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Interfacial properties of polymethyl α-cyanoacrylate and polybutyl α-cyanoacrylate*

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Several physical properties of two polyalkyl α-cyanoacrylates relevant to their use in pharmaceutical dosage forms have been investigated. Formation of polymer films at several oil-water interfaces reveals films of diverse morphology. The retardation of solute transfer across an oil-water interface caused by the presence of polymer films formed *in situ* from the monomers has revealed that the methyl derivative forms the more effective barrier to the test solute, gentian violet. The emulsion-stabilizing properties of the methyl polymer have been studied, and the film-forming properties of the monomers spread from benzene onto water surfaces have been examined using a surface balance.

Biodegradable polymers are of particular interest in the design and fabrication of prolonged-acting dosage forms, particularly those intended for implantation or subcutaneous or intramuscular injection. Leonard, Kulkarni & others (1967) reported that polyalkyl α-cyanoacrylates are biodegradable, the rate of breakdown *in vivo* and *in vitro* decreasing with increasing alkyl chain length. The lower homologues (methyl, ethyl) are metabolized *in vivo* over a period of weeks and because of the relatively fast production of formaldehyde are more toxic than higher homologues. The butyl derivative is used as an adhesive in surgery; the monomer, applied to moist tissues, rapidly polymerizes forming bonds between neighbouring tissues.

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During work aimed at producing long-acting injections of phenothiazines, the need for biodegradable polymers for use even in experimental animals became clear (Florence & Jenkins, 1975). Promising pharmacology of nylon 6–10 microcapsules (which have unknown but possibly unacceptably slow biodegradability) led us to consider the possibility of employing alkylcyanoacrylate monomers to prepare polymer microcapsules. This work describes our preliminary investigations of the film-forming properties of the methyl and butyl cyanoacrylate monomers.

MATERIALS AND METHODS

Methylcyanoacrylate monomer was prepared using the method described by Jeremias (1960). The liquid monomer thus obtained was sealed into dry ampoules and stored in a refrigerator before use.

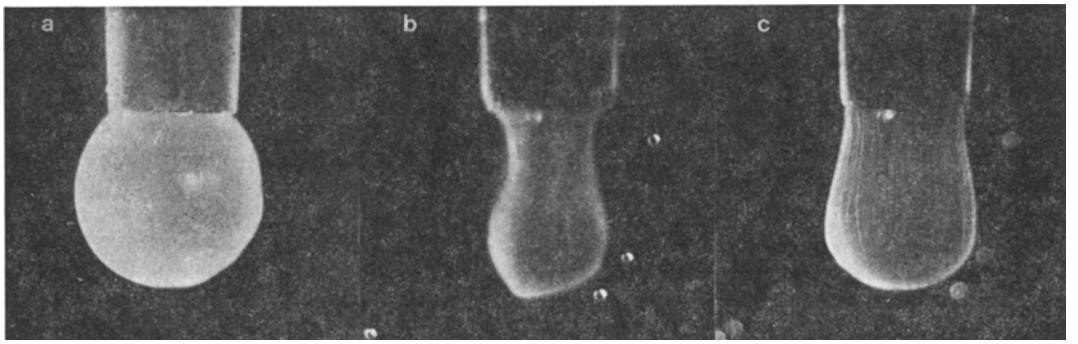

FIG. 1. Photographs of a droplet of di-n-butylphthalate containing 2·5% methylcyanoacrylate in an aqueous medium (a) several hours after formation (b) on reduction of droplet volume by withdrawal into syringe (c) on addition of further oil. Higher concentrations of monomer produce clearly visible films which crack on increase in droplet surface area with gradual renewal of the visible film.

Butylcyanoacrylate monomer was obtained as Histoacryl from Armour Laboratories Ltd. This material contains a low concentration of stabilizer to maintain its bulk storage properties.

Solutions of the monomers were prepared as required in di-n-butyl phthalate, carbon tetrachloride, benzene and chlorobenzene. Polysorbate 80 was obtained from Honeywill-Atlas.

Formation and barrier properties of interfacial polymer films. Solutions (2·5–5%) of the monomer in non-aqueous solvents were filled into a dry Agla syringe. A dye, gentian violet (1·85%), was added to each system and release of the dye from the oil droplet into water was measured. The syringe was assembled so that an oil droplet formed directly in an aqueous phase (15 ml) in a 2 cm glass cell placed in an SP 600 spectrophotometer. The optical density at 580 nm was determined at intervals.

Films for scanning electron microscopy were prepared under similar conditions. Solutions of monomer in three non-aqueous solvents were layered in contact with water. The monomer spontaneously polymerizes on contact with the aqueous phase and after equilibration the films were separated, dried, vacuum coated with gold/palladium and viewed by scanning electron microscopy (Cambridge Stereoscan Mark IIA).

Emulsions of di-n-butyl phthalate in water were prepared by ultrasonication for 30 s using 5 ml oil and 10 ml aqueous phase. Where monomer was incorporated in the emulsion it was as a 0·1% solution in the oil phase.

Particle size distributions of the resulting dispersions were measured as a function of time, using a light microscope.

Interfacial tensions were determined by the pendant drop method described previously (Elworthy & Florence, 1969). Each drop was photographed on 35 mm film and the dimensions of the drop determined from the negative using a Cambridge measuring machine. The tables of Stauffer (1965) were used in the calculation of interfacial tension. A value of 38·1 mN m^{-1} was found for the chlorobenzene-water interfacial tension (literature value, 37·41 mN m^{-1} at 25°). (The monomer dissolved in chlorobenzene displayed little surface activity when the surface tension of the droplets was measured in air; in the presence of the aqueous phase, polymer is formed at the interface, and perhaps caution has to be exercised in the application of the pendant drop equations when a visible film is present.)

Surface pressure studies. A benzene solution of the monomer (0·01%, 0·02 ml) was pipetted carefully onto the swept surface of water in a glass trough (32 × 14 cm). So that the rate of formation of an equilibrium film could be obtained, the barrier was fixed at different positions and the change in surface pressure (π) following application of the monomer solution was determined. Normal π-A isotherms were determined by compression of the surface film and monitoring of surface pressure, using a Wilhelmy plate and torsion balance.

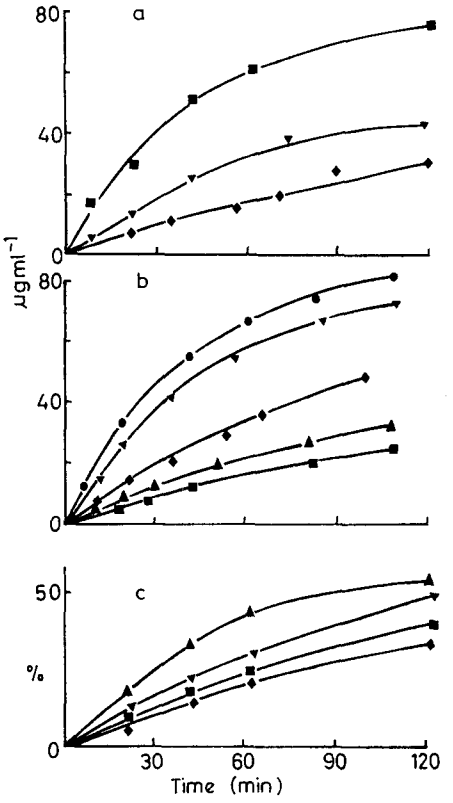

FIG. 2. (a). Plots of dye (gentian violet) released (μg ml^{-1}) from a drop of di-n-butylphthalate into water (■) in the absence of methylcyanoacrylate (MCA) ▼ in the presence of 2·5% MCA in the oil phase and ◆ 5% MCA in the oil phase.

(b). As above, but drop of chlorobenzene, (●) in absence of monomer with additional results with ▲ 2·5% butylcyanoacrylate and ■ 5% butylcyanoacrylate.

(c). Comparison of methyl and butyl monomers as film formers on release of gentian violet—above results plotted as a percentage of the release in absence of the polymer using the 2 h release values as 100% (120 min value = 100%). This shows the film formed on the chlorobenzene drop (■, ◆) to be more effective at identical monomer concentration than the film at the butylphthalate droplet interface (▲, ▼).

RESULTS

When a sufficiently concentrated solution of cyanoalkylacrylate contacts water, visible polymer film formation takes place within seconds. The films have considerable thickness and rupture on stretching but possess a degree of elasticity when the droplets are reduced in size. These properties may be inferred from the series of photographs of oil drops coated with polymer film shown in Fig. 1. The formation of the films not unexpectedly leads to retardation of solute transport out of the butyl phthalate droplets. Fig. 2 shows the effect of two concentrations of methylcyanoacrylate on the diffusion of gentian violet from butylphthalate drops, and these are compared with some results on diffusion from chlorobenzene droplets. At equal monomer concentrations, the polymethylcyanoacrylate derivative forms a more effective barrier than the butyl derivative. This might be due either to the greater affinity of the dye for the more hydrophobic butyl film or due to differences in film structure. The methyl derivative performs equally at both the butylphthalate and chlorobenzene interfaces.

The electron microscopy shows that the morphology of methylcyanoacrylate films prepared at different oil-water interfaces is not identical; Fig. 3 shows the different representative structures formed at carbon tetrachloride, benzene and butylphthalate interfaces with water.

Surface pressure-area isotherms are plotted in Fig. 4a for both methyl and butyl cyano acrylates. The extrapolated area per monomer unit is 12·5 Å^2 for the methyl derivative and 11 Å^2 for the butyl derivative. Isotactic polymethylmethacrylate (PMMA) has been found in similar experiments to give 27 Å^2 per monomer unit while syndiotactic PMMA produced values as low as 13 Å^2 per monomer unit (Beredjick, Ahlbeck & others, 1960). Catalin molecular models of the polymethylcyanoacrylate suggest that in a monolayer each monomer should occupy 21 Å^2. However, theoretical values will only be achieved if the polymer forms a conventional monolayer and if chain folding occurs as in some helical configurations of isotactic PMMA (Beredjick & others, 1960) apparently low values of area/monomer will be obtained and possibly inflexions in the π-A isotherm will appear as folding-unfolding transitions occur on compression. The butyl derivative shows such a transition at about a surface pressure of 9 mN m^{-1}. The relation between

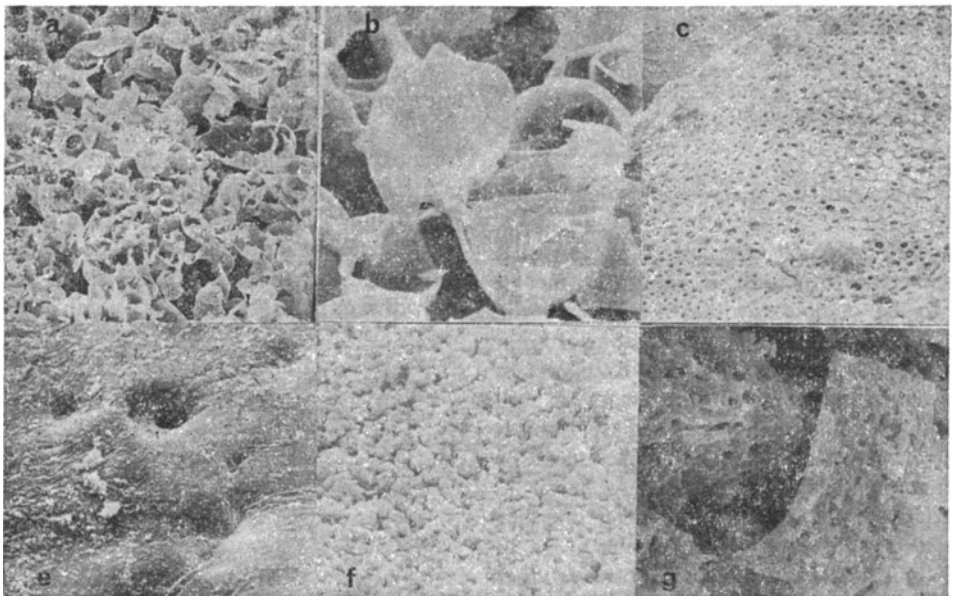

FIG. 3. Scanning electron micrographs of polymethylcyanoacrylate films formed at several oil-water interfaces. (a) and (f) are films prepared in same manner on different occasions (original magnification stated) (a) carbon tetrachloride/water interfacial film, × 950 (b) same, but at × 5000 thickness of walls of ruptured portions 100–500 nm (c) benzene–water films × 100 aqueous face (e) benzene–water film, organic face × 2000 (f) film prepared at the carbon tetrachloride–water interface × 2000 (g) liquid monomer dropped into water, polymerized and allowed to solidify shows porous appearance (× 1900).

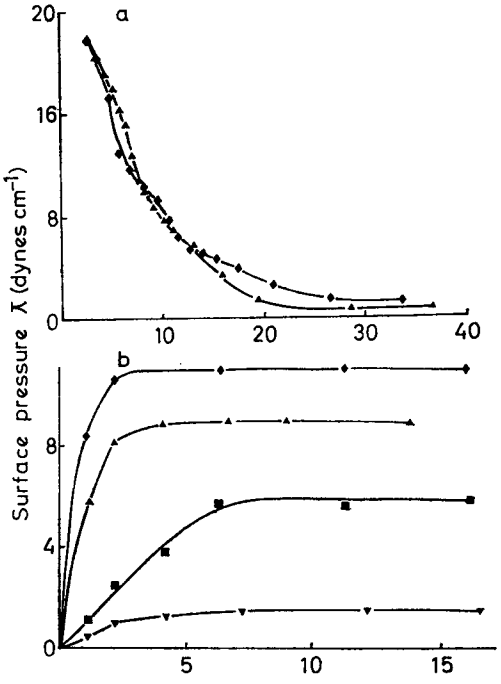

FIG. 4. (a). Surface pressure (π)-area (apparent area/monomer, Å²) isotherms for ▲ methylcyanoacrylate ◆ butylcyanoacrylate.

(b). Change in surface pressure with time (min) after spreading butylcyanoacrylate from benzene onto water at different initial apparent area/monomer ◆ area 7·7 Å²/monomer ▲ 8·6 Å²/monomer ■ 10·4Å²/monomer ▼ 13·7Å²/monomer.

the monolayers and the macroscopic films is not clear.

The surface pressure experiments suggest that equilibrium film formation is rapid; in fact it appears to be complete within 1 min with the methyl derivative but may take up to about 10 min with the higher homologue (Fig. 4b). As expected, at higher film areas, where the monomers are well spaced, equilibrium takes longer to achieve, but it is to be noted that even at the highest area studied the minimum area/monomer is about 13·7 Å².

Interfacial tensions (σ) at the oil-water interface are reduced in the presence of polymer (Fig. 5). Although limited data is available it is observed that the lowering is concentration-dependent and tentative application of Gibbs' adsorption equation in the form

$$\Gamma = -\frac{1}{2{\cdot}303\ RT}\left(\frac{d\sigma}{d\log c}\right) (\text{mol cm}^{-2})$$

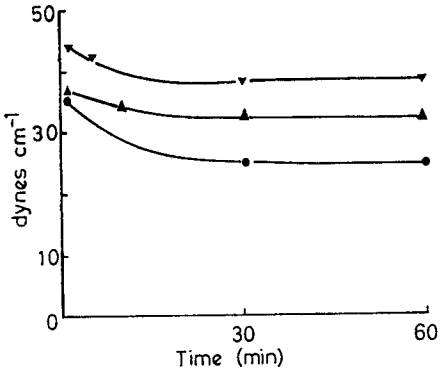

FIG. 5. Interfacial tensions (dynes cm^{-1}) as a function of time at the chlorobenzene–water interface ▼, no additives; ▲, 5×10^{-4}% methylcyanoacrylate in the chlorobenzene; ●, 2×10^{-3}% methylcyanoacrylate in the chlorobenzene.

gives an area/molecule of 85 Å² from a surface excess (Γ) of 2×10^{-10} mol cm^{-2}. This conclusion is dependent on the validity of the application of Gibbs' equation to the system being studied. Lankveld & Lyklema (1972) who have discussed this problem in relation to polymer adsorption at an oil-water interface, have concluded that although polymer adsorption is largely irreversible, hence disallowing the application of Gibbs' equation, segment adsorption could well be reversible.

Whatever the merits of the case, the lowering of interfacial tension and the presence of a discrete film at the interface at higher monomer concentrations, where multiple layers obviously form, results in an ability of the polymer to stabilize emulsions. Fig. 6 shows how the mean volume diameter for several emulsions of butyl phthalate in water alters with time when the stabilizer is either the methyl derivative or polysorbate 80 or a combination of the

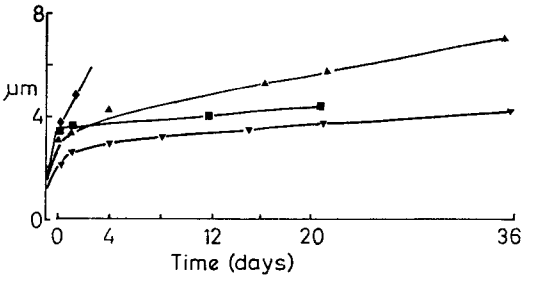

FIG. 6. The change in mean volume diameter (μm) in emulsions of di-n-butylphthalate in water ◆ with no stabilizer; ▼ with 0·1% methylcyanoacrylate ■ with 0·1% polysorbate 80, and ▲ with 0·1% methylcyanoacrylate in 0·1% polysorbate 80.

two. Higher homologues of the monomer have yet to be examined. A measure of stability is conferred by the polymer but it is less efficient than the non-ionic stabilizer polysorbate. Polymer and polysorbate 80 show synergism.

DISCUSSION

The difference in the speed of formation of films from the methyl and butyl monomers may be of importance in the formation of microcapsules; the limited data on permeability shows that the membranes are not as effective barriers as might be required in microcapsules containing small drug molecules. The scanning electron micrographs indicate considerable heterogeneity in the films when these were formed at some oil-water interfaces and this suggests that any investigation of microcapsule formation with these materials must involve a study of non-aqueous solvent effects on membrane properties, particularly strength and permeability.

The spread monolayers are not necessarily related structurally to the visible polymer films, but the technique of spreading monomers from a benzene solution onto water allows a study of the rate of formation of the film in a way which cannot be investigated by other methods. If microencapsulation is to produce high encapsulant yields then film formation must be rapid. A measure of the permanence of formed film can be obtained from studies of coalescence of oil globules. A discrete, permanent film should prevent coalescence. Polymethyl-α-cyanoacrylate alone is not an efficient stabilizer of butylphthalate in water emulsions. This failure suggests that the films formed around the droplets can fuse and allow coalescence of the oil.

Acknowledgements

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