel et al., 1987; Nagai, 1986; Singla et al., 2000; Junginger, 1991; Mortazavi and Smart, 1994; Bouckaert and Remon, 1993; Minghetti et al., 1998). However, the hydration of these polymers results in the formation of an outer gel layer and the increase in the size of tablets affects negatively patients' compliance and in some cases the drug bioavailability (Singla et al., 2000). To overcome these drawbacks new low-swellable mucoadhesive materials were developed by salification with NaOH and KOH of polymethylmethacrylate (Cilurzo et al., 2003). Nevertheless, the in vivo permanence time of placebo tablets and patches was limited by the fast dissolution rate of the copolymers which was affected by the molar proportions of monomers (Cilurzo et al., 2003). Indeed, the intrinsic dissolution rate of the copolymer salts whose molar ratio methacrylic acid:methylmethacrylate was 1:1 (Eudragit® L100) is faster than that of the corresponding copolymers with the molar ratio 1:2 (Eudragit® S100).

The reduction of the dissolution rate of these materials, maintaining their mucoadhesive and low swelling properties, appears of interest to produce buccal dosage forms.

Small amounts of zinc sulphate caused aggregation and precipitation of polymethylmethacrylates in aqueous solution (Minghetti et al., 2003). Moreover, the addition of bivalent ions was found to affect the drug release and mucoadhesion properties of dosage forms made of polyacrylic acid (Lee and Chien, 1996) and starch graft acrylic acid copolymers (Geresh et al., 2004). Therefore the addition of bivalent cations could be a suitable approach to reduce the dissolution rate of these polymethylmethacrylate salts.

In this work the effects of the addition of zinc, magnesium, and calcium ions on mucoadhesion, swelling properties and intrinsic dissolution rate of Eudragit S sodium salt (EuSNa) were investigated; the effects of salt concentration and the type of contra-ion were evaluated.

Ten blends were prepared by adding 5 or 10% (m/m) $CaCl_2$, $MgCl_2$, $MgSO_4$, $ZnCl_2$ and $ZnSO_4$ to EuSNa. The mechanism responsible of mucoadhesion was investigated by attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) and texture analysis. Finally, to assess the feasibility of such formulative approach, tablets made of the suitable inorganic salt/copolymer blends were tested in vivo evaluating the permanence time and volunteer compliance.

2. Materials and methods

2.1. Materials

Eudragit® S100, poly(methacrylic acid, methylmethacrylate), molar proportions of the monomer units 1:2, molecular weight ≈ 135,000 Da (Röhm, G); Methocel® K4M (HPMC K4M), substitution: methoxyl = 22%, hydroxypropoxyl = 8.1%, nominal viscosity 2% in water: 4000 cP (Colorcon, I); cellulose acetate propionate (CAP) (CAP 482 P East-Kodak, US); crude (Type II) mucin from porcine stomach (Sigma Chemical Co., US); magnesium chloride, magnesium sulphate, zinc chloride, zinc sulphate, calcium chloride and aluminium chloride (ACEF, I).

2.2. Preparation of sodium Eudragit® S100 sodium salt

Eudragit® S100 sodium salt (EuSNa) was obtained by adding 10% (m/m) NaOH aqueous solution to 7.5% (m/m) polymer aqueous suspension till complete salification and spray-drying the solution as previously described (Cilurzo et al., 2003).

2.3. Tablet preparation

Tablets of 25 and 80 mg made of blends of EuSNa and 5 or 10% (m/m) inorganic salts (Table 1) were compressed on an instrumented single punch tablet press (Korsch, type EK0, G) equipped with 6 mm diameter flat punch. The compression procedure was carried out manually. The upper punch was assessed in order to obtain tablets with a resistance to crushing of about 5 kp.

Table 1
In vitro bioadhesive performance of the EuSNa/inorganic salt blends (mean ± S.D., $n = 5$)

Blend no. (% inorganic salt)	Work of adhesion (mJ)	Maximum detachment force (N)
1 (5% $MgCl_2$)	3.251 ± 0.866	3.338 ± 0.589
2 (10% $MgCl_2$)	4.771 ± 0.653	4.098 ± 0.731
3 (5% $MgSO_4$)	4.531 ± 1.548	4.300 ± 0.499
4 (10% $MgSO_4$)	4.574 ± 2.000	4.345 ± 0.420
5 (5% $ZnCl_2$)	3.212 ± 2.066	2.670 ± 0.314
6 (10% $ZnCl_2$)	2.324 ± 0.660	2.868 ± 0.728
7 (5% $ZnSO_4$)	5.585 ± 1.608	3.135 ± 0.179
8 (10% $ZnSO_4$)	4.502 ± 0.849	3.073 ± 0.085
9 (5% $CaCl_2$)	4.861 ± 1.724	3.588 ± 0.381
10 (10% $CaCl_2$)	2.608 ± 0.537	3.563 ± 0.375
100% EuSNa	5.110 ± 1.019	6.172 ± 0.278
Stainless steel punch[a]	0.650 ± 0.009	2.808 ± 0.201
HPMC K4M[b]	1.513 ± 0.256	3.973 ± 0.12

[a] Negative control.
[b] Positive control.

2.4. Tablet swelling

Swelling and erosion processes of EuSNa and the relative blends were evaluated by gravity method. Tablets of 80 mg were attached by cyanoacrylate glue to a glass plate and immersed in 30 ml of deionised water under constant stirring. At predetermined time intervals, polymeric tablets were removed out of beaker, weighed and photographed after gently medium removal. The variation of tablet weight (Δweight) over time, namely water uptake and mass loss, was calculated according to the following equation:

$$\Delta\text{weight} = \frac{\text{WT}_t\,(\text{mg}) - \text{DT}_0\,(\text{mg})}{\text{DT}_0\,(\text{mg})} \quad (1)$$

where WT_t represents the wet weight of tablet at the time t and DT_0 stands for the initial dry weight of the tablet.

2.5. Study of EuSNa/inorganic salts interaction

The interactions between the different inorganic salts and EuSNa upon hydration were investigated by ATR-FTIR spectroscopy. The test was performed using tablets of 80 mg prepared as described in Section 2.3. The tablet was incubated in purified water and after 20 min the hydrated layer was carefully removed from the tablet and it was directly applied on the ATR accessory of an FT-IR spectrometer (Perkin Elmer, US) equipped with a diamond crystal. Sixty-four scans were collected at a resolution of $2\,\text{cm}^{-1}$ over the wavenumber region 4500–650 cm^{-1}. The spectrum of dry EuSNa was also recorded.

2.6. In vitro study of mucoadhesive properties

2.6.1. Texture analysis

2.6.1.1. Compact preparation. Compacts of 170 mg made of blends of EuSNa and the selected inorganic salt were obtained by using a hydraulic press (Glenrothes, UK) equipped with flat faced punches and having a die diameter of 11.28 mm. The compression force (10 t for 30 s) was kept constant.

2.6.1.2. Experimental conditions. A software-controlled dynamometer (AG/MC1, Acquati, I) with a 5 daN force cell was used for tensile mucoadhesive experiments. The compacts were attached to the mobile steel punch by cyanoacrylate glue. Mucin compacts, weighting 130 mg, were obtained applying a compression force of 11 t for 60 s. The compact was attached with cyanoacrylate glue to a steel plate fixed at the bottom of the tensile apparatus and hydrated with 80 μl water upon 5 min, in order to obtain a jelly superficial stratum.

Upon making contact between the polymeric compact and hydrated mucin, a constant force of 1.3 N was imposed for 360 s. The mucoadhesive performance of the blends was determined by measuring the detachment force required to separate the compact from the support (maximum detachment force) upon an elongation of 10.00 mm at the constant rate of 0.1 mm/s. The areas under the curve of the detachment force in function of the elongation were determined to represent the work (or energy) required for the detachment of the two compacts.

The stainless steel punch was selected as negative control and HPMC K4M as positive one.

2.6.2. ATR-FTIR spectroscopy

The interactions between EuSNa and mucin upon hydration and the effect of the blending with the inorganic salts were investigated by means of ATR-FTIR spectroscopy.

2.6.2.1. Sample preparation. Two hundred milligrams of mucin was hydrated in 1 mg of purified water and mixed with a solution of EuSNa (0.2 g/ml) or the blends containing 10% of the inorganic salts. The gel was spread on a stainless steel plate and dried until constant weight.

The spectra were collected as described in Section 2.5.

2.6.3. Intrinsic dissolution rate

Compacts (250 mg, 13 mm diameter) made of blends of EuSNa and inorganic salts were prepared using a hydraulic press (RIIC hydraulic press, UK) with 10 t compaction force and a 10 min holding period. In order to expose a single face with constant area to the medium, all surfaces except one base were coated by partial immersion in 8% (m/m) dichloromethane CAP solution.

The dissolution test was performed in a modified USP 25 dissolution apparatus 2, fixing the coated compact eccentrically under the paddle at the distance of 1.8 cm from the rotating axis (Cilurzo et al., 2003). Five hundred milliliters of deionised water thermostated at $37.0 \pm 0.5\,^{\circ}C$ were used as dissolution medium. Stirring speeds of 25, 50 and 100 rpm were tested. The dissolved amounts of EuSNa were spectrophotometrically assayed at $\lambda = 213$ nm.

Intrinsic dissolution rate (G) was determined from the slope, calculated by linear regression, of the curve obtained by plotting the dissolved amount of the copolymer per unit area (mg/cm^2) versus time (min) (US Pharmacopoeia, 2002). The linear regression was calculated until 70% was dissolved because of the high solubility of the specimens. As the experimental values of intrinsic dissolution rate are affected by the hydrodynamic condition the intrinsic dissolution rate at infinite rotation speed (G_∞) was extrapolated as described by Nicklasson et al. (1985):

$$G = G_\infty + \frac{k}{r\sqrt{\omega}} \tag{2}$$

where G is the intrinsic dissolution rate, G_∞ the intrinsic dissolution rate at infinite rotation speed, k a proportionality factor, r the distance from the rotating axis and ω is the angular velocity of the matrix. The angular velocity of the compact can be calculated as follows:

$$\omega = 2\pi\nu \tag{3}$$

where ν is the number of revolution per minute (rpm).

G_∞ is obtained by measuring G as a function of r and ω and extrapolating to $(r\sqrt{\omega})^{-1} = 0$.

2.7. In vivo mucoadhesion study

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and followed the ICH-GCP guidelines of 17-1-1997, and was in compliance with local regulatory requirements. All subjects were completely informed concerning the pertinent details and the purpose of the study. A written consent form was supplied, understood and signed by each subject prior to dispensing test materials. The study was conducted on six healthy human volunteers (aged 25–28 years) using 25 mg tablets attached to upper buccal sulcus, in the region of the top canine tooth. Volunteers were allowed to drink during the study, while food intake and smoking were prohibited. Volunteers were asked to record the time of insertion and time of end of the adhesion (permanence time), mucosal irritation, comfort, smarting sensation in mouth and the buccal cavity.

2.8. Statistical analysis

Tests for significant differences between means were performed by Student's t-test or one-way ANOVA by using the software SPSS 11 (SPSS Inc., US). In order to identify the parameters which affected the in vivo permanence time, a multilinear regression analysis was also carried out using the same software. Differences were considered significant at the $p < 0.05$ level.

3. Results and discussion

3.1. Tablet swelling

The blends exhibited a different performance upon hydration depending on the type of the inorganic salt mixed with EuSNa. When 5% $MgCl_2$, $MgSO_4$ and $CaCl_2$ were added, the tablets dissolved without swelling. This behaviour was comparable to that of pure EuSNa (Fig. 1). When the zinc salts were mixed with EuSNa, the tablets (blend nos. 5–8) showed an evident swelling layer without erosion and their weight

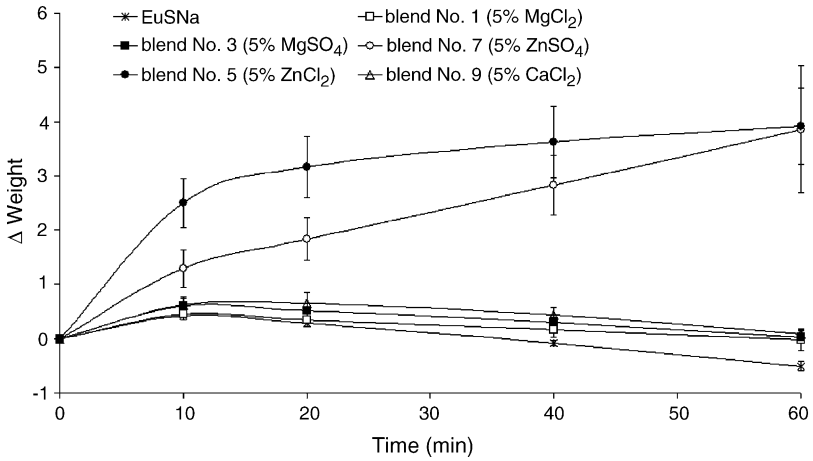

Fig. 1. Water uptake or mass loss of tablets made of EuSNa and the blends containing 5% inorganic salts upon hydration.

increased of 6–7-fold in 60 min (Fig. 1). The behaviour of the blends upon hydration can be attributed to the electronegativity of the Zn^{2+} ion (1.6) that is higher in comparison with that of Mg^{2+} and Ca^{2+} (1.2 and 1.0, respectively). In order to verify this hypothesis, the performance of a blend made of $AlCl_3{\cdot}6H_2O$ and EuSNa (Al^{3+} electronegativity 1.6) was assayed: upon hydration the tablet showed the same behaviour of those made of blend nos. 5–8 (Δweight after 60 min: 2.64 ± 0.19).

The influence of the electronegativity of the inorganic ion on the swelling of EuSNa was supported by ATR-FTIR analyses. As an example, spectra of dry and hydrated EuSNa and blend nos. 1 (5% $MgCl_2$), 5 (5% $ZnCl_2$) and 9 (5% $CaCl_2$) are shown in Fig. 2. After hydration the COO^- and C=O esteric groups of EuSNa shifted from 1562 to 1544 cm^{-1} and from 1720 to 1712 cm^{-1}, respectively. The shifts can be attributed to the formation of H-bond interactions between these functional groups and water.

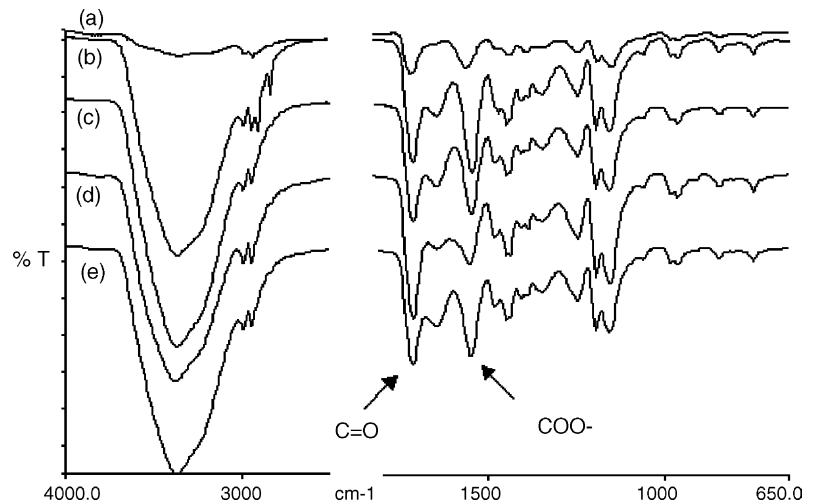

Fig. 2. ATR-FTIR spectra of: (a) dry, (b) hydrated EuSNa and hydrated blends containing (c) 5% (m/m) $MgCl_2$, (d) 5% (m/m) $ZnCl_2$ and (e) 5% (m/m) $CaCl_2$.

As far as blends are concerned, the COO^- antisymmetric stretching vibration band was detected at 1553 cm^{-1} in the case of Zn ions and 1548–1549 cm^{-1} in the case of Mg and Ca ions. The shift was attributed to the interaction between the bivalent cation and EuSNa. The shifts of the band were independent of the type of contra-ion and the percentage of the inorganic salt in the blend (data not shown).

The shift of the COO^- band in presence of all inorganic salts was also associated to a reduction of the intensity of the band with respect to the band at 1712 cm^{-1} attributed to the ester moiety of the copolymer. The reduction was much more evident in presence of Zn ions (Fig. 2).

3.2. In vitro mucoadhesive properties

3.2.1. ATR-FTIR spectroscopy

The effect of the addition of the inorganic salts on the structure of the mucin was preliminarily investigated. The spectrum of hydrated mucin showed two main bands at about 3300 cm^{-1} and about 1630–1635 cm^{-1} which were attributed to water (data not shown). The other relevant band detectable in the spectrum was attributed to the stretching vibration of the carboxyl moiety of the sialic acid at 1552 cm^{-1} (Saiano et al., 2002).

The addition of the inorganic salts to hydrated mucin mainly caused a decrease of the intensity of the peak at 1552 cm^{-1} (data not shown). This phenomenon was attributed to an interaction between the ionised COO^- of sialic acid and the inorganic salts. Furthermore, when the inorganic salts were added to the mucin, the intensities of the primary and secondary alcohol bands at 1058 and 1118 cm^{-1}, respectively, were reduced probably because of a decrease of the electrostatic charge of the glycoprotein. The modifications of the hydrated mucin spectra were more evident when Ca and Zn salts were added.

As exemplified in Fig. 3 when EuSNa and mucin were mixed the main differences detectable in the spectrum were the shift of the hydrated EuSNa band from 1712 to 1723 cm^{-1} and the reduction of its intensity. The shift suggests the formation of an interaction between the C=O of the ester group of EuSNa and mucin via H-bond formation which could be responsible of the mucoadhesive properties of the copolymer. The interaction between EuSNa and mucin was verified also in presence of the inorganic salts and a similar shift of the co-bands was registered (data not shown).

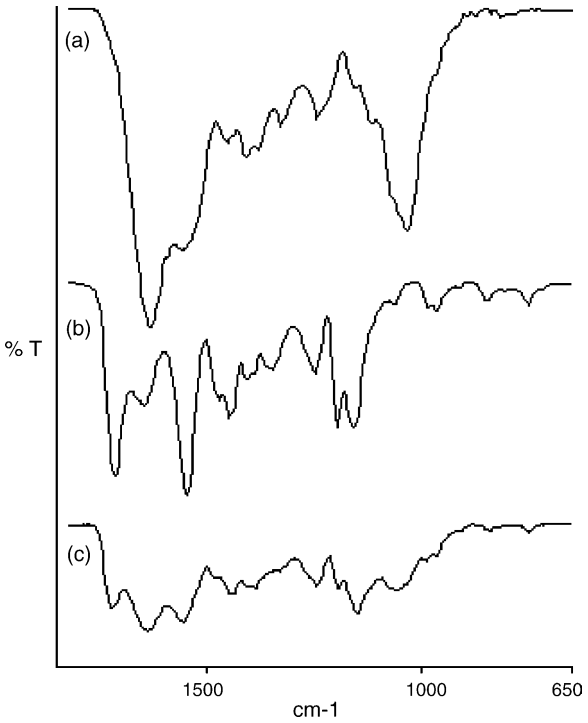

Fig. 3. ATR-FTIR spectra of: (a) mucin, (b) EuSNa and (c) EuSNa/mucin mixture upon hydration.

3.2.2. Texture analysis

The texture profiles are reported in Fig. 4. The force versus elongation graphs obtained by texture analysis can be divided in four portions (Cilurzo et al., 2003). The main differences in the profiles of EuSNa and the relative blends were detected in the early portion of the curve when the detachment force rose to the maximum value. In the first portion of the curve the main event involves nucleation followed by growing of microcavities. Both of them are related to the visco-elastic properties of the hydrated EuSNa/mucin mixture and occur under low strain applied on a confined interface. In the case of EuSNa, the detachment force during the nucleation phase increased faster because at the interface EuSNa/mucin the viscous modulus of the gel layer is greater than those at the interface between EuSNa-inorganic salts blend and mucin. This hypothesis is

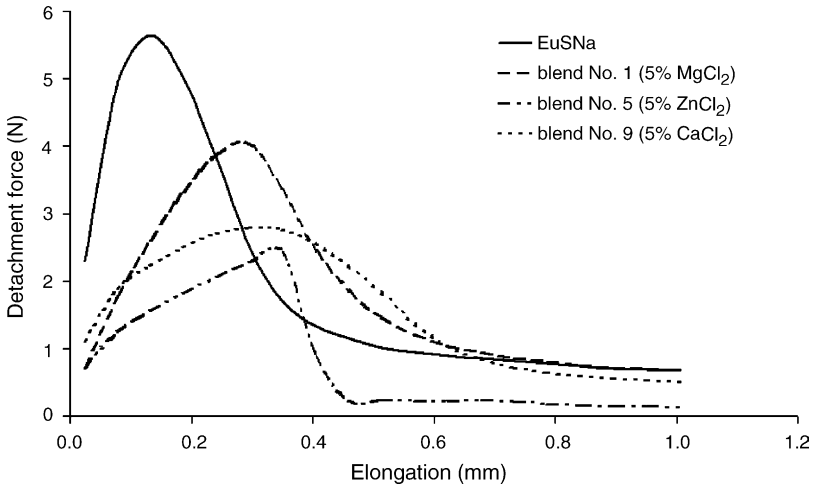

Fig. 4. Detachment force pattern as a function of elongation at the constant rate of 0.1 mm/s. Experiments carried out on EuSNa and the blend nos. 1 (5% $MgCl_2$), 5 (5% $ZnCl_2$) and 9 (5% $CaCl_2$).

supported by the physical cross-linking of the linear chain of EuSNa due to the interaction between the bivalent cations and the copolymer verified by ATR-FTIR analysis. The addition of inorganic salts also induced a changing of the mucin fold (Leung and Robinson, 1998; Shrivastava et al., 2003). This may result in a reduction of the expanded nature of the hydrated three-dimensional network and consequently the visco-elastic properties of the mucin gel formed upon hydration of the compact. The work of adhesion was calculated as the area under the detachment force/elongation curve and therefore, in this case, its value underwent minor variation than that of the maximum detachment force (Table 1). Indeed, the work of adhesion values were always statistically higher than that registered with the negative control ($p > 0.05$). The addition of the inorganic salts caused a statistically significant decrease of the maximum detachment force of EuSNa ($p < 0.02$).The maximum detachment force of the blend nos. 5 (5% $ZnCl_2$), 6 (10% $ZnCl_2$) and 8 (10% $ZnSO_4$) resulted not statistically different from the negative control; the maximum detachment force of blend no. 7 (5% $ZnSO_4$) was significantly higher than that of the negative control ($p = 0.01$), and significantly lower than that of HPMC K4M, selected as positive control ($p = 0.022$). The maximum detachment force values of the other blends were not significantly different from those of HPMC ($p > 0.187$).

The results showed that only the addition of Zn ions caused a significant reduction of mucoadhesive properties of EuSNa.

3.3. Intrinsic dissolution rate

As the tablets containing Zn salts showed an evident swelling layer upon contact with water, the intrinsic

Table 2
Intrinsic dissolution rate (mg/cm^2/min) at different rotation speed (rpm) and extrapolated at infinite rotation speed (G_∞) (mean ± S.D., $n = 3$)

Speed (rpm)	EuSNa	Blend no. (% inorganic salt)					
		1 (5% $MgCl_2$)	2 (5% $MgCl_2$)	3 (5% $MgSO_4$)	4 (10% $MgSO_4$)	9 (5% $CaCl_2$)	10 (10% $CaCl_2$)
25	0.208 ± 0.003	2.006 ± 0.009	1.919 ± 0.104	2.581 ± 0.118	1.701 ± 0.299	1.979 ± 0.123	1.667 ± 0.111
50	0.372 ± 0.007	2.334 ± 0.076	2.429 ± 0.079	2.726 ± 0.375	2.551 ± 0.392	2.604 ± 0.260	2.184 ± 0.216
100	0.503 ± 0.011	4.502 ± 0.394	3.551 ± 0.226	3.328 ± 0.543	3.164 ± 0.400	3.348 ± 0.321	3.097 ± 0.516
$1/G_\infty$	0.137 ± 0.024	0.178 ± 0.042	0.203 ± 0.028	0.221 ± 0.021	0.231 ± 0.021	0.236 ± 0.022	0.253 ± 0.034
(r^2)	(0.940)	(0.889)	(0.947)	(0.881)	(0.881)	(0.905)	(0.875)
G_∞	7.299	5.618	4.926	4.524	4.329	4.237	3.952

Table 3
In vivo permanence time of tablets (mean ± S.D., $n = 6$)

Blend no. (% inorganic salt)	Permanence time (min)
1 (5% $MgCl_2$)	163 ± 16
3 (5% $MgSO_4$)	158 ± 24
9 (5% $CaCl_2$)	175 ± 25
EuSNa	125 ± 9

dissolution rate was determined only for the blend nos. 1–4, 9 and 10. The values of the intrinsic dissolution rate at the different rotation speeds are reported in Table 2.

As expected, the blends containing the inorganic salts dissolved slower than EuSNa and this feature may be due to the physical cross-linking of EuSNa. The reduction of G_∞ value was at least about 25% and followed the rank order: $MgCl_2 < MgSO_4 < CaCl_2$. In all cases the increase of the inorganic salt/EuSNa ratio from 5:95 to 10:90 (%, m/m) reduced the intrinsic dissolution rate in a not significant way ($p > 0.39$).

3.4. In vivo permanence time

To perform the in vivo study, tablets made of the blend nos. 1, 3 and 9, containing the lowest amount of inorganic salt, were chosen to minimize possible irritation. All tablets remained adherent to the gingival tissue and never detached. Volunteers reported no episodes of irritation following the administration of all the tablets. Moreover, no volunteers felt any uncomfortable or unpleasant sensation during the application period.

The tablet permanence times are reported in Table 3. As expected, the addition of the inorganic salts to EuSNa increased significantly the permanence time in respect to the pure EuSNa ($p < 0.05$). Moreover, the permanence time were comparable to that of hydroxypropylmethylcellulose with a low nominal viscosity (147 ± 40 min) (Cilurzo et al., 2003).

The potential predictors of the in vivo permanence time (Pt), i.e. work of adhesion, maximum detachment force (MDF) and intrinsic dissolution rate, were analysed by multiple regression analysis. The following equation was obtained:

$$\mathrm{Pt} = 235 \pm 10 - 10 \pm 3\mathrm{MDF} - 14 \pm 4G_\infty$$
$$(r^2 = 0.976,\ F = 20.3,\ p = 0.155,\ n = 4)$$

The work of adhesion cannot be considered as a predictor of the in vivo permanence time.

The MDF and G_∞ values showed a good sound of correlation, but the obtained equation was not significant. Moreover, the MDF cannot be considered a consistent predictor because, according to the equation, the increase of its value would cause a decrease of the in vivo permanence time.

To verify the predictivity of G_∞, a further in vivo experiment was performed by using tablet containing 10% (m/m) $MgCl_2$ (Pt = 159 ± 13 min). A significative correlation between in vivo permanence time and the predictor was observed:

$$\mathrm{Pt} = 230 \pm 20 - 20 \pm 4G_\infty$$
$$(r^2 = 0.826,\ F = 14,\ p = 0.032,\ n = 5)$$

4. Conclusion

The features of the blends containing EuSNa and inorganic salts depended on the type of the selected salt. Calcium and magnesium salts yielded a reduction of the dissolution rate of EuSNa of at least 25% without modifying the swelling and mucoadhesive properties of the copolymer. When the zinc salts were mixed with EuSNa, the tablets showed an evident swelling layer and a significant reduction of mucoadhesive properties of EuSNa.

Swelling and mucoadhesive properties of the linear polymethylmethacrylate salt were affected by a physical cross-linking due to bivalent cations. The extent of such interaction may be mainly ascribed to the different electronegativity of the cations. ATR-FTIR spectroscopy and texture analysis supported this hypothesis.

The addition of magnesium and calcium salts to EuSNa can be considered a useful approach to reduce the dissolution rate of EuSNa and therefore prolong the permanence time. The lack of swelling, mucosal irritation and unpleasant sensation recorded during the in vivo study confirmed the suitability of the tablets made of blends of EuSNa and magnesium or calcium salts for buccal administration.

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