Solubility parameter effects on microencapsulation in the presence of polyisobutylene

M.G. Moldenhauer, J.G. Nairn*

Faculty of Pharmacy, University of Toronto, Toronto, Ont., Canada, M5S 2S2

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Abstract

A nonsolvent/solvent evaporation method of microencapsulation using ethylcellulose and ion-exchange resin–drug complex was used to show that solubility parameters of the microencapsulation system affect the ability of polyisobutylene (PIB) to promote mononucleated microcapsules. Microencapsulations using solvent systems which had solubility parameters well within the PIB soluble region of a two-dimensional solubility parameter map produced nonaggregated microcapsules which exhibited similar morphological characteristics. Whereas multinucleated microcapsules were produced when solvent systems were used which had solubility parameters close to the region of insolubility for PIB. Further examination of solubility parameter maps of ethylcellulose as affected by polyisobutylene demonstrated that PIB altered the phase changes of ethylcellulose. The formation of two liquid phases induced by polyisobutylene can be used to explain how mononucleated microcapsules are produced using the adjunct polymer PIB. The use of a solubility parameter map for the coating polymer ethylcellulose, as affected by the adjunct polymer, polyisobutylene, can be used to choose solvent systems providing related phase changes and consequently similar microcapsule coats.

Keywords: Polyisobutylene, Solubility parameters, Microencapsulation, Ethylcellulose

1. Introduction

The adjunct polymer, polyisobutylene (PIB), has been used to prevent aggregation and multinucleation from occurring during some microencapsulation processes [1–9]. This adjunct polymer has been studied in procedures employing ethylcellulose as the coating polymer [1–6] and in procedures using Eudragit RS and Eudragit RL as the coating polymer [7–9]. It was found that a minimum concentration was required before PIB was effective at promoting mononucleated microcapsules [1–4]. It was postulated that PIB induced the formation of a coacervate as opposed to other phase types [3], and stabilized the coacervate drops thereby promoting smooth single cored microcapsules [2]. Above certain levels PIB decreased coating polymer utilization producing microcapsules with thinner coats and faster release rates [2,3]. The decreased coating polymer utilization was believed to be due to increased PIB adsorption which decreased the size of the coacervate drops and in combination with the increased viscosity prevented the addition of more coacervate drops to the growing microcapsule walls [2].

In a microencapsulation system using Eudragit RS Benita et al. [8] found it necessary to try several solvents before finding an appropriate solvent to form
suitable microcapsules. They also showed that the viscosity imparted by PIB was not the main factor responsible for preventing aggregation [8,9]. They showed this by using liquid paraffins [8,9] and low molecular weight PIB [9] with a viscosity equivalent to their microencapsulation system and found that an unsatisfactory product, either an aggregated mass or matrix type microcapsules, were formed.

The production of suitable microcapsules often involves a consideration of many solvent systems and possibly the coating polymer. In the past this has meant a large number of experiments were needed to obtain an acceptable microcapsule morphology and the desired release characteristics. The solubility parameter concept has allowed the rational choice of solvent systems for reverse osmosis membranes and it was felt that this system could also be employed for microencapsulation systems [6,10].

Previously, microcapsules were prepared with different solvents. The solubility parameters of the solvent systems were calculated and compared to a solubility parameter map for the coating polymer, ethylcellulose. The solubility parameters of the microencapsulation systems were correlated with morphological characteristics and release rates [6]. The morphology ranged from smooth mononucleated microcapsules to large multinucleated microcapsules. As PIB influenced microcapsule multinucleation it was felt that further study of PIB solubility as affected by solubility parameters might improve the understanding of the morphology change. PIB has also been implicated in altering phase changes in microencapsulation systems therefore the changes that occurred in ethylcellulose solubility with varying PIB concentrations was also studied.

2. Experimental

Materials and methods are described in a previous paper [6] and only methods pertaining to the present
work are reported here. The procedures were all carried out at room temperature.

2.1. Polyisobutylene solubility parameter map

Samples, 0.25 g, of polyisobutylene (PIB), medium molecular weight (Aldrich Chemical Co., Milwaukee, WI), were placed into glass culture tubes. A solvent or solvent mixture, 10 ml, was added and the mixture was shaken for 1 week. In order to obtain a suitable solubility parameter map the solvents were pure or a mixture of two of the following solvents acetone, cyclohexane, methyl acetate, 95% ethanol, 1-butanol, ethyl acetate, methyl ethyl ketone, n-pentane, light liquid paraffin, n-heptane or toluene. The mixture was then visually assessed as soluble or insoluble.

A 2-dimensional solubility parameter map of the dispersive parameter, $\delta_d$, versus the polar and hydrogen bonding parameters, $\delta_{ph}$, was plotted. The polar parameter, $\delta_p$, and the hydrogen bonding parameter, $\delta_h$, were combined for plotting and the solubility parameters for the mixed solvents were calculated as described in a previous paper [6]. The solubility parameters of the pure solvents were taken from Handbook of Solubility Parameters and Other Cohesion Parameters [11].

2.2. Ethylcellulose solubility parameter maps in the presence of PIB

Solutions of ethylcellulose (Ethocel Premium, Ethoxy Standard, Viscosity 100; The Dow Chemical Company, Midland, MI), 0.001–0.004 g/ml, and polyisobutylene, 0.014–0.050 g/ml, were prepared with a solvent or solvent mixture and samples were placed into glass culture tubes, shaken for 1 minute, and allowed to settle for one month. The mixture was then visually assessed. The solvents were a mixture of cyclohexane, ethyl acetate and light liquid paraffin.

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**Fig. 2** Solubility parameter map for ethylcellulose and polyisobutylene showing the solubility border and the initial and final microencapsulation solubility parameters. ■ using ethyl acetate, cyclohexane and light liquid paraffin, ▲ using methyl ethyl ketone, cyclohexane and light liquid paraffin, ● using ethyl acetate and light liquid paraffin, and ○ using methyl ethyl ketone and light liquid paraffin.
2.3. Microencapsulation method [6]

As described previously [6], theophylline-resin complexes (DRC) were dispersed in a solution containing polyisobutylene using cyclohexane, light liquid paraffin (LLP) or a mixture of cyclohexane and LLP. These solvents formed the nonsolvent for ethylcellulose. A solution of ethylcellulose in ethyl acetate or methyl ethyl ketone, was added to the PIB and DRC dispersion, the mixture was then stirred in a reaction kettle until 47 g of the ethylcellulose solvent evaporated over 6 h ± 15 min. The microcapsules were collected by vacuum filtration, then washed with cyclohexane to remove any excess PIB.

2.4. Scanning electron micrographs

Samples of microcapsules were fastened to the holder using double sided tape and then gold sputter coated for 195 s at 20 mA. All photographs were taken.
at 20 kV. The magnification on the screen ranged from 30 to 1500 and the scale for the photograph is in the bottom right hand corner of the micrographs (Hitachi S-250, Tokyo, Japan).

3. Results and discussion

Previous work has shown that changing the solvent system alters the ability of PIB to promote mononucleated microcapsules [6]. To improve the understanding of the effect of PIB on microencapsulation, a solubility parameter map for PIB (Fig. 1) using Hansen's parameters [12] was prepared as described previously. The map indicates that PIB is soluble at high dispersive values and in solvents with low polarity and hydrogen bonding. As the polarity and hydrogen bonding capability of the solvents increases, the PIB forms a narrow area where two liquid phases occur, followed by an area where the polymer becomes swollen and

Fig 4. Scanning electron micrograph of microcapsules produced using methyl ethyl ketone, cyclohexane and light liquid paraffin.
finally the PIB becomes totally insoluble. This type of phase separation demonstrates the formation of initially a polymer solution then two liquid phases, a polymer-rich phase and a phase consisting of mostly solvent [18]. As the solvent systems become poorer the polymer-rich phase, of the two phases, becomes more viscous then gel-like and eventually a solid. The change in solubility is much more abrupt as the dispersive parameter is decreased. The PIB goes from a solution to a solid without any other apparent phase changes occurring.

In order to determine how PIB solubility affects microencapsulation the boundary of the PIB soluble area was overlaid on a solubility parameter map showing the solubility boundary of ethylcellulose and the solubility parameters of the initial and final concentrations of solvent systems used in several microencapsulation processes [6] (Fig. 2). The microcapsules
which were formed well within the PIB soluble region, where the polymer is loosely coiled, were either predominantly mononucleated (Fig. 3) or consisted of both mononucleated and small multinucleated microcapsules (2–5 core particles) (Fig. 4). Microcapsules formed by solvent systems on the edge of the PIB soluble region were large and multinucleated (Fig. 5 and 6).

The microencapsulation systems in the lower part of the map (Fig. 2) were formed at the limit of the PIB soluble region where the PIB is more tightly coiled and thus may have less affect on the microcapsule morphology. Microcapsules were also made using ethyl acetate and light liquid paraffin as described previously but without the inclusion of PIB. These microcapsules had the same large multinucleated morphology as the microcapsules made with PIB using this solvent system. These results suggest that the large multinucleated microcapsules are formed because PIB did not influ-
Fig 7(a-b) see 7e for legend
Fig 7(c–d) see 7e for legend
ence the microencapsulation process as PIB is dissolved in a poor solvent and is tightly coiled.

PIB has been shown to alter the phase changes which occur in microencapsulation systems [2,3,8,9]. To study how PIB affects ethylcellulose phase changes, solubility parameter maps of ethylcellulose were made in the region where mononucleated microcapsules were formed (Fig. 2) using various concentrations of ethylcellulose and PIB as noted above. These concentrations are similar to the concentrations used for the microencapsulation process. The solubility map previously published for ethylcellulose did not include PIB and did not demonstrate a two liquid phase region [6]. The solubility parameter maps made for ethylcellulose in the presence of PIB all demonstrate a two liquid phase region (Fig. 7). In the region where PIB is completely soluble, that is at the top of the map, increasing the PIB concentrations decreases the area where ethylcellulose forms an adhesive precipitate (Figs. 7a and 7b) perhaps due to an increased steric effect and/or a change in the solvent available to the ethylcellulose. The adhesive precipitate is always at the lower edge of the maps which corresponds to the edge of the PIB soluble region. The two liquid phase region increases with increasing PIB concentration from 1.5% to 2.4–3.2% then the region decreases (Fig. 7). At the higher PIB concentrations the PIB causes the ethylcellulose soluble region to expand.

The alteration of the phase changes of ethylcellulose by PIB can be explained by polymer thermodynamics [15,17,18]. It has been established that solvent systems containing two dilute high molecular weight polymers often undergo a phase separation forming two liquid phases [15–18]. This change can be explained thermodynamically due to the low entropy of polymer mixing and the large interaction energy between large molecules [17,18]. When the polymers have little attraction for each other the separation occurs such that
each liquid phase contains the majority of one of the polymers [16–18]. It is likely that in the present system each liquid phase consists of principally one polymer. Increasing the concentration of the PIB should cause phase separation to occur sooner and over a wider range [17]. However with the concentrations used in the present microencapsulation system two liquid phases are not observed when the ethylcellulose and polyisobutylene concentrations are increased (Fig. 7) perhaps because of high viscosity of the PIB solution and the low interfacial tension which exists between the two phases [16]. These factors tend to prevent the coalescence of the ethylcellulose solution drops and the observation of the formation of the two phases.

During the microencapsulation process, which corresponds to the solubility parameters maps with 1.5% and 2.4% PIB (Figs. 7a and 7b), there is initially a solution containing ethylcellulose and PIB. As solvent evaporation takes place the polymer concentrations increase and the composition of the microencapsulation system moves into an area where, due to the presence of two polymers in higher concentration, a two liquid phase region exists. Due to the agitation an emulsion of ethylcellulose solution in PIB solution would occur. The low interfacial tension between the ethylcellulose solution and the PIB solution would make the drops fairly stable and able to coat the resin. Due to its loosely coiled structure PIB would likely interfere with approach and multinucleation of the ethylcellulose coated resin because the PIB acts as a steric barrier as the solubility parameter becomes less favorable during evaporation. PIB is postulated to prevent microcapsule multinucleation by altering the way ethylcellulose undergoes precipitation, namely the formation of two liquid phases, and by sterically interfering with the approach between growing microcapsules.

4. Conclusion

PIB prevents microcapsule multinucleation by altering phase changes of ethylcellulose solution. In the presence of PIB and solvents, the system separates into two liquid phases which concentrates the ethylcellulose in one phase and forms an emulsion whose drops are attracted to the core particles. Due to the low interfacial tension between the two liquid phases little coalescence of the ethylcellulose drops occurs. In addition PIB forms a steric barrier preventing ethylcellulose coated complexes from sticking together. In the absence of PIB the coated core material adheres and forms multinucleated microcapsules.

The use of a solubility parameter map incorporating the adjunct polymer PIB can be used to choose alternate solvent systems to form microcapsules with similar properties. The solubility parameter map demonstrates the necessary phase changes and allows the choice of solvents in the same area to obtain the same phases changes.

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