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Three-ply walled w/o/w microcapsules formed by a multiple emulsion technique

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A new method of microencapsulation is described. Interfacial rheological studies had shown the formation of a rigid bipolymer film at the interface between an aqueous solution of a water-soluble polymer and a non-aqueous solution of an oil-soluble polymer. This led to the idea that small spherical bodies might be formed on making a w/o/w emulsion from these solutions. The present work has shown that ethyl cellulose/acacia microcapsules are formed when the organic solvent ethyl acetate is removed from the multiple emulsion drops. These microcapsules may be obtained as a free-flowing powder.

Controlled drug delivery systems have the aim of attaining sustained, relatively constant effective drug levels. Synthetic polymers developed for drug delivery take the form of films or capsules, which can be applied to the skin, implanted subcutaneously, or inserted into body cavities. The rate of release from such devices will depend on the physical properties of the polymer matrix and of the drug itself.

Microcapsules are an example of such a polymeric delivery system, where the active agent is contained within an envelope of polymer material. To exert an effect, either the agent must diffuse out of the capsule, or the substrate on which the agent will act, must diffuse into the capsule. Of the various ways to manufacture microcapsules, those successfully employed include air suspension, coacervation, spray drying and congealing, electrostatic deposition, pan coating techniques and microencapsulation by interfacial polymerization. The most recent patents have been collated by Gutcho (1979).

We wish to describe a novel method of microencapsulation that by its nature gives rise to three-ply walled microcapsules, composed of three layers of polymer material. The three-ply walls allow for more variables than with the conventional one layer walled microcapsules, and by adjustments in the formulation more desirable rates of release might be obtained. These microcapsules are small, having a diameter with a range up to 50 μm, and a mode of 10 μm, on a statistical weight basis and so could be prepared for parenteral use. The microcapsules are formed by a multiple emulsion (w/o/w) method (Warburton 1981).

Multiple emulsions have themselves been used as controlled release delivery systems (Brodin et al 1978; Brodin & Frank 1978; Versteeg 1978; Birol 1979). However, such emulsions are liquids, difficult to transport and prone to degradation. With the method described by Warburton (1981), microcapsules are automatically formed by loss of volatile and slightly water soluble solvent from the hydrophobic layer of multiple emulsion droplets and are subsequently obtained as a free-flowing powder.

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GENERAL APPROACH

From surface tension studies, it has been found that in solution, both acacia, a water soluble polymer, and polychloroprene, an oil soluble polymer, are surface active. Interfacial rheological studies have shown that the interface between an aqueous solution of a water-soluble polymer and a non-aqueous solution of an oil-soluble polymer could become rigid, with the formation of an interfacial film formed from both polymers (Warburton 1976). When droplets of an aqueous solution of acacia are dispersed in oil containing polychloroprene, as in the formation of a water-in-oil emulsion, both the acacia and the polychloroprene form adsorbed films at the interface of the aqueous droplet and organic continuous phase, a film of acacia forming on the inner aqueous side, and a film of polychloroprene on the outer, organic side. The presence of these adsorbed polymers provides a physical barrier to coalescence. Thus the wall of the w/o droplet consists of two layers, an inner water-soluble polymer (acacia) layer and an outer oil-soluble polymer (polychloroprene) layer (Fig. 1a). The continuous phase in this emulsion is organic solvent (xylene) plus dissolved oil-soluble polymer. When this w/o emulsion is mixed with further acacia solution to form a multiple emulsion, a fresh water/oil surface is created. Again oil-soluble

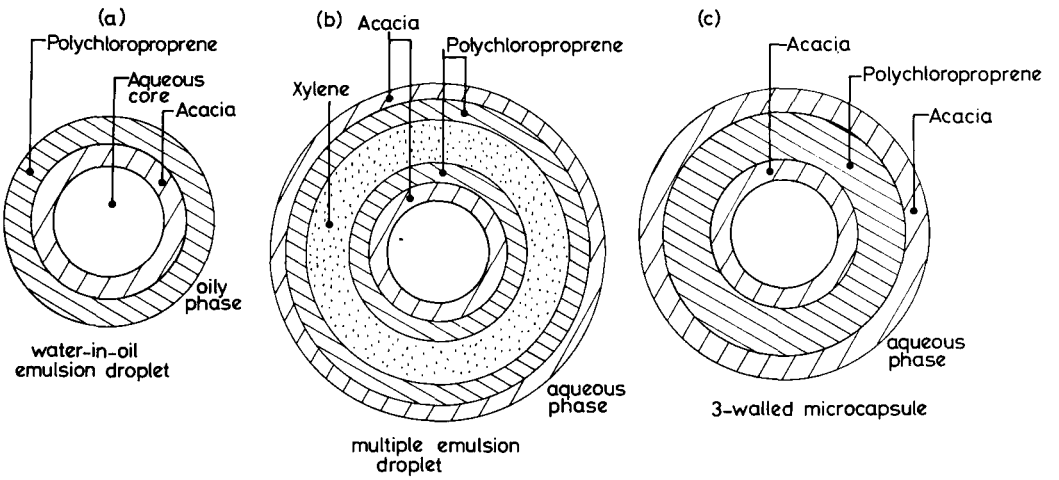

FIG. 1. Representations of the structures of (a) a w/o emulsion droplet; (b) a w/o/w multiple emulsion droplet, and (c) a microcapsule, formed in the manufacture of w/o/w microcapsules.

polymer and acacia molecules are drawn to it, forming a double polymer film, which can be visualized as possessing two walls, an inner and an outer, each composed of the two polymers (Fig. 1b). The inner wall is stronger than the outer, because the acacia solution in the core is trapped, hence the acacia layer of the inner wall remains firm (elastic). However, the acacia component of the outer wall is vulnerable and can easily be removed, for example by washing, thus weakening the outer wall. This idealized structure is of a multiple emulsion droplet with only one aqueous core, in fact, the number of inner aqueous droplets ranges from none to many.

Fig. 1b shows the organic solvent to lie in a layer between two layers of oil-soluble polymer. This is not exact because these layers meet at points, and so contain the solvent in pockets, or vacuoles. The walls are permeable to both organic solvent and aqueous core solution allowing them to diffuse out of the droplet, and enabling aqueous continuous phase to diffuse in. Because the organic solvent used is volatile, as it diffuses out it is lost by evaporation causing the outer walls to contract and eventually to come into contact with the inner walls (see Fig. 1c), the two double polymer films coming together so that the two inner oil-soluble polymer layers meet. In this way, the resulting microcapsule has a wall consisting of three polymer layers: an inner and outer layer of water-soluble polymer (acacia) and a middle layer of oil-soluble polymer. By examination of sectioned microcapsules under the electron microscope, there is support for the suggested three-ply wall structure (Fig. 2).

The phenomenon of loss of solvent from multiple emulsion droplets is apparent in Fig. 3. If the organic solvent is less dense than water, the multiple emulsion droplets cream to the surface. After losing solvent, microcapsules form which are denser than the surrounding liquid, and so sediment. The micrographs reveal that changes in structure have occurred which we assume to have been brought about by loss of solvent entrapped in the vacuoles (Fig. 3a). Because the system is open to the air, multiple emulsion droplets may lose their organic solvent by evaporation following diffusion, thus becoming microcapsules, and consequently sedimenting. It is believed that Fig. 3a shows multiple emulsion droplets, and Fig. 3b shows microcapsules. The core is not lost because of the mutual diffusion of water molecules from both the aqueous core and aqueous continuous phase.

MATERIALS AND METHODS

Materials

Acacia (Macarthys, Essex); di-n-butyl phthalate, xylene (BDH Chemical Ltd, Poole); ethyl acetate (Hopkins & Williams, Essex); ethyl cellulose, type T10 (Hercules Inc., Wilmington, U.S.A.); polychloroprene, *cis*-isomer (B.P. Chemicals, Sunbury, Middx.); water, double-distilled, from an all-glass still.

Methods

Microcapsules were produced from the multiple emulsion by two methods. The first began with an

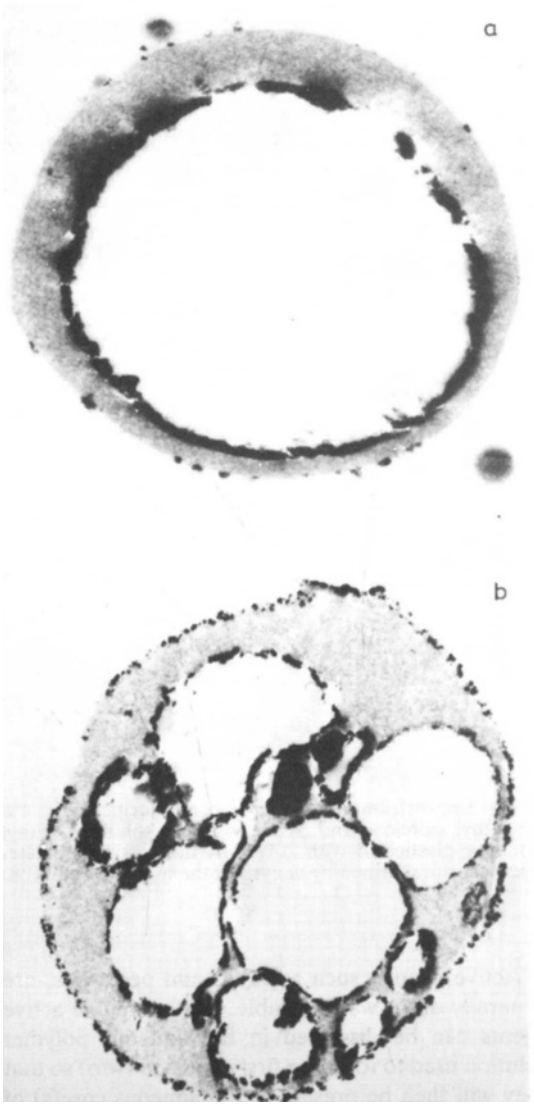

FIG. 2. Electron micrographs of two types of microcapsule (sectioned).
(a) A uni-cored three-ply walled microcapsule, a representation of which was shown in Fig. 1(c). Most of the outer layer of acacia has been lost through preparation for the electron microscope.
(b) A multi-cored microcapsule, showing all three layers. The microcapsules were formed from 4% w/v polychloroprene, dissolved in xylene, and 5% w/v acacia solution. The black areas are assumed to be acacia, the grey, polychloroprene.

aqueous solution of acacia and a solution of polychloroprene in xylene, the xylene being removed in the latter stages by bubbling air through a w/o/w multiple emulsion. However, the procedure proved to be lengthy and was thought to damage the wall of the microcapsules. The non-aqueous solvent and polymer used were also toxic, and so the whole method was superseded by a second procedure

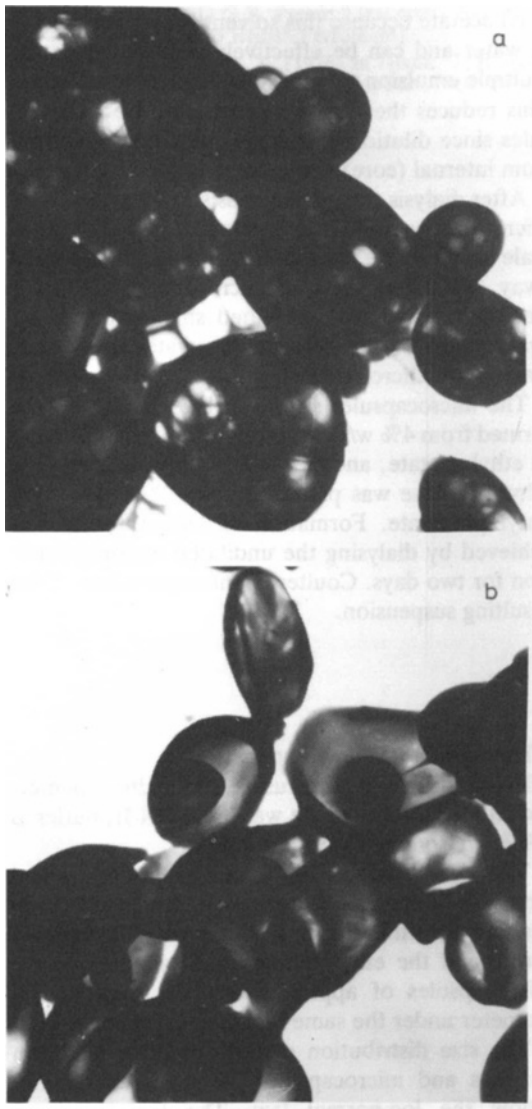

FIG. 3. Structures found in the cream (a) and sediment (b) of a multiple emulsion that had been allowed to stand, exposed to air, for six weeks. It is believed that these show multiple emulsion droplets and microcapsules, respectively.

Multiple emulsion formed from 4% w/v ethyl cellulose (T10), dissolved in ethyl acetate, and 5% w/v acacia solutions. The ethyl cellulose was plasticized by the addition of di-n-butyl phthalate 20% w/v, relative to the total weight of plasticizer and polymer.

which involved a polymer and solvent which were pharmaceutically acceptable.

A highly substituted grade of ethyl cellulose (49·8%) was selected because its low permeability to water was required as the microcapsule core is aqueous and a hydrophobic wall is needed for delayed release. Ethyl cellulose was dissolved in ethyl acetate because this solvent is partially soluble in water and can be effectively removed from the multiple emulsion droplets by dialysis after dilution. This reduces the time for production of microcapsules since dilution encourages diffusion of solvent from internal (core) and external aqueous phase.

After dialysis the system consists of a sediment of microcapsules and a supernatant liquid. For small scale manufacture, most of the supernatant is poured away, leaving a slurry of microcapsules. If this is transferred to a wide-mouthed shallow container, evaporation of the surrounding water can occur, leaving dry microcapsules.

The microcapsules shown in Figs 3a and b were formed from 4% w/v ethyl cellulose (T10), dissolved in ethyl acetate, and 5% w/v acacia solutions. The ethyl cellulose was plasticized with 20% w/w di-n-butyl phthalate. Formation of microcapsules was achieved by dialysing the undiluted multiple emulsion for two days. Coulter counts were taken of the resulting suspension.

Microcapsule size distributions

Microcapsules were sized using the Coulter Counter, model B. The electrolyte was ISOTON II, buffered 0·9% w/v sodium chloride solution.

The size distributions of microcapsules formed from solutions of 4% w/v ethyl cellulose and 5% w/v acacia is shown in Fig. 4. Both the polychloroprene/acacia and the ethyl cellulose/acacia systems gave microcapsules of approximately the same modal diameter under the same manufacturing conditions.

The size distribution of both multiple emulsion droplets and microcapsules we prepared did not follow the log-normal law. The law has been reported to be obeyed by many particulate systems, including microcapsules (Takenaka et al 1980; Senjkovic & Jalsenjak 1981) although other workers with microcapsules (Nixon & Hassan 1980) have not found the law applicable. In the manufacture of w/o/w microcapsules there are varying degrees of core capture by the second emulsification, so the deviance is perhaps not surprising.

POTENTIAL OF W/O/W MICROCAPSULES

The technique is not restricted to the polymers described (Watanabe & Hayashi 1976; Nozawa & Higashide 1978; Nozawa & Fox 1981). Emulsions, and thus microcapsules, should be able to be formed from any two immiscible polymer solutions. In microcapsule manufacture, the two aqueous solutions can be different so that three different wall materials are present.

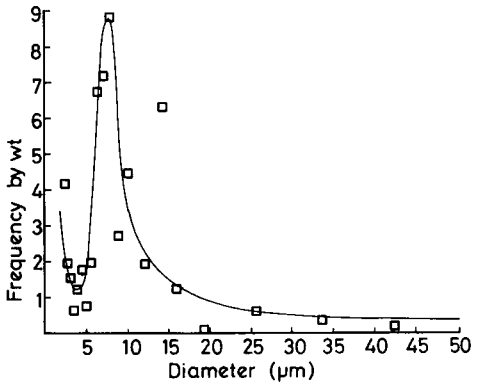

FIG. 4. Size distribution of microcapsules formed from 4% w/v ethyl cellulose and 5% w/v acacia solutions. Ethyl cellulose plasticized with 20% w/w di-n-butyl phthalate. Microcapsules formed by dialysis of the multiple emulsion.

Active agents, such as drugs and pesticides, are generally oil or water soluble. Water soluble active agents can be dissolved in the aqueous polymer solution used to form the first emulsion (w/o) so that they will then be present in the aqueous core(s) of the microcapsules. Oil soluble active agents may also be encapsulated, this time by entrapment in the wall of the microcapsule if they are added to the organic polymer solution. Active agents that are finely divided may also be encapsulated similarly.

There is thus considerable scope for varying both wall materials and the encapsulated active materials with the method.

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