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Review Article

Technical aspects of preparing PEG-PLGA nanoparticles as carrier for chemotherapeutic agents by nanoprecipitation method

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ABSTRACT

Nanoprecipitation is a simple and increasingly trending method for nanoparticles preparation. The self-assembly feature of poly (ethylene glycol)-poly (lactide-co-glycolic acid) (PEG-PLGA) amphiphilic copolymer into a nanoparticle and its versatile structure makes nanoprecipitation one of the best methods for its preparation. The aim of this study is to review currently available literature for standard preparation of PEG-PLGA nanoparticles using nanoprecipitation technique in order to draw conclusive evidenceto draw conclusive evidence that can guide researchers during formulation development.

To achieve this, three databases (Web of Science, Scopus and PubMed) were searched using relevant keywords and the extracted articles were reviewed based on defined inclusion and exclusion criteria. Data extraction and narrative analysis of the obtained literature was performed when appropriate, along with our laboratory observations to support those claims wherever necessary. As a result of this analysis, reports that matched our criteria conformed to the general facts about nanoprecipitation techniques such as simplicity in procedure, low surfactants requirement, narrow size distribution, and low resulting concentrations. However, these reports showed interesting advantages for using PEG-PLGA as they are frequently reported to be freeze-dried and active pharmaceutical ingredients (APIs) with low hydrophobicity were reported to successfully be encapsulated in the particles.

1. Introduction

Nanoprecipitation was first reported by (Fessi et al., 1989). They used the term “interfacial deposition” to describe their method in which a mixture of Poly (lactic acid) (PLA), benzyl-benzoate and phospholipids in hot acetone was used to encapsulate indomethacin (a hydrophobic compound) and the mixture was added dropwise into water with poloxamer as a surfactant. The solvent was then evaporated under reduced pressure. The resulting particles were described as a capsule consists of a film of mainly PLA and a core of benzyl-benzoate containing the drug.

Nanoprecipitation is the simplest laboratory based polymeric nanoparticle preparation method ever steadily reported to date. In an optimum case of an amphiphilic polymer based particles prepared using this method; preparation does not require high sheer homogenization techniques, ultracentrifugation or surfactants. However, this method is hindered by significant drawbacks such as; low concentration preparation, the arguably inability to freeze dry the particles (Bodmeier et al., 1991). Table 1. summarises the pros and cons of choosing nanoprecipitation to prepare PEG-PLGA nanoparticles.

As the research in nanomedicine grows, the trends in publications of nanoprecipitation and nanoparticles has continued going up especially in the last five years as presented in Fig. 1.

On top of the difficulties that conventional chemotherapeutics should pass through to get approved by regulatory agencies worldwide which make it exceptionally expensive, nanotechnology also involves several additional special manufacturing steps, requiring elongated time for batch preparation and specially trained personnel. The process usually lacks robustness and reproducibility, and may result in continuous shortage of supplies even for the oldest formulations in the market (Barenholz, 2012; Food and Administration, 2015). For this reason, simplicity of nanoprecipitation is anticipated to reduce batch to batch variabilities and ensure consistency of the manufacturing process.

Zhu, (2013) Answered the debate about block copolymer nanoparticles formed by flash nanoprecipitation proposing that they are an accumulation of polymer structures that were kinetically frozen in a non-equilibrium thermodynamic state, hence they are neither micelles nor micellar particles that are composed of clearly identified layers with

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Table 1
Advantages and disadvantages of nanoprecipitation method to prepare nanoparticles from amphiphilic polymers.

Characteristic	Advantages	Disadvantages
Water miscible solvents	• Less toxic (nonhalogenated) (Sah and Sah, 2015) • Able to encapsulate less hydrophobic drugs.	• Depends solely on the ouzo effect which limits the polymers that can be used. • Incomplete solvent removal causes particle aggregation hence they are more difficult to be freeze dried or collected by ultracentrifugation. • Difficult to encapsulate hydrophilic drugs using simple nanoprecipitation techniques.
Spontaneous (dropwise) particle formation	• Simple single step process for hydrophobic drug encapsulation. • Narrowly dispersed particle size.	• Low concentration of the dispersed phase (high concentration will result in an uneven and large particle distribution).
No surfactant Needed	• Avoid toxicity of surfactants. • Avoid surface characteristics effects. • Lower centrifugation speed is enough to collect the particles with high yield	• Metastable system can aggregate over period of time. • Sedimentation and aggregation can occur and affect physical stability.
Low energy mixing	• No high sheer homogenization, making scaling up easier Francois and Katz (2005).	• Improper mixing can disturb particle size distribution.

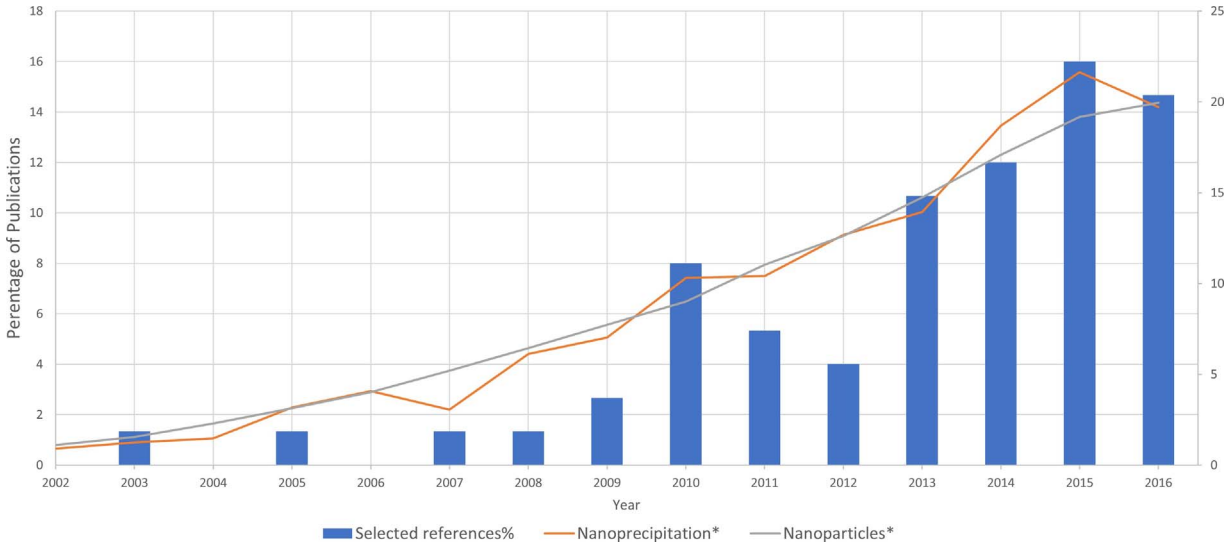

Fig. 1. Trends and comparison of publications of nanoprecipitation and nanoparticles. *Data was extracted from Web of Science.

a high thermodynamic stability and smaller particle size, with some of the PEG chains trapped inside the hydrophobic core and some sticking out of the particle to form the hydrophilic surface. Fig. 3 illustrates the difference between a nanoparticle and a micelle.

Fig. 2 shows the phase diagram of a system composed of a hydrophobic solute, polar miscible solvent and water, namely single phase, nucleation and separation phase. A single-phase region is just a stable solution (lowest water and salute concentrations), while nucleation

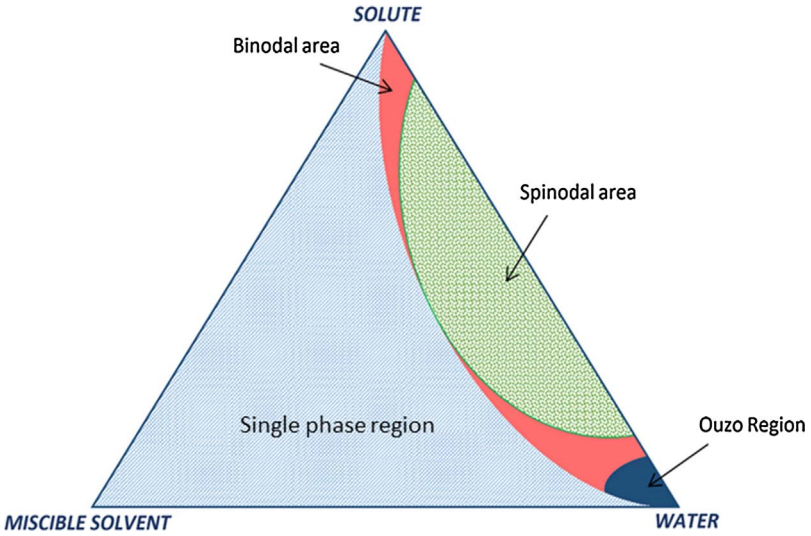

Fig. 2. Phase diagram of ternary system: the nucleation area is determined by the red colour and bordered by the spinodal and the bimodal lines. The system is monodispersed and best metastable in the Ouzo region. Adopted with slight modification from (Botet, 2012). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)