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An investigation of the effects of some process variables on the microencapsulation of propranolol hydrochloride by the solvent evaporation method

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Abstract

The effects of four process factors: pH, emulsifier (gelatin) concentration, mixing and batch, on the % w/w entrapment of propranolol hydrochloride in ethylcellulose microcapsules prepared by the solvent evaporation process were examined using a factorial design. In this design the minimum % w/w entrapments of propranolol hydrochloride were observed whenever the external aqueous phase contained 1.5% w/v gelatin at pH 6.0 (0.71–0.91% w/w) whereas maximum entrapments occurred whenever the external aqueous phase was composed of 0.5% w/v gelatin at pH 9.0 (8.9–9.1% w/w). The theoretical maximum loading was 50% w/w. Statistical evaluation of the results by analysis of variance showed that emulsifer (gelatin) concentration and pH, but not mixing and batch significantly affected entrapment. An interaction between pH and gelatin concentration was observed in the factorial design which was accredited to the greater effect of gelatin concentration on % w/w entrapment at pH 9.0 than at pH 6.0. Maximum theoretical entrapment was achieved by increasing the pH of the external phase to 12.0. Marked increases in drug entrapment were observed whenever the pH of the external phase exceeded the pK_a of propranolol hydrochloride. It was concluded that pH, and hence ionisation, was the greatest determinant of entrapment of propranolol hydrochloride into microcapsules prepared by the solvent evaporation process.

Keywords: Microencapsulation; Solvent evaporation process; Propranolol; pH; Gelatin; Factorial design; ANOVA ; Interaction

1. Introduction

Microencapsulation is the term that describes the various techniques used to wrap either individual particles or aggregates of particles within a polymeric coat or matrix (Krowczynski, 1987). A popular method for the microencapsulation of water-insoluble drugs within water-insoluble polymers is the solvent evaporation process (Beck et al., 1979). In this method, the core material is dissolved or dispersed in a polymer solution of a volatile organic solvent. Following emulsification of this polymeric phase into a continuous immiscible aqueous phase containing an emulsifier, the

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organic solvent is removed using heat, solvent extraction, freeze-drying or a vacuum. The polymeric material shrinks around the core material to produce solid, drug-loaded microcapsules. The collection of microcapsules is then performed by filtration, centrifugation, decantation and then dried (Bakan, 1986).

There are several process variables in the solvent evaporation process that may influence the characteristics of the microcapsules. These include, the aqueous solubility of the drug, type of organic solvent or solvent mixture, phase ratio of the emulsion system, drug loading, temperature, type and concentration of emulsifier (Benita et al., 1984; Bodmeier and McGinity, 1987a,b, 1988). Generally, however, the efficiency of microencapsulation of water-soluble drugs by the solvent evaporation process has been low due to drug loss from the polymeric phase to the aqueous phase (Bodmeier and McGinity, 1988).

There have been several attempts to optimise the solvent evaporation process to efficiently encapsulate water-soluble drugs. Bodmeier and McGinity (1987a,b) adjusted the pH of the aqueous phase to minimise drug solubility in that phase and thus reduced drug loss from the polymeric phase. Wada et al. (1990) microencapsulated doxorubicin hydrochloride and insulin within a lactic acid homopolymer using the solvent evaporation process by formation of an o/o emulsion. High entrapment efficiencies were reported (80–90%) and the release profiles were not accompanied with a significant burst effect. However, one drawback in the process is the use of oil as the external phase as this presents problems in the final washing of the microcapsules. Other workers have used a water in oil in water (w/o/w) emulsification in the solvent evaporation process to encapsulate highly water-soluble drugs (Ogawa et al., 1988; Alex and Bodmeier, 1990). In these the water-soluble drug is dissolved in water and this solution is emulsified in an organic solution of the polymer to be used for the wall material. This primary emulsion is then emulsified in an aqueous phase to form a w/o/w emulsion. After evaporation of the organic solvent an aqueous suspension of microcapsules is produced.

The aim of this investigation was to examine the contribution of some process variables on the entrapment efficiency of propranolol hydrochloride, a water-soluble drug, within ethylcellulose microcapsules using the solvent evaporation process and a factorial design. Factorial designs are commonly used in experiments to evaluate the effects of certain variables (Factors) on experimental results. In addition to elucidating the effects of primary variables, factorial designs are necessary to reveal any interactions between factors and also to allow maximum use of the data produced during the course of experimentation (Bolton, 1984).

2. Materials and methods

2.1. Chemicals

Propranolol hydrochloride BP was a gift from Oregin (NZ) Ltd (Palmerston North) and was sieved through a 180 μm mesh prior to use. Gelatin type B was donated by Davis Gelatin NZ Ltd (Christchurch). Ethylcellulose N4, dichloromethane (GPR) and hydrochloric acid (GPR) were purchased from BDH Chemicals (Poole, UK).

The buffer system used was a Prideaux buffer (Jordan, 1980), the constituents of which, potassium hydroxide AnalaR, anhydrous potassium chloride AnalaR, glacial acetic acid AnalaR, orthophosphoric acid AnalaR and boric acid AnalaR, were purchased from BDH Chemicals (Poole, UK).

2.2. Preparation of microcapsules

Microcapsules were prepared using a modification of the method described by Wakiyama et al. (1982). In brief, ethylcellulose N4 (1 g) was dissolved in dichloromethane with stirring (Nuova II hot plate/stirrer, Medical Supplies Limited, NZ) and into this propranolol hydrochloride (1 g) was thoroughly dispersed. This drug/polymer organic dispersion was emulsified with mixing at 800 rpm using either non-baffled (Nuova II hot plate/stirrer) or baffled (Heidolph R1RZ, Wiar-

ton, Ontario) stirring into an aqueous external phase composed of gelatin type B (0.5, 1.5% w/v) at the required pH at room temperature (18–20°C). The final volume of the two phases was 200 ml, the phase/volume ratio (organic:aqueous) was 1:10 and the rate of addition of organic phase to aquoeus phase was constant throughout the factorial design. Stirring of the resultant o/w emulsion was continued until evaporation of dichloromethane occurred. The microcapsules were collected by filtration, washed with deionised water and dried in a desiccator for at least 48 h. The dried microcapsules were sieved and those within the size range 250–500 μm retained and stored at room temperature for further analysis.

2.3. Determination of the proranolol hydrochloride content of microcapsules

The propranolol hydrochloride content of microcapsules was determined as described by Senjkovic and Jalsenjak (1982) and Singh and Robinson (1988). At least triplicate samples of microcapsules (50 mg) were placed in a mortar and thoroughly triturated with a pestle. The drug was extracted using 50 ml of 0.1 M HCl in a 100 ml Erlenmeyer flask. After thoroughly rinsing all equipment, the total mixture was filtered through a Buchner funnel fitted with a sintered glass filter. Further dilutions were performed using 0.1 M HCl and analysis was performed spectrophotometrically (λ = 290 nm) using a Hewlett-Packard 8452A diode array spectrophotometer. The calibration curve for propranolol hydrochloride was linear over the range 0.5–10.0 mg/ml (r = 0.99 with zero intercept). The theoretical drug content within the microcapsules was 50% w/w. Ethylcellulose did not interfere with the analytical method.

2.4. Statistical analysis of results

For the purpose of the statistical analyses of the results, the % entrapment of propranolol hydrochloride within ethylcellulose microcapsules was calculated. Statistical analysis was performed using analysis of variance (Statview, Abacus Concepts Inc., CA, USA).

3. Results and discussion

In this study ethylcellulose microcapsules containing propranolol hydrochloride were prepared by the solvent evaporation process. In this process, the organic solvent is lost from the surface of the droplets whilst emulsified in the aqueous external phase. There is a subsequent increase in the concentration of polymer until a critical point is reached where the concentration of the polymer exceeds the solubility of the polymer in the organic phase. The polymer then precipitates to produce microcapsules (Bodmeier and McGinity, 1988).

Four factors were statistically examined in this study, namely, pH of external phase, concentra-

Table 1
The effect of process variables on the entrapment (% w/w) of propranolol hydrochloride within ethylcellulose microcapsules (N4) prepared by the solvent evaporation process

pH [a,b]	Concentration of gelatin (%/ w/v) [a,b]	Propranolol hydrochloride entrapment (% w/w) ± S.D. of microcapsules prepared by the solvent evaporation process using:			
		Baffled mixing [c]		Non-baffled mixing [c]	
		Batch 1 [c]	Batch 2 [c]	Batch1 [c]	Batch 2 [c]
6	0.5	1.34 ± 0.05	1.36 ± 0.05	1.19 ± 0.04	1.27 ± 0.07
6	1.5	0.72 ± 0.04	0.71 ± 0.02	0.91 ± 0.06	0.90 ± 0.03
9	0.5	9.14 ± 0.42	8.91 ± 0.14	8.93 ± 0.42	8.90 ± 0.39
9	1.5	3.57 ± 0.22	3.40 ± 0.12	3.28 ± 0.17	3.56 ± 0.21

[a] pH and gelatin concentration were significant factors in the factorial design ($p < 0.05$).
[b] pH and gelatin concentration exhibited a significant interaction in the factorial design ($p < 0.05$).
[c] Mixing type and batch were non-significant in the factorial design ($p > 0.05$).

tion of emulsifier (gelatin) in the external phase, nature of mixing (baffled or non-baffled) and batch. The pH of the external phase was adjusted using a Prideaux buffer (Jordan, 1980). This buffer was selected as it provides a constant ionic strength over a wide range of pH values and thus eliminates potential variations due to ionic strength differences.

The % w/w loadings of ethylcellulose microcapsules with propranolol hydrochloride following manufacture using different process variables are shown in Table 1. The maximum % w/w loadings were achieved whenever the external aqueous phase was composed of 0.5% w/v gelatin at pH 9.0 (8.9–9.1% w/w propranolol hydrochloride). The minimum % w/w loadings were observed whenever the external aqueous phase contained 1.5% w/v gelatin at pH 6.0 (0.71–0.91% w/w propranolol hydrochloride). The analysis of variance of the results obtained in the factorial design showed that two experimental factors, pH and gelatin concentration, exhibited a significant effect on drug loading ($p < 0.05$) whereas mixing type and batch were insignificant ($p > 0.05$) (Table 2). Thus, good batch-to-batch reproducibility was observed in this study. It has been reported that the solvent evaporation process is associated with good batch-to-batch reproducibility (Bodmeier and McGinity, 1987a; Sprockel and Prapaitrakul, 1990).

The parameter investigated in this study (% w/w drug loading of microcapsules) is of fundamental importance to this process. Failure to achieve acceptable loadings may preclude the use of this method for economic reasons. To ensure an efficient process it is essential that the core drug material is retained within the polymeric phase until the solid microcapsule is produced (Bodmeier and McGinity, 1988). The drug used in this study, propranolol hydrochloride, is a weak base ($pK_a = 9.45$) which is soluble in water (Moffat, 1986) and exhibits a pH-dependent solubility in water. At pH 9.0 the percentage of unionised molecules increases (compared to pH 6.0) and relative hence partitioning into the aqueous phase will decrease. Therefore, the lower entrapment efficiency observed at pH 6.0 is due to the greater degree of drug partitioning from the organic phase to the aqueous phase prior to the solidification of the polymeric droplets. These observations conform to the suggestion by Bodmeier and McGinity (1987a,b) that the degree of ionisation and thus the pH of the external phase is an important determinant in the entrapment of ionisable drugs.

Table 2
Analysis of variance of the effect of process variables on the % w/w entrapment of propranolol hydrochloride within ethylcellulose microspheres prepared by the solvent evaporation process

Source	Degrees of freedom	Sum of squares	Mean square	F value
pH (A)	1	265.79	265.79	3742.73 [a]
Gelatin (B)	1	89.47	89.47	1259.86 [a]
AB	1	63.08	63.08	888.28 [a]
Mixing (C)	1	0.007	0.007	0.103
AC	1	0.037	0.037	0.514
BC	1	0.077	0.077	1.086
ABC	1	0.037	0.037	0.517
Batch (D)	1	0.001	0.001	0.021
AD	1	0.006	0.006	0.089
BD	1	0.012	0.012	0.175
ABD	1	0.039	0.039	0.553
CD	1	0.077	0.077	1.085
ACD	1	0.052	0.052	0.732
BCD	1	0.005	0.005	0.075
$ABCD$	1	0.019	0.019	0.262
Error	26	1.846	0.071	

[a] Significant at $p < 0.05$.

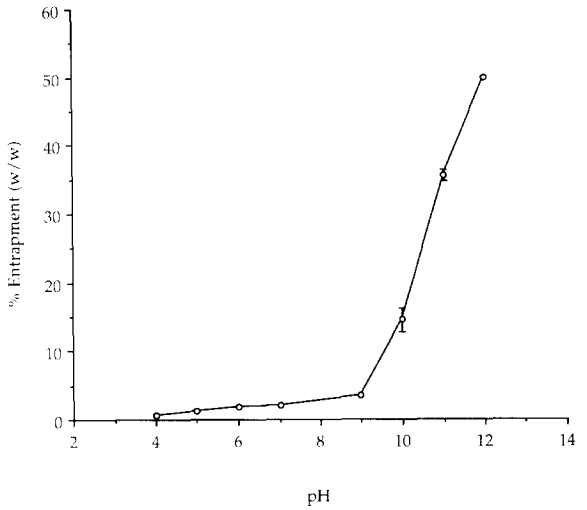

Fig. 1. The effect of pH of external phase (containing 1.5% w/v gelatin) on the mean (±S.E.) % w/w entrapment of propanolol hydrochloride in ethylcellulose microcapsules prepared by the solvent evaporation process.

To further examine this, ethylcellulose microcapsules containing propranolol hydrochloride were prepared over a range of external pH values (4–12) using non-baffled stirring and gelatin (1.5% w/v) as the emulsifier (Fig. 1). The relationship between % w/w entrapment of propranolol hydrochloride and pH of the external phase was biphasic. Two linear portions can be identified on this graph, namely the regions described by pH 4.0–9.0 ($r^2 = 0.978$) and from pH 10.0–12.0 ($r^2 = 9.88$). Intersection and extrapolation of these two linear portions to the x-axis yields a pH value of approx. 9.4. This denotes the inflection point on the graph and coincides with the pK_a of propranolol hydrochloride, thus further indicating the importance of ionisation and hence pK_a on the entrapment of ionisable drugs by the solvent evaporation process. Increasing the pH of the external phase beyond the pK_a resulted in a marked increase in drug entrapment. At pH 12, i.e., whenever the percentage ionisation of propranolol hydrochloride was 0.281, the % entrapment was approx. 50% w/w (100% theoretical entrapment).

In the solvent evaporation process, emulsifiers (e.g., gelatin, methylcellulose, polyvinyl alcohol, polyoxyethylene sorbitan monooleate) are incorporated to stabilise the suspended droplets over the duration of the process (Benita et al., 1984; Juni et al., 1985; Cavalier et al., 1986; Bodmeier and McGinity, 1988). The effect of emulsifiers on the physical appearance of microcapsules prepared by the solvent evaporation process has been reported previously (Benita et al., 1984; Cavalier et al., 1986), however, there are few reports concerning the effect of the concentration of emulsifier on the subsequent drug loading of microcapsules. Bodmeier and McGinity (1987b) reported that increasing the concentration of polyoxyethylene sorbitan monooleate in the aqueous phase led to a small reduction in the quinidine content of microcapsules prepared by the solvent evaporation process. In this present study, microencapsulation performed using the lower concentration of gelatin (0.5% w/v) resulted in a significant increase in the propranolol hydrochloride content of microcapsules ($p < 0.05$) in comparison to microcapsules prepared using 1.5% w/v gelatin. As gelatin is an emulsifier it will form a layer around the organic microdroplets at the o/w interface. Therefore, whenever the higher concentration of gelatin is used, this may result in the generation of either a more complete and/or thicker diffusion layer around the microdroplets, and subsequently, a reduced rate of organic solvent loss from the droplet. Reduced solvent loss increases the duration of existence of emulsified microdroplets, thus presenting a greater time for drug partitioning from the microdroplet to the external phase. In addition, the higher gelatin concentrations may enhance the solubility of propranolol hydrochloride in the aqueous phase and led to increased drug loss to this phase.

Interestingly, pH and gelatin concentration were observed to exhibit an interaction within the factorial design ($p < 0.05$) (Fig. 2). Post-hoc statistical examinations of this interaction (one-way analysis of variance, $p < 0.05$ denoting significance) revealed that the pH of the external aqueous phase significantly effects loading of microcapsules with propranolol hydrochloride at each gelatin concentration investigated ($p < 0.05$). At pH 9.0 there was a significant difference in the

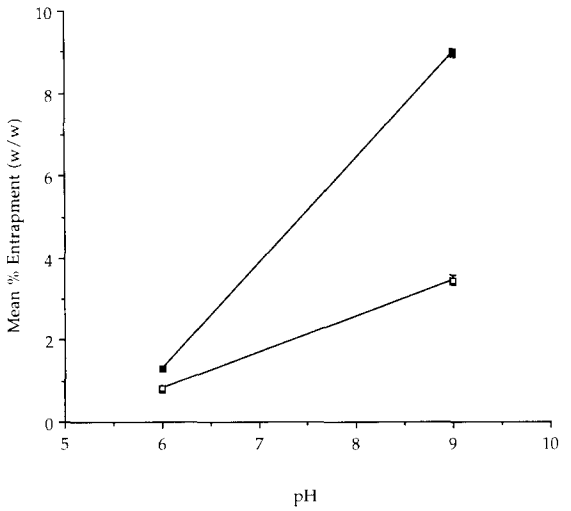

Fig. 2. Graphical illustration of the interaction between pH and gelatin concentration of external phase. y-Axis shows the mean (±S.E.) % entrapment of propanolol hydrochloride within ethylcellulose microcapsules prepared using gelatin 0.5% w/v (■) and 1.5% w/v (□) at two pH values (x-axis).

effect of the two gelatin concentrations on drug loading, however, at pH 6.0 this difference was less marked. This accounts for the interaction effect, displayed as a lack of parallelism in Fig. 2. A possible explanation for the interaction may involve the effect of pH on the partitioning of propranolol hydrochloride. At pH 6.0, due to potentially enhanced ionisation, the rate of partitioning from the organic polymeric phase to the external aqueous phase is relatively rapid and thus gelatin concentration has little effect on the final drug content of the microcapsules. It has previously been reported that drug content within microcapsules stabilises almost instantaneously (Bodmeier and McGinity, 1988) and this supports the above suggestion that drug partitioning at pH 6.0 is relatively rapid. At pH 9.0, due to the reduced solubility of propranolol within the external aqueous phase, the rate and extent of partitioning into the aqueous phase will be decreased. This allows sufficient time for the effect of gelatin concentration to become significant in the entrapment process.

In the factorial design two types of mixing were investigated. During the emulsification and evaporation stages extensive vortex formation is undesireable as it may lead to sticking or lumping of microcapsules. The use of baffled stirring has been suggested to eliminate strong vortex formation and provide effective mixing (Bodmeier and McGinity, 1987a). The blade of the Heidolph mechanically driven stirrer is designed to produce baffled stirring whereas the magnetic stirrer produced vortex mixing. In this study there was no significant difference in the drug loading of microcapsules prepared by the two mixing techniques which is in agreement of the findings of Bodmeier and McGinity (1987b).

In conclusion, this study has shown that pH and gelatin concentration in the aqueous phase, but not mixing type or batch, significantly affected propranolol hydrochloride loading of ethylcellulose microspheres prepared by the solvent evaporation process. However, pH was the greatest determinant of drug loading and this reflects the importance of ionisation on the entrapment of water-soluble drugs.

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