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Review Article

Design attributes of long-circulating polymeric drug delivery vehicles

Moritz Beck-Broichsitter, Julien Nicolas, Patrick Couvreur *

Institut Galien UMR CNRS 8612, Faculté de Pharmacie, Université Paris-Sud XI, Châtenay-Malabry, France

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ABSTRACT

Following systemic administration polymeric drug delivery vehicles allow for a controlled and targeted release of the encapsulated medication at the desired site of action. For an elevated and organ specific accumulation of their cargo, nanocarriers need to avoid opsonization, activation of the complement system and uptake by macrophages of the mononuclear phagocyte system. In this respect, camouflaged vehicles revealed a delayed elimination from systemic circulation and an improved target organ deposition. For instance, a steric shielding of the carrier surface by poly(ethylene glycol) substantially decreased interactions with the biological environment. However, recent studies disclosed possible deficits of this approach, where most notably, poly(ethylene glycol)-modified drug delivery vehicles caused significant immune responses. At present, identification of novel potential carrier coating strategies facilitating negligible immune reactions is an emerging field of interest in drug delivery research. Moreover, physical carrier properties including geometry and elasticity seem to be very promising design attributes to surpass numerous biological barriers, in order to improve the efficacy of the delivered medication.

1. Introduction

Systemic drug application enables the biologically active compound to distribute throughout the body, which is currently *state-of-the-art* for the treatment of numerous severe diseases (e.g. cancer, infectious and metabolic diseases or pathologies of the central nervous system). Current therapy regimens are however often associated with a short duration of action, drug resistance, a lack of organ specificity and as a consequence, a random and non-targeted drug distribution which manifests in significant toxicities [1]. To rectify the primary limitations of conventional therapeutic approaches, which can be serious enough to interrupt a treatment, and moreover, to increase the therapeutic efficacy of the delivered medication, drug delivery research is providing tailored vectors able to selectively accumulate in the target organ, tissue or cells [2,3].

The motivation for structural refinements of drug delivery vehicles to the nanoscale was to approximate the idealized concept of *magic bullets* proposed by Paul Ehrlich, which were first introduced in the mid 1970s [4,5]. Nowadays, various biological processes can be accessed or manipulated by application of nanomaterials [6,7]. Thus, the considerable interest in the potential of nanomedicine over the past decades made several polymer-based nanoparticulate treatment modalities for cancer clinically available (e.g. Abraxane®, Genexol®-PM, and Livatag® (Phase III)) [8–12]. These formulations hold great promise to deliver the encapsulated drug to the desired site of action, resulting in an increased therapeutic benefit and an improved quality of life [13–16].

To profit from the versatility of nanomedicines, such as increased organ/tissue accumulation, employing passive or active targeting strategies [17], formulations need to display prolonged residence times within the blood compartment [18–20]. After intravascular administration, drug carriers face numerous effective defense mechanisms significantly affecting their biological half-life in circulation [21–24]. The elimination of foreign materials is initiated by adsorption of plasma proteins (the so-called *opsonization*) [25,26] and activation of the complement system [27]. The tagged formulations are then recognized and taken up by macrophages of the mononuclear phagocyte system (MPS) [28]. Design attributes with influence on the residence time within circulation comprise physical (e.g. size, shape and mechanical properties (i.e.

Abbreviations: ABC, accelerated blood clearance; EPR, enhanced permeability and retention; MPS, mononuclear phagocyte system; NP, nanoparticles; PACA, poly(alkyl cyanoacrylate); PEG, poly(ethylene glycol); PLA, poly(lactide); PLGA, poly(lactide-*co*-glycolide); PPG, poly(propylene glycol); PRINT®, Particle Replication In Non-wetting Templates.

* Corresponding author at: Institut Galien UMR CNRS 8612, Faculté de Pharmacie, Université Paris-Sud XI, 5, rue Jean-Baptiste Clément, F-92296 Châtenay-Malabry, France. Tel.: +33 146835396; fax: +33 146835946.

E-mail address: patrick.couvreur@u-psud.fr (P. Couvreur).

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elasticity)) and chemical (e.g. surface chemistry) carrier characteristics [29–31].

Numerous studies underlined the rapid elimination of plain polymeric nanoparticles (NP) by the immune system [18–20]. By contrast, coating with hydrophilic polymers (e.g. poly(ethylene glycol) (PEG)) protected the carrier surface from unwanted opsonization, what in turn led to a delayed clearance from circulation [18–20,32]. Although PEGylation of colloidal drug carriers is still considered the *gold standard* for intravenous administrations, scientific evidence accumulated that the benefit of this surface modification approach is limited, especially with respect to activation of the immune system (e.g. complement cascade and *accelerated blood clearance* (ABC) phenomenon) [27,33,34]. In this context, identification of novel coatings would be highly desirable for the design of enhanced drug delivery systems [35,36].

Apart from the quest for drug delivery, the development of NP with additional functionalities [37,38], such as susceptibility (*stimuli-responsive*) [39–41] or traceability (*theranostic*) [42–44] to external triggers, would further contribute to a more specialized therapy and diagnosis of diseases. The confinement of two (or more) functionalities in the same vehicle enables dual (or more) treatment modalities following a single administration.

This review article will summarize the current knowledge on design attributes that make polymeric drug delivery vehicles long-circulating in blood, a prerequisite for highly efficient medications.

2. Preparation of polymeric drug delivery vehicles

Beside liposomal formulations [45,46], NP consisting of macromolecular materials (polymers) have been most frequently employed to accelerate intravascular drug administration [47]. Commonly, sizes of around 100 nm in diameter are regarded as relevant [18–20]. In 1976, Birrenbach and Speiser were the first introducing cross-linked polyacrylamide NP for vaccination purposes [48]. Polymer drug nanocarriers were later applied for the systemic administration of drugs which needed to replace the non-degradable polyacrylamide NP matrix by bioresorbable polymers [49,50]. Poly(alkyl cyanoacrylate) (PACA) nanoparticles were first developed in the late 1970s [49] followed by polylactide (PLA) and poly(lactide-*co*-glycolide) (PLGA) which emerged in the early 1980s [50]. Both classes have become the most prominent polymers for targeted drug delivery applications [51–53], owing to their well-known biocompatibility and biodegradability [54,55].

Several manufacturing techniques have been described for the production of spherical polymeric NP [56,57]. Conventionally, two main procedures can be distinguished: the first method involves polymerization reactions of monomers [51,58], whereas the second makes use of preformed, synthetic (or natural) polymers [59]. Moreover, there is an increasing interest in the fabrication of non-spherical particles for diverse applications in drug delivery and diagnostic imaging [2,29,60–64]. Among the existing methods to manipulate the shape of polymeric drug delivery vehicles, template-assisted soft lithography techniques seem to be the most promising with respect to precision and reproducibility [65–69]. Overall, the choice of suitable manufacturing technique not only depends on the physicochemical properties of the polymer, the active compound to be encapsulated in the nanoformulation and the therapeutic goal to be reached, but also on the scalability of the fabrication process allowing for a clinical translation of the most promising nanomedicines [70–73].

2.1. Polymerization techniques

NP formation by polymerization techniques necessitates the dissolution or dispersion of a suitable monomer in a continuous aqueous phase. The polymerization reaction is then carried out by an energy (e.g. UV- or γ-irradiation) input or initiator (e.g. bases, nucleophiles or radical starters) addition [51,56,58]. The first types of polymeric NP prepared by this approach consisted of non-degradable polyacrylamide and poly(methyl methacrylate) matrices [48,74], which significantly limited their use for intravascular applications. To overcome these limitations, Couvreur et al. [49] introduced NP made from biodegradable PACA [55,75]. PACA synthesis is mainly performed by anionic emulsion polymerization reactions in an acidified aqueous medium, due to the exceptional reactivity of these monomers [76,77]. Variation of the polymerization reaction allowed for a preparation of NP with tunable size in the range of approximately 30–300 nm [78,79]. Alternatively to anionic polymerization, radical emulsion polymerization has been reported for PACA NP synthesis [80,81]. For the latter, polymerization reactions generally require large quantities of organic solvents and surfactants. Furthermore, the presence of unreacted monomers, initiators and surfactants in the polymerization medium necessitates a tedious purification of the colloidal suspension.

2.2. Precipitation techniques

Alternatively to polymerization reactions, polymeric NP may be obtained by precipitation of preformed, synthetic polymers (e.g. PACA, PLA, and PLGA) in a non-solvent (usually water), as for example used in the solvent evaporation, salting-out, emulsification–diffusion, and nanoprecipitation techniques [56,57,59]. The solvent evaporation methodology relies on the emulsification of a polymer dissolved in a water-immiscible organic solvent (e.g. methylene chloride) in an aqueous phase containing surfactants, followed by evaporation of the organic solvent [82]. Process parameters affecting the final product quality include the choice of the organic solvent, the polymer molecular weight, the concentration in the organic phase, the type and amount of stabilizing agent, the ratio of continuous and dispersed phase, the method and duration of emulsification, and the temperature and pressure during solvent evaporation [59]. Gurny et al. [50] were the first using this method for the preparation of testosterone-loaded PLA NP. Since then, numerous modifications have been reported that improve the physicochemical quality and biological performance of the preparation obtained with this technique [59,83]. Another approach, the salting-out method is based on the phenomenon that highly-concentrated aqueous solution of salts (e.g. $MgCl_2$) or sugars prevents normally water-miscible organic solvents (e.g. acetone) from being miscible with water [59,84]. Following emulsification of an acetone-based polymer solution, sufficient addition of water allows for a diffusion of the organic solvent into the aqueous phase, inducing polymer precipitation in the form of NP [85,86]. However, time-consuming purification steps limit the use of such NP formulation strategy. The emulsification–diffusion process, originally considered as a modification of the salting-out method, makes use of partially water-soluble organic solvents (e.g. benzyl alcohol and propylene carbonate) to obtain polymeric NP [87]. After emulsification of the organic polymer solution in an aqueous stabilizer solution, addition of an excess of water promotes solvent diffusion into the aqueous phase and subsequent NP formation according to a *diffusion-stranding* mechanism [59,84,88,89]. A convenient nanoprecipitation process was proposed by Fessi et al. [90]. In contrast to the solvent evaporation, salting-out, and emulsification–diffusion process, the nanoprecipitation technique enables the formation of polymeric NP without prior energy input (i.e. emulsification step) [91,92]. Here, the progressive addition of a polymer dissolved in a mutually water-miscible organic solvent (e.g. acetone) to the aqueous non-solvent phase leads to the formation of colloidal suspensions in a comparable manner as the spontaneous emulsification (*ouzo effect*) [91–94].