Semipermeable composite microcapsules

Ehud Shchori* and Kenneth F. O'Driscoll
Department of Chemical Engineering, University of Waterloo, Waterloo, Ontario, Canada
(Received 17 January 1978; revised 11 April 1978)

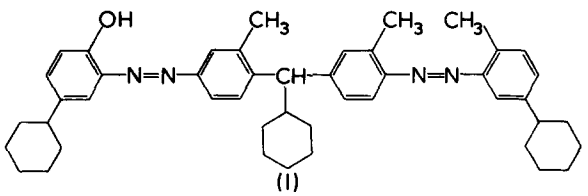
An interfacial polycondensation technique is described for preparing microcapsules from polyamides with a thin but dense surface supported by a strong porous layer of polymer. The permeation rate out of the capsules was measured for a compound with molecular weight ~100 and compared with permeation rates for a compound with molecular weight ~1000. Relative permeabilities of up to 10^4 were observed. It is suggested that composite microcapsules may find application for the immobilization of homogeneous catalysts of high molecular weight acting upon substrates of low molecular weight.

INTRODUCTION

In the process of microencapsulation small liquid droplets are coated by a spherical polymeric film[1]. One can distinguish between two types of microcapsules: those in which the polymeric film is so dense and non-permeable that the contents of the microcapsules are released only after the film is degraded by mechanical or chemical means[2] and those where the polymeric film is intentionally made permeable so that low molecular weight compounds can rapidly diffuse and equilibrate between the interior of the microcapsule and its supernatant liquid[3].

Applications for permeable microcapsules include controlled release of drugs[4,5], entrapment of adsorbent materials and catalysis by enzymes entrapped in the microcapsules[3,6–8]. Nylon-6,10 or collodion membranes which have been used for the latter purpose are semipermeable, since they allow the rapid permeation of substrates of low molecular weight but can retain the extremely high molecular weight enzymes. Typically, the substrates have molecular weights of the order of 10^2 while the enzyme has a molecular weight of the order of 10^5. It would be desirable to have microcapsules with more selectivity in their semipermeability. This might permit, for example, the restriction of access of some harmful materials to entrapped enzymes, or it might lead to the useful immobilization within the capsules of homogeneous organometallic catalysts having formula weights of the order of 10^3 (e.g. Wilkinson's hydroformylation catalyst $RhCl[P(C_6H_5)_3]_3$, $MW = 924$]. The present technique of immobilizing such homogeneous catalysts involves covalent binding between a support and one or more of the ligands of the catalyst[9]. Such utilization of the ligands may seriously affect the activity and selectivity of the catalyst with regard to product formation. Useful microencapsulation of homogeneous catalysts can be envisaged as requiring an encapsulating membrane highly permeable to ordinary reaction substrates and products of molecular weight ~100, but essentially impermeable to the bulkier catalyst of molecular weight ~1000.

In this report we describe 'composite microcapsules' which are prepared by interfacial polycondensation. They consist of a very thin and selective membrane supported by a thicker but highly permeable porous film. The composite microcapsules appear to have the desired combination of high permeabilities for model substrates [*o*-dichlorobenzene (DCB) of molecular weight 147] together with a high selectivity. The selectivity in this case is described as the ratio of permeabilities of the substrate (DCB) and of the bulky dye compound, oil yellow (I), $MW = 681$, which serves in this preliminary study as a model for an encapsulated catalyst.



(I)

The basic principle and the advantage of the composite structure over the non-composite structures are illustrated in *Figure 1*. The composite capsule is described as a thin dense membrane supported by a porous or swollen thick film. This unique structure gives the capsules a selectivity comparable to that of the dense-walled capsules, and a permeability for low molecular weight substrates as fast as with the porous capsules.

EXPERIMENTAL

The acid chlorides for interfacial polymerization, sebacoyl chloride (SC) and 1,3,5-benzenetricarboxylic acid chloride

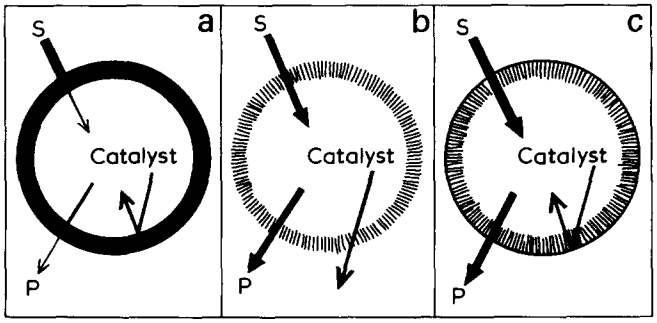


Figure 1 Schematic comparison of permeability in composite vs. non-composite microcapsules. (a) Dense membrane; (b) porous membrane; (c) composite membrane

* Present address: Polaroid Corporation, Cambridge, Mass., USA.

0032–3861/78/1909–1074$02.00

(BTC) were obtained from Eastman and Aldrich respectively and were used without further purification. The amines, 1,6-hexanediamine (HD), diethylenetriamine (DETA) and triethylenetetraamine (TETA), all from J. T. Baker, and *N*-(2-aminoethyl)piperazine (AEP) from Aldrich were also used as received. Solvents, from J. T. Baker, were of reagent grade.

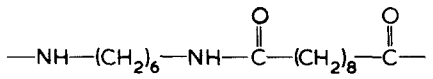
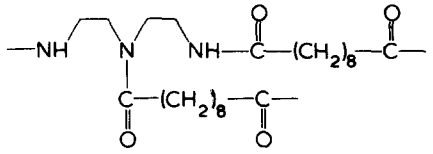
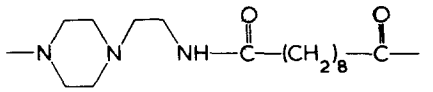
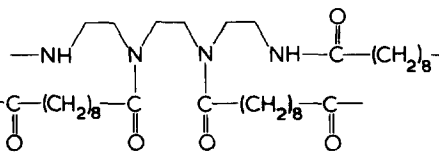
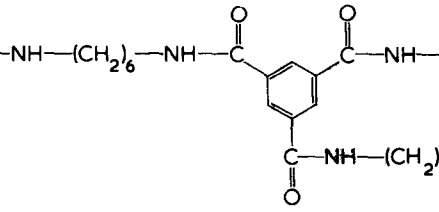
In a typical microencapsulation of oil yellow dye (Matheson, Coleman and Bell), a solution in *o*-dichlorobenzene (DCB) was prepared containing 0.8% oil yellow, 0.16 M SC and 2.5% poly(ethylene glycol) (molecular weight, 20 000). This solution was emulsified in an aqueous poly(vinyl alcohol) solution (1.0% Elvanol 50-42, DuPont) at 5°C using a magnetic stirrer. On addition of one or more polyamines to the aqueous phase (to a final concentration of 4.6% amine in water) a polyamide was formed encapsulating the oil yellow in the DCB phase. The reaction was stopped after 30 min of agitation. The capsules were washed with water and fractionated according to size by sedimentation. Average particle sizes were measured microscopically on capsules swollen in dioxane. Typically, 50–80% consumption of the acid chloride was noticed with the various preparations.

To measure the permeability of an encapsulated compound, the capsules were first washed with dioxane to remove excess water and DCB, and then suspended with stirring in a solvent such as dioxane, water or benzene. The supernatant solvent was separated from the capsules after an appropriate time period and the concentration of permeant in the solvent measured spectrophotometrically at 270 nm for DCB and at 350 nm for oil yellow. Selectivity is defined as the ratio between the permeation rate for DCB and that for oil yellow. The permeation rate is defined as the slope of a plot of the natural logarithm of the permeant content of the capsules vs. time.

To measure the permeability of DCB, either the diffusion of the residual DCB was monitored after washing with dioxane, or the washed capsules were equilibrated with a 10% solution of DCB in dioxane and then the DCB permeation measured into fresh supernatant.

Quaternization of free amino groups was carried out by treatment with 15% methyl iodide in methanol for 3 days. The bound iodide was displaced with hydrochloric acid and analysed as free iodine after reacting with potassium iodate and extraction into carbon tetrachloride.

Table 1 structures and designations of polyamide repeating units

Repeating unit	Designation
	HD–SC
	DETA–SC
	AEP–SC
	TETA–SC
	HD–BTC

RESULTS

Microcapsules were prepared by interfacial polycondensation of various polyamines with (mostly) sebacoyl chloride. The various repeating units of the resulting polyamides are shown in *Table 1*. *o*-Dichlorobenzene (DCB) was used both as the organic solvent and as a model compound for the permeability measurements. Permeabilities were studied in the relatively non-polar 1,4-dioxane. This solvent was used in most preliminary investigations due to its ability to remove both water and DCB from the interior of the microcapsules and also due to its optical transparency in the ultra-violet region. The results of permeability measurements on a variety of preparations are given in *Table 2*. The permeation rates were obtained from data such as those shown in *Figure 2*.

Some experiments were carried out to assess the effect of the solvent on the permeation rate and the results are summarized in *Table 3*.

Table 2 Permeability and selectivity of polyamide microcapsules in dioxane

Expt	Main support	Thin film[a]	SC concentration (M)	Average diameter (μm)	Permeation rate (min^{-1} × 100) DCB	Permeation rate (min^{-1} × 100) Oil yellow	Normalized permeation rate[b] (min^{-1} × 100) DCB	Normalized permeation rate[b] (min^{-1} × 100) Oil yellow	Selectivity
1	HD–SC	–	0.20	500	15.7	4.45	26	7.4	3.5
2	DETA–SC	–	0.20	680	0.3	3×10^{-5}	0.68	6.8×10^{-5}	10 000
3	DETA–SC	–	0.08	300	4.5	1.7×10^{-3}	4.5	1.7×10^{-3}	2 650
4	TETA–SC	–	0.16	320	1.35	2.4×10^{-3}	1.45	2.6×10^{-3}	560
5	HD–SC/BTC[c]	–	0.16	250	1.8	2.0×10^{-3}	1.5	1.7×10^{-3}	900
6	AEP/DETA–SC	–	0.16	320	21	1.2	22.4	1.3	17.5
7	HC–SC	DETA–SC	0.20	600	6.1	8.3×10^{-3}	12.2	16.6×10^{-3}	740
8	AEP/DETA–SC	DETA–SC	0.16	220	24	3.6×10^{-3}	17.6	2.6×10^{-3}	6 700
9	AEP/DETA–SC	TETA–SC	0.16	400	17	2.5×10^{-3}	22.6	3.3×10^{-3}	6 800

[a] Capsules in expts 7–9 are composite as described in text; [b] permeation rate normalized to capsules of 300 μm in diameter, based on an inverse proportion between the rate and capsule size; [c] mole ratio SC/BTC = 92.5/7.5 in the acid chloride solution

DISCUSSION

In all cases in *Table 2* the steady state permeation rate of DCB into a supernatant of dioxane is compared with that of oil yellow. An initial rapid decline in permeant content of many of the preparations can be seen in *Figure 2*. This is partly attributed to the existence of imperfections in some capsules and was often confirmed by the observation of the fraction of capsules without any dye at the end of an experiment (experiment numbers 8 and 9 in *Figure 2*). The early initial loss of permeant which is demonstrated in experiments 2 and 4 (*Figure 2*) is, however, a consequence of the effect of water on the permeability in dioxane. This effect is further discussed below.

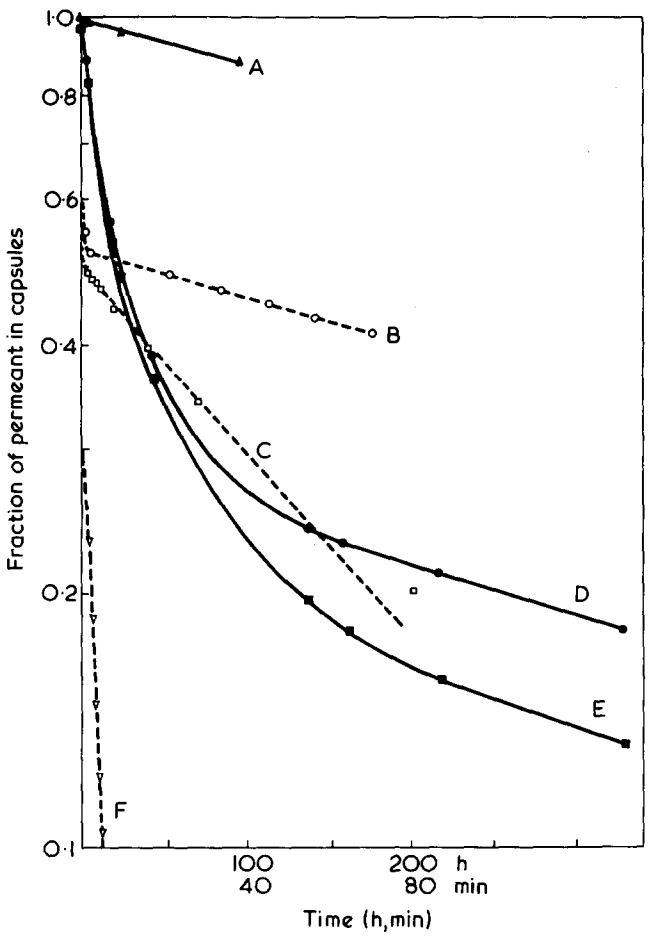


Figure 2 Permeation of DCB (— — — —) and oil yellow (———) in microcapsules in dioxane. The numbers refer to the experiments listed in Table 2: A, 5; B, 2; C, 4; D, 8; E, 9; F, 6

Two classes of polyamide membranes were studied. One class was of porous or swollen films which were characterized by a high permeability for both DCB and oil yellow and with a very low selectivity. The second class was of dense or less swollen polyamides which were characterized by lower permeabilities for both dye and DCB but with a high selectivity with respect to permeability of the lower molecular weight substrate.

Nylon-6,10 microcapsules (HD–SC) are typical of the first class (experiment 1). The interfacial polycondensation reaction to form this type of polyamide was extensively studied by Morgan[10] and more recently by Enkelmann and Wegner[11]. The reaction takes place at the interface between the organic phase and the water swollen film. The rate at which the film is formed is governed by the affinity of the amine for the organic solvent and its ability to diffuse through the film. The nylon-6,10 film is highly swollen. As prepared, it contains as much as 90% of its weight of water. Also, it is oriented perpendicular to the interface, which is not favourable for a strong film. Upon crystallization a porous but rather weak film is formed[11]. When the hexane diamine (HD) was replaced by the triamine, diethylenetriamine (DETA), (Experiments 2 and 3) extensive crosslinking occurred: only 2.5 mol % of free amino groups could be detected by quaternization with methyl iodide and subsequent analysis for bound iodide ions. The DETA–SC were observed to be much thinner and more transparant than are the HD–SC capsules. The transparency was taken as an indication of non-porous and non-crystalline structure. DETA–SC film is much stronger than HD–SC film and also much more flexible. As seen in *Table 2*, it has a lower permeability to DCB than in HD–SC film but it has a very high selectivity. Ratios of permeabilities of up to 10^4 have been achieved for the two substrates differing by a factor of only 4.6 in their molecular weights. Lower values reported in other experiments (experiment 3) reflect the significance of imperfections in the membrane on the permeability of slow-diffusing substrates. Crosslinking was also achieved through the use of a trifunctional acid chloride. 1,3,5-Benzene tricarboxylic acid chloride (BTC, 7.5 mol %) added to the sebacoyl chloride and reacted with HD gave similar effects of reducing absolute permeabilities while raising selectivity (experiment 5).

To obtain both high permeability *and* high selectivity, microcapsules were constructed by allowing DETA to react with the emulsion containing SC for a very short period (60 sec) and then adding HD. Based on existing descriptions of interfacial polymerizations we believe that this two step

Table 3 Effect of solvents on permeability of microcapsules

Expt	Composition	Average diameter (μm)	Permeant	Molecular weight	Solvent	Permeation rate (min^{-1} X 100)
1	DETA–SC	250	Sudan III	352	Benzene	7.5×10^{-3}
2	DETA–SC	400	Sudan III	352	Dioxane	3.7×10^{-3}
3	DETA–SC	400	Sudan III	352	5% H_2O/dioxane	3.55
4	DETA–SC	300	Congo red	697	H_2O, pH = 11	1.1
5	HD–SC	150	Congo red	697	H_2O, pH = 11	1.1
6	HD–SC/BTC[a]	250	Oil yellow	681	Dioxane	2×10^{-3}
7	HD–SC/BTC[a]	250	Oil yellow	681	25% H_2O/dioxane	42×10^{-3}
8	HD–SC/BTC[a]	250	DCB	147	Dioxane	1.8
9	HD–SC/BTC[a]	250	DCB	147	25% H_2O/dioxane	20

[a] Mole ratio SC/BTC = 92.5/7.5 in the acid chloride solution

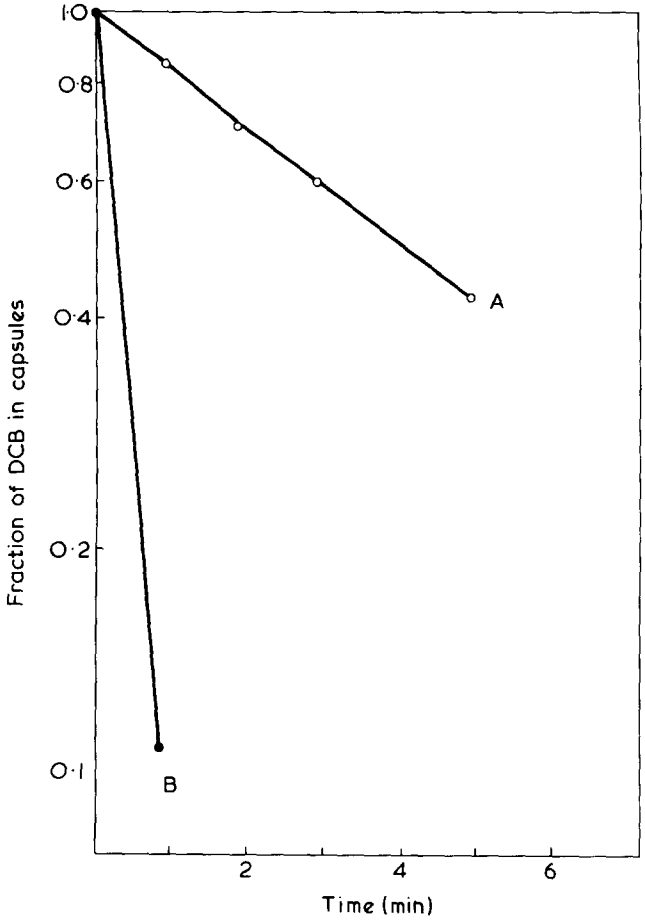


Figure 3 Permeation of DCB in composite microcapsules (expt 9, *Table 2*) in dioxane and 10% v/v H_2O in dioxane. A, Dioxane; B, 10% v/v H_2O/dioxane

technique created a 'composite' microcapsule which has an inner, thick layer of highly permeable HD–SC polyamide supporting the initially formed, thin, continuous and relatively impermeable DETA–SC polyamide. This composition (experiment 7) gave encouraging results, having nearly the same permeability for DCB as did the HD–SC of experiment 1, but a selectivity 200 fold greater.

The unsatisfactory mechanical properties of HD–SC films led us to a search for a better porous support. This was done by keeping a crosslinked structure and with a reduction of the hydrogen bonding content of the polymer, so to allow for a better swelling in a non-polar solvent. A good combination of mechanical properties and swellability was provided by a primary–secondary diamine, *N*-(2-aminoethyl)piperazine (AEP), $H_2N–CH_2CH_2–N(CH_2CH_2)_2NH$, which also contains a tertiary amino group. Highly strong, flexible and transparent microcapsules were obtained when a one to one (w/w) mixture of AEP and DETA was reacted with SC. DETA served to enhance the good mechanical properties of the membranes in this composition. The resulting copolyamide was found by the quaternization analysis to contain 38/62 mol ratio of AEP/DETA, in accordance with the initial ratio of 40/60 mol ratio used in the amine mixture and as a reflectance of the structural similarity between the two diamines. The AEP/DETA–SC microcapsules did not exhibit any marked selectivity (experiment 6) but they did show good mechanical properties, similar to those of pure DETA–SC.

The 'composite' technique was applied using first DETA solution with SC and after 5 sec adding AEP to establish an AEP:DETA ratio of 1:1 by wt. The resulting microcapsules exhibited both good mechanical properties and high permeability and selectivity (experiment 8). Similar results were obtained using a higher homologue, triethylenetetramine (TETA), which was allowed to react with SC for 15 sec before adding a mixture of AEP/DETA. TETA reacts more slowly than DETA and, therefore, allows a better control of the thickness of the first deposited film. It was also assumed that TETA does not compete with AEP and DTA on the formation of the supporting layer.

The permeation rates which are summarized in *Table 2* are expressed as the fraction of the substrate released per min. For a better comparison these values should be normalized to constant average size of capsules. Experimentally, the rate of permeation was found to be inversely proportional to the average diameter of the capsules. Composite microcapsules having a TETA–SC or DETA–SC skin show the same high permeability for DCB as that exhibited by the swollen support itself. The thin skin, although playing only a minor part in restraining the permeation of the DCB, is the only functioning layer inhibiting the release of the bulkier dye compound. The resulting selectivity obtained with the composite microcapsules is of the same order of magnitude and even higher than that obtained with the thick dense films.

Considering the data given in *Table 3*, it is apparent that replacing dioxane by similarly non-polar benzene did not change the permeability appreciably. Changing to water as solvent resulted in a high increase in permeability. This is especially pronounced with the highly hydrophilic DETA–SC. Permeability of Congo red in DETA–SC exceeds that in HD–SC. This was also observed in the release of sodium pentobarbital in aqueous solution[5]. Surprisingly, even as little as 5% water added to dioxane resulted in an increase of three orders of magnitude in the permeation of a dye, Sudan III, in DETA–SC capsules. This effect of the water is also seen with the initial fast release observed when the wet capsules are washed with dioxane (*Figure 2*, experiments 2, 4).

To achieve composite microcapsules and semipermeable microcapsules operating in aqueous or other polar solutions, other, less hydrophilic, structures should be used. An example for such is given by nylon-6,10 which is crosslinked with 1,3,5-benzene tricarboxylic acid chloride. The influence of water on the permeability in this system is relatively small (*Table 3*, experiments 6–9) and the selectivity factor is reduced by a factor of only 2.

A comment should be made concerning the limit of permeability in microcapsules. One would notice that a diffusion process in these systems comprises diffusion from a stirred exterior solution through a polymeric membrane followed by a second diffusion process through the unstirred interior of the capsule. In all our experiments the diffusion through the polymeric membrane was the rate-determining step. This was demonstrated by a simple experiment (*Figure 3*) in which the composite microcapsules (TETA and AEP/DETA–SC) were swollen in 10% water in dioxane. The permeation rate for DCB increased by more than an order of magnitude as compared with the rate in pure dioxane. For practical systems, such as encapsulated homogeneous catalysts, diffusivity at the interior of the capsule may govern the rate of the whole process. To achieve this limit, a more permeable supporting film can be used. Increasing the AEP content in the AEP/DETA mixture may serve this purpose. The crosslinked AEP/DETA–SC film can also replace nylon-6,10 for encapsulating enzymes and absorbent

materials. This structure may offer a better mechanical stability with a better permeability and convenient control of selective permeability.

ACKNOWLEDGEMENT

Support of this research by the National Research Council of Canada is appreciated. We are grateful for an experimental introduction to the technique of microencapsulation by Professor T. M. S. Chang of McGill University.

REFERENCES

1 Herbig, J. A. 'Encyclopedia of Polymer Science and Technology', Interscience, New York, 1968, Vol 8, p 719
2 Gutcho, M. 'Capsules Technology and Microencapsulation' Noyes Data Corp., Park Ridge, New York, 1972
3 Chang, T. M. S. 'Artificials Cells' Thomas, Springfield, Illinois, 1972
4 Luzzi, L. A. *J. Pharm. Sci.* 1970, **59**, 1367
5 DeGennaro, M. D., Thompson, B. B. and Luzzi, L. A. Coatings and Plastics Preprints, 171st ACS Meeting 1976, **36**, 376
6 Chang, T. M. S. and Poznansky, M. J. *J. Biomed. Mater. Res.* 1968, **2**, 187
7 Chang, T. M. S. *Biomed. Eng.* 1973, **8**, 334
8 Chang, T. M. S. *Kidney Int.* 1975, 7, 5
9 Grubbs, R. H. *Chem. Tech.* 1977, 7, 512
10 Morgan, P. W. 'Condensation Polymers by Interfacial and Solution Methods' Interscience, New York, 1965
11 Enkelmann, E. V. and Wegner, G. *Appl. Polym. Symp.* 1975, **26**, 365 and *Makromol. Chem.* 1976, **177**, 3177