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Effect of sodium chloride on the mechanical and osmotic properties of silicone matrices

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Summary

Sodium chloride has been suggested as a hydrophilic osmotic additive for controlling drug release from silicone polymers. In this study, the effect of sodium chloride on the mechanical and osmotic properties of silicone matrices and release of model drug from these matrices was evaluated. The addition of sodium chloride reduced the tensile strength of the matrices, shortened their elongation at break and increased the elastic modulus. Although the matrices became less flexible and brittle, their mechanical properties were acceptable for controlled release systems. In the beginning of sodium chloride release the crystals on the surface of the matrix dissolved rapidly. Then water was osmotically imbibed into the matrix and a continuous network of water channels was formed. This process was dependent on the amount and size of sodium chloride particles in the matrix. Sodium chloride was released at a constant rate when fixed osmotic pressure was maintained inside the network. When the sodium chloride particles in the matrix had dissolved, the release rate decreased until sodium chloride had diffused from the matrix. Corresponding phases were noticed during swelling of the matrices. The rates of matrix swelling and sodium chloride release were lower in vivo on the skin surface than they were in vitro. This was due to the smaller amount of water available.

Introduction

Chemically inert and biocompatible silicone medical grade elastomers (polydimethylsiloxanes) are widely used in different therapeutic systems (Chien, 1976; Sanvordeker et al., 1982; Rankin, 1985). These materials are hydrophobic and thus are suitable for controlling especially the release of relatively non-polar and lipophilic drugs. However, it has been demonstrated that the release of hydrophilic drugs from polymer matrices can be accelerated by using osmotically active agents (McGinity et al., 1979; DiColo et al., 1982; Hsieh et al., 1985). Although the rate of drug release from osmotic matrices has most often been observed to depend on time, systems with constant rates of drug release have also been described (Gale et al., 1980; Wright et al., 1981).

In this study we evaluated the effect of osmotically active sodium chloride on water sorption into silicone matrices in vitro and in vivo on the skin. Also, the mechanical properties of the corresponding matrices and the release of sodium chloride and sulphanilamide from the osmotic matrices were studied.

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Materials and Methods

Preparation of matrices

Sulphanilamide (3.1% w/w, 92 ± 17 μm) with or without sodium chloride was carefully dispersed in silicone elastomer (Silastic 382, Dow Corning, Midland, MI). Stannous octoate (10 mg/g) (Catalyst M, Dow Corning) was added as a curing agent in the mixture. Thereafter, matrices were prepared by compressing the mixture between the plastic plates by means of a hydraulic press (Carver model C laboratory press, Carver, Menomonee Falls, WI) for 30 min at a pressure of 0.94 MPa. After curing 2.5×2.5 cm pieces with a thickness of about 600 μm were cut from the matrices. Different concentrations (0, 5, 10 and 20% w/w) and particle sizes (20 ± 9, 59 ± 12 and 127 ± 35 μm) of sodium chloride were used in matrices. The elastomer containing 5% w/w of sodium chloride with a particle size of 59 μm was selected as the base material for matrices containing drug.

Determination of mechanical properties of the matrices

Specimens for testing mechanical properties were prepared with standard die C according to the American Society for Testing and Materials (ASTM) specification no. D412 (1981). The JJ Tensile Tester (type T5002, J.J. Lloyd Instrument, Southampton, U.K.) was used at a strain rate of 6 mm/min and initial grip separation of 50 mm. The stress-strain curve was monitored using an *XY*-plotter. Six measurements were taken for each formulation.

Elongation of the sample at break (%) was used as an indicator of the ductility of the matrices. Tensile strength was calculated according to Eqn. 1 (Allen et al., 1972):

$$\text{Tensile strength} = \frac{F}{ab}\left(1 + \frac{\Delta L}{L}\right) \qquad (1)$$

where F is the breaking force, a is the initial width, b is the initial thickness of the strip, ΔL is the elongation at break and L is the original length of the strip. The elastic modulus was determined as the slope of the initial linear part of the stress-strain curve. The slope was calculated by means of the least-squares method using at least five measurement points. The work done in breaking the matrix was the area under the stress-strain curve. The Mann-Whitney U-test was used for statistical testing.

In vitro release studies

For in vitro release tests, the matrices were introduced into flasks containing 50 ml of distilled water. The stoppered flasks were shaken at 160 rpm in a thermostated room (37 °C) during the test. At different times, samples were withdrawn and replaced by pre-warmed blank solution. The amount of sodium chloride released was measured with an osmometer (Osmostat OM-6020, Daiichi Kagaku, Kyoto). The concentration of sulphanilamide in the samples was determined spectrophotometrically at 257 nm. Sink conditions prevailed in the experiments. Six matrices were tested in each case.

Swelling experiments

Swelling of matrices was evaluated by weighing the matrices at fixed times after immersion in water. The swollen matrices were gently dried with filter paper and weighed. Swelling was expressed as the ratio of swollen matrix weight to initial weight.

The amount of water absorbed into the matrices was calculated from their weights. The values were corrected with respect to the amount of sodium chloride released. The rate of water absorption was calculated using the corrected values from the linear parts of the plots between 4 and 12 h from the beginning of the test. Each experiment was repeated three times.

The structure of polydimethylsiloxane matrices containing sodium chloride was evaluated before and after dissolution test using a scanning electron microscope (Jeol JSM-30, Japan). Scanning electron micrographs were taken from the top and broken surfaces of the matrices.

In vivo sorption measurements

The matrices containing 5% w/w of sodium chloride with a particle size of 59 μm were used in the in vivo tests. In tests, the matrices were applied to the skin on the arms of ten healthy

volunteers. An aluminium foil disc was placed over the silicone matrix as an occlusive baseplate. The aluminium foil disc with the adhesive free matrix was attached to the skin with silicone adhesive B (Dow Corning, Brussels). The matrix was detached from the skin after 8, 24, 48 and 72 h. Water sorption into the matrix during the test period was determined as the difference between the weights of the swollen and dried matrix. The amount of sodium chloride released was calculated as the difference between the total and residual amounts of sodium chloride in the matrix. Released sodium chloride was taken into account when the amount of absorbed water was calculated.

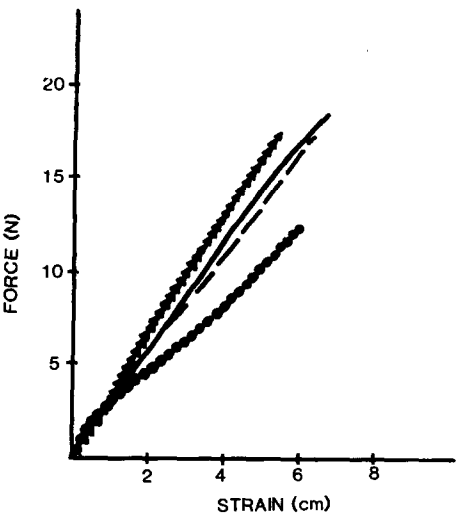

Fig. 1. Typical stress-strain curves for silicone matrices containing 0% (———), 5% (▶▶▶), 10% (- - - - - -) and 20% (●●●) of sodium chloride with a particle size of 59 μm.

Results and Discussion

Mechanical properties of the matrices

In the stress-strain test the plain polydimethylsiloxane matrix was rather strong and flexible (Fig. 1). When the concentration of sodium chloride was less than 10%, the viscoelastic behaviour obeyed Hooke's law. When the matrices contained 20% w/w of sodium chloride there was a knee point in the stress-strain curves with all particle sizes. The concentration of sodium chloride had no significant effect on elongation of the matrices at break, whereas decreasing particle size led to an increase (Table 1). Matrices containing sodium chloride with a particle size of 20 μm were the most ductile of the matrices.

The tensile strength diminished with increasing sodium chloride content of silicone matrices (Table 1). The influence of sodium chloride on tensile

TABLE 1

The effect of the amount and particle size of sodium chloride on the mechanical properties of polydimethylsiloxane matrices (n = 6)

Particle size (μm)	Amount of NaCl in matrices (%)	Elongation at break (%)		Tensile strength (MPa)		Elastic modulus (MPa)		Work done (MPa)	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
–		120	3	5.52	0.20	4.92	0.05	2.51	0.09
20	5	128	5	4.72 *	0.21	3.44 **	0.08	2.10	0.17
	10	124	3	4.37 *	0.21	3.27 **	0.10	1.83 *	0.20
	20	127	6	4.15 **	0.28	3.01 **	0.14	1.92 *	0.24
59	5	112	5	4.81	0.35	4.15 **	0.28	1.90	0.24
	10	115	4	5.01	0.28	4.02 *	0.19	1.86	0.15
	20	111	6	3.75 **	0.34	3.05 **	0.11	1.50 *	0.20
127	5	110 *	2	4.23 **	0.12	3.53 **	0.17	1.58 **	0.12
	10	113	6	4.29 *	0.33	3.48 **	0.06	1.83	0.26
	20	108 *	3	3.36 **	0.07	2.80 **	0.07	1.24 **	0.07

* $p < 0.05$ Mann-Whitney's U-test compared to matrices without NaCl.
** $p < 0.01$ Mann-Whitney's U-test compared to matrices without NaCl.

strength was greatest for matrices containing 20% w/w of sodium chloride and a particle size of 127 μm.

Increasing sodium chloride content significantly reduced the elastic modulus of matrices (Table 1), in contrast to the particle size which had no effect.

The work done in breaking the matrices (toughness) was reduced as the amount and particle size of osmotic additive were increased. The effect was most evident ($p < 0.01$) with matrices containing sodium chloride with a particle size of 127 μm.

In this study, we observed similar trends to those reported by Pfister et al. (1985), who used different silicone polymer and solid additives. The addition of solid particles reduced the tensile strength and elastic modulus of polydimethylsiloxane matrices and shortened the elongation at break. Although the matrices became less flexible and brittle, they were still considered as suitable for controlled release systems.

Release of sodium chloride and swelling of matrices

The rate of release of sodium chloride from matrices was calculated from the near-linear parts of the release plots after the initial burst. Sodium chloride release became faster for greater amounts and larger particle sizes of this additive being dispersed in silicone matrices (Figs. 2 and 3). The rate of water absorption into matrices decreased as particle size increased (Figs. 2 and 3). Matrices containing 20% w/w of osmotic additive showed the most rapid rate and extent of swelling among the matrices tested.

The dissolution and diffusion of sodium chloride from the matrices can be divided into four phases (Fig. 3). From the very first moment sodium chloride particles at the surface of the matrix were released rapidly. The initial, rapid release was seen in all release plots.

The second phase concerns the osmotic inhibition of water into matrices. This phase was particularly evident and long-lasting when matrices contained small amounts of small particles of sodium chloride (Fig. 2). In these cases, sodium chloride particles are more efficiently separated from each other by the polymer. The imbibition of water into the matrices containing sodium chloride particles is possible when the walls between the capsules are ruptured by osmotic pressure and a continuous diffusion network is formed. During this phase, sodium chloride is released slowly and the matrices swell effectively (Fig. 2). Swelling was greatest when the sodium chloride particles were more encapsulated and separated further, the volume of the network formed by rupturing being greater as a result.

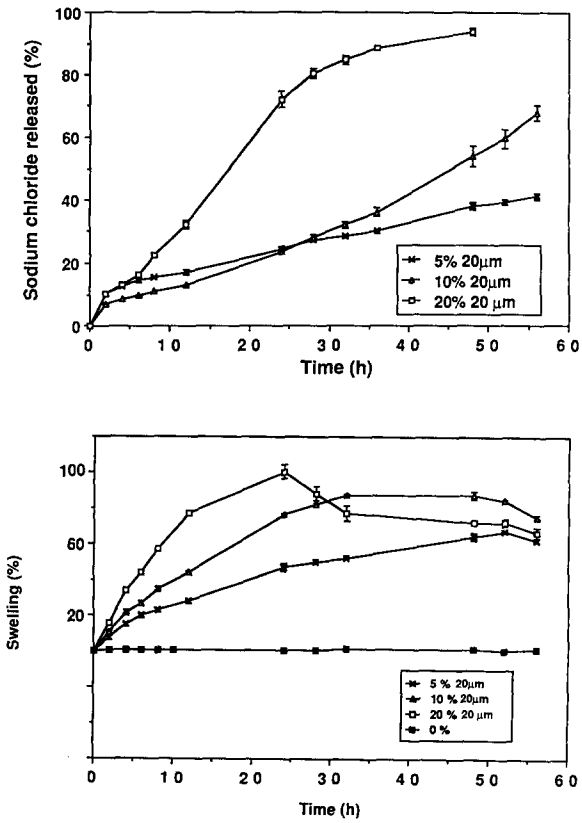

Fig. 2. Typical plots of release of sodium chloride from silicone matrices (upper) and swelling of the corresponding matrices (lower) as a function of time. Means ± SE of three determinations are presented.

After formation of the diffusion network, water is more readily absorbed into the matrix. During this phase the absorbed water gradually dissolves the sodium chloride. Efflux of the saturated solution from the matrix occurs due to the osmotic pumping effect. The osmotic pressure remains practically constant provided solid sodium chloride is present in the matrix. During this phase the

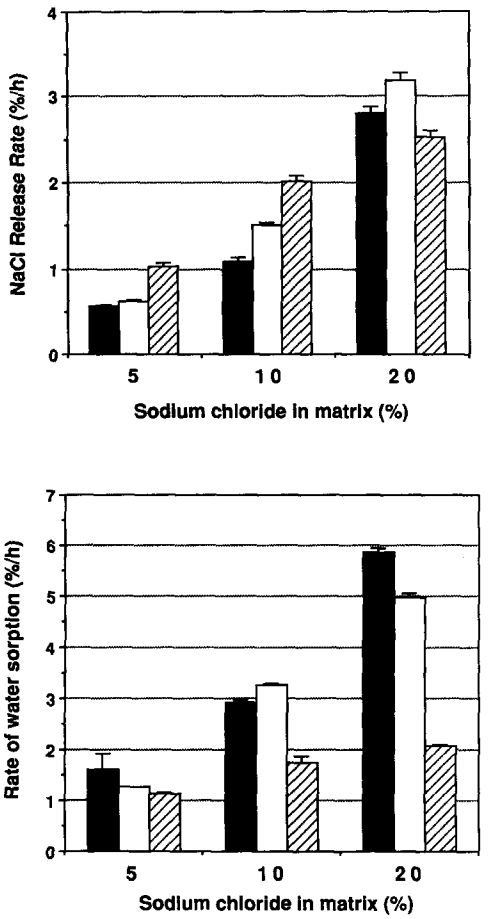

Fig. 3. Rate of sodium chloride release from silicone matrices (upper) and rate of water sorption in the corresponding matrices (lower). Particle size of sodium chloride: filled bars, 20 μm; unfilled bars, 59 μm; hatched bars, 127 μm. Means $\pm$ SE of three determinations are presented.

form of the matrix stays almost unaltered and sodium chloride is released at a constant rate (Fig. 2). In the last phase solid particles of sodium chloride were no longer present in the matrix and the release rate decreased until all sodium chloride had diffused from the matrix (Fig. 2). Due to the decrease in osmotic pressure, the pressure of the silicone polymer was able to shrink the matrix.

In vivo release of sodium chloride from matrices

Swelling of matrices and release of sodium chloride from them were of lesser extent in vivo than in vitro (Fig. 4). This was probably due to the smaller available amount of water surrounding the matrices. However, the shapes of the swelling and release profiles were almost identical in vivo and in vitro (Fig. 4). When occlusion was adequate, the absorption of water from the skin by the matrices studied was sufficiently large to trig-

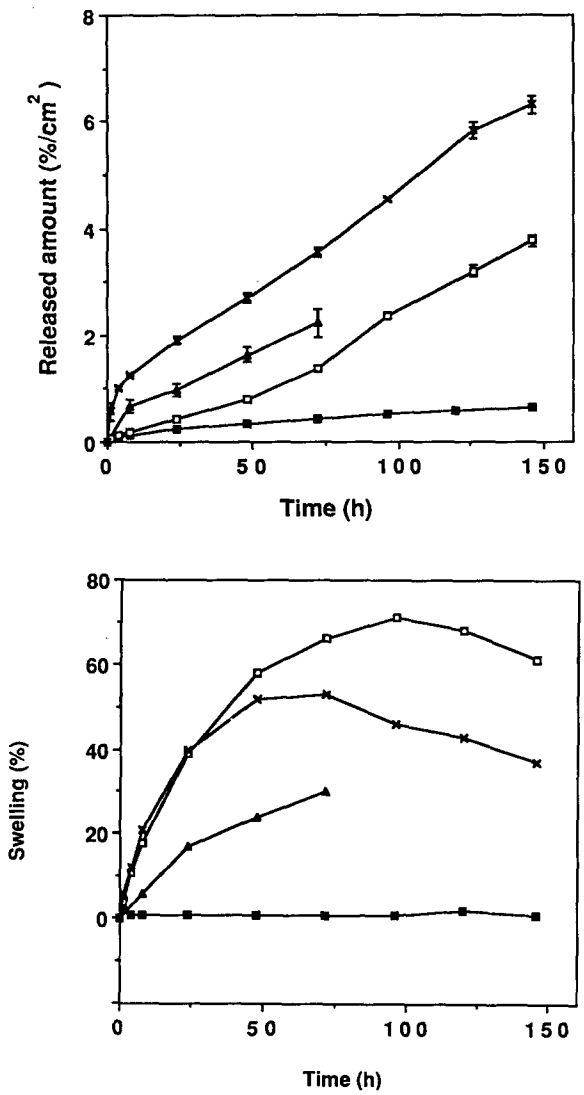

Fig. 4. In vivo release of sodium chloride and in vitro release of sulphanilamide and sodium chloride from the silicone matrices (upper) and swelling of the corresponding matrices (lower) as a function of time. (▲) Sodium chloride in vivo, (x) sodium chloride in vitro, (■) sulphanilamide, (□) sulphanilamide with 5% w/w of sodium chloride. Means $\pm$ SE of 10 (in vivo) and 6 (in vitro) determinations are presented.

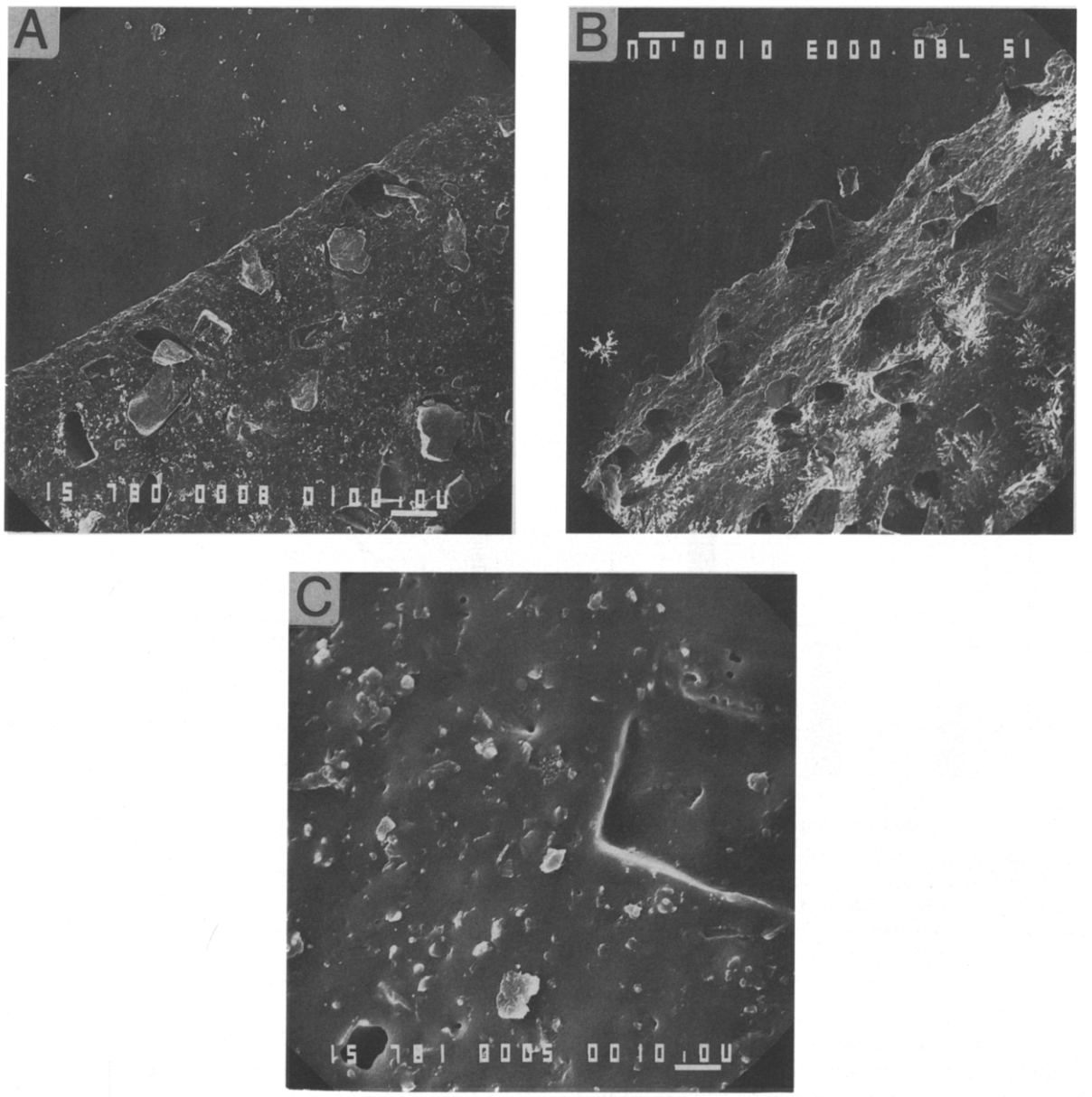

Fig. 5. Scanning electron micrographs taken from the silicone matrices containing 20% w/w of sodium chloride with a particle size of 59 μm before (A) and after (B, C) the dissolution test. Pictures show intact (upper) and cut (lower) surfaces of the matrix. Bar = 100 μm (A, B) and 10 μm (C).

ger a constant pumping effect in the matrices. Thus, sodium chloride was released following nearly zero-order kinetics after the initial burst. The individual anatomical and physiological factors affected especially the extent of swelling of matrices. On the other hand, deviations in the amounts of sodium chloride released were relatively small.

Release of sulphanilamide from silicone matrices

The rate of release of sulphanilamide was calculated from the near-linear part of the release

plot. Sulphanilamide was released extremely slowly from matrices in the absence of sodium chloride (Fig. 4). The moderately hydrophilic sulphanilamide did not dissolve to a sufficient extent in silicone for release from matrices. After a test period of 1 week, only 9% of the sulphanilamide had been released. Sulphanilamide matrices without sodium chloride did not swell (Fig. 4). We noticed only a slight weight increase, which was probably caused by water absorption onto the surface of the polymer matrix.

For 2 days, the release of sulphanilamide occurred very slowly from matrices with 5% of sodium chloride (Fig. 4). Subsequent to this period of water sorption, the rate of release of sulphanilamide was nearly equal to that of sodium chloride. During this phase the matrices remained practically unchanged in a swollen form, with sulphanilamide being released at a nearly constant rate due to the osmotic pressure inside the network undergoing no variation.

Microscopic evaluation of the matrices

According to the scanning electron micrographs taken before the dissolution test, the surface of all the polydimethylsiloxane matrices containing sodium chloride was intact (Fig. 5a). Thus, irrespective of particle size, all sodium chloride particles near the surface of the matrix were covered with a polymeric film. Also, according to SEM micrographs inside the matrices containing small amounts of sodium chloride, all particles were completely covered with a polymeric film; furthermore, at greater concentrations and especially for a particle size of 127 μm, the particles were partially interconnected. Thus, one can clearly understand that in matrices containing large amounts of 127-μm particles the continuous diffusion network was easily formed by means of dissolution without extensive mechanical rupturing of the polymeric material. On the other hand, in matrices containing totally encapsulated small particles, the formation of a continuous diffusion network demands the rupturing of polymeric bridges between particles. From scanning electron micrographs taken after dissolution tests, it is possible to observe numerous small shrunken capillaries inside the matrix and even some disc-shaped openings at the surface (Fig. 5b and c). Thus, the variations in the profiles of release and swelling between different matrices can at least partially be explained by the differences in the formation of the diffusion network.

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