International Journal of Pharmaceutics, 2 (1979) 91–99

ENCAPSULATED MICROCAPSULES

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(Received May 31st, 1978)
(Accepted June 6th, 1978)

SUMMARY

A microencapsulation procedure has been developed which allows an oil slurry of microcapsules to be filled into soft gelatin capsules. Ethylcellulose solutions in ethyl acetate can be desolvated by the addition of light liquid paraffin so that an ethylcellulose coat is deposited on a core material such as aspirin. Approximately 1% of the aspirin is imperfectly encapsulated. The use of light liquid paraffin enables the slurry to be filled directly into soft gelatin capsules without the usual filtering, drying, and redispersion steps.

Different release characteristics can be devised by varying the ratio of ethylcellulose to drug. In vitro release into a simulated gastric juice shows that essentially first-order kinetics exist for periods up to 12 hours.

INTRODUCTION

Microencapsulation can be defined as the application of a thin coating to individual core materials which have an arbitrary particle size range from 5 to 500 μm. The function of this coating may be to protect, separate or to change the physical properties or availability of the core material. Although initially developed as a means of producing 'carbonless' copy paper (Green and Schleicher, 1956), microencapsulation is rapidly becoming established as a way of presenting active drugs. This paper outlines the technology of presenting microencapsulated drugs in soft gelatin capsules which involves a continuous process of manufacture and filling.

Pharmacologically active materials can be microencapsulated by interfacial polymerization, electrostatic deposition, air suspension and spray drying or congealing methods (Bakan and Anderson, 1976). None of these are particularly suitable for efficient in-line manufacture and filling into soft gelatin capsules.

The most popular method of microencapsulation, phase separation and coacervation, can be readily adapted to the in-line requirements. The four stages of this method of microencapsulation are shown in Figure. 1.

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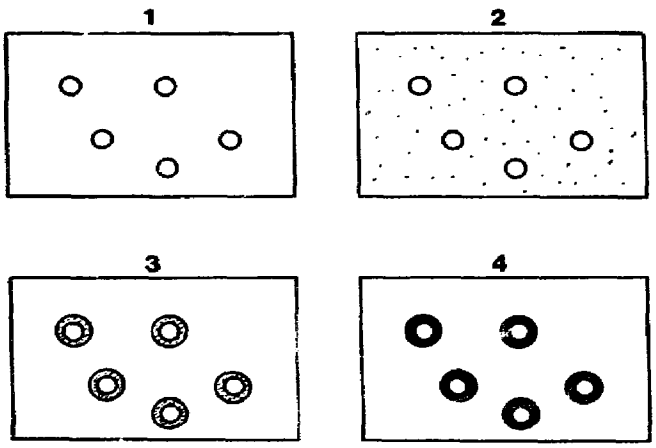

Fig. 1. Stages in the coacervation method of microencapsulation. 1: dispersion of the core material in a homogeneous phase containing dissolved wall material. 2: coacervation of the wall material by a change in system conditions. 3: deposition of the coacervate onto the core material. 4: rigidization of the deposited coacervate.

The conditions which can cause coacervation include a change in temperature, pH or the addition of a competing solute or of a liquid in which the coating material is not soluble, i.e. a non-solvent. Typical coating materials which are used in the procedure include gelatin, albumin, starch derivatives, styrene, maleic acid, acrylamide and polyethylene glycol (Gutcho, 1972; El-Egakey et al., 1974). Using this phase separation procedure, ethylcellulose has been used to produce ammonium nitrate, ammonium dichromate and magnesium hydride microcapsules (Gutcho, 1972).

Salicylates have been a favoured model drug to study microencapsulating procedures. Athough salicylic acid and aspirin have been encapsulated in gelatin (Tanaka et al., 1963; Paradissis and Parrott, 1968), ethylcellulose with its solubility in non-aqueous solvents would be a preferred coating material for aspirin. Microencapsulated aspirin has been presented in a tablet (Measurin by Bayer), but there must be doubt about the physical coherence of the coating material as a result of normal tabletting procedures. The efficiency of the microencapsulation of aspirin can be readily tested if the product is presented in a water containing dosage form. Since aspirin assay methods are well established the in vitro and in vivo sustained release characteristics of a dosage form containing aspirin microcapsules can be readily determined.

The Scherer Rotary Die method of manufacturing soft gelatin capsules has enabled this dosage form to be regularly used in pharmaceutical practice. Soft gelatin capsules present drugs in an elegant easily swallowed form and because they contain a solution or a suspension, they can accurately and reproducibly present a given amount of drug. However, soft gelatin capsules have four main disadvantages as a dosage from:

(1) strongly hydrophilic liquids cannot be filled because the gelatin wall would dissolve. Most fill liquids are oils;

(2) low molecular weight volatile organic compounds should not be encapsulated because they could migrate through the wall;

(3) suspensions or solutions made from strong acids, bases and their salts often cannot be filled because the inside of the gelatin wall is tanned and the products are poorly released from the capsule; and

(4) moisture sensitive materials like aspirin are unsuitable because the gelatin wall contains water.

These disadvantages are removed if the unsuitable material is microencapsulated. The inclusion of a physically and chemically stable microcapsule slurry in a soft gelatin capsule would have major manufacturing advantages over the incorporation of the microcapsules into other dosage forms. Firstly, the microcapsules would not be subjected to any physical attack as in tabletting. Secondly, if the microencapsulation procedure employed resulted in an oily slurry of hardened microcapsules, these could be directly filled into the soft gelatin capsules without the tedious and costly collection, drying, and redispersion of the microcapsules. The use of such a direct filling procedure would require that non-toxic reagents be chosen for the microencapsulation procedure or the removal of any toxic substances used in the procedure.

MATERIALS AND METHODS

Materials

Monsanto No. 2 ASA aspirin was sieved through Endecott stainless steel sieves on a Cheers sieve shaker. The +180/−250 micrometer fraction was collected and used. Ethylcellulose N100 was used as supplied (A.C. Hatrick, Melbourne). Light liquid paraffin (LLP) was used as supplied as Ondina 17 (Shell Chemicals, Melbourne). Ajax 'Univar' grade ethyl acetate and chloroform were used for the solvent for the ethylcellulose and in the aspirin assay of the microcapsule slurry respectively.

Manufacturing procedure for aspirin microcapsule slurry

The microcapsule slurry was manufactured in a glass 3 dm^3 tall form beaker which had an internal diameter of 14 cm. A 10.5 cm diameter disc type stirrer with 12 blades set at a pitch of approximately 45° driven be a Caframo variable speed stirrer (type RZ R1-64) was used. The following manufacturing procedure was adopted.

(a) Preparation of a solution of ethylcellulose in ethyl acetate: 4–10 g ethylcellulose was added slowly to 600 cm^3 of ethyl acetate with gentle agitation (about 80 rpm).

(b) Initial desolvation: when the ethylcellulose was completely dissolved, 350 cm^3 of LLP was added and the mixture rapidly agitated at 1500 rpm.

(c) Addition of aspirin: after exactly 30 min, 40.0 g of aspirin was added. The volume of the reaction mixture was approximately 750 cm^3.

(d) Final desolvation: after a further 60 min, when the total volume was approximately 550 cm^3, 2 dm^3 of LLP was added and the stirring continued for a further 60 min.

(e) Concentration of the microcapsule slurry: after the microcapsules had been allowed to settle overnight, the excess vehicle was decanted. The concentrated slurry was collected for assay, in vitro testing and filling into soft gelatin capsules.

(f) Recycling: the decanted vehicle could then be used for the desolvation steps in the succeeding batches of microcapsules.

Assay of the microcapsule slurry

A Beer–Lambert plot of the spectral absorbance of aspirin in chloroform and of suitable reagent blanks at 278 nm was prepared using a Coleman model 55 spectrophotometer.

A sample of 700–1000 mg of the microcapsule slurry was dissolved in 100 cm^3 of chloroform and diluted 1 in 100. The absorbance of the diluted solution was measured and the amount of aspirin in the slurry estimated directly from the Beer–Lambert plot.

In vitro release characteristics

(a) One dm^3 of simulated gastric juice USP, sine pepsin, was heated at 37°C in a water jacketed beaker.

(b) A sample of microcapsules with a total aspirin content of 200 mg was added and the system stirred by a teflon-coated cylindrical (0.8 × 5.0 cm) magnetic stirrer bar at 220 rpm.

(c) A Watson Marlow type 200 flow inducer continuously drew 25 ml/min of the incubating fluid from the jacketed beaker through a 350 μm stainless steel pre-filter to a flow-through cell in a Perkin Elmer 402 UV-vis spectrophotometer set at 278 nm. The fluid was then returned to the jacketed beaker.

Estimation of free aspirin

Whilst keeping the total aspirin content at 600 mg, different amounts of free aspirin were added to separate lots of the microcapsule slurry. The in vitro release of aspirin from these lots was then measured for 20 min, using the procedure described above. The free aspirin in the microcapsule was estimated by a back extrapolation procedure.

Estimation of residual ethyl acetate

A series of solutions containing known amounts of ethyl acetate in light liquid paraffin was prepared. One μl of these solutions and 1 μl samples of recycled LLP were then analyzed on a Perkin Elmer 900 gas chromatograph. The amount of ethyl acetate in the samples of recycled LLP was estimated from the peak heights obtained when nitrogen, at a flow rate of 30 ml/min, was used as the carrier gas in a 6 ft, 0.25 in. inner diameter glass column packed with Apiezon L 4% on Chromasorb W AW-DMCS and operated at 60°C.

RESULTS

Microencapsulation procedure

The procedure did not cause any significant change in the particle size distribution of the aspirin crystals. By decanting the excess vehicle a content of 300 mg of aspirin per gram of microcapsule slurry is easily achieved.

Residual ethyl acetate

The amount of ethyl acetate remaining in the samples of recycled LLP (the eventual vehicle for the microcapsules) ranged from not detectable to 0.8%.

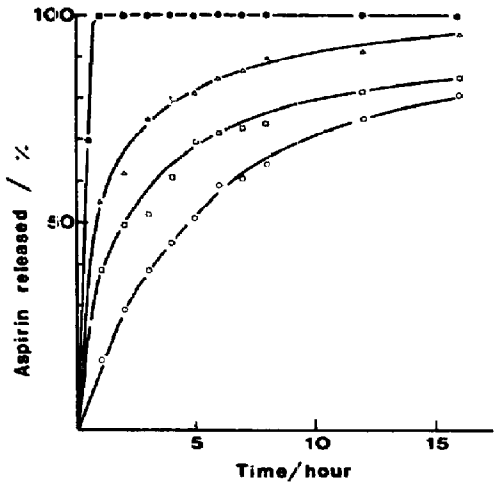

Fig. 2. Percentage of aspirin released from products microencapsulated with different percentages of ethylcellulose. •, unencapsulated aspirin; △, 10% ethylcellulose; □, 17.5% ethylcellulose; ○, 25% ethylcellulose.

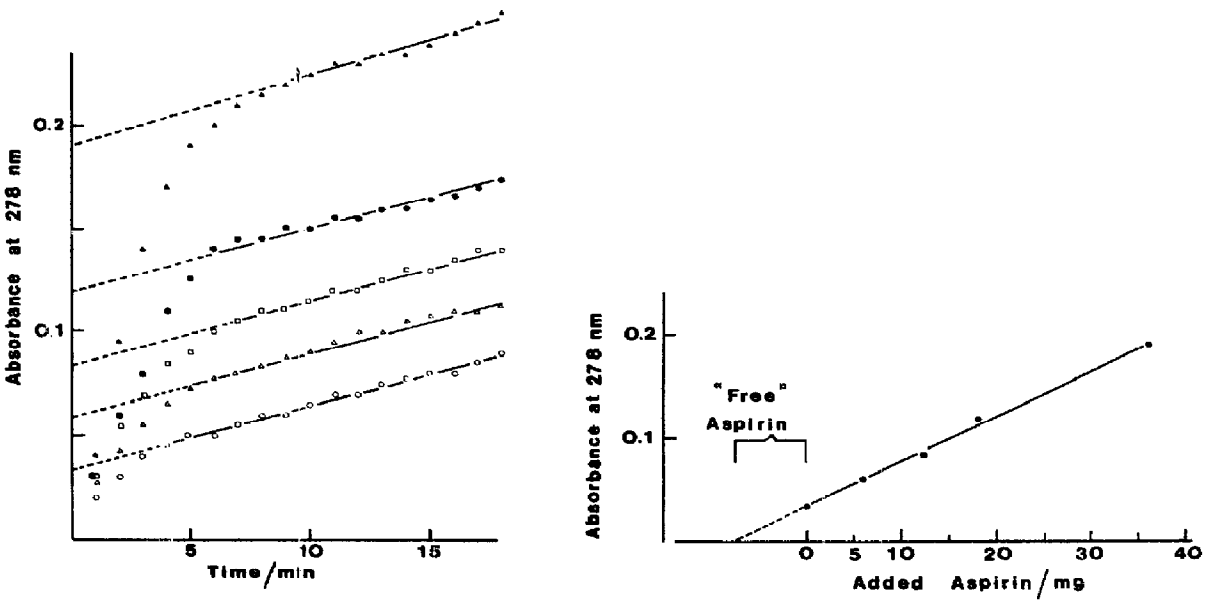

Fig. 3. Time release profile (as determined by absorbance at 278 nm) for 600 mg batches of microcapsules to which different amounts of uncoated aspirin, drawn from the same batch of aspirin, have been added. ○, no added aspirin; △, 6 mg; □, 12 mg; •, 18 mg; ▲, 36 mg.

Fig. 4. Determination of free aspirin in the batch of microcapsules using the intercepts on Fig. 3, by extrapolation to zero absorbance at 278 nm. The negative intercept on the horizontal axis gives the free aspirin content of the microcapsule batch.

In vitro release

The in vitro release from batches of microcapsules is shown in Fig. 2. As the ratio of ethylcellulose to aspirin is increased, slower in vitro release was observed. The batch prepared with a ratio of 17.5% ethylcellulose relative to aspirin released 38.6 and 49.1% of the total aspirin content after 1 and 2 h respectively. These release characteristics were considered suitable for the final dosage form and so this batch was chosen to be replicated many times and then pooled for filling into soft gelatin capsules. The amount of aspirin released at any time from any of these replicated batches was generally within a 5% band of the mean amount released.

'Free' aspirin

Fig. 3 demonstrates the in vitro release of the series of microcapsules to which uncoated aspirin was added. The intercepts on the vertical axis relate to the amount of 'free' aspirin.

Fig. 4 shows the straight line relationship between the amount of added aspirin and the intercepts on the vertical axis in Fig. 3. The amount of 'free' aspirin in the batch of microcapsules was found to be 7 mg or 1.2%. This amount was found to be typical for all the batches studied. At no time did the amount of free aspirin exceed 2%.

DISCUSSION

Solubility of core material

The success of a microcapsulation procedure using coacervation or phase separation is dependent on, amongst other factors, the insolubility of the core material in the solvent and non-solvent for the wall material. Whilst aspirin is insoluble in LLP, it has limited solubility in ethyl acetate. To minimize the dissolution of aspirin and its later re-precipitation as a molecular dispersion, the aspirin was added after the separation of ethylcellulose induced by first addition of LLP. The proportion of LLP to ethyl acetate was a balance between keeping the coacervated ethylcellulose in a liquid state, so it could envelop the added aspirin, and ensuring that a minimum of the added aspirin dissolved in the microencapsulation reaction mixture.

Whilst many solvent/non-solvent combinations could be used for the microencapsulation of aspirin by ethylcellulose, the limitations of the objective of a direct filling of the slurry into soft gelatin capsules severely limits the possible combinations. Another possible combination would be ethyl acetate and dimethicone.

Particle size

The particle size of aspirin crystals used in the process was determined by the need to sieve an amount sufficient for microencapsulating and then filling into soft gelatin capsules on a small production scale. Small aspirin crystals are very cohesive and it was found that +180/−250 μm fraction was the smallest particle size that could reasonably easily be collected in quantity from bulk aspirin supplied. Furthermore, Sirine (1967) suggested that to attempt to microencapsulate solid particles to 100 μm or smaller via a coacervation technique from non-aqueous systems is difficult and may result in highly aggregated systems. Our preliminary experiments support this suggestion.

Agglomeration of discrete microcapsules

As the ethyl acetate was evaporated with rapid agitation, the proportion of the non-solvent (LLP) relative to the solvent (ethyl acetate) was increased, which progressively solidified the ethylcellulose deposited on the aspirin cores. If the evaporation of the ethyl acetate was allowed to continue, the agglomeration of single microcapsules into aggregates was common. This resulted in a slurry containing particles which would have been too large to readily flow from the feed line used to fill the soft gelatin capsules. However, it was found that adding a large excess of non-solvent immediately prior to the point at which agglomeration took place, minimized the occurrence of oversized aggregates of microcapsules. This point could be pre-determined by trial runs. This technique of large scale rapid desolvation also avoided the need for dispersants, which otherwise would have to have been incorporated into the microencapsulating system. Such dispersants may have caused a decrease in the efficiency of the coating step.

Content of active material

A content of 300 mg/g of microcapsule slurry was easily obtainable. This compares favourably with previously published data of Paradissis and Parrott (1968). However, after the addition of flow improvement agents to the slurry and filling into an easily swallowed size of soft gelatin capsule (e.g. the 16 minim oblong), the single dose unit will contain approximately 200 mg of aspirin. The low aspirin per gram of slurry is due to the presence of excess vehicle which could not be removed by the simple process of decanting. If a more strenuous collecting method, e.g. vacuum assisted draining, is used, then a more concentrated slurry, and therefore a higher aspirin per unit dose, would result. The aspirin capsules would serve as effective model system to develop the technology required for the in-line process. The technology can now be used to present other problem drugs (D'Onofrio, 1977).

In vitro studies.

As expected, the in vitro dissolution of aspirin crystals was more rapid than the microencapsulated variety. Furthermore, as the ratio of ethylcellulose to aspirin was increased, slower in vitro release was observed. This concurs with data attributed to The National Cash Register Company by Bakan and Anderson (1976). Fig. 2 shows that while first-order kinetics apply to batches of microcapsules made with 25% coating, those made with 17.5% and 10% show first-order kinetics only after the first hour. One would expect that first-order release should be observed from all microcapsules made with ethylcellulose because it appears that the release from such is by a physical leaching effect. However, it would be expected that as the level of ethylcellulose is reduced, the thickness of the microcapsule wall is decreased. If so, some microcapsules now may have all or part of their walls so thin as not to be able to withstand the increased internal pressure resulting from the surrounding solvent diffusing into the microcapsule. These microcapsules may burst or develop leaks thus causing a more rapid release of aspirin in the initial stages. This effect should be more pronounced as the ratio of ethylcellulose to aspirin is decreased and this was observed (Fig. 2).

Free aspirin

Aspirin crystals which are largely uncoated should dissolve very rapidly compared to intact microcapsules. Fig. 3 shows that the first 15 min of in vitro release from the microcapsule slurries to which free aspirin has been added is bi-phasic and that the first rapid phase is dependent on the amount of free aspirin present. Fig. 4 shows how the amount of free aspirin in the original microcapsule slurry can now be estimated by an extrapolation technique and the result compares favourably with previous data (El-Egakey et al., 1974) on the content of free drug in microencapsulated products. Whilst this determination was performed on a batch of microcapsules made with 25% coating, it can be shown that the other batches have free aspirin contents of a similar order. This rapid dissolution of uncoated drug compared to the intact microcapsules may serve as a quality control test of microencapsulation efficiency.

Residual ethyl acetate

The maximum allowable daily intake of ethyl acetate varies from 2.5 to 25 mg/kg/day depending on the particular regulatory authority. Assuming a soft gelatin capsule content of 1 cm^3, a daily intake of 40 capsules is required to reach the most restrictive limit (Council of Europe, 1974). This suggests that the residual level of ethyl acetate is so low as to be of insignificant toxicity.

Stability

No stability testing of the aspirin microcapsules was undertaken. Two hundred mg of aspirin was microcapsulated and incorporated into soft gelatin capsules. The same amount of free aspirin was incorporated into soft gelatin capsules in a control experiment. After 6 months storage at 37°C the controls gave some 'leaky' soft gelatin capsules. The microcapsule product gave no 'leaky' capsules. Both types of soft gelatin encapsulated product gave less than 5 mg salicylic acid produced after 6 months storage at 37°C.

ACKNOWLEDGEMENTS

G. D'Onofrio acknowledges the award of a Commonwealth Postgraduate Scholarship. The authors thank R.P. Scherer Pty Ltd. for support of the research programme.

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