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Review

Polymeric nanoparticles: A study on the preparation variables and characterization methods

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ABSTRACT

Since the emergence of Nanotechnology in the past decades, the development and design of nanomaterials has become an important field of research. An emerging component in this field is nanomedicine, wherein nanoscale materials are being developed for use as imaging agents or for drug delivery applications. Much work is currently focused in the preparation of well-defined nanomaterials in terms of size and shape. These factors play a significantly role in the nanomaterial behavior *in vivo*. In this context, this review focuses on the toolbox of available methods for the preparation of polymeric nanoparticles. We highlight some recent examples from the literature that demonstrate the influence of the preparation method on the physicochemical characteristics of the nanoparticles. Additionally, in the second part, the characterization methods for this type of nanoparticles are discussed.

Contents

1. Introduction

Polymeric nanoparticles (PNPs) have attracted considerable interest over the last few years due to their unique properties and behaviors resulting from their small size [1]. As asserted by different authors, these nanoparticulate materials show potential for a wide range of

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applications such as diagnostics and drug delivery [2–4]. Advantages of PNPs as carriers include controlled release, the ability to combine both, therapy and imaging (theranostics), protection of drug molecules and its specific targeting, facilitating improvements in the therapeutic index [5–7].

The uptake of nanoparticles into cells usually involves endocytotic processes, which depend primarily on their size and surface characteristics [8,9]. These properties can be tuned by the nanoparticle preparation method [10,11]. Depending upon the preparation method and composition of the organic phase, nanocapsules or nanospheres can be obtained [3]. A nanocapsule particle has core-shell morphology with an aqueous or oily cavity in which the active compounds are confined and surrounded by a polymer shell. Nanospheres have a matrix-like structure in which the active compounds and the polymer are uniformly dispersed.

The classic mechanism for controlling drug release from PNPs is achieved by regulation of the rates of polymer biodegradation and drug diffusion out of the polymer matrix [12]. More recently, exogenous and endogenous stimuli triggered drug release is of particular interest, as it is selective to the microenvironment of specific diseases [3,12].

The technology of polymeric drug delivery relies heavily in the biodegradability and biocompatibility of the polymers. Biodegradable polymers have advantages since they are completely eliminated from the body by natural metabolic pathways [13]. Natural polymers are usually biocompatible and biodegradable; however their use has been limited due to batch-to-batch variations in properties and could be mildly immunogenic. On the other hand, synthetic polymers are well-known for their controlled chemical composition. Several synthetic or natural polymers have been used for the preparation of PNPs, such as proteins, sugars or other natural macromolecules, biodegradable polymers and non-biodegradable, but pharmaceutically acceptable polymers [14–16]. To self-assemble these materials into PNPs, several preparation techniques has been successfully developed [17]. The choice of a specific method is usually determined by the type of polymer, the drug's physicochemical properties and the final desired characteristics of the PNPs. Nevertheless, all these methods share a common step which is polymer precipitation. This can occur either through addition of a non-solvent or after a decrease of polymer solubility. Besides, in most of these methods PNPs are produced in an aqueous suspension form, in which their chemical and physical stability is poor. Freeze-drying has been the most commonly drying method used to overcome the instability of nanoparticles suspension, improving their long-term stability and facilitating handling and storage [18]. As this process is highly stressful for nanoparticles, cryoprotectants during freezing and lyoprotectants during drying may be used to minimize the damages [18].

Effective post-synthesis purification of nanoparticles is also an important step for controlling their quality and characteristics and therefore their suitability for a biomedical application. Depending on the preparation method, several impurities will be present in the nanoparticle suspension and adsorbed to the nanoparticles. These potentially toxic impurities include organic solvents, salts, particle aggregates, and reagent residues. Filtration, centrifugation and dialysis techniques are commonly used purification methods [19].

Herein the preparation techniques and characterization of PNPs are reviewed. The aim is to collect and compile the information, and also to update and highlight recent developments. We hope the information covered in this review will stimulate the development of novel nanomedicines that are easier to handle, compatible with physiological media and suitable for further clinical developments.

2. Preparation of polymeric nanoparticles

Polymeric nanoparticles have been synthesized by several methods depending on the requirements of their application and the physicochemical characteristics of the drug [20]. The choice of the most suitable method plays a vital role in order to obtain PNPs with the desired properties for a particular application.

Several preparation methods have been developed and these can be divided into two groups, namely, those based on the polymerization of monomers and those taking advantage of preformed polymers (Fig. 1) [17]. These methods can be further classified into two categories: two-step procedures involving the preparation of an emulsification system followed by formation of nanoparticles in the second step of the process and one-step procedures where emulsification is not required for the formation of nanoparticles.

For the polymerization methods, the monomers are polymerized to form the encapsulating polymer. This process can be carried out in two ways, either using emulsion polymerization techniques or interfacial polymerization [10,11]. Some drawbacks have been reported which have limited the use of polymerization methods for the synthesis of PNPs [10,11]. Not only are most PNPs formed from slowly biodegradable or nonbiodegradable monomers, but also non-biocompatible byproducts may be generated with these methods. Toxic residues such as monomers and initiators may persist which require extensive purification work to result in a pharmaceutically acceptable product. Another challenge is the requirement for free-radical polymerization or UV light to trigger polymerization, which prevents the addition of proteins or peptides during polymerization [21]. Considering the limitations of polymerization techniques, attention is focused on describing the methods involving preformed polymers, as many of the problems involved in the former method can be avoided.

2.1. Two-step procedures based on emulsification

Emulsion based colloidal delivery systems are widely used in the food and pharmaceutical industries to encapsulate, protect, and deliver bioactive components.

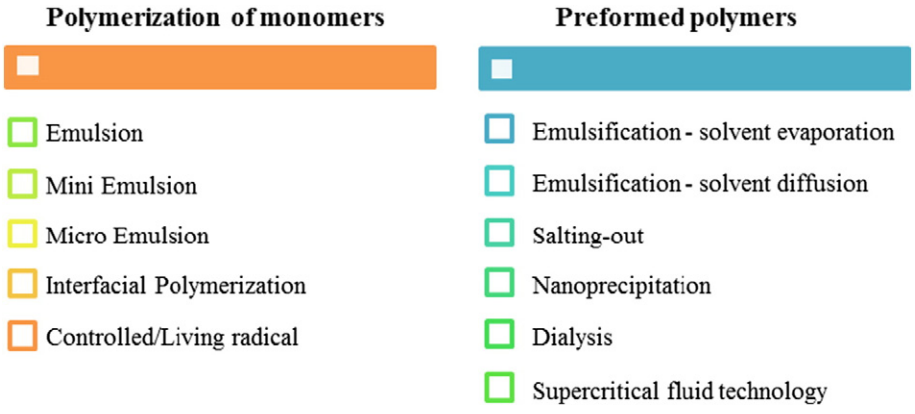

Fig. 1. Schematic representation of several techniques for the preparation of PNPs.