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COMMUNICATIONS

Polycyanoacrylate nanocapsules as potential lysosomotropic carriers: preparation, morphological and sorptive properties

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We have shown previously (Couvreur et al 1977) that polyacrylamide nanocapsules are a new type of lysosomotropic carrier, but unfortunately they are unlikely to be digested by lysosomal enzymes. This article describes the preparation and the morphology of polyalkylcyanoacrylate nanocapsules since polycyanoacrylate may be biodegradable, as suggested by its use in surgery (Collins et al 1969; Heisterkamp et al 1969) and by its chemical properties (Cameron et al 1965; Leonard et al 1966 a, b; Pani et al 1968).

We also present results of the sorption of small molecules on these nanocapsules.

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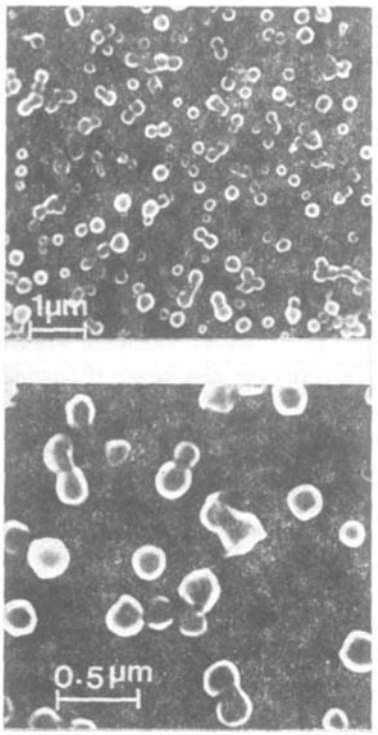

FIG. 1. Morphological appearance of polymethylcyanoacrylate nanocapsules by scanning electron microscopy.

Polymethyl and polyethylcyanoacrylate nanocapsules were prepared by polymerization. To Tween 20 (0·25 g), HCl 0·1 M (5·0 ml) in distilled water (50·0 ml) was added 0·6 ml of either of the monomers (methyl-or- ethylcyanoacrylate). After mechanically stirring for 30 min the mixture was passed through a fritted glass filter (pore size 9–15 μm) and then distilled water added to 200 ml. After preparation, nanocapsules form milky suspensions displaying a Tyndall effect. The particles pass through a Millipore filter with 0·45 μm pores. This method is rapid and easy and avoids the destructive γ-irradiation used in the preparation of polyacrylamide nanocapsules (Couvreur et al 1977).

Scanning electron microscopy shows spherical particles with a diameter of about 200 nm (Fig. 1). Variation of the Tween 20 concentrations did not affect the morphological appearance and size. Particles obtained without surfactant seem to be more agglomerated and larger than those with surfactant.

Suspension of nanocapsules prepared with Tween 20 (0·1%) were spray frozen (Bachmann & Schmitt-Fumian 1973) and examined by the electron microscope after freeze fracture. The use of fixatives and cryoprotectants are avoided by this method, while surfactants do not appreciably interfere. Fig. 2 shows that the inner structure appears to be highly porous, de-

FIG. 2. The appearance of the internal structure of polymethylcyanoacrylate nanocapsules by the electron microscopy after spray freezing and cryofracture (see (Bachmann et al 1973) for details).

veloping a large specific area favourable to sorption processes. No continuous limiting envelope surrounding the particle could be identified.

The sorption of fluorescein at pH values between 2 and 8 both on methyl and on ethylcyanoacrylate nanocapsules was assessed immediately after preparation of the capsules and 1, 2 and 4 days later to confirm the in vitro degradability of the polymer described in the literature (Cameron et al 1965; Leonard et al 1966; Pani et al 1968). The capsule suspensions were kept at 37 °C. Fluorescein was determined by fluorimetry in both sediment and supernatant after ultracentrifugation of the suspensions at 50 000 rev min^{-1} for 1½ h. Immediately after preparation of the samples, 65% of the fluorescein is sorbed on polyethylcyanoacrylate capsules at pH values between 2 and 4 (Fig. 3b, solid line). In the same conditions and at the same pH values the methylpolycyanoacrylate nanocapsules sorb about 50% of the fluorescein (Fig. 3a, solid line). At pH values between 4 and 6·5 fluorescein is desorbed from both methyl and ethylpolycyanoacrylate nanocapsules (Fig. 3a, b, solid lines). At more alkaline pH values sorption of fluorescein becomes negligible.

These results suggest that non-ionized fluorescein tends to be sorbed on the capsules and more so on the ethyl than methylcyanoacrylate capsules.

After the storage of the suspensions at 37 °C and ultracentrifugation, no sediment was observed in the samples buffered at pH beyond 7 after 1 day for the methylcyanoacrylate and after 4 days for the ethylcyanoacrylate. Furthermore the zone of desorption is shifted towards the acid pH (see Fig. 3a, b).

This shift is more important for the methyl than for the ethylpolycyanoacrylate probably because of the more rapid degradability of the methyl product suggested in the literature (Leonard et al 1966).

The second type of drug tested for sorption was an alkaline antimitotic drug, daunorubicin. Unlike fluorescein, this is highly sorbed at alkaline pH, but only slightly sorbed at acid pH. The desorption zone corresponds to the pK_a (8·2) of the drug. These results are in agreement with the basic character of the molecule.

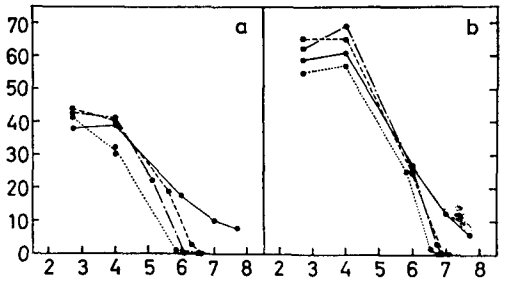

FIG. 3. Adsorption of fluorescein (ordinate: %) on methyl (a) and ethylpolycyanoacrylate (b) nanocapsules after 0 (●——●), 1 (●- - - -●), (●—·—●) and 4 (●·····●) days. Abscissa: pH.

However, determination of daunorubicin at more basic pH values is not reliable because of the drug's instability.

Both with fluorescein and daunorubicin, our results show that the sorptive capacity of the polymethyl and polyethylcyanoacrylate nanocapsules depends on the pH of the solutions and the pK_a of the drug sorbed. Furthermore, the high sorptive capacity of these nanocapsules is in agreement with the porous structure of capsules observed after cryofracture by electron microscopy.

Thus, polycyanoacrylate nanocapsules of about 200 nm diameter or less can be successfully used to sorb material of low molecular weight depending on the pH of the suspension and the pK_a of the drug. The results suggest that they could be potentially useful as lysosomotropic carriers owing to their size, structure and sorptive properties. The main interest in these capsules is that they may be biodegradable. However, their degradability in lysosomes and their stability in biological fluids remains to be assessed.

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