ABSTRACT SUMMARY
The macromonomer used in the fabrication of nanoparticles was synthesized by ring opening polymerization of ε-caprolactone and characterized. Stealth poly(ε-caprolactone) nanoparticles were synthesized by in-situ dispersion polymerization. Morphology of the nanoparticles was investigated by using different molar ratios of monomer to initiator. The lowest molecular weight macromonomer, for tailored applications, is functionalized to give it a polymerizable end-group.

Statistical experimental design involving mixture methodology is a good method for investigating the effects of the formulation variables on the properties of nanoparticles. Following the use of D-optimal statistical experimental design for the runs, dispersion polymerization method was used to fabricate the nanoparticles. Scheffe polynomial models were generated to predict particle size (nm) and zeta potential (mV) as functions of the composition of the formulation. Simultaneous numerical optimization was carried out using the empirical models.

EXPERIMENTAL METHODS
The macromonomer was synthesized by ring opening polymerization of ε-caprolactone in the presence of HEMA as an initiator and stannous octoate as a catalyst. Characterization was by GPC, FT-IR and 1H-NMR. The macromonomer, PEG and the cross-linking agent were dissolved in a mixture of acetone and water. Following purging with nitrogen for ten minutes, the initiators were injected into the system, and then the polymerization was allowed to continue overnight. The nanoparticles were purified by dialysis using Spectra/Por® molecular porous membrane tubing (MWCO 12-14,000) and freeze dried. The nanoparticles external morphology was examined by scanning electron microscopy (FEI Quanta 200F environmental scanning electron microscope). The average particle size, particle size distribution and zeta potential were determined by dynamic light scattering (DLS) using Zetasizer Nano-ZS (Malvern Instruments, USA). The statistical D-optimal mixture experimental design was used for optimization because the formulation components add up to unity. The validity of the models was checked by diagnostic plots. Simultaneous numerical optimization was carried out on the empirical models. Three of the solutions from the numerical optimization were compared with laboratory data.

RESULTS AND DISCUSSION
Increase in the amount of HEMA resulted in decrease in the molecular weight of the end-functionalized macromonomer (Table 1). Similar behavior was reported previously for ε-caprolactone, indicating that it is possible to control the molecular weight of macromonomer, for tailored applications, by using different molar ratios of monomer to initiator. The lowest molecular weight macromonomer was used in this work. It was observed that the choice of appropriate solvent system for dispersion polymerization is very critical in determining the formation and morphology of stealth polyε-caprolactone nanoparticles (Figure 1). Solvent systems with different polarities and solubility parameters produced different effects. Confirmation of nanoparticle formation was shown by electron micrograph (Figure 1) and by particle size determination (Figure 2). Particle size distribution studies gave values in the nanometer range, which provides hope for nanotechnology platform in the design of drug delivery systems. The average particle size and average zeta potential values range from 131.4 nm to 691.5 nm and -36.6 mV to +0.112 mV respectively depending on formulations (thirty formulations were investigated).

Mixture statistical experimental design (D-optimal mixture design) was used in this work. Based on preliminary data, constraints were introduced to the
proportions of the components to allow the fabrication of smooth spherical particles within the nanometer size range. In D-optimal mixture design, there are restrictions on component proportions such that a lower and an upper limit should be specified. The responses (particle size and zeta potential) are functions of the proportions of the formulation variables tested: macromer, initiator, PEG, and crosslinker. Aided by a statistical software, we examined the effects of the combinations of the variables on particle size and zeta potential. To improve the models, insignificant terms were removed by backward elimination, as customary in regression analysis. Diagnostic plots (Figure 3) show the validity of the models. Simultaneous numerical optimization was carried out using the two models (Scheffe polynomials). Three of the solutions provided were used for verification by confirmatory fabrication of nanoparticles using the suggested solutions and comparing the results with the predicted particle values. The results show that nanoparticles of desired physical properties (size and surface charge) can be determined a priori using the empirical models and simultaneous numerical optimization.

Table 1: Characteristics poly(ε-caprolactone -HEMA) macromonomers (Macro)

<table>
<thead>
<tr>
<th>Macro</th>
<th>Mole Ratio of Caprolactone /HEMA</th>
<th>Mn (1H NMR)</th>
<th>Mn (GPC)</th>
<th>Mw/Mn (GPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro 1</td>
<td>14.96</td>
<td>1916</td>
<td>3014</td>
<td>2.13</td>
</tr>
<tr>
<td>Macro 2</td>
<td>7.53</td>
<td>1455</td>
<td>2272</td>
<td>1.64</td>
</tr>
<tr>
<td>Macro 3</td>
<td>4.98</td>
<td>1360</td>
<td>1960</td>
<td>1.68</td>
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<tr>
<td>Macro 4</td>
<td>3.75</td>
<td>1084</td>
<td>978</td>
<td>1.08</td>
</tr>
</tbody>
</table>

CONCLUSION

Crosslinked, biodegradable, stealth poly (ε-caprolactone) nanoparticles were prepared by free radical dispersion polymerization. D-optimal mixture statistical experimental design was used to generate empirical models for numerical optimization.

REFERENCES


ACKNOWLEDGMENTS

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