Cellulose acetate phthalate microcapsules: method of preparation

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Cellulose acetate phthalate has been used for enteric coating pharmaceutical dosage forms for many years. Such coatings are intended to prevent the release of the drug from the coated dosage form in the acidic gastric environment but to disintegrate and release the contents in the relatively basic intestinal medium. Recently, Madan & Minisci (1976) found that a number of commercially available enteric-coated tablets released their drug in the acidic environment. Since the release in some cases approximated zero order (Madan, 1977), it was believed that cellulose acetate phthalate would have microcapsule forming properties. We report the use of cellulose acetate phthalate as a possible microcapsule wall-forming material for the controlled release of the drug from the coated particles.

All materials were of U.S.P. or analytical grade and were used as received.

Microencapsulation procedure. A solution of cellulose acetate phthalate was prepared by dissolving 8 g in 100 ml of a 2% solution of sodium salicylate. Spherical droplets of the dispersion were prepared by a method similar to the capillary method reported by Madan, Luzzi & Price (1972). A fine capillary tube, C (Fig. 1) having an internal diameter of 200 μm was attached to a reservoir, R, in which was placed the dispersion to be encapsulated. Air pressure was applied to the reservoir to force the dispersion through the capillary tube at a steady rate of 60 drops min^{-1}. The droplets leaving the capillary tube were collected in a 5 M solution of hydrochloric acid which had been saturated with salicylic acid, separated from the solution and allowed to air dry at room temperature.

Release rates. The release of sodium salicylate from the microcapsules was determined by examining duplicate samples containing approximately 25 mg of the drug using the modified flask dissolution method This employed a 500 ml, three-necked round bottom flask with a 6 cm hole cut in the centre to accommodate the entrance of the 40 mesh screen basket assembly as used in the U.S.P. dissolution method. 300 ml of dissolution medium, preheated to 37°, was added to the flask maintained at 37° ± 0·5°. The basket containing the microcapsules was immersed in the dissolution medium, centered, and rotated at 100 rev min^{-1}. Samples of the dissolution medium were withdrawn at predetermined times by a pipette fitted with a cotton plug. The sample volume taken was replaced by an equal volume of the dissolution medium. In each case the cotton plug was added to the dissolution mixture. Concentrations were determined spectrophotometrically at 304 nm after appropriate dilutions.

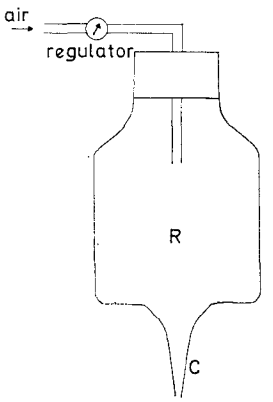

FIG. 1. Schematic diagram of apparatus.

Assay. Triplicate samples of approximately 100 mg of the microcapsules were accurately weighed and placed in a 150 ml homogenizing flask containing 50 ml of the dissolution medium. The samples were then completely ruptured using a Virtis blender operated at its maximum speed. In each case, two samples were blended for 10 min and complete rupture was insured by blending a third sample for 15 min with no observed increase in the drug content. Complete collection from the flask assembly was insured by washing with 50 ml of the dissolution medium.

Results. Sodium salicylate was used because of its ease of analysis. Ideally, microcapsules should be round, uniform in size and monodisperse. The apparatus produced uniform and monodisperse droplets at a rate not exceeding 100 droplets min^{-1}. Above this rate there was a change in the mean diameter and in the scatter of the microcapsules and monodispersity was lost. By varying the internal diameter of the capillary tube or air pressure, or both, the diameter of the droplets produced could be changed. A capillary tube having an internal diameter of 200 μm and an air pressure sufficient to produce 60 droplets per min^{-1} was preferred because the microcapsules so produced, 540 μm in diameter, were easily handled and remained in the dissolution basket during the release rate studies.

To attain uniformity, all experiments were conducted under identical conditions, using the same capillary tube and air pressure to achieve the 60 droplets min^{-1} rate.

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The microcapsules, unlike those of gelatin, were not sticky (Madan, Luzzi & Price, 1974) and did not form agglomerates (Madan, Madan & Price, 1976). However, after drying they ceased to be perfect spheres because of loss of solvent due to evaporation. There was no liquid inside the core suggesting that the drug content was in a crystalline form distributed in the centre of the microcapsule and/or throughout the collapsed sphere and, unlike gelatin microcapsules, the product neither returned to spherical shape nor increased in size when hydrated (Madan, Price & Luzzi, 1974).

Release characteristics. The release characteristics of the microcapsules are shown in Fig. 2. The data were plotted using the following equation to compensate for the portion of the drug removed from the dissolution flask at each withdrawal of the sample for concentration determination:

$$C_{corr} = C_{read} + \frac{5}{300}\sum_{s=1}^{n-1} C_{uncorr}$$

Where C_{corr} = corrected concentration of the sample at time 't'. C_{read} = spectrophotometrically measured concentration at time 't'. 5/300 = 5 ml of the sample withdrawn from 300 ml of the dissolution medium. $\sum_{s=1}^{n-1} C_{uncorr}$ = sum of the uncorrected concentration of the previous runs.

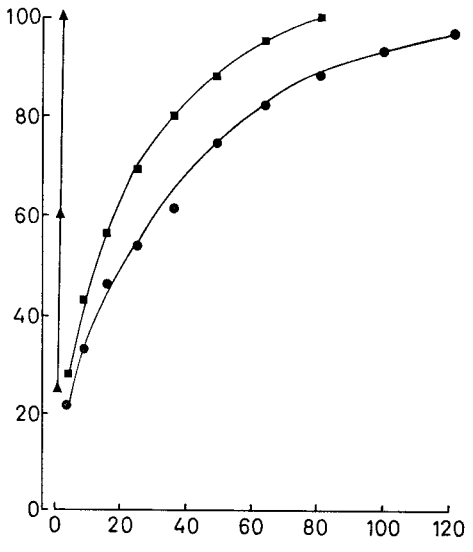

FIG. 2. Release of sodium salicylate from ▲—unencapsulated drug particles. ●—Microcapsules in 0·1 M HCl. ■—Microcapsules in phosphate buffer (pH = 8·0). Ordinate: Cumulative sodium salicylate released (%). Abscissa: Time (min).

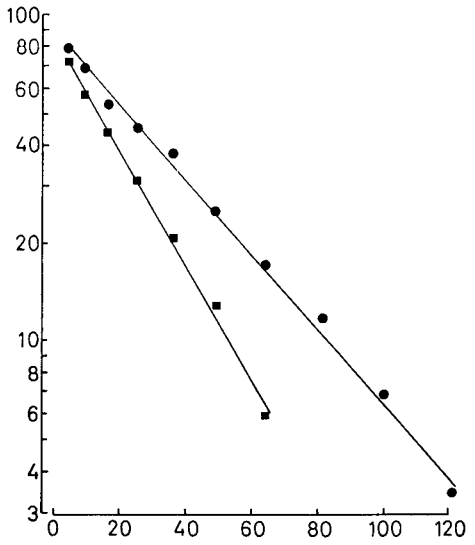

FIG. 3. First order plot of sodium salicylate released from the microcapsules in ●—0·1 M HCl. ■—Phosphate buffer (pH = 8·0). Ordinate: Sodium salicylate remaining (%). Abscissa: Time (min).

From Fig. 2 it can be seen that the process produced microcapsules that showed controlled release of sodium salicylate in both acidic and basic media. Unencapsulated drug particles of 100/120 mesh (average size 137 μm) dissolved completely in less than 2 min but drug release from the microcapsules in the acidic environment took over 2 h.

Since cellulose acetate phthalate is soluble in the alkaline medium, it would be expected that the release of drug from the microcapsules under alkaline conditions would be analogous to the dissolution of drug particles but Fig. 2 shows that release from the microcapsules in phosphate buffer at pH = 8·0 was similar to that in the acidic environment, only not as slow.

The controlled release of the drug from the microcapsules in the phosphate buffer indicates that the capsule shell was not soluble in the alkaline medium. It is possible that the cellulose acetate phthalate was modified during its treatment with hydrochloric acid solution to render it insoluble in both acidic and basic media. The shell did not dissolve and maintained its geometry in both media even over extended periods (observation made for at least 48 h).

The release of the salicylate followed first order kinetics (Fig. 3) in the acidic and the basic environment over all except the initial range of the dissolution process, and this represented about 20–25% of drug released. The non-linearity of this initial portion shows what appears to be a large surge of release almost as soon as the dissolution determinations were started and could be due to drug retained on the microcapsule wall during the microencapsulation process or to drug

Table 1. *Release of salicylate from the microcapsules in 0·1 N HCl and at pH 8 in phosphate buffer.*

Time, min	Cumulative % salicylate released* 0·1 N HCl	pH 8
10	34·23 ± 0·08	45·80 ± 0·50
20	49·30 ± 0·05	62·40 ± 0·34
30	60·00 ± 0·20	74·38 ± 0·26
40	68·50 ± 0·08	82·26 ± 0·80
50	75·22 ± 0·50	87·50 ± 0·48
60	80·50 ± 0·40	90·46 ± 0·36
70	84·84 ± 0·35	
80	88·00 ± 0·70	
90	90·60 ± 0·90	
100	93·02 ± 0·84	

* Average of two observations.

that may have migrated to the periphery of the microcapsule wall during the drying stage due to the solvent migration effect. Either one or a combination of both these phenomena would make some drug immediately available.

The drug content of the microcapsules as determined by extraction was 18% w/w compared with the theoretically calculated value of 20% w/w. This 10% difference could have resulted from some of the drug dissolving in the collecting fluid during the preparation of the microcapsules. Possibly because the addition of the alkaline cellulose acetate phthalate-drug dispersion into the acidic, drug-saturated collecting fluid would tend to make the collecting fluid less acidic (and therefore subsaturated with respect to salicylate), some of the drug from the microcapsules would be likely to dissolve in the collecting fluid resulting in a decrease in the drug being encapsulated.

The process of microencapsulation reported gave a remarkable degree of reproducibility. Release rates were within a narrow range, the maximum observed being less than 3% (Table 1). In addition, the process is simple, economical, and amenable to industrial application.

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LETTER TO THE EDITOR

'Immunogenic impurities' in acetylsalicylic acid

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Aspirin has wide use and it is obvious that methods for measuring and determining impurities in it are of importance but the clinical relevance of these impurities should be made clear. In 1976 Bundgaard published a paper entitled 'Colorimetric Analysis of Immunogenic Impurities in Acetylsalicylic Acid' in which he states that 'impurities in acetylsalicylic acid rather than the drug substance itself are held responsible for the appearance of anti-salicyloyl antibodies in patient's treated with acetylsalicylic acid'. The use of the term 'immunogenic impurities' and 'anti-salicyloyl antibodies in patients' is unsatisfactory in that it implies that the immunogenicity of these impurities has some clinical significance. Furthermore, the bibliography is incomplete and some references are quoted in a misleading manner.

In a few patients therapeutic doses of aspirin elicit a syndrome which clinically resembles a systemic allergic (anaphylactic) reaction of the immediate type. Bundgaard and his colleagues (see references quoted by him) claimed this syndrome is in fact anaphylactic and due to an immunogenic impurity in aspirin, namely acetyl-

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