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Effect of variables on the preparation of shellac microcapsules by solvent evaporation technique: Part 1

D.S. Sheorey, A.S. Shastri and A.K. Dorle

Department of Pharmaceutical Sciences, Nagpur University, Nagpur 440 010 (India)

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Summary

Shellac microcapsules were prepared by phase separation by solvent evaporation using sulphadiazine as a model drug. Appropriate mixtures of the drug were made in solution of shellac in isobutanol and emulsified in aqueous bentonite suspension. The microcapsules were obtained by evaporating the solvent at elevated temperatures. The effect of variables such as the amount of drug, bentonite concentration and stirring speed were studied. The proposed method is simple and free from agglomeration and coalescence.

Introduction

The microencapsulation technique originally developed for carbonless copy papers has been diversified into various applications. It has recently received increasing attention as a means of formulating pharmaceuticals for controlled release purposes. Of the various ways to manufacture microcapsules, those successfully employed include air suspension, coacervation, spray drying and congealing, electrostatic deposition, pan coating, interfacial polymerisation, etc.

Various natural and synthetic polymers have been developed and are being investigated for their usefulness in this field. This has led to the development of different encapsulation techniques, which in some cases are the modifications of the existing techniques to suit the core and coat material. Shellac is widely used in pharmaceutical industry for its excellent film forming and acid resistance properties. It is also used in the production of sustained release formulations. Shellac microcapsules containing encapsulated erythromycin propionate (Scapinelli, 1982), vitamin B-12 (Gupta and Rao, 1985) have been prepared by the emulsion technique. In another technique, prolong release sulphaethylthiadiazole microcapsules were obtained by spray drying an aqueous ammonia solution of shellac and the core material (Asker and Baker, 1966).

We wish to describe a new method of microencapsulation using shellac as the polymeric wall material. It is based on the method originally developed for rosin and rosin derivatives as wall

Correspondence: D.S. Sheorey, Dept. of Pharmaceutical Sciences, Nagpur University, Nagpur 440 010, India.

materials (Sheorey and Dorle, 1990). Sulphadiazine was chosen as a model drug because of its ease of estimation.

Materials and Methods

Shellac IP, Sulphadiazine IP (both supplied by H. Jules & Co., India), bentonite IP (J.J. Chemicals, India) and isobutanol (Sarabhai, India) were used.

Preparation of microcapsules

The microcapsules were prepared by the following general method. Shellac (acid value 72) was dissolved in isobutanol by gentle heating. Sulphadiazine, the model drug, was suspended in the above solution. With constant stirring, this was added slowly in a thin stream into a freshly prepared aqueous bentonite suspension maintained at 70 °C. Phase separation and consequent coating of the drug occurred on evaporation of the solvent. The temperature of the system was maintained at 70 °C throughout the experiment. The microcapsules were separated by filtering through a 150 mesh stainless-steel sieve, washed with water and air dried. The effect of variables such as the amount of drug, bentonite concentration and the rate of stirring were examined with regard to the drug content, particle size and size distribution and dissolution characteristics.

Drug content of microcapsules

Microcapsules, accurately weighed, were thorougly triturated in a glass mortar. The resulting powder was transfered to a 100 ml beaker. After thorough rinsing of the mortar and pestle with 10% HCl, the powder was suspended in about 50 ml of 10% HCl, gently warmed and agitated with a magnetic stirrer for 30 min to effect complete dissolution of the drug. After filtration, the volume was adjusted to 100 ml with distilled water and after suitable dilutions analysed for drug content (Bratton and Marshall, 1939).

Particle size analysis

The microcapsule size and size distribution were determined by evaluating a minimum of 400–500 microcapsules under a microscope fitted with a micrometer. The cumulative frequency undersize

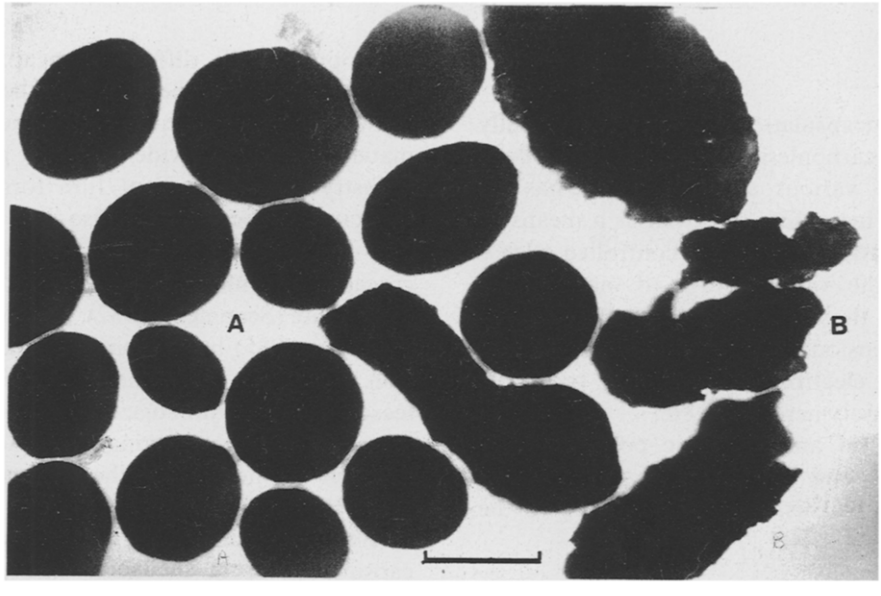

Fig. 1. Photomicrograph of shellac microcapsules containing encapsulated sulphadiazine prepared by solvent evaporation technique showing the effect of bentonite on microcapsule formation (scale bar, 250 μm). (A) With bentonite, (B) without bentonite.

data was plotted on log probability graph paper from which the mean diameter and the geometric standard deviation were calculated.

Dissolution studies

The in vitro dissolution studies were carried out in 1000 ml of simulated gastric fluid USP (without enzyme) using the standard dissolution rate equipment USP XIX model (Campbell Electronics, India), at 37 ± 1°C and 150 rpm. Microcapsules equivalent to 20 mg of the drug were employed in each case to maintain sink conditions. Aliquot portions were removed after suitable time intervals and analysed for drug content.

Results and Discussion

In the preliminary experiments, it was observed that unlike rosin and rosin derivatives, a dry product could be obtained without employing bentonite but the majority of the product was almost in the form of irregular flakes or needles, as compared to free flowing, spherical microcapsules when bentonite was used. Electron micrographs show the absence of aggregation, suggesting that no coalescence or aggregation occurs at any stage during the process (Figs 1 and 2). It was also observed that in all the cases a negligible fraction of bentonite, if at all, was incorporated into the microcapsules. This indicates that the bentonite particles always remained on the outer surface of the growing polymer membrane and maintained the shape and integrity of the spherical dispersed globules until completion of the process.

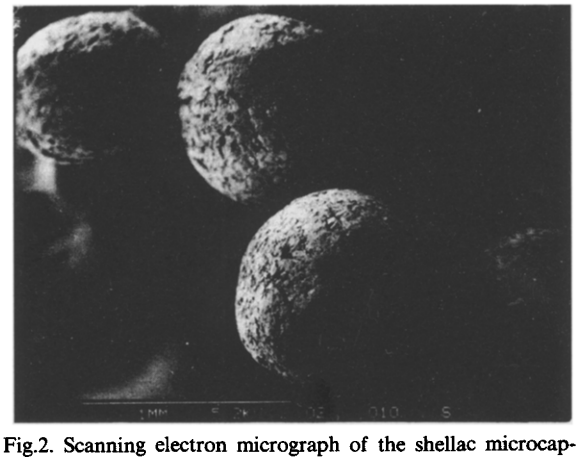

Fig.2. Scanning electron micrograph of the shellac microcapsules. (Cambridge Stereoscan S 250, Mark III, scan time 60 s).

TABLE 1

Effect of amount of drug on micromeritic and dissolution properties [a]

Amount of drug (g)	Mean diameter (μm)	Geometric standard deviation	% drug content [b] (± SD)	% drug released [b] in 3 h
4	1161	1.1048	85.34 ± 3.80	15.52
6	482	1.1680	90.44 ± 1.91	24.90
8	449	1.1649	95.35 ± 1.09	30.44

[a] Encapsulation conditions: Temperature, 70°C; 100 ml of 5% w/v bentonite suspension; 50 ml of 2% w/v shellac in isobutanol; speed, 1000 rpm.
[b] Average of three readings.

The experimental data show that the micromeritic and the release characteristics were influenced by the process variables taken into account for this study, viz. amount of drug, amount of bentonite and speed of agitation. Table 1 lists the effect of drug on the micromeritic and release properties of the microcapsules. At the same speed,

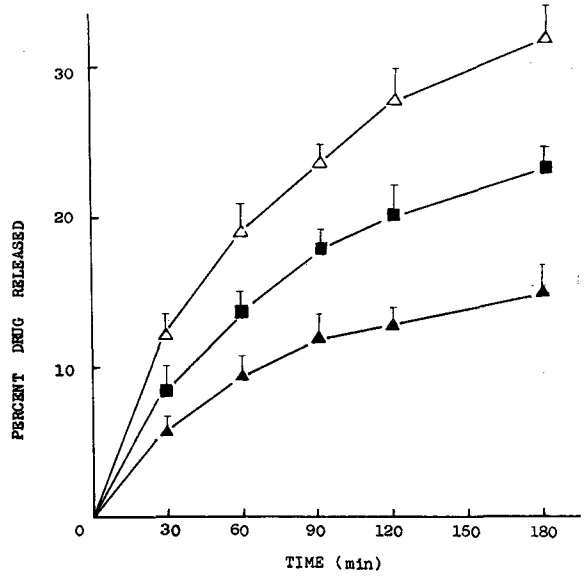

Fig. 3. Effect of amount of core material on the release characteristics of sulphadiazine in gastric fluid pH 1.2. Drug: 4 g (▲); 6 g (■); 8 g (△). Bars indicate ± SD.

increase in the amount of drug shifted the size distribution curves towards the smaller microcapsules with subsequent increase in the drug content of the microcapsules. The microcapsule size distribution was found to be log normal in all the cases. The increased drug content and the decreased microcapsule size indicate a decrease in the wall thickness of the microcapsules which is reflected in the release characteristics. At a core-to-coat ratio of 4:1, about 15% of the drug was released in 3 h. The release increased 2-fold when the amount of drug in the system was doubled (Fig. 3). This increase in the release is the result of the combined effect of decreased wall density and the microcapsule size. The decrease in the microcapsule size increased the surface area of the microcapsules available for dissolution.

The amount of dispersing agent and the speed of agitation govern the emulsification of the drug and the polymer solution and hence the final microcapsule size and size distribution. At higher bentonite concentration smaller microcapsules with narrow size distribution were obtained. A change in the dispersion medium caused by an increase in the bentonite concentration changes both the viscosity of the dispersion medium and the interfacial tension between the dispersed phase and the dispersion medium. The increased viscosity of the dispersion medium, however, prevents the subdivision of the drug/polymer droplets, reduces the coalescence and aggregation of the globules during the process and consequently influences the size distribution of the microcapsules. A slight increase in the drug content was also observed when bentonite concentration was increased from 5 to 10 g (Tables 1 and 2). The effect of preparative speed of agitation on the microcapsule characteristics is given in Table 3. The mean microcapsule size decreased slightly as the speed of agitation was increased. Although the

TABLE 2

Effect of bentonite on micromeritic and dissolution properties [a]

Amount of bentonite (g)	Mean diameter (μm)	Geometric standard deviation	% drug content [b] ($\pm$SD)	% drug released [b] in 3 h
6	382	1.2089	90.59$\pm$1.31	27.30
8	310	1.2129	91.32$\pm$0.91	32.40
10	265	1.1277	93.89$\pm$0.81	41.86

[a] Encapsulation conditions: Temperature, 70°C; 100 ml of bentonite suspension; 50 ml of 2% w/v shellac in isobutanol; drug, 6 g; speed, 1000 rpm.
[b] Average of three readings.

TABLE 3

Effect of rate of stirring on micromeritic and dissolution properties [a]

Speed (rpm)	Mean diameter (μm)	Geometric standard deviation	% drug content [b] ($\pm$SD)	% drug released [b] in 3 h
1000	265	1.1277	93.89$\pm$0.81	41.86
2000	240	1.1389	92.30$\pm$2.09	50.60
4500	235	1.2324	91.35$\pm$1.05	65.08

[a] Encapsulation conditions: Temperature, 70°C; 100 ml of 10% w/v bentonite suspension; 50 ml of 2% w/v shellac in isobutanol; drug, 6 g.
[b] Average of three readings.

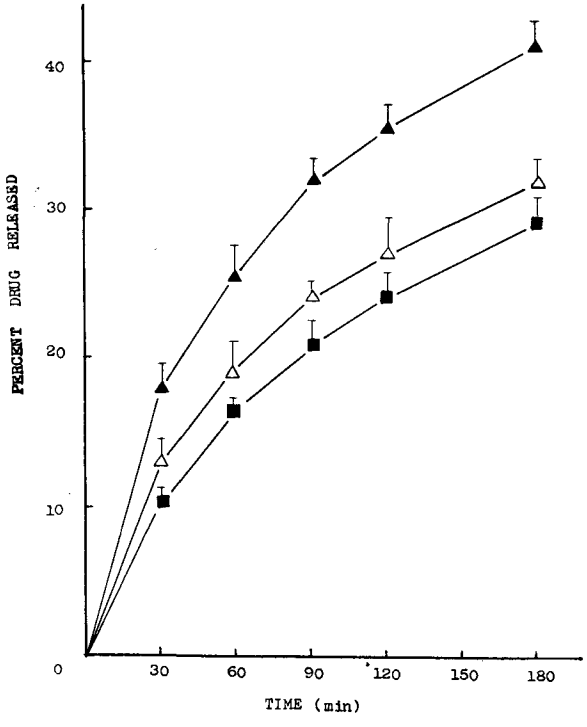

Fig. 4. Effect of bentonite concentration on the release characteristics of sulphadiazine in gastric fluid pH 1.2. Bentonite: 6 g (■); 8 g (△); 10 g (▲). Bars indicate $\pm$SD.

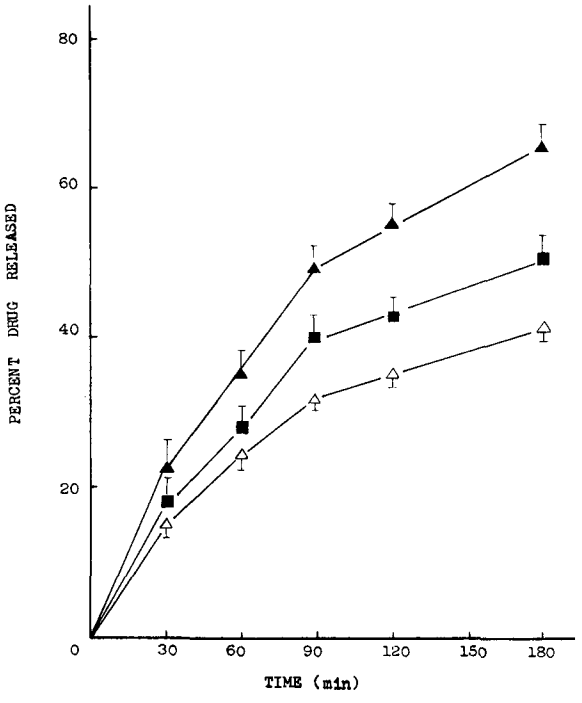

Fig. 5. Effect of rate of stirring on the release characteristics of sulphadiazine in gastric fluid pH 1.2. Speed: 1000 rpm (△); 2000 rpm (■); 4500 rpm (▲). Bars indicate ± SD.

mean microcapsule diameters obtained at 2000 and 4500 rpm were strikingly similar, particles obtained at the lower speed were more narrowly distributed than those obtained at the higher speed. Thus, the latter batch contains a greater fraction of small sized microcapsules than the former. This difference in drug content, particle size and size distribution was reflected in the release characteristics of the encapsulated drug (Figs 4 and 5). Microcapsules prepared at higher speeds of agitation and those prepared by using higher amounts of bentonite significantly released greater amounts of drug.

The data clearly show that the described encapsulation process is able to produce microcapsules with varying core-to-coat ratios. This is a fundamental requirement for controlling the release rates by shell thickness. In all cases, the variation in drug content and amount of drug released was minimum, showing the efficiency of the proposed method. The release of the drug was uniform and gradual and no burst effect was observed. Microcapsules retained their shape and size even after dissolution which indicates that the release is by diffusion/leaching of the drug through the polymer walls of the microcapsules. In contrast to earlier reports on encapsulation by the solvent evaporation technique, in which a dispersed phase having a boiling point lower than that of the dispersion medium is utilised, we have successfully employed a dispersed phase (isobutanol) having a higher boiling point than the continuous phase (water). The data also demonstrate that simple variations in the encapsulation process can significantly affect the drug release rates. Such knowledge would allow the manufacturer to determine the best conditions for encapsulation with respect to the objectives. The procedure is simple and could be employed to encapsulate water-insoluble substances. The proposed method was also found to be applicable to other film formers such as shellac derivatives, ethyl cellulose, etc., with relative ease.

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