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Microencapsulation of ion-exchange resins by interfacial nylon polymerization

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Summary

Microcapsules of nylon containing ion-exchange resins have been prepared, using an interfacial polycondensation procedure. A complex formed by anion-exchange resins (Dowex-1) and sodium fluoresceinate was used as a model resinate. Observation of the microcapsules by optical microscopy permitted us to confirm the continuity of the polymeric film around the particles of resin, as well as their perfect individualization. In vitro release studies revealed that the degree of reticulation of the resins, as well as the presence of the polymeric coat of nylon, delayed the release of the drug.

Introduction

Since Adams and Holmes synthesized the first ion-exchange resins in 1935, proposing their use in the isolation and purification of products from solutions, investigations that have been carried out using this system have led to a considerable increase in the number of possible applications. This is especially true in the field of pharmacy where it has led to the filing of important patents (Keating, 1961; Hays, 1962; Keating, 1964).

Among the advantages of including drugs in ion-exchange resins, so that they can be used as new drug delivery systems, we can cite the following (Keating, 1961): (i) a delay in the release of the drug that will permit a longer duration of its effects; (ii) an increase in its stability; and (iii) the masking of possible disagreeable organoleptic characteristics.

If, in addition to a delay, a true control over the rate of release of the drug is desired, it will be necessary to coat the particles of the drug-resin complex, this coating acting as a limiting factor in the release of the drug.

A suitable procedure for attaining the above is microencapsulation. This technique, although it has been used extensively (Luzzi, 1970; Nixon and Walter, 1971; Madan et al., 1972), has seldom been applied to the coating of resin particles (Raghunathan et al., 1981; Motycka et al., 1985; Irwin et al., 1988).

One of the main failings of microencapsulation of resins is the rupture of the coating caused by swelling of the dried particles on rehydration. To solve this problem, it was proposed that impregnating agents such as poly(ethylene glycol), propylene glycol, mannitol, lactose and methylcellulose (Raghunathan et al., 1980) be used, that

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were capable of maintaining the particles swollen before coating.

The formation of a coating of nylon by interfacial polycondensation, in addition to being a relatively simple microencapsulation technique, has the advantage that it can be carried out on the hydrated resins and therefore eliminates the necessity of using impregnating agents.

This investigation is aimed at achieving the encapsulation of particles of ion-exchange resins with nylon film, in order to obtain adequate control of the release rate of the drugs.

Materials and Methods

Materials

Anion-exchange resins (Dowex ion-exchange resins; Dow, Midland, MI) in the chloride form (1-x4 and 1-x8; 200–400 mesh) were used as the model resin and fluorescein sodium salt (Sigma, La Verpillière, France) was used as the model drug. Hexamethylenediamine and sebacoyl chloride (Sigma) were the monomeric reactants and sorbitan trioleate (Glytanox-4034; Glyco Ibérica, Barcelona) was the emulsifying agent. Chloroform and cyclohexane were analar grade and used without further purification.

Methods

Purification of the resins The resins in the chloride form were conditioned by decantation to remove the floating beads. A slurry of 5 g of the resins was then treated with 3×50-ml portions of deionized water, 2×50 ml of 95% ethanol, 1×50 ml of 50% ethanol, and 1×85 ml of deionized water. Each stage of treatment takes at least 1 h using a batch process with magnetic stirring. Purification is achieved by recycling the ion exchanger twice between its basic and acidic forms, respectively, with 60 ml of 2 M NaOH and 60 ml of 2 M HCl. This procedure was repeated once, and finally the resins were recovered by vacuum filtration and washed thoroughly with deionized water. They were then dried to constant weight at 50 °C in an electronic moisture balance (Shimadzu, Kyoto) and placed in a desiccator.

Preparation of the drug-resin complexes The particles of resin were suspended in a charging solution consisting of a 0.018 M solution of sodium fluorescein containing an excess, in terms of equivalents, and stirred continuously for 24 h. The drug-resin complex was collected by vacuum filtration and washed free of any unreacted drug with deionized water, followed by drying to constant weight. The filtrate was assayed spectrofluorimetrically (Kontron, Zürich) at an excitation wavelength of 485 nm and an emission wavelength of 515 nm (USP XXI). The drug load of the resin complex was calculated by subtracting the amount of fluorescein in solution after filtering and rinsing, from the initial value. This drug load was 63.88% for Dowex 1-x4 resin and 61.51% for Dowex 1-x8 resin.

Coating procedure The resins were coated by interfacial nylon polymerization according to the method described by Chang et al. (1966), as slightly modified. For the preparation of microcapsules, 6 ml of 1 M hexamethylenediamine in 0.45 M $NaHCO_3$-Na_2CO_3 buffer (pH 9.8) was added to 3 g of wet resin beads and the suspension was stirred for 30 min.

After soaking the resins, the supernatant liquid was discarded and the slurry was injected in 60 ml of a 0.144 M solution of sebacoyl chloride in organic phase (chloroform/cyclohexane, 1 : 4) containing 10% v/v of sorbitan trioleate. The reaction vessel was cooled by immersion in an ice bath prior to the addition of the resins and the system was stirred at 1200 rpm (IKA stirring motor RW 20 DZM, IKA-Labortechnik, Stanfen, F.R.G.). The polymerization reaction was continued for 5 min and then quenched by the addition of 120 ml of organic phase. The microcapsules formed were allowed to settle, the supernatant was decanted, and then, the microcapsules were rinsed twice, each with 120 ml of organic phase. They were collected by vacuum filtration and washed thoroughly with deionized water. Encapsulated beads were stored in their hydrated state at 4 °C.

The coating procedure may be carried out either on the drug-resin complex or on the uncharged resin. In the present work, the resins were exchanged with the drug after encapsulation and the

drug load attained was 63.36% for the Dowex 1-x4 resin and 54.34% for the Dowex 1-x8 resin.

Observation of coated resins The microcapsules were examined using an optical microscope (Optiphot, Nikon).

In vitro drug release studies To evaluate the release behaviour of the drug from coated and uncoated resins the in vitro test was performed as follows: 50 mg of product were suspended in 4 l of dissolution medium (0.2 M Na_2HPO_4-NaH_2PO_4 buffer, pH 7.4) with an ionic strength of 1 under agitation at 1000 rpm (IKA stirring) and 37 °C.

Aliquots were withdrawn for analysis at fixed time intervals and the drug concentration was measured by spectrofluorimetry.

In order to minimize possible degradation of fluoresceinate anion, due to the effects of light, the processes for binding and for release were performed in the dark and the withdrawn samples were also stored in the dark.

Results and Discussion

The release of fluorescein from the resins was observed to be strongly influenced by the effect of the ionic strength of the dissolution medium used.

TABLE 1

Effect of ionic strength on the percentage of drug released after 1 and 24 h from Dowex 1-x4 resinates

Time (h)	Fluorescein released (%)		
	$\mu = 0.8$	$\mu = 1.0$	$\mu = 1.2$
1	38.73	64.35	71.99
24	51.25	68.66	82.58

This effect had already been described for other types of resins (Irwin et al., 1987; Sprockel and Prapaitrakul, 1988). Fig. 1 shows the release profiles obtained from Dowex 1-x4 resins, in H_2NaPO_4/HNa_2PO_4 buffer with different ionic strengths: 0.8, 1.0 and 1.2. As can be observed, an increase in the ionic strength produces an increase in the release of fluorescein from the resinates, unmistakably reflecting the influence of the increase in concentration of competitive ions in the medium. This effect is of decisive importance when selecting the dissolution test that is going to be used in the in vitro tests.

Table 1 lists the values of the percentages of drug released at 1 and 24 h, using the different ionic strengths, values which motivated the selection of the dissolution medium of ionic strength 1 as the most appropriate for carrying out release

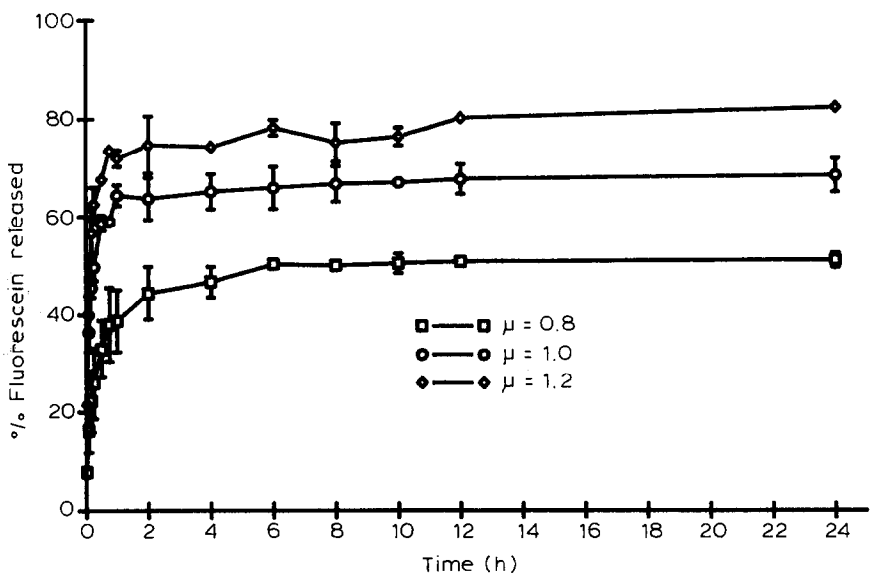

Fig. 1. Effect of ionic strength on the fluorescein release profiles from Dowex 1-x4 resinates.

studies of the drug, as the quantities of drug released in this case are sufficiently high for later use in carrying out comparative studies with the encapsulated complexes.

The interest in the technique of interfacial polymerization for the preparation of microcapsules has become evident in the elaboration of the so-called artificial cells used as extracorporeal systems of blood purification (Chang, 1966, 1969; Chang et al., 1966) and as carriers for the treatment of enzymatic deficiencies (Chang and Poznansky, 1968). Although in the literature, a wide variety of acid diamines and acid halides have been suggested for the preparation of different polyamides (Madan, 1986), in the encapsulation of pharmaceuticals, nylon 6-10 is the one that has been investigated most as a builder of the microcapsular wall (Chang, 1966; Florence and Jenkins, 1975; McGinity et al., 1981) this being the reason for its selection. The attempt to carry out the coating of resins, mentioned by Chang in some of his early studies (Chang, 1966), gave a satisfactory result when using concentrations of monomers higher than those normally proposed for the formation of nylon microcapsules. The necessity for using such high concentrations of monomeric reactives could be justified by taking into account that the attempt to form the nylon film, is not to surround a drop of emulsion w/o (as happens in the normal elaboration of microcapsules), but a porous particle of resin. In this case, the solution of hexamethylenediamine does not constitute the internal phase of the emulsion, but incorporates itself by impregnating the structure of the resin, so that the polymerization reaction is produced completely around the particle, the concentrations of both monomers having to be increased greatly. An individual and uniform coating is attained under these conditions, as can be seen in Fig. 2, where the nylon coating that has been achieved can be observed very clearly.

In order to prevent possible losses of the drug during the polymerization process, formation of the resin-fluorescein complex was carried out, in this case, after elaboration of the microcapsules. In Fig. 3 one can see the release profiles obtained from the 1-x4 and 1-x8 resins, both coated and uncoated, and the effects of both the degree of crosslinking and the nylon film coating can be observed. In order to confirm the significance of

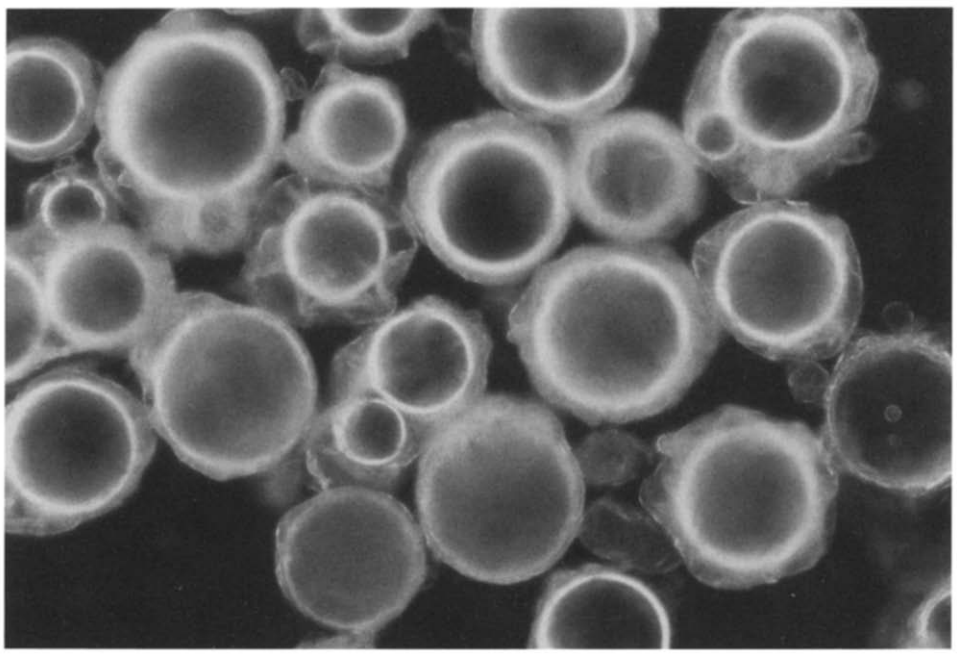

Fig. 2. Optical photomicrograph of encapsulated drug-resin complex (magnification: ×125).

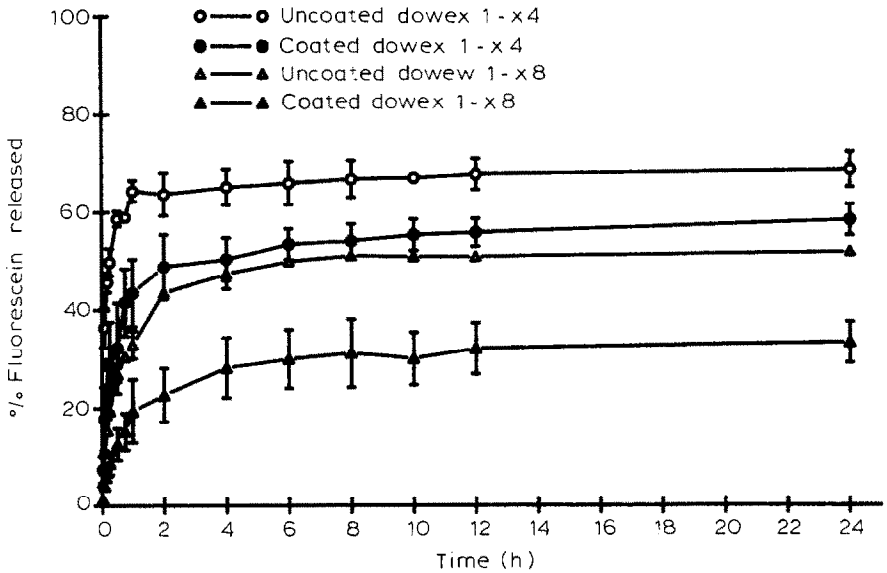

Fig. 3. Release profiles of fluorescein from coated and uncoated Dowex 1-x4 and 1-x8 resinates.

these effects, the corresponding analysis of variance for the percentages of drug released after 1 and 24 h was performed. These parameters were selected in order to obtain a correct characterization of the release profiles. The values corresponding to these parameters are listed in Table 2. The influence of crosslinking on drug release, indicated previously for this and other types of

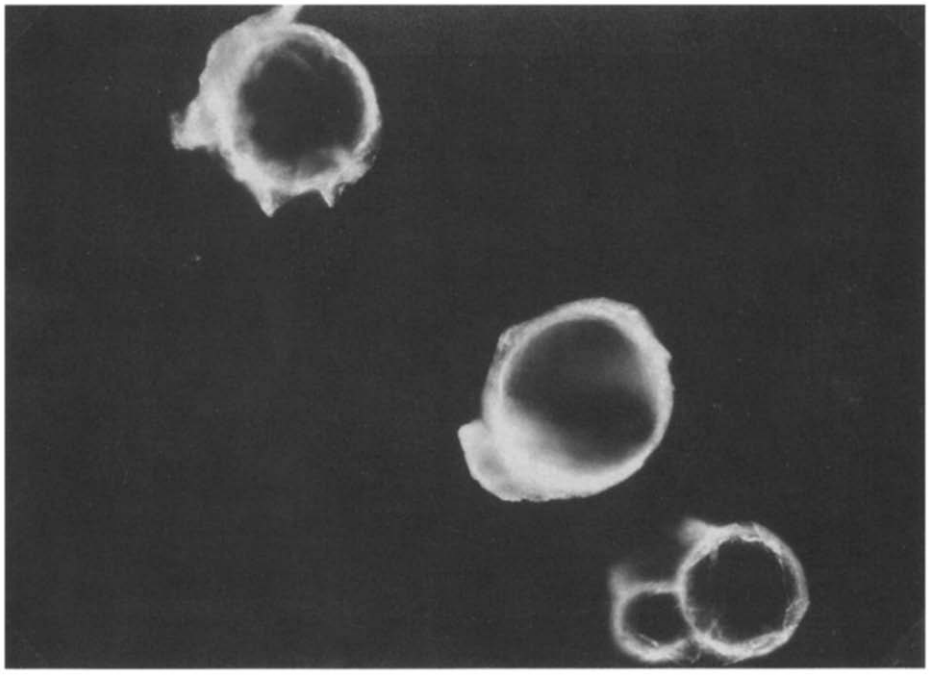

Fig. 4. Optical photomicrograph of encapsulated drug resin complex after in vitro release study (magnification: ×125).

TABLE 2

Effect of crosslinking degree and coating on the percentage of drug released after 1 and 24 h from Dowex 1-x4 and 1-x8 resinates

Time (h)	Fluorescein released (%)			
	Dowex 1-x4		Dowex 1-x8	
	Uncoated	Coated	Uncoated	Coated
1	64.35	43.78	32.91	19.39
24	68.66	58.47	51.93	33.36

resins (Geneidi and Hamacher, 1980; Irwin et al., 1987; Farag and Nairn, 1988), was of marked significance in our case for the amount of drug released not only after 1 h ($F = 88.83$ with 1 degree of freedom, $\alpha = 0.01$), but also after 24 h ($F = 126.9$ with 1 degree of freedom, $\alpha = 0.01$). It was also possible to confirm the significant influence of the polymeric coating on the two previous parameters ($F = 43.07$ and $F = 59.76$ with 1 degree of freedom, $\alpha = 0.01$), which becomes more pronounced in the 8% crosslinked resins. A possible explanation for this observation would be the formation of a more uniform polymeric film around the less porous particles, which would lead to an increased delay in liberation.

One of the most conspicuous factors in the behaviour of the microcapsules during the liberation process is the resistance of the nylon coating that has been formed. This is reflected in Fig. 4, showing that it is possible to observe the state of the microcapsules after 24 h in the dissolution medium. Therefore, the coating of the swollen resins prevents the bursting of the film, which would normally result from the swelling of the dried resins as they rehydrated (Raghunathan et al., 1981), and this also means that it is not necessary to use impregnating agents (Raghunathan, 1980; Raghunathan et al., 1981).

In order to be able to produce a good sustained release formulation, it is essential to understand the controlling mechanism of release. The release of the drug from the resins could be controlled by the resistance to pore diffusion (also referred to as 'particle diffusion control') or by the resistance of the film surrounding the particle, ('film diffusion control'). Thus, whilst the most appropriate parameter for comparing the release profiles in the case of particle diffusion control is the diffusion coefficient, the film thickness is the most pertinent factor in the other case. In cases where the rate-limiting step is particle diffusion, assuming that resin particles are uniform spheres of radius r, and that sink conditions are maintained, the fraction of drug released as a function of time is given by the following equation, proposed by Boyd et al. (1947):

$$F = 1 - Q/Q_0 = 1 - 6/n^2 \sum_{n=1}^{\infty} 1/n^2 \exp(n^2 Bt) \quad (1)$$

where
$B = n^2 D/r^2$, and F represents the drug released from the resinate at time t, Q, the drug content of the resinate at time t, Q_0, the initial drug content of the resinate, B, the rate constant, D, the effective diffusion coefficient of the ion exchange process and t, the time.

For F values lower than 0.85 and after different transformations, Reichenberg (1953) obtained a simplified approximation for Eqn. 1, tabulating the corresponding values of Bt for different values of F. By plotting Bt values vs experimental values of time, a straight line passing through the origin with a slope equal to B should be obtained. From this B value the effective diffusion coefficient, D, could be calculated. This method has been used by Chaudhry and Saunders (1956), Gyselinck et al. (1981) and Schacht et al. (1982) for the characterization of their resinates. A simpler procedure has been recently developed by Bhaskar et al. (1986) to test the particle diffusion controlled release of drug, which avoids the repeated consultations of Reichenberg's standard table. In the equation that they have proposed, it is suggested that the simple checking of the linearity between $-\ln(1-F)$ and $t^{0.65}$ is sufficient to establish which is the determining mechanism of the liberation process:

$$-\ln(1-F) = \ln(Q_0/Q) = 1.59(3/r)^{1.3} D^{0.65} t^{0.65} \quad (2)$$

The corresponding plots of $\ln(Q_0/Q)$ vs $t^{0.65}$ for the different resinates are shown in Fig. 5. As can be observed, in all cases a linear relationship is maintained, which confirms the fact that the release rate is controlled by particle diffusion, irrespective of whether the resins are encapsulated.

In this graph, attention is focussed on the existence of the independent term in the equation of plot *Bt-t* corresponding to the uncoated Dowex 1-x4 resinates. The explanation of this could be based on the rapid initial release of fluorescein, caused by the high concentration of ions used in the dissolution medium ($\mu = 1$). This supposition is supported by a comparison of the straight lines obtained by plotting $\ln(Q_0/Q)$ vs $t^{0.65}$ for these resinates released at different ionic strengths, which are shown in Fig. 6. In this graph, it can be seen how the increase in counterions in the medium promotes a fast exchange of the fluoresceinate ion. In the complexes formed by the resins that have the highest degree of crosslinking, as well as in the encapsulated complexes, the value of the independent term is practically zero, which demonstrates that the delay in the release due to crosslinking and the presence of the coating counteracts the accelerating effect caused by the high concentration of counterions.

With regard to these results, the ion-exchange resins coated with nylon 6-10 appear to be potential sustained release formulations, whose wide range of particle size could permit their use, independently of the oral administration usually used for this type of particles (Chaudhry and Saunders, 1956; Raghunathan et al., 1981), in other new fields such as parenteral or ophthalmic applications.

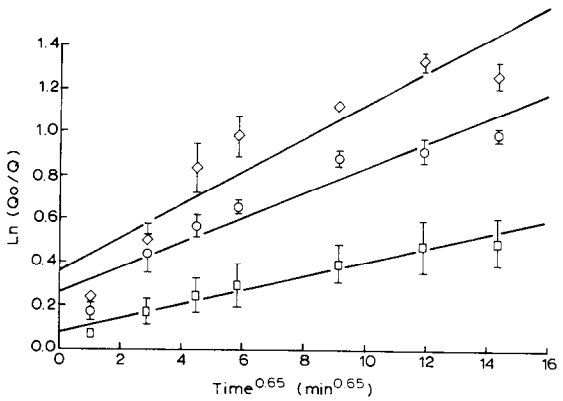

Fig. 6. Effect of ionic strength on the plot to check particle diffusion-controlled drug release from Dowex 1-x4 resinates. Key as in Fig. 1.

Complementary Results

Results of drug release studies

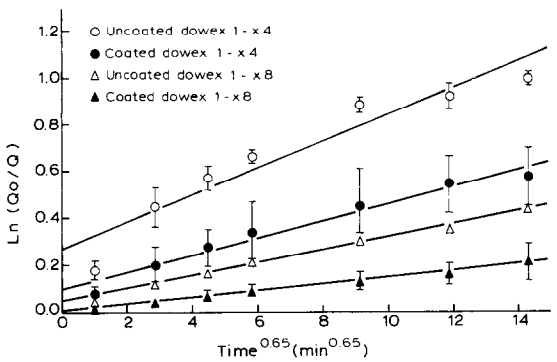

Fig. 5. Plot to check particle diffusion-controlled drug release from coated and uncoated Dowex 1 resinates. Key as in Fig. 3.

Time (min)	Mean values (S.D.) of % fluorescein		
	$\mu = 0.8$	$\mu = 1.0$	$\mu = 1.2$
1	7.77 (0.95)	16.32 (3.18)	21.52 (1.18)
5	16.30 (4.60)	36.37 (4.03)	39.80 (4.10)
10	22.18 (6.25)	45.60 (1.95)	56.54 (4.84)
15	25.92 (7.25)	49.79 (2.79)	62.53 (3.46)
30	32.94 (5.90)	58.67 (1.54)	67.61 (0.34)
45	38.00 (7.63)	58.98 (1.03)	73.59 (1.20)
60	38.73 (6.42)	64.35 (2.14)	71.99 (1.72)
120	44.46 (5.38)	63.66 (4.33)	74.76 (5.84)
240	46.74 (3.11)	65.11 (3.63)	74.34 (1.16)
360	50.35 (0.61)	65.90 (4.36)	78.31 (1.60)
480	50.09 (1.20)	66.71 (3.69)	75.25 (3.95)
600	50.52 (2.01)	67.00 (1.29)	76.51 (1.82)
720	50.83 (1.37)	67.72 (3.10)	80.25 (1.36)
1440	51.25 (1.47)	68.66 (3.52)	82.58 (0.42)

Time (min)	Mean values (S.D.) of % fluorescein			
	Dowex 1-x4	μcDowex 1-x4	Dowex 1-x8	μcDowex 1-x8
1	16.32 (3.18)	7.41 (2.70)	4.76 (0.21)	1.33 (0.38)
5	36.37 (4.03)	17.78 (6.56)	11.22 (0.41)	4.10 (0.97)
10	45.60 (1.95)	23.82 (6.00)	15.37 (1.31)	6.90 (1.85)
15	49.79 (2.79)	28.47 (9.08)	19.49 (0.94)	8.70 (2.26)
30	58.67 (1.54)	32.23 (9.24)	26.92 (1.56)	12.62 (3.23)
45	58.98 (1.03)	41.55 (6.90)	30.38 (0.23)	15.19 (3.77)
60	64.35 (2.14)	43.48 (6.90)	32.91 (2.86)	19.39 (6.44)
120	63.66 (4.33)	48.81 (6.62)	43.52 (1.15)	22.67 (5.43)
240	65.11 (3.63)	50.36 (4.40)	47.38 (3.05)	28.21 (6.14)
360	65.91 (4.36)	53.42 (3.18)	49.94 (1.08)	29.99 (5.96)
480	66.71 (3.69)	54.08 (3.53)	51.10 (1.03)	31.16 (6.97)
600	67.00 (1.29)	55.37 (3.23)	50.92 (0.65)	30.05 (5.38)
720	67.72 (3.10)	55.83 (2.88)	50.92 (1.26)	32.12 (5.27)
1440	68.66 (3.52)	58.47 (3.20)	51.93 (1.03)	33.36 (4.20)

ANOVA of percentage of drug release at 1 h

Source of variance	Sum of squares	Degree of freedom	Mean square	F	α
Treatments	3128.33	3	1042.78	43.96	< 0.01
Crosslinking	2106.75	1	2106.75	88.83	< 0.01
Coating	1021.58	1	1021.58	43.07	< 0.01
Interaction	17.52	1	17.52	0.74	
Error	189.73	8	23.72		
Total	3318.06	11			

ANOVA of percentage of drug release at 24 hours

Source of variance	Sum of squares	Degree of freedom	Mean square	F	α
Treatments	1933.95	3	644.65	62.22	< 0.01
Crosslinking	1315.03	1	1315.03	126.98	< 0.01
Coating	618.92	1	618.92	59.76	< 0.01
Interaction	52.33	1	52.33	5.05	
Error	82.85	8	10.36		
Total	2016.80	11			

Acknowledgement

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