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Effect of ethylcellulose grade and sealant treatments on the production and in vitro release of microencapsulated sodium salicylate

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Sodium salicylate was microencapsulated with ethylcellulose 100 cp by polymer deposition from cyclohexane by temperature change to give a finer product, with slower drug release, than that obtained with 10 cp grade of ethylcellulose. Scanning electron microscope and polymer disc swelling studies confirmed that larger microcapsules after drug release ruptured into smaller particles with swollen surfaces containing pores. Treatment of microcapsules with paraffin wax solution retarded release of core material, the release being affected by the percentage of sealant used and the particle size of the product. The mechanism of release from the sealed microcapsules was complex involving mainly diffusion, but polymer erosion and drug binding were also involved. Other sealant materials were less effective in retarding dissolution.

Many different coating materials and processes of application are used in microencapsulation. Several general reviews of microencapsulation have been recently published (Bakan & Anderson 1970: Fanger 1974; Luzzi 1976).

A procedure for producing microcapsules of water-soluble drugs was outlined in the U.S. patent assigned to The National Cash Register Co. (Fanger et al 1970) and involved ethylcellulose coating by polymer deposition from cyclohexane by temperature change. Recently Jalsenjak et al (1976) have described certain details of the process when used for the microencapsulation of phenobarbitone sodium. Whereas acceptably fine particles of product were obtained by careful control of the coating procedure, the in vitro dissolution of the core material was rapid, despite attempts to delay it by increase in coating: core ratio and particle size. In this investigation further details of the coating procedure have been investigated and an attempt has been made to prolong the in vitro release from ethylcellulose-encapsulated sodium salicylate by the application of various sealant treatments.

MATERIALS AND METHODS

Materials

Sodium salicylate U.S.P.(Merck), ethylcellulose standard 100 and 10 cp (Dow Chemical), cyclohexane, practical (Eastman Kodak), paraffin wax (Standard Oil), ceresin, white (Sargent-Welch), spermaceti, white beeswax and carnauba wax (Gazzola Drug), chloroform and hydrochloric acid (BDH, analar) and distilled water were used.

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Methods

Preparation of microcapsules

The method was developed from those described by Fanger et al (1970) and Jalsenjak et al (1976). The coating vessel used was 1 litre capacity and fitted with a flanged 4 port cover. Through the centre port was mounted a 3 blade P.T.F.E. stirrer connected to the chuck of a variable speed motor. The remaining ports were used to provide the coating vessel with a reflux condenser, a thermometer and an entry point. The lower part of the vessel was heated by immersion in an oil bath. To prepare a batch of microcapsules 6 g of sodium salicylate, 6 g of the appropriate grade of ethylcellulose and 600 ml cyclohexane were added to the reaction vessel and heated to 80–81 °C over 1 h with stirring at a stirrer speed of 750 rev min^{-1}. After being maintained at this temperatre for 1 h the product was slowly cooled over 3 h to 35 °C with constant agitation, removed and allowed to sediment at room temperature. The excess cyclohexane was decanted and the product was washed 3 times with 300 ml cyclohexane (10 °C) after 15 min agitation before being filtered and air dried overnight. The yield was always greater than 96%.

Sealant treatments

Samples (3 g) of ethylcellulose microencapsulated drug were agitated at 150 rev min^{-1} with 50 ml solu-

tions of paraffin wax, ceresin or spermaceti in cyclohexane at room temperature, filtered and air-dried overnight. A similar procedure was employed for white beeswax or carnauba wax with the exception that the process was carried out at 60 °C at which temperature each wax was in solution in the cyclohexane.

Particle size separation of microcapsules

The various batches obtained were fractioned into suitable particle size ranges using a nest of standard sieves mounted on a moving sieve shaker for 3 min.

Dissolution studies

Samples (200 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 50 rev min^{-1} in 400 ml dissolution medium at 37° ± 0·5 °C contained in a 500 ml round bottomed flask. This arrangement minimized the tendency of particles to float to the top of the dissolution medium, escape from the basket was negligible, there was no sign of mesh blockage and near perfect sink conditions were produced. At periodic intervals 10 ml volumes were removed, filtered through a Millipore filter fitted with a 0·22 μm pore size membrane and assayed spectrophotometrically at 296 nm. An equivalent quantity of dissolution medium was added to the dissolution vessel immediately after each volume was withdrawn and this factor was allowed for in the calculation of the amount of drug released.

Total drug content of microcapsules

To determine the total drug content in the various size fractions, 40 mg samples were washed with 5 ml chloroform which dissolved off all the coating materials used. These samples were then extracted 10 times with 7 ml volumes of water and the pooled aqueous washings were assayed.

Scanning electron microscopy

Samples of microcapsules were mounted onto stubs using double sided adhesive tape and vacuum-coated with gold film approximately 30 nm thick. A Mini-Sem, model v scanning electron microscope was used.

Polymer swelling measurements

Discs containing 0·3 g ethylcellulose or ethylcellulose treated with paraffin wax (not microcapsules) were compressed at a force of 6125 kg cm^{-2} under vacuum to remove air. Compression at forces exceeding this value did not significantly affect the rate of swelling. A 1·3 cm diameter flat-face punch and die assembly and a R11C Hydraulic Press C30 were used. Each disc was mounted on a sample holder using a film of hard paraffin in an apparatus similar in design to that described by Heyd et al (1969) which was fitted with a small glass stirrer driven at 50 rev min^{-1}. To determine swelling the percentage increase in thickness of discs after variable periods of immersion in agitated water at 37 °C, compared with their unwetted thickness, was measured using an optical micrometer.

RESULTS AND DISCUSSION

The preparation of microcapsules using ethylcellulose by polymer deposition following cooling below the critical phase separation temperature, requires careful attention to details of the procedure in order to avoid obtaining a product that is largely comprised of coarse aggregated masses of the starting materials. To obtain a fine well coated product vigorous agitation and a slow rate of cooling around the phase separation temperature must be employed. Also, washing the product with cold cyclohexane tends to lessen aggregation.

The grade of ethylcellulose used is also important. Standard ethylcellulose having a high ethoxy content is preferred and is available commercially in a range of different apparent viscosities, determined on 5% w/w solutions in 80:20 toluene:ethanol at 25 °C. Table 1 shows sieving analysis results from products obtained using ethylcellulose standard 10 or 100 cp. The 100 cp grade obviously produced less coarse particles. Scanning electron micrographs of samples of the two products are shown in Fig. 1. The general appearance of both samples is similar as shown in Fig. 1 A and B. Apart from single capsules larger microcapsules are clearly seen in Fig. 1 C to be

Table 1. Sieving analysis of microencapsulated sodium salicylate prepared using ethylcellulose standard 10 or 100 cp and variable % paraffin wax treatment.

Size range (μm)	% Fraction Ethylcellulose grade (cp) 10	100	100	100	100
	% Paraffin wax treatment 0	0	5	10	20
>1190	32·60	18·48	8·04	16·16	49·63
1190–840	12·24	9·57	4·04	6·91	23·82
840–500	22·26	27·53	25·08	29·60	23·71
500–297	13·95	22·27	31·48	29·30	2·58
297–250	3·77	6·46	18·96	15·68	0·22
250–177	4·93	8·34	11·79	2·32	0·04
<177	10·25	7·35	0·61	0·03	0·00

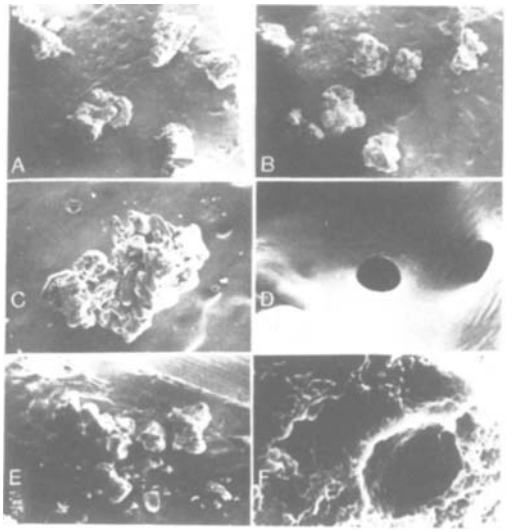

FIG. 1. Scanning electron micrographs of 500–297 μm microcapsules containing sodium salicylate coated with ethylcellulose standard 10 cp (A) or 100 cp (B,C,D,E,F) before (A,B,C,D) or after (E,F) dissolution studies. A,B,E. about × 10; C about × 35; D,F about × 1750.

aggregates of coated particles held together by polymer bridging. Watanabe & Hayashi (1976) reported a similar aggregated appearance of ethylcellulose-coated aspirin prepared by a polymer precipitation method. Fig. 1D shows a portion of the surface of an ethylcellulose 100 cp coated capsule which like the surface of 10 cp coated material exhibits both rough and smooth areas with the presence of pores some of which may extend through the coating to the core material.

Dissolution studies are often used to indicate possible differences in bioavailability of pharmaceutical products. Fig. 2 shows dissolution curves for the release of sodium salicylate from equivalent size range microcapsules prepared using the two

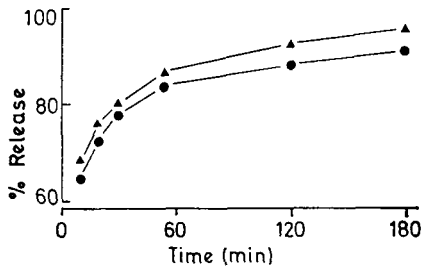

FIG. 2. Release of sodium salicylate from 500–297 μm microcapsules coated with a ▲ 10 cp or ● 100 cp ethylcellulose standard.

grades of ethylcellulose. The ethylcellulose 100 cp-coated capsules had the slower release. However, in both cases, over 90% of the core material was released within 3 h which confirms the poor capacity of these coatings to retard dissolution of water soluble drugs from microcapsules. A similar rapid release of phenobarbitone sodium from an ethylcellulose microencapsulation was reported by Jalsenjak et al (1976) and from ethylcellulose-coated granules containing various drugs by El-Sayed et al (1978). Fig. 3 shows the results of swelling experiments on discs prepared from both grades of ethyl-

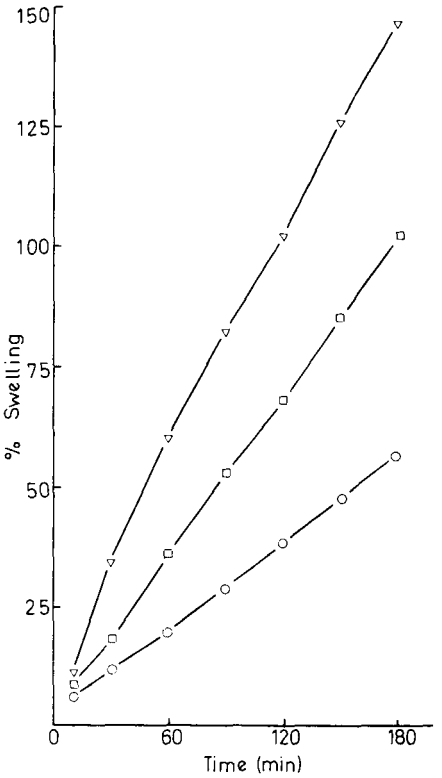

FIG. 3. Swelling in water at 37 °C of ▽ 10 cp, □ 100 cp or ○ 100 cp ethylcellulose standard treated with 10% paraffin wax solution.

cellulose, indicating that the polymers swelled markedly, the 10 cp grade to a greater extent over the 3 h period. Fig. 1E shows a micrograph of microcapsules after 3 h dissolution treatment which in contrast to Fig. 1B shows that the microcapsules have ruptured into many fragments. Fig. 1F shows a portion of the surface of a microcapsule after dissolution which in contrast to Fig. 1D shows a swollen rough surface with an enlarged pore present.

The faster release of core material from the 10 cp coated capsules is probably due to their greater fragmentation and porosity associated with the increased swelling of the polymer.

For the production of prolonged action preparations, as distinct from other applications of microencapsulation, it is desirable that the release of the encapsulated drug should be further retarded. Because of its capacity to produce a finer particulate product with a greater tendency to prolong release, ethylcellulose 100 cp was chosen to prepare several batches of microcapsules which were thoroughly mixed. Samples of the mixed material were then sealed by agitation with solutions of various waxy materials in cyclohexane, as previously described, before size fractionation. Fig. 4 shows that by

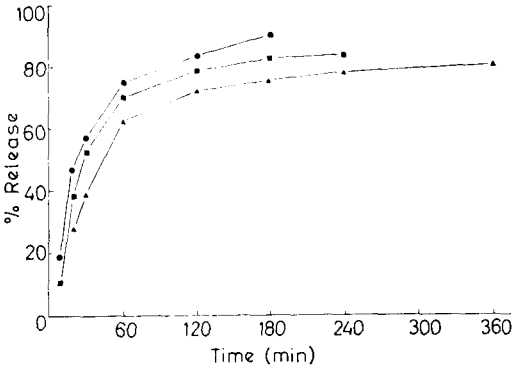

FIG. 4. Release of sodium salicylate from 500–297 μm ethylcellulose 100 cp coated microcapsules sealed with ● 5%, ■ 10% or ▲ 20% paraffin wax.

increasing the % of paraffin wax in the sealant treatment it is possible to delay the release of the core material from equivalent size range microcapsules. However the results of sieving analysis shown in Table 1 confirm the tendency of increasing wax treatment to produce an excessively coarse product. Microcapsules obtained using 5% paraffin wax-treatment had a narrower and finer size range than the corresponding unsealed capsules. Concentrations over 20% or wax treatment of the drug alone tended to produce a product which was unacceptably greasy and adhesive. A similar sealant treatment was outlined by Powell (1971) for ethylcellulose encapsulated *N*-acetyl-*p*-aminophenol. Fig. 5A shows a scanning electron micrograph of a 10% paraffin wax treated microcapsule which is obviously composed of an aggregate of smaller particles. A portion of the surface is shown in greater magnification in Fig. 5B having a wavy, wax-impregnated appearance and no

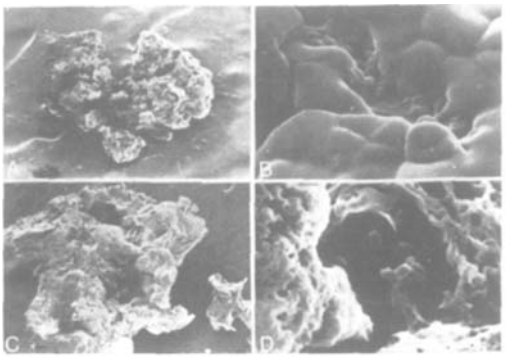

FIG. 5. Scanning electron micrographs of 500–297 μm microcapsules containing sodium salicylate coated with ethylcellulose 100 cp and sealed with 10% paraffin wax treatment, before (A, B) and after (C, D) dissolution studies. A, C about ×35; B about ×700; D about ×1050.

obvious pores are present. Fig. 5C shows a microcapsule which after 3 h dissolution treatment had swollen and become more porous but not appreciably fragmented. The swollen surface containing several pores is shown in greater detail in Fig. 5D. The results of the polymer swelling experiments shown in Fig. 3 indicate that discs compressed from 10% paraffin wax treated ethylcellulose swell less than untreated ethylcellulose.

Fig. 6 shows the influence of particle size on the release of sodium salicylate from microcapsules sealed with 10% paraffin wax treatment. As the particle size decreases the release of the drug increases because smaller microcapsules have more drug molecules close to their surface for dissolution into the surrounding medium.

Various mechanisms and mathematical models to interpret controlled release data from solid dosage dispersions have been reviewed by Baker & Lonsdale

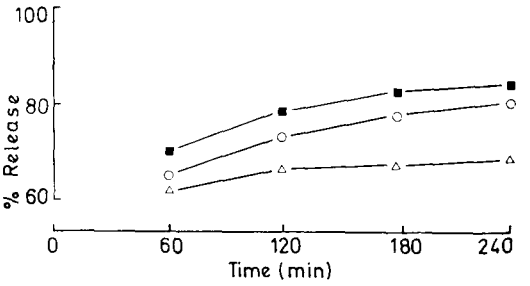

FIG. 6. Release of sodium salicylate from ■ 500–297 μm, ○ 840–500 μm or △ 1190–840 μm ethylcellulose 100 cp coated microcapsules sealed with 10% paraffin wax treatment.

(1974). Nang & Carlier (1976) reviewed aspects of diffusion from microcapsules. It is probable that the mechanism of drug release from microcapsules is complex, involving leaching, diffusion and erosion compounded by polymer swelling, the presence of air in the coating and drug binding. Accordingly, it would be unlikely that any simple mathematical model based on diffusion would perfectly fit the release data.

Schwartz et al (1968) studied the release of drugs from wax matrices and found a complex release pattern with square root of time release profiles giving the best fit of the experimental data. Fig. 7 shows such plots for the paraffin wax-treated micro-

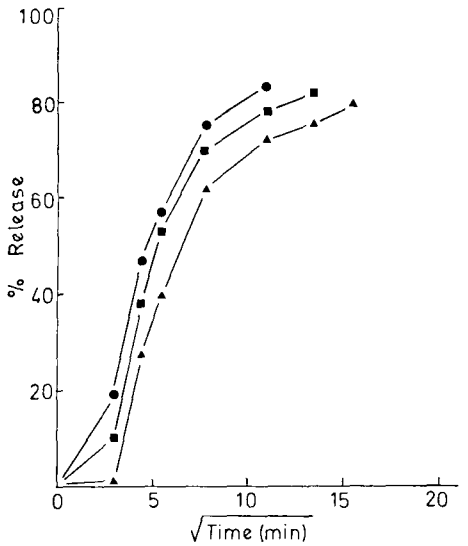

FIG. 7. Release of sodium salicylate as a function of the square root of time from 500–297 μm ethylcellulose 100 cp-coated microcapsules sealed with ●5%, ■ 10% or ▲20% paraffin wax treament.

capsules. The initial lag in release increases with increasing % of wax treatment and probably corresponds with that required by the dissolution medium to penetrate the surface and capillaries of the wax-impregnated coating and for the drug to diffuse outward from the core. At intermediary times the plots are roughly linear, being indicative of a diffusion controlled mechanism of release from a matrix. As dissolution proceeds, progressive swelling of the coating occurs with increase in porosity and decrease in tortuosity. Eventually the swelling, assisted by rupture of microcapsules, should lead to an increased rate of release. However, as the drug is very water soluble, with over 60% released in the first 60 min in all cases the remaining amount of drug in the microcapsules is probably not sufficient to maintain the concentration equal to its saturated aqueous solubility. Hence the final lag in release rate observed when fractions remaining to be released become small. This lag and the total release pattern is affected by binding between the drug and the ethylcellulose, less than 3% available drug being bound when a 10% w/v suspension of ethylcellulose 100 cp in 10% w/v sodium salicylate solution was agitated at 37 °C for 3 h. Binding between drugs and methylcellulose have been reported by Tillman & Kuramotto (1957).

Lapidus & Lordi (1966, 1968) investigated the release of various drugs from hydrophilic matrices composed of different cellulose derivatives. The polymers investigated, like ethylcellulose, swelled rapidly in water. Provided the integrity of the hydrated layer formed was maintained and not eroded by attrition, the release of drug was diffusion-controlled, being linearly related to the square root of time.

Fig. 8 shows plots of log % remaining drug to be released against time for 500–297 μm microcapsules

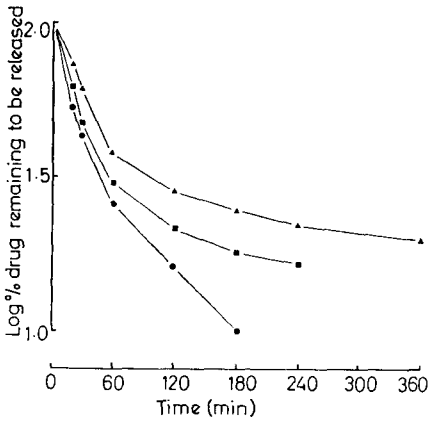

FIG. 8. Release of sodium salicylate plotted according to first order kinetics from 500–297 μm ethylcellulose 100 cp-coated microcapsules sealed with ● 5%, ■ 10% or ▲ 20% paraffin wax treatment.

sealed with variable % paraffin wax treatment. The plots show an initial apparent first order release rate which progresses to a more complex order as dissolution proceeds. Wagner (1969) reported a departure from apparent first order kinetics for the dissolution behaviour of drugs from tablets and capsules and proposed a distribution plot concept as an alternative way of evaluating such data. Fig. 9 shows such plots for drug % remaining to be dis-

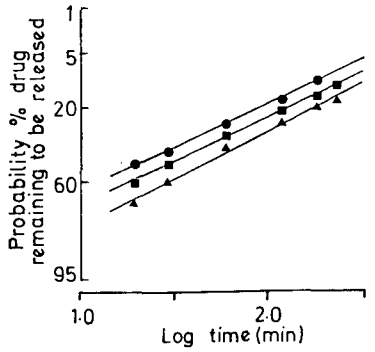

FIG. 9. Probability—log time plots for the release of sodium salicylate from 500–297 μm ethylcellulose 100 cp microcapsules sealed with ● 5%, ■ 10% or ▲ 20% paraffin wax treatment.

solved on a probability scale for 500–297 μm microcapsules sealed with variable % of paraffin wax treatment. The plots obtained are approximately linear and accordingly their median and standard deviation may be used to accurately predict the time required for any unknown drug % to be released.

Release of sodium salicylate was also studied in 0·1 M hydrochloric acid and was only slightly slower indicating that the pH of the external medium over the normal physiological range should have little effect. Desai et al (1965) reported a similar effect for the release of sodium salicylate from a polyethylene matrix.

A variety of other waxy substances were examined for suitability as sealants to cause prolongation of drug release. The release of drug from 500–297 μm microcapsules sealed with 10% treatment of the substances showed none of the sealants to produce as great a diminution in release of drug at comparable percentage treatment as paraffin wax.

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