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Optimization of poly (butylcyanoacrylate) nanoparticulate size and polydispersity using central composite design

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Poly(butylcyanoacrylate) nanaoparticulate systems have been studied extensively as a potential means for drug delivery and targeting. Several well established methods of preparation have been described, including emulsification polymerization, solvent dispersal with interfacial deposition (Fessi et al 1989) and interfacial polymerization. In the final method, polymerization of monomer occurs at the interface between an aqueous nanodroplet and an organic continuous medium. It is, therefore, particularly useful for nanoencapsulation of peptides and hydrophilic molecules and is the method studied in this work. Encapsulation using the other methods can result is loss of peptide activity and low levels of drug entrapment.

Nanoparticles were prepared by adding butylcyanoacrylate monomer (500 µl) to 20 ml of cyclohexane:chloroform solution (4:1) containing Span 60. Phosphate buffer (1 ml) was added quickly and the emulsion sonicated for a defined period of time. Three factors considered to play a significant role in particle formation were chosen for investigation, namely, buffer pH, surfactant concentration and sonication time. Two responses, particle size and polydispersity, were observed.

Multiple regression analysis (MRA) was used to fit the data to one of three models. The initial model used first order factors only, the next was a second order model and the final model used both second order and interaction terms. A 3^3 central composite design was used, with five replicates at the design centre point and six axial points lying along the design axes and outside the experimental design region.

MRA showed that particle size was best described using a second order model with interaction terms (R= 0.427). Analysis of variance (ANOVA) showed that first order surfactant concentration was the most relevant factor for influencing particle size. Figure 1 shows the second order response surface (with interaction terms).

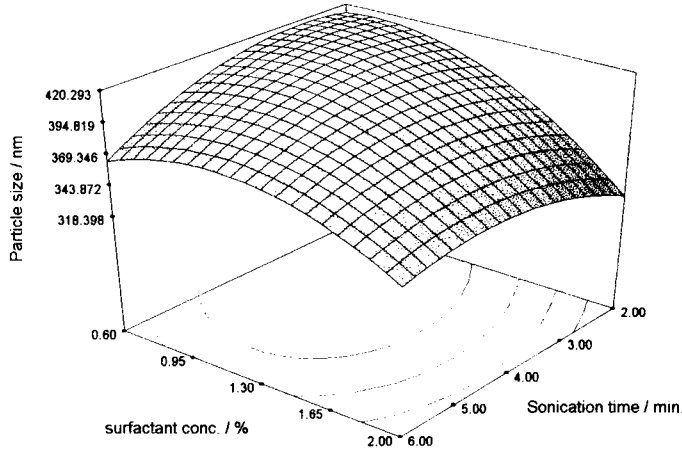

Figure 1. Response surface showing relationship between surfactant concentration and sonication time.

MRA also showed that, with respect to polydispersity of particle size, the R value was increased noticeably (R= 0.780) when interaction terms were included into the second order model. ANOVA showed that the first order pH term was significant (p=0.0198) and also the factor most relevant in influencing the polydispersity.

The results of this work showed that both nanoparticle size and polydispersity can be described using second order models with the inclusion of interaction terms. Particle size depended primarily on the surfactant concentration in the organic phase. Polydispersity was highly dependent on the pH of the aqueous dispersed phase.

Fessi, H., Puisieux, F., Devissaguet, J.P., Ammoury, N. and Benita, S., Nanocapsule formation by interfacial deposit-ion following solvent displacement. Int J. Pharm. 55 (1989) R1-R4.