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Formulation and in vitro evaluation of HPMCP-microencapsulated drug-resin complexes for sustained release of diclofenac

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Abstract

Microcapsules containing diclofenac-resin complexes were prepared by a non-aqueous emulsion method using hydroxypropyl methylcellulose phthalate (HPMCP). The effect of the addition of various surfactants on the characteristics of microcapsules including resin particles with different degrees of crosslinking, was investigated. The microencapsulation process was evaluated with respect to total yield and coat to core ratio, and the microcapsules with respect to particle size and dissolution efficiency. Statistical analysis of the results demonstrated that both the degree of crosslinking and the presence of the polymer coating significantly retard release, indicating that the effect of the type of surfactant on the release rate is inappreciable.

Keywords: Ion-exchange resin; Microencapsulation; Hydroxypropyl methylcellulose phthalate; Sodium diclofenac; Sustained release

Ion-exchange resins (IER) behave, for some drugs, as reliable controlled drug delivery systems (Schlichting, 1983). However, improvements of their release properties can be effected by coating the resin beads and further controlling the rate of drug release (Ragunathan et al., 1981; Motycka et al., 1985; Prapaitrakul and Whitworth, 1989; Moldenhauer and Nairn, 1990). In these forms the pattern of drug release is governed by the degree of crosslinking of the resins and by the properties of the coat. Usually, resins are coated with insoluble polymers which control the release of drug by a diffusion mechanism, however, microencapsulation with an enteric polymer may also represent a useful tool for improving their release and protective properties.

In this study, we have designed a system based on the coating of diclofenac-resin complexes with the polymer HPMCP (grade HP-55), which dissolves at pH 5.4. This system was specially intended for nonsteroidal anti-inflammatory drugs, such as diclofenac, which have to be formulated in an enteric and also controlled release dosage form, due to their gastrointestinal side effects and their short half-life, respectively. The aim of this work was to evaluate the in vitro behaviour of these enteric systems and also to study the

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effect of some formulation variables on the release of diclofenac, such as the degree of crosslinking of the resins and the type of surfactant used.

The diclofenac-resin complexes were prepared by suspending the previously purified ion-exchange resins (IER) (Dowex 1x4 and 1x8, 200–400 mesh; Dow Chemical Co., Midland, MI) in a 0.01 M solution of sodium diclofenac in an ethanol-water mixture (1:1, v/v) containing a 25% excess of equivalents, and stirring for 24 h. The complexes were microencapsulated with HPMCP (grade HP-55; Shin-Etsu Chemical Ind. Co., Tokyo) by a non-aqueous emulsion method in an acetone/liquid paraffin system. To study the effect of surfactants with different HLB values on the microencapsulation process, Span 20, Span 80 and Span 85 were incorporated into the external phase of the emulsion. Briefly, the core material (about 0.5 g dry weight) was dispersed in 100 ml of light liquid paraffin containing the surfactant agent. The suspension was stirred at 500 rpm (IKA stirring motor RW DZM, IKA-labortechnik, Stafen, Germany) and 10 ml of 12% (w/w) HPMCP solution in acetone was added. Simultaneously to the addition of the polymer solution, 5 ml of pure solvent was added to reproduce the concentrations selected on a previously constructed phase diagram (García-Encina et al., 1992): 1.03% w/w HPMCP, 11.65% w/w acetone and 87.32% w/w light liquid paraffin. After stirring for 30 min, 100 ml of petroleum ether was added and stirring was then continued for an additional 15 min to harden the product. The product was filtered under vacuum, washed with petroleum ether and air dried for 12 h.

For each batch of micocapsules the yield of the process was determined in duplicate. The final coat/core ratio was calculated in triplicate by extracting the coat of the microcapsules in a Soxhlet apparatus with acetone, and then drying the extract to constant weight. From this ratio the drug load of the microcapsules was evaluated. The mean diameter of the microcapsules was determined by measuring 50 particles under an optical microscope (Olympus BH2-PC) and scanning electron microscopy (Model S-250 Hitachi, Tokyo) was used to evaluate the quality of the coating obtained under the various conditions studied. The release characteristics of both the diclofenac-IER complexes and their microcapsules (about 0.1 g dry weight) were examined in triplicate in a continuous-flow apparatus (Llabrés et al., 1978). The first eluent, 0.1 M HCl, was pumped for 2 h and was then replaced with a 0.2 M buffer phosphate (pH 6.8). Samples were assayed spectophotometrically at 276 nm.

The microcapsules were spherical, multinucleate and displayed a spongy appearance. Differences in the thickness of the polymer coating were noticeable from microscopical examination (results not shown), with the more hydrophobic surfactant (Span 85) leading to a greater coating thickness. Table 1 shows the process yield, final coat/core ratio and particle size of the studied microcapsule formulations. These results seem to confirm the conclusions suggested by the microscopical analysis. The two-way ANOVAs carried out on the first two parameters indicated that the factor 'type of surfactant' has a significant effect ($F = 5.76$ with 2 and 6 df, $\alpha < 0.05$, for process yield; and $F = 811.56$ with 2 and 12 df, $\alpha < 0.01$,

Table 1
Parameter values of various formulations of microcapsules (mean ± SD)

Core material	Type of surfactant	Yield (%)	Coat/core ratio	Particle size (μm)
Dowex 1x4	Span 20	53.95 ± 21.95	0.63 ± 0.04	703.5 ± 191.8
	Span 80	78.72 ± 5.25	1.77 ± 0.12	849.5 ± 156.2
	Span 85	96.85 ± 7.52	1.87 ± 0.09	889.5 ± 151.6
Dowex 1x8	Span 20	58.74 ± 0.64	0.61 ± 0.02	680.5 ± 188.8
	Span 80	83.08 ± 4.74	2.01 ± 0.05	826.0 ± 137.0
	Span 85	82.93 ± 12.76	2.22 ± 0.06	869.5 ± 166.6

for coat/core ratio). The degree of crosslinking was not significant with regard to the parameter process yield, however, it was in respect of the final coat/core ratio ($\alpha < 0.01$). This significant effect can be considered to be of little importance, as supported by its low F value (35.29, with 1 and 12 df), in comparison with that obtained for the factor, type of surfactant.

Process yield, final coat/core ratio and particle size were all considerably lower when the surfactant used was Span 20. This latter effect being unexpected in the light of previous studies carried out without core material, in which greater aggregation and larger particle sizes were observed (García-Encina, 1992). In this work, when Span 20 was used, the inclusion of resins led to a considerable loss of polymer, as can be seen from the values of the process yield and final coat/core ratio parameters. This loss is especially appreciable during the microencapsulation process when the nonsolvent is added, leading to the insolubilization of the polymer on the walls of the vessel and on the surface of the external phase. The direct result of this loss is a thinner polymer coating, which is more transparent and spongy in appearance than that obtained using any of the other surfactants. The comparative statistical test confirmed the significance of the differences mentioned above, distinguishing the formulations prepared with Span 20 from the others, in terms of either process yield or core/coat ratio. Thus, the least significant difference (LSD) test applied to the yield data led to the following grouping for the 1x4 and 1x8 microcapsule (MC) formulations:

$\underline{MC_{Span\ 20}\ MC_{Span\ 80}\ MC_{Span\ 85}}$

and to final coat/core ratio data were as follows:

$\underline{MC_{Span\ 20}\ MC_{Span\ 80}\ MC_{Span\ 85}}$

(core: Dowex1x4)

$\underline{MC_{Span\ 20}\ MC_{Span\ 80}\ MC_{Span\ 85}}$

(core: Dowex1x8)

These statistical results indicate that, in general, the other two surfactants (Span 80 and Span 85) behave similarly during the microencapsulation process, although with respect the final coat/core ratio the test separates the 1x8 formulation prepared with Span 85 from the others.

Release profiles were characterized using the parameter dissolution efficiency (Khan and Rhodes, 1972), whose values together with that of drug loading are listed in Table 2. As can be seen from Fig. 1, once the pH began to increase (about 3 h), there was a marked difference between the drug release profiles from coated and uncoated diclofenac-IER complexes. Prior to this, there was scarcely any difference between the two dissolution curves, and there was hardly any drug release from any of the formulations. This was to be expected for the HPMCP microcapsules but not for those of resin, since in an acidic medium the latter would be expected to start the ion exchange. However, the observations can be explained on the basis of the pH-dependent solubility of sodium diclofenac, which shows the maximum value from about pH 4. Therefore, all drug released is precipitated at pH < 2 and only at higher values do differences become evident. The fact that small differences between microcapsules with the same degree of crosslinking were ob-

Table 2
Drug loading and dissolution efficiency (DE) values of various formulations (mean ± SD)

Core material	Type of surfactant	Drug loading [a] (%)	DE
Dowex 1x4	–	43.73 ± 0.29	0.3492 ± 0.0022
	Span 20	26.87 ± 0.58	0.2502 ± 0.0219
	Span 80	15.78 ± 0,66	0.2368 ± 0.0136
	Span 85	15.26 ± o.45	0.2177 ± 0.0208
Dowex 1x8	–	36.61 ± 0.33	0.2751 ± 0.0098
	Span 20	23.11 ± 0.26	0.1835 ± 0.0136
	Span 80	12.32 ± 0.20	0.1681 ± 0.0144
	Span 85	15.52 ± 0.19	0.1625 ± 0.0200

[a] (Weight of diclofenac/weight of dry complex or microcapsules) × 100.

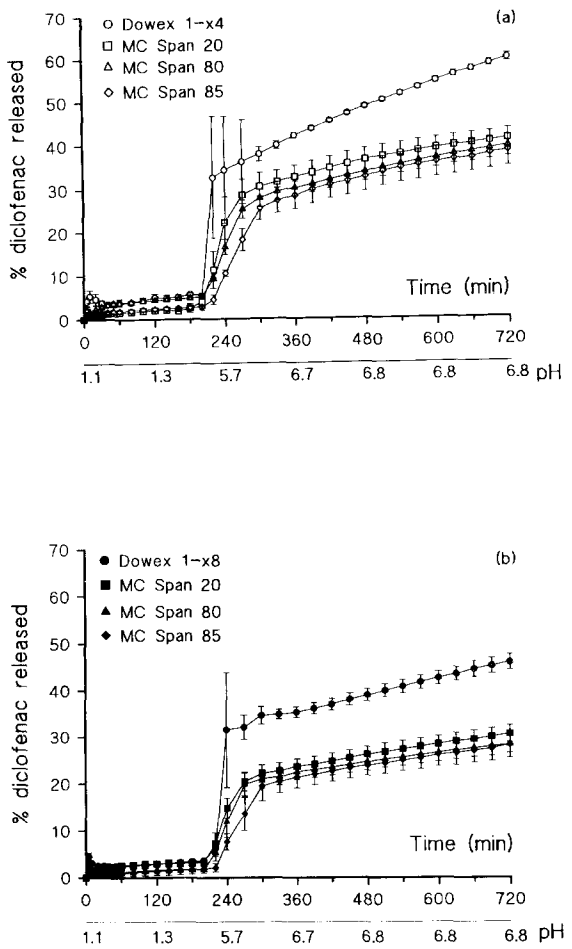

Fig. 1. In vitro diclofenac release profiles from drug-IER complexes and HPMCP microcapsules. Core material: (a) Dowex 1x4; (b) Dowex 1x8.

served from the third hour onwards supports this hypothesis, whereas in both cases (1x4 and 1x8 resin) the delay in the release of diclofenac caused by the enteric coating could be clearly seen.

The two-way ANOVA applied to the DE values showed that both 'degree of crosslinking' and type of surfactant are significant factors ($F = 105.6$ with 1 and 16 d.f. and $F = 74.55$ with 3 and 16 d.f.; $\alpha < 0.01$). The LSD test indicated the following grouping for the 1x4 and 1x8 formulations:

resins $\underline{MC_{Span\ 20}\ MC_{Span\ 80}\ MC_{Span\ 85}}$

From these results it can be concluded that the type of surfactant has little effect on the release of diclofenac from the HPMCP microcapsules containing ion-exchange resins. The release-limiting step is that of HPMPC dissolution, which does not appear to depend on coating thickness although, on the grounds of the above, this factor does depend on the type of surfactant used, this being indicated by the ANOVAs carried out on the coat/core ratio and by the morphological and size analysis of the microcapsules. Finally, the delay in release brought about by the enteric coating, even in the case of resins with the high degree of crosslinking, is worth noting and confirms the usefulness of employing ion-exchange resins as microencapsulation core material in enteric formulations. In this way, it may be possible to improve the release characteristics of ionic complexes and to avoid the harmful effects of drugs like diclofenac on the gastric mucosa.

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