Polymer Nanoparticles as Formulation Agents

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ABSTRACT

An approach to produce polymer nanoparticles with tailored characteristics to accommodate different nanoformulation applications is presented. Polymer nanoparticles are made from the collapse of polyelectrolytes in the presence of counterions and/or different solvents. The size, hydrophobic/hydrophilic character, as well as surface interaction characteristics of collapsed polyelectrolyte nanoparticles can be controlled by varying the degree of crosslinks and the degree of chemical modification of the parent polyelectrolyte chain. Depending on the characteristics of the polymer nanoparticle (i.e. size, hydrophobic/hydrophilic character, degree of crosslinking, etc.) different molecules like dyes, pigments, agricultural and pharmacological active ingredients, and aromatics can be loaded into the polymer nanoparticles. Polymer nanoparticles made with this approach are typically smaller in size (10-50 nm) than those achievable using other methods. Data illustrating the different characteristics of the polymer nanoparticles and the interactions of the polymer nanoparticles with different active ingredients will be presented.

Keywords: polymer nanoparticles, nano formulations, active ingredients, hydrophobic/hydrophilic character

1 SYNTHESIS AND CHARACTERIZATION OF POLYMERIC NANOPARTICLES

Water dispersible nanoparticles are produced using counterion-induced collapsed polyelectrolyte chains. Polyelectrolytes are polymers having monomer units with ionizable groups such as amines, carboxylic acids, or sulfonic acids. Their conformation in aqueous solution is governed by electrostatic interactions between the charged moieties in the chain. Under conditions of high ionization and low ionic strength, the individual polyelectrolyte chains assume a highly extended, swollen coil conformation arising from repulsive electrostatic interactions along the chain. The addition of ionic species results in the screening of these repulsive interactions by the counterions, causing the highly extended polyelectrolyte coils to collapse into globules. These globules contain the counterions used to induce collapse, and can range in size from ~ 1-50 nm [1]. Crosslinking the collapsed polymer chain results in a stabilized globular structure even after removal of the ions used to collapse the polyelectrolyte. This process is summarized in figure 1.
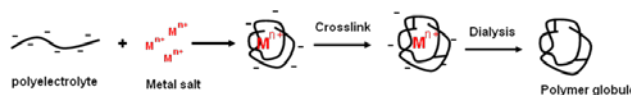

Figure 1. -ion induced collapse of polyelectrolytes to form polymer nanoparticles/globules.

Transmission Electron Microscopy (TEM) and Atomic force microscopy (AFM) was used to characterize the structure and size of these polymer nanoparticles. Figure 2 shows the TEM images of polymer nanoparticles that have been dialyzed to remove most of the collapsing ions. Figure 3A shows an AFM image of $Al(OH)_3$ collapsed polyacrylic nanoparticles and figure 3B shows the same nanoparticles that were dialyzed against acid to remove the Al^{3+} ions.
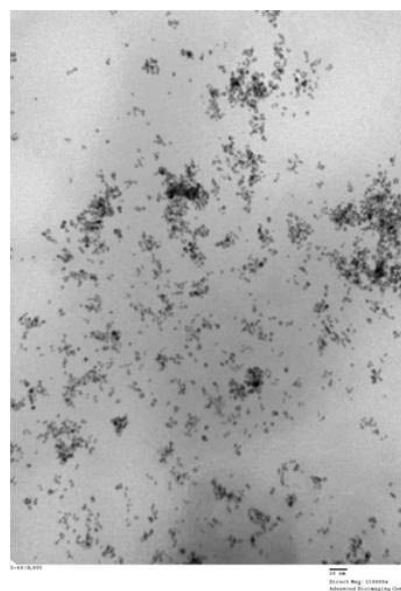

Figure 2. TEM image of polyacrylic acid nanoparticles (note: contrast comes from residual metal ions (Fe^{3+}) not entirely removed by dialysis)
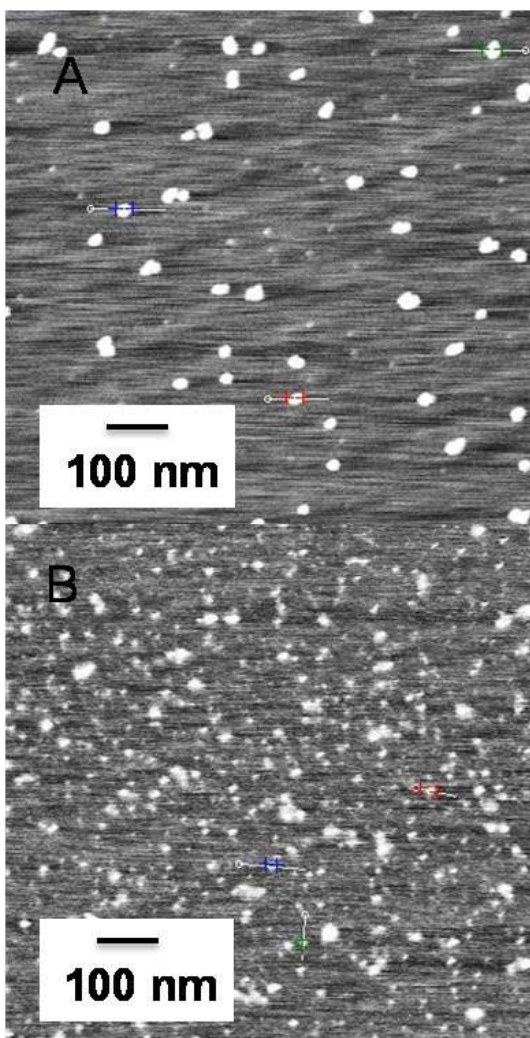
Figure 3. A) Al^{3+} collapsed polyacrylic acid nanoparticles.
(B) Dialyzed nanoparticles to remove Al^{3+}.

2 RELATIVE POLARITY OF DIFFERENT POLYMER NANOPARTICLES

The relative hydrophobicity of the polymer nanoparticle microenvironment can be characterized using an environment-sensitive fluorescent probe such as pyrene. The intensity ratio of the first and third vibronic bands (I1/I3) in the emission spectra of the pyrene monomer is very sensitive to the monomer's microenvironment, and can be used as a metric to gauge the hydrophobic nature of different polymer nanoparticles produced using the methods described here. As shown in figure 4, we measured the hydrophobic character of the nanoparticles as a function of the solution pH and the polymer used to make the polymer nanoparticles. At pH 3-6, a polymer nanoparticle microenvironment similar to o-dichlorobenzene [2] was achieved using polymer nanoparticles from poly(methacrylic acid) (PMAA) or poly(methacrylic acid-co- ethyl acrylate) (P(MAA-co-EA)), while a less hydrophobic microenvironment similar to dioxane was achieved from Zn2+- collapsed polyacrylic acid nanoparticles. A microenvironment similar to glycerol was achieved by using Na+- collapsed polyacrylic nanoparticles. Similarly, in the pH range 6-10 different microenvironments were achieved using different polymers make the nanoparticles. A microenvironment similar to methylene chloride was achieved from PMMA or P(MAA-co-EA) nanoparticles while a less hydrophobic microenvironment similar to glycerol was achieved from Na+ collapsed polyacrylic acid nanoparticles.
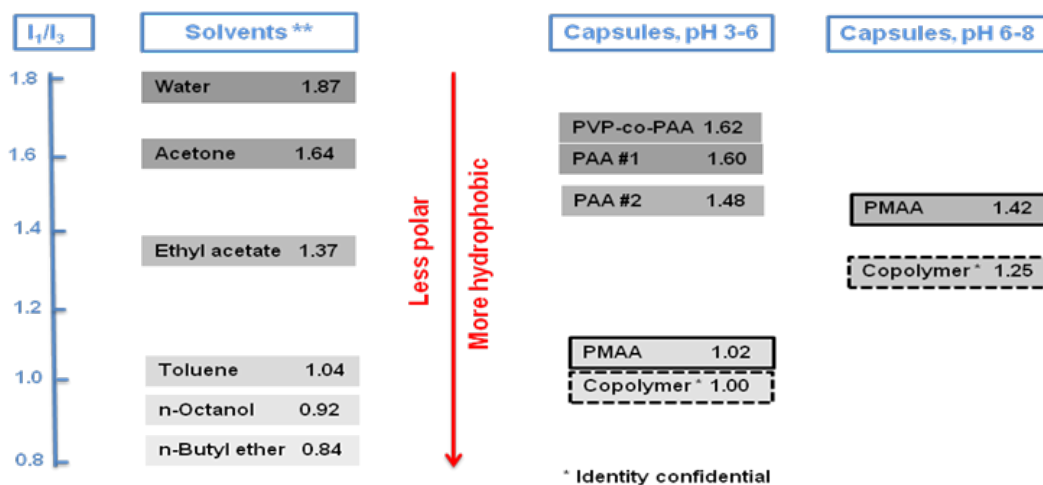
Figure 4. . Summary of relative hydrophobicty of the polymeric nanoparticles using pyrene as a microenvironment sensitive probe.
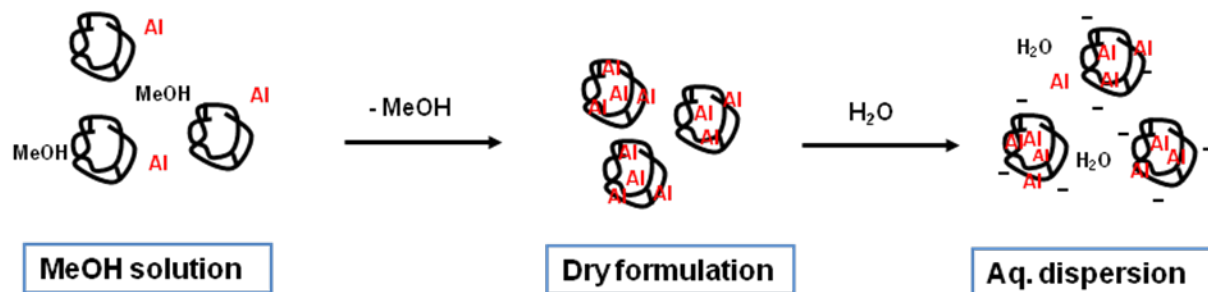
Figure 5. .   Proposed mechanism for loading hydrophobic active ingredients into polymer nanoparticles.

AIs	Solubility in water (mg/mL)	AI wt% loaded *	Polymer capsules	Improved solubility In water (mg/mL) *
Imazethapyr	1.40	50	PMAA	6.7
Trifluralin	2.2×10^{-4}	33	PMAA	1.0
		33	PAA/PVP	1.0
		50	Copolymer	6.5

* Data shown as tested – does not represent upper limit.

Table 1.

3   LOADING OF ACTIVE INGREDIENTS INTO POLYMER NANOPARTICLES

To illustrate the utility of these polymeric nanoparticles in formulations, we have loaded several types of active ingredients into these nanoparticles.   A simplified version of the loading protocol is illustrated in figure 5. Polymeric nanoparticles are dispersed in a solvent that is able to disperse both the hydrophobic active ingredient of interest and the polymeric nanoparticles.   As the solvent is removed, the active ingredients associate with the polymeric nanoparticles until the point where a dry formulation is formed.   This dry formulation is then redispersed in water to form an aqueous dispersion of the polymer nanoparticle/active ingredient formulation. Once in aqueous solution, the hydrophobic active ingredient remains associated with the polymer nanoparticles.

Using this method, the solubility of hydrophobic active ingredients in water can be greatly improved without the use of any additional surfactants and solvents.   We have demonstrated this for an active ingredient that has parts per trillion (ppt) solubility in water by improving its solubility in water by 6 orders of magnitude (data not shown due to confidentiality restrictions).   Table 1 shows two of the different active ingredients we have investigated.

REFERENCES
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