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THE INFLUENCE OF COLLOIDAL PROPORTIONS ON THE RELEASE OF PHENOBARBITONE FROM MICROCAPSULES

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SUMMARY

The effect of preparative conditions on the ability of gelatin–gum acacia systems to produce microcapsules has been studied. The influence of these conditions on the size, size distribution and release characteristics of the microcapsules is reported.

INTRODUCTION

Phenobarbitone, either alone or in combination with phenytoin, is used in the treatment of Grand Mal epilepsy and whilst the former material has a naturally occurring extended activity it has been found that the reported contra indications occur less frequently when it is given in microencapsulated form. It was also desired to combine both phenytoin and phenobarbitone microcapsules in the same formulation and to study the possible substitution of phenobarbitone by other barbituric acid derivatives. For this purpose factors affecting the microencapsulation process had to be elucidated.

The normal method of microencapsulating water-insoluble medicinal compounds is by complex coacervations using the two colloids gelatin and gum acacia. Early work by Bungenberg de Jong (1936, 1947) and his co-workers (1949) indicated that there was a limit to the amount of colloid which could be used successfully, although this has been put at various values from 4% to 8% total colloid. A 6% total colloid appears to be the practical limit due to the suppressive effect of neutral salts present, or formed, during the coacervate process. Although it is normally assumed that all the colloid is present in the coacervate phase this is not strictly correct (Nixon and Khalil, 1968) as the quantity and proportion of the individual colloids varies depending on the relative colloid proportions, but it would appear most probably that the colloid in excess will be the one which appears in the equilibrium liquid. Yoshida and Thies (1966) suggested that not all the excess colloid appears in the equilibrium liquid, but that some might be associated with the

coacervate phase. It appears to us that if this latter condition applies it would undoubtedly affect the preparation of microcapsules and also the release characteristics of microcapsule core material. However, there appears to be no information available regarding the effect of varying the concentration and proportions of the colloids used in preparing the microcapsules.

MATERIALS AND METHODS

Gelatin (Richard Hodgson, Beverley, Yorkshire). Acid pretreated pigskin material; Bloom strength 256. Viscosity (62/3% w/w at 40°C) 7.4 cP. pH (2%) 4.35. Isoionic point pH 9.0.

Acacia (Evans Medical), Phenobarbitone (B.D.H.). These materials complied with British Pharmacopoeia specifications.

Preparation of microcapsules

The phenobarbitone was dispersed in the required concentration of gum acacia at 40°C. A similar quantity of gelatin solution was added and stirred at 250 rpm. The pH was adjusted to 3.9 and stirring continued for 50 min to allow formation of the microcapsules. Where required, hardening was by means of 10 ml of 40% formaldehyde solution added to the system prior to cooling. The system was rapidly cooled to 4°C and the microcapsules isolated and washed with isopropanol to dehydrate the outer coat before finally drying in a stream of nitrogen. Variations in the quantities of gelatin and gum acacia were used to prepare other samples of microcapsules.

Determination of equilibrium liquid viscosity

The viscosity was determined by means of a type B British Standard U tube viscometer (B.S. 188/1957). The amount of colloid in the equilibrium liquid was compared with reference to a calibration curve for gelatin. It was impossible to differentiate between the gelatin and gum acacia present in excess and it is more appropriate to refer to increasing viscosity of the equilibrium liquid as being due to the presence of unspecified excess colloid.

Particle size analysis

The microcapsule size was measured using both a projection microscope and the Model B Coulter Counter fitted with a 400 μm diameter orifice.

Dissolution studies

These were carried out at 37°C using two litres of dissolution media in a 3-necked flask at a stirring speed of 100 rpm. A 500 mg charge of microcapsules was used. Samples were taken at suitable intervals, filtered through a millipore Swinnex adaptor and phenobarbitone assayed at 255 nm, the filter and a suitable volume of dissolution media being re-added to the flask. Dissolution media consisted of aqueous solutions adjusted to pH 5, 9 and 13 with HCl or NaOH.

RESULTS AND DISCUSSION

Table 1 shows the characteristics of microcapsules prepared at varying concentrations of gelatin and gum acacia and indicates that conditions of equal amounts of gelatin and gum acacia produced the best microcapsules. Whenever unequal amounts of either colloid were used there was a tendency for the microcapsules to aggregate or gel on cooling, possibly due to the adhesive effect of excess colloid present during the extraction stage. At colloid concentrations in excess of a total 6% there is a probability of the resulting microcapsules aggregating into a viscous mass and treatment with isopropanol did not dehydrate the outer surface sufficiently rapidly to prevent adhesion. It appears that 6% represents a limiting total colloid concentration for the preparation of free flowing non-aggregated microcapsules.

The presence of excess acacia resulted in darker microcapsules, though the reason for this was not obvious. The equilibrium liquid from these systems could be demonstrated to contain excess colloid, which produced a hard glassy mass on evaporation. This residue complied with the B.P. identification tests for gum acacia (B.P. 1963). A 4 : 1 excess of acacia resulted in an inability to extract any microcapsules from the system.

Table 2 indicates that the equilibrium liquid, even in the systems which did not produce recoverable microcapsules, contained only relatively small amounts of colloid. It has been shown that under ideal conditions the equilibrium liquid contains no colloid. The flow times in the U-tube viscometer for systems containing excess gum acacia show that there is a small increase in the colloid present in the equilibrium liquid over that contained when equal amounts of the two colloids are used to prepare the coacervate. However, the most notable increase in equilibrium liquid colloid concentration occurred when excess gelatin was present. This resulted in the entrapment of any microcapsules that formed in a gel network on cooling.

TABLE 1

EFFECT OF COLLOID CONCENTRATION ON THE MICROCAPSULES PRODUCED

Colloid concentration (% w/v)		Observation
Gelatin	Gum acacia	
1.0	1.0	Free-flowing microcapsules
1.5	1.5	Free-flowing microcapsules
2.0	2.0	Free-flowing microcapsules
2.5	2.5	Free-flowing microcapsules
3.0	3.0	Free-flowing microcapsules
4.0	4.0	Microcapsules gelled on cooling
3.0	4.0	Microcapsules aggregate
2.0	4.0	Microcapsules aggregate
1.0	4.0	Microcapsules aggregate
4.0	3.0	Microcapsules gelled on cooling
4.0	2.0	Microcapsules gelled on cooling
4.0	1.0	No microcapsules

TABLE 2

DETERMINATION OF THE AMOUNT OF COLLOID PRESENT IN THE EQUILIBRIUM LIQUID (WITH REFERENCE TO THE VISCOSITY OF GELATIN SOLUTIONS)

Colloid concentration (% w/v)		Mean time of flow through viscometer (secs)	Equilibrium liquid colloid concentration (% w/v)
Gelatin	Gum acacia		
1.0	1.0	78	0.095
1.5	1.5	80	0.11
2.0	2.0	81.5	0.125
2.5	2.5	86	0.17
3.0	3.0	84	0.15
4.0	4.0	88	0.19
3.0	4.0	84.5	0.155
2.0	4.0	92.7	0.24
1.0	4.0	99.5	0.30
4.0	3.0	108	0.385
4.0	2.0	342	1.20
4.0	1.0	1070	3.65

The excess gelatin does not appear to take any part in forming the microcapsule wall, but because of the small amount of the excess acacia associated with the equilibrium liquid it is probable that the excess may take part in the formation of, or be entrapped within, the coacervate wall. It is not firmly bonded and due to leaching out results in a more rapid dissolution of the drug through the now very porous microcapsule wall. The excess acacia did not produce an aggregate containing embedded microcapsules as did excess gelatin.

Besides a possible effect on the release of the drug from the microcapsules, the presence of different concentrations of colloid might be expected to have an influence on size. Figs. 1–3 illustrate the relationships between the concentration of colloid used in

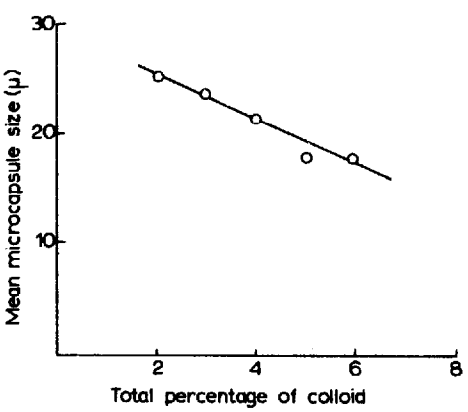
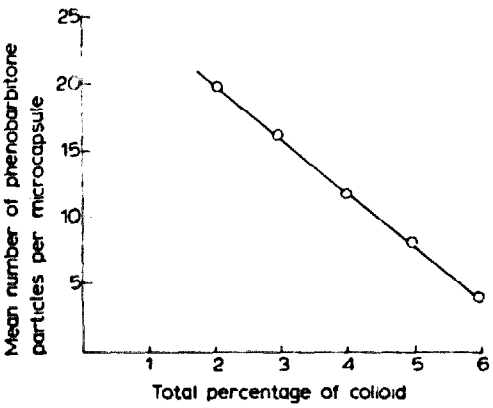


Fig. 1. Mean particle size of microcapsules in relation to the percentage of colloids used in their preparation.



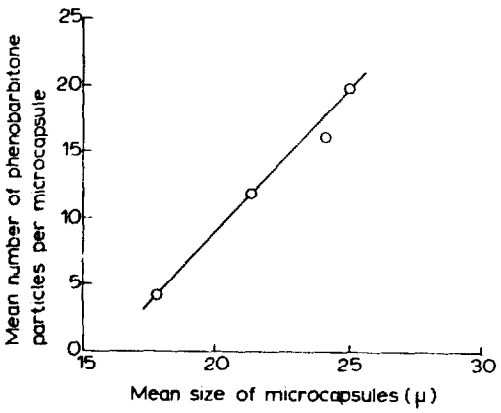


Fig. 2. The effect of colloid concentration on the mean number of phenobarbitone particles per microcapsule.

Fig. 3. The relationship between the number of phenobarbitone particles contained in a microcapsule and the microcapsule size.

the microcapsule preparation, the mean size of the microcapsules and the number of core particles per microcapsule. For a given set of preparative conditions the higher the colloid concentration the smaller the mean size of the resulting microcapsules and the smaller the number of entrapped core particles. It would appear that there is an increase in the number of coacervate droplets with an increase in colloid concentration rather than an increase in the size of the drops. The figures show the average of 5 individual experiments. The maximum experimental variation was 11.6% with most showing a variation of approximately 6%. The plots allow a straight line to be drawn through the points.

These results have important implications in the preparation of microcapsules. It might be expected that the most probable effect of an increase in colloid concentration would be solely to produce thicker microcapsule walls. At higher colloid concentrations the surface tension is reduced sufficiently to allow the core material to separate thus producing more, but smaller 'seeds', around which the colloid can deposit. Alternatively at higher colloid concentrations the colloid may deposit on microcapsules formed from a smaller number of 'seeds' produced by the aggregation of the core particles within the more viscous system thus producing larger microcapsules with thicker walls. As a third alternative, at colloid concentrations above 6%, large amounts of colloid may remain in the equilibrium liquid and eventually supress the isolation of individual microcapsules. Our observations appear to indicate that this latter condition may occur at high colloid concentrations or when gelatin is in excess. The size shown in Figs. 1–3 is a mean value and in all cases a size distribution curve shows a sigmoidal shape. There is a tendency for an increase in the number of large aggregates (above 300 μm) and very small individual microcapsules (under 1 μm) at high colloid concentrations. In some systems the very small microcapsules make a large numerical contribution but because of their size contain only a small percentage of the core material and may be completely empty.

The release characteristics follow a normal pattern, producing a rapid release up to between 50 and 60% followed by a much slower release of the remaining contents at all

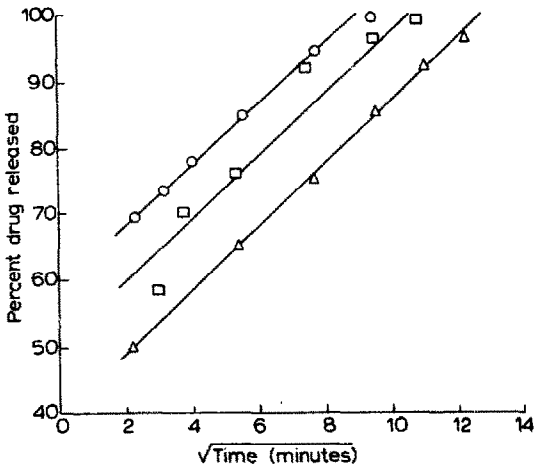


Fig. 4. The relationship between the release of phenobarbitone from microcapsules and the square root of time. pH 13. Temperature 37°C. Colloid concentration: ○, 1% gelatin: 1% gum acacia; □, 2% gelatin: 2% gum acacia; △, 3% gelatin: 3% gum acacia. Microcapsule charge 500 mg. Phenobarbitone % in microcapsules, ○, 33%; □, 20%; △, 14%.

these pHs studied. It has been suggested that this rapid removal of contents is brought about by the release of core material trapped in vacuoles or associated with the wall of the microcapsule (Nixon and Walker, 1971; Nixon and Matthews, 1974; Nixon and Nouh, 1977). The portion which is released slowly is removed from the microcapsules by diffusion of the saturated solution of the solid core through the walls. A specimen plot of per cent drug released against $\sqrt{\text{time}}$ at pH 13 for the slower release portion of the curve (Fig. 4) produced a straight line graph. Similar results were found at other pHs. The effect of colloid concentration shows a diminishing progress from fastest release with low colloid concentration. The lines on the $\sqrt{\text{time}}$ plot appear to be parallel, but not enough replicate data is available for a significant statistical analysis to be performed. However, it would appear that the amout released is an artifact of the colloid concentration and that low colloid concentrations produce a poor microcapsule wall which allows rapid release of the bulk of the contents. If this release was solely dependent upon the surface area of the microcapsules and the core then from Figs. 1 and 2 it might be expected that the reverse to the above observation would occur as smaller microcapsules, with the core more widely distributed, are present at higher colloidal concentrations. These conditions would be expected to produce an increased surface area for diffusional release. Microscopic examination showed that with the higher colloid concentrations the thickness of the hydrated microcapsule wall was greater. It would appear that the thickness of the wall is the important factor in the primary release of core material. Neither the colloid concentration nor the surface area of the microcapsules or core appear to be the controlling factor in the slow release of the remaining drug, which appears to progress at an uniform rate independent of the preparative conditions.

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