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Influence of coating and core modifications on the in vitro release of methylene blue from ethylcellulose microcapsules produced by pan coating procedure

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Core pellets containing methylene blue, a highly water-soluble drug, lactose and polyvinylpyrrolidone (PVP) were produced and coated by pan technology with ethylcellulose 7 cp. Scanning electron microscopy revealed that larger microcapsules were aggregates of smaller microcapsules which remained intact during the dissolution testing. The coating appeared porous with rough and smooth areas. Polymer disc studies confirmed a lack of swelling of the ethylcellulose used when in contact with the dissolution medium. Modifications of the coating applied included addition of hydroxypropylmethylcellulose (a cofilm former), diethyl phthalate, di-n-butylphthalate and castor oil (plasticizers), talc (an extender and anti-tack agent) and paraffin wax and hydrogenated castor oil (waxy sealants) to the coating solution. Most products had released 50% drug after about 20 min dissolution treatment although the inclusion of the waxy sealants in the coating markedly retarded release during the first 60 min. In contrast, the inclusion of hydrogenated castor oil or polyethylene powder in the core, retarded dissolution of the drug over 3 h but tended to produce a coarser product. Other modifications of the core were addition of hydroxypropylmethylcellulose, carnauba wax–beeswax (1 : 1) and carnauba wax, with little retardation of drug release. The mechanism of drug release from the microcapsules was complex involving mainly diffusion.

Ethylcellulose is a water insoluble polymer widely used as a film former for microencapsulation. However, Jalsenjak et al (1976) and Deasy et al (1980) have found that ethylcellulose-coated microcapsules containing water-soluble drugs such as phenobarbitone sodium or sodium salicylate have poor capacity to retard drug release. The temperature change-phase separation procedure employed by both groups of workers resulted in the formation of an irregular, porous coating. Apart from surface sealant treatments with waxes to retard drug release, the procedure does not facilitate ready modification of core or coating. Accordingly, microencapsulation by the more flexible procedure of pan coating was carried out. Methylene blue, another highly water-soluble drug was chosen as a model compound to facilitate visual assessment of various stages during the manufacture and evaluation. Coating or core was modified, using different combinations of film formers, plasticizers, extender and anti-tack agent, and waxes in an attempt to prolong the in vitro release of methylene blue.

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MATERIALS AND METHODS

Materials

Methylene blue (microscopic grade, Merck), ethylcellulose standard 7 cp (Dow Chemical), lactose, (DMV–200 mesh milled; 99–100% $<160\,\mu m$), polyvinylpyrrolidone (PVP, Plasdone, GAF Ltd.), hydroxypropylmethylcellulose (HPM, 50 cp Celacol, British Celanese), diethyl phthalate and di-n-butyl phthalate (BDH lab. reagents), castor oil B.P. (Lennox), purified talc (B.P.), paraffin wax and hydrogenated castor oil (Standard Oil), polyethylene powder (BASF AM 3), carnauba wax (Brome and Schimmer), carnauba wax–beeswax (1 : 1, Leo Lab.), sodium carboxymethylcellulose 75 cp (courlose gum, British Celanese), toluene and methylene chloride-methanol 1 : 1 (BDH lab. reagents), hydrochloric acid (BDH Analar reagent) and distilled water were used.

METHODS

Preparation of microcapsules

Initially, core pellets containing methylene blue, lactose and PVP were prepared by a method similar to that of El-Sayed et al (1978). Methylene blue (10%) and lactose (90%) were thoroughly mixed in a

cube mixer. Samples (100 g) were introduced into a copper coating pan (mounted on a shaft driven by an Erweka varispeed motor) and made to roll by rotating the pan at 30 rev min^{-1}. The binding solution, 10% PVP in water in the form of a fine mist, was sprayed tangentially onto the powder bed from a Burgess Electric Airless Spray gun (V220, model 969). The concentration of binder in the dried product was usually about 3%. As the powders commenced to agglomerate, the rotation speed was gradually reduced to about 15 rev min^{-1} and the cores were allowed to roll for 5–10 min. This speed reduction facilitates the growth in size of the cores. Hot air was then directed into the pan, care being taken to prevent loss of fine cores.

The cores were then coated in the pan revolving at 40 rev min^{-1} with 10% w/w ethylcellulose sprayed from a 2·5% w/v solution in toluene. About 40 ml of the solution was delivered for each layer of coating which was followed by intermittent drying. Approximately ten coating applications were required. For the last two applications the rate of drying was reduced in an attempt to smooth the coat. Unless otherwise stated, the amount of coating applied was 10% w/w of product applied from dispersions of varying % compositions in suitable organic solvents indicated in Table 1. Core compositions are outlined in Table 2.

The various batches of microcapsules were fractionated into suitable particle size ranges (mean

Table 1. Variations in the composition of the coat applied to the core.

	Coating	% w/w	Function	Solvents used
(a)	Ethylcellulose 7 cp	2·5	Film former	Toluene
(b)	Ethylcellulose 7 cp	1·25	Film former	Toluene
	Hydroxypropylmethylcellulose	1·25	,, ,,	Methylene chloride Methanol mix (1 : 1)
(c)	Ethylcellulose 7 cp	1·25	Film former	Toluene
	Diethyl phthalate	1·25	Plasticizer	
(d)	Ethylcellulose 7 cp	2·375	Film former	Toluene
	Di-n-butylphthalate	0·125	Plasticizer	
(e)	Ethylcellulose 7 cp	1·25	Film former	Toluene
	Di-n-butylphthalate	1·25	Plasticizer	
(f)	Ethylcellulose 7 cp	2.375	Film former	Toluene
	Castor oil	0·125	Plasticizer	
(g)	Ethylcellulose 7 cp	2·25	Film former	Toluene
	Talc	0·25	Extender and anti-tack	
(h)	Ethylcellulose 7 cp	2·25	Film former	Toluene
	Paraffin wax	0·25	Waxy sealant	
(i)	Ethylcellulose 7 cp	1·25	Film former	Toluene
	Hydrogenated castor oil	1·25	Waxy sealant	

Table 2. Variations in the core composition.

	% w/w	Core compositions	% w/w		% w/w
(a)	Methylene blue 9·61	Hydroxypropylmethyl–cellulose	86·54	PVP solution	3·85
(b)	Methylene blue 9·61	Sodiumcarboxymethyl–cellulose	86·54	PVP solution	3·85
(c)	Methylene blue 9·61	Powdered hydrogenated castor oil	87·48	PVP solution	2·91
(d)	Methylene blue 9·61	Polyethylene powder (BASF AM 3)	86·54	PVP solution	3·85
(e)	Methylene blue 9·61	Carnauba wax	86·54	PVP solution	3·85
(f)	Methylene blue 9·61	Carnauba wax–Beeswax (1 : 1)	86·54	PVP solution	3·85

size: 337·5; 367·5; 885; 1340 and 1840 μm) using a nest of standard Endecott sieves (200–2000 μm) mounted on a moving sieve shaker table for 3 min.

Dissolution studies

Samples (150 mg) of selected particle size ranges were weighed into a U.S.P. dissolution basket assembly, the base of which was lined with a disc of greaseproof paper, and agitated at 140 rev min^{-1} in 400 ml of 0·1 M hydrochloric acid at 37°C. At intervals of 5, 10, 20, 30, 40, 60, 90, 120 and 180 min, 5 ml samples were removed, filtered through a Millipore filter, with a 0·22 μm pore size and assayed at 663 nm. After each sample withdrawal the volume loss was made up with 0·1 M prewarmed acid.

Total drug content of microcapsules

Method 1. 150 mg microcapsule samples, washed with 5 ml chloroform to dissolve off coating material were extracted 10 times with 7 ml volumes of water and the combined aqueous washings assayed spectrophotometrically.

Method 2. 150 mg microcapsule samples were ground finely (mortar and pestle), diluted appropriately, filtered (Millipore) and assayed.

Both methods gave similar results.

Free film diffusion studies

Free ethylcellulose films, of thickness 30–60 μm, were pre cast onto a mercury substrate and mounted between two adapted conical flasks, fitted with Teflon rings, as described by Goldberg & Higuchi (1968). The joined flasks were subsequently placed into a heated water bath (37 °C ± 1 °C), and were filled simultaneously with 250 ml of a preheated solution of 0·006% w/v methylene blue in 0·1 M hydrochloric acid (flask 1) and 250 ml of 0·1 M hydrochloric acid alone (flask 2) with continuous stirring. The introduction of the two solutions into the flasks was taken as time = 0 and at 5, 10, 20, 30, 40, 60, 90, 120 and 180 min, 5 ml samples were withdrawn from flask 2 for assay. Each sample withdrawal from flask 2 was replaced with 0·1 M acid. If the drug diffuses across the membrane, the dye content of flask 2 should increase.

Scanning electron microscopy

Surface morphology of the microcapsules was examined before and after dissolution tests using a scanning electron microscope. Dry samples were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film approximately 30 nm thick. With some products, it was necessary to cool the coater by a water jacketed system to prevent melting of the waxes. Maximum magnification was 2000X.

Polymer swelling measurements

Discs containing 0·3 g ethylcellulose 7 cp were compressed at forces ranging from 508 to 6111 kg cm^{-2}, under vacuum to remove air with a 1·3 cm diameter flat-face punch and die assembly and a R11C Hydraulic press C30. The discs were mounted on a sample brass holder using paraffin wax B.P. in an apparatus similar to that of Heyd et al (1969) which was fitted with a small glass stirrer driven at 50 rev min^{-1}. Comparisons of the thickness of the discs after variable periods of immersion in agitated water at 37 °C, with their unwetted thickness, were made (micrometer) to determine the degree, if any, of polymer swelling.

RESULTS AND DISCUSSION

The preparation of microcapsules by pan coating is apparently easy, although time consuming. The product obtained tends to be large with the greatest % yield of microcapsules in the 1680–2000 μm range. Poor flow was frequently observed in the coating pan during core formation and gave rise to irregular coarse cores possibly because of the differences in physical properties such as particle size, shape and density between the drug and the diluents. Scanning electron microscopy showed that many of the products appeared to be aggregates of smaller coated particles held together by polymer bridging with pores and both rough and smooth areas present on the surface. Similar products were obtained by Deasy et al (1980) and Watanabe & Hayashi (1976) using the phase separation procedure.

Dissolution tests were carried out to distinguish between promising and unpromising formulations. Figs 1, 2 show dissolution curves for products with modified coats. Addition of 10% paraffin wax to the coating solution was more effective in delaying the overall release of methylene blue, see Fig. 2, than either coats consisting of ethylcellulose 7 cp alone or in combination with 5% castor oil, 50% hydrogenated castor oil or 10% talc. However, none of the products could be considered satisfactory as a means of prolonging drug release. Scanning electron microscopy studies revealed no apparent differences in the various coats observed. Post dissolution micrographs showed that apart from considerable erosion of the coating there was no appreciable fragmentation or polymer swelling, unlike that obtained by Deasy et al (1980) using ethylcellulose from a different batch.

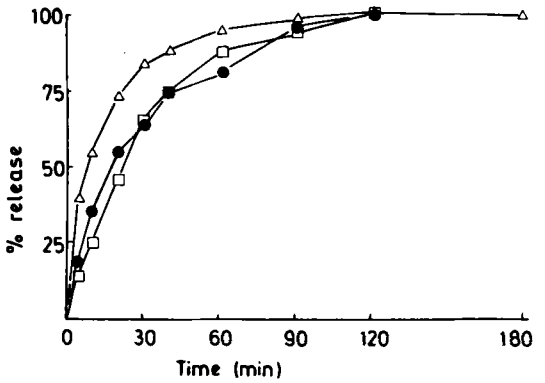

FIG. 1. Release of methylene blue from microcapsules (mean size 855 μm) coated with 10% w/w ethylcellulose standard 7cp (●), 9·5% w/w ethylcellulose standard 7cp and 0·5% w/w di-n-butylphthalate (△) or 9·5% w/w ethylcellulose standard 7cp and 0·5% w/w castor oil (□).

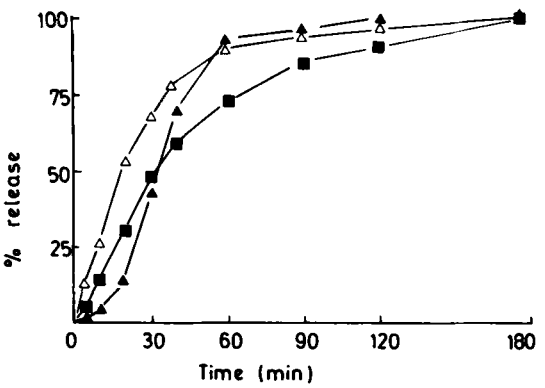

FIG. 2. Release of methylene blue from microcapsules (mean size 855 μm) coated with 9% w/w ethylcellulose standard 7cp and 1% w/w talc (△), 9% w/w ethylcellulose standard 7cp and 1% w/w paraffin wax (■) or 5% w/w ethylcellulose standard 7cp and 5% w/w hydrogenated castor oil (▲).

Polymer swelling studies on discs prepared from ethylcellulose 7 cp confirm a lack of swelling when in contact with water.

In comparison, when hydroxypropylmethylcellulose (HPMC) was added to the core, considerable swelling and erosion of the microcapsules took place as expected (see Fig. 3A). In addition, release of the drug was retarded over the first 60 min of dissolution suggesting diffusion of the drug through a gel barrier which later erodes. Similar findings were reported by Lapidus & Lordi (1966).

Other modifications of the core were more useful

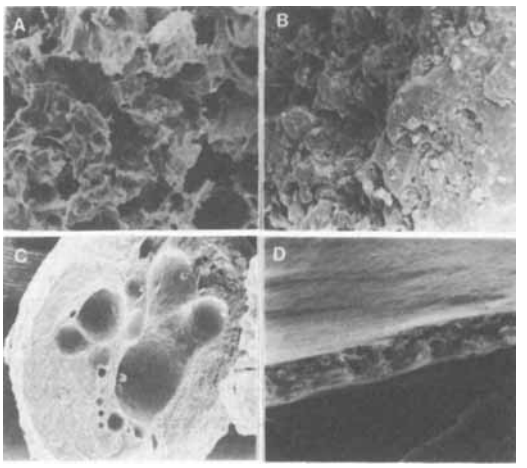

FIG. 3. Scanning electron micrographs of an ethylcellulose standard 7cp film (D) and ethylcellulose 7cp coated microcapsules, containing methylene blue, hydroxypropylmethylcellulose and PVP. (A) or methylene blue, hydrogenated castor oil and PVP (B) or methylene blue, carnauba wax–beeswax mix (1 : 1) and PVP (C) in the core, before (B,C) and after (A) dissolution studies. A,C, about × 100; B, about × 200; D, about × 510.

in delaying drug release. Fig. 4 shows that the addition of hydrogenated castor oil or polyethylene powder to the core had the greatest effect on the release with only 75% drug released after 120 min dissolution treatment. However, the scanning electron

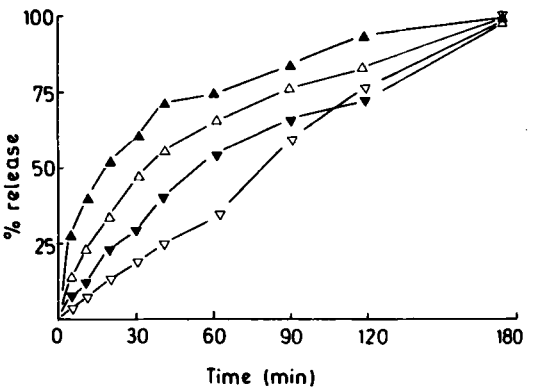

FIG. 4. Release of methylene blue from ethylcellulose standard 7cp coated microcapsules (mean size 855 μm) containing methylene blue, carnauba wax and PVP (▲) or methylene blue, carnauba wax–beeswax (1 : 1) and PVP (△) or methylene blue, hydrogenated castor oil and PVP (▼) or methylene blue, polyethylene powder and PVP (▽) in the core.

micrograph (Fig. 3B) reveals a very coarse ethylcellulose 7 cp coated microcapsule surface after addition of hydrogenated castor oil to the core.

The disappointing effect of carnauba wax–beeswax mix (1 : 1) in the core to delay drug release may be due to the large pores present in the matrix and the uneven deposition of the coating in parts as seen in a cross section of the microcapsule (Fig. 3C). A scanning electron micrograph of a free cast ethylcellulose film 5–10 μm approx. in thickness, see Fig. 3D, reveals a porous type network in the interior. The absence of pores on the surface suggests perhaps that if such ethylcellulose films could be cast without surface pores onto the core, the release rate of the drug could be significantly reduced. This is supported by the fact that when the diffusion of methylene blue through such pre cast ethylcellulose films was studied there was negligible permeation of the drug observed.

The addition of sodium carboxymethylcellulose or carnauba wax alone were disappointing in their capacity to delay drug release.

To quantitatively describe the release profiles of the microcapsules observed is not easy. In the usual manner, for plastic and wax matrices (time)$^{\frac{1}{2}}$ release plots of the products were examined (Desai et al 1965; Schwartz et al 1968). Sigmoidal shapes were generally obtained and could be attributed in part to the high solubility of the methylene blue and the presence of air in the matrix.

In addition, as polymeric matrices may sometimes show apparent first order kinetics, first order release plots were also examined. The products tended to show an initial apparent first order release which progressed to a more complex order as dissolution proceeded. Modifications of the core gave rise to a greater departure from apparent first order release.

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