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Opinion

Novel Design Perspectives of PLA Nanoparticles for Drug Delivery

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Opinion

Polylactide (PLA) is a bio-based chiral polymer that has largely been investigated from the 90s as a result of the development of Ring-Opening Polymerization (ROP) synthetic routes to attain high molecular weight polymeric derivatives. The featured promising physicochemical properties of PLA along with its low price made it an environmental-friendly alternative to traditional petroleum-derived polyolefins. In addition, PLA is a biocompatible material as lactic acid is generated from its hydrolyses in physiological media which is an endogenous molecule metabolized in water and carbon dioxide [1]. Furthermore, the physicochemical properties of PLA depend on the chain stereoregularity architecture, which can be tuned by controlling the polymerization process. Particularly, isotactic homochiral PLA is a semicrystalline and stiff polymer whilst atactic PLA is an amorphous and elastic polymer [2]. Likewise, several crystalline phases of PLA (α, α', β, γ, stereocomplex phase) exhibiting different thermal and mechanical properties are obtained depending on the processing conditions, offering the possibility to tailor the properties of the final material for specific applications [3]. In particular, the Food and Drug Administration approved the use of PLA for biomedical purposes back in 1960, leading to reach the clinical level for several applications such as sutures, dermal fillers, tissue engineering or Drug Delivery Systems (DDS) [4-6]. Drug encapsulation has emerged as a promising pharmaceutical technology approach to enhance the therapeutic efficacy as well as facilitating treatment compliance by diminishing the fluctuations of blood drug concentrations whilst increasing the cellular uptake as well as enhancing the drug stability. The design of DDS based on PLA derivatives allows tuning the release rate of the drug by modifying the synthesis and post-synthesis processing of PLA [7]. Nowadays, more than 15 microparticles PLA-based products have already reached the market to control drug delivery [4] and in particular, PLA nanoparticles have been applied for the treatment of several pathologies such as cancer [8,9], Chagas disease [10], Alzheimer disease [11] or insulin-dependent diabetes [12]. Besides, PLA is usually blended with other polymers such as PGA or PEG to increase the hydrophilicity character. Furthermore, the surface of polymeric nanoparticles is functionalized with antibodies [13] or cell-penetrating peptides [14,15] as a synthetic approach to target specific tissues or cells and both increase the therapeutic effect and decrease side effects.

However, the absence of a clinical application for PLA nanoparticles despite the research abundance on the drug load/release might be due to the lack of know-how transfer between the fundamental research on the DDS design and clinical trials. The synthesis of PLA at the industrial level is mainly accomplished using Sn(Oct)2 as the catalyst, due to its cheapness and ease of handling [16]. Although Sn(Oct)2 is accepted as a food additive by the FDA, avoiding post purification of the polymers for applications such as packaging [17], tin

compounds are potentially harmful as tend to accumulate in lungs and brain tissue. The amount of tin residue in polymers used for biomedical applications must remain below 20ppm [18], limiting its applicability in the nanomedicine field. New catalytic alternatives are being urged to avoid the toxic effects of Sn-based catalysts such as organometallic compounds featuring metals found in the human body, such as recently employed Zn or Mg [16]. However, the polymerization of PLA at an industrial scale needs to be implemented. Moreover, the mechanistic relationship found between the parameters of nanoparticles formulation at the laboratory level (such as the method, the solvent, polymer and drug concentration, etc) and the final properties of the nanoparticles (such as nanoparticle size, porosity, drug entrapment, etc), which control the drug release rate, remains unclear and is frequently found serendipitously. Recently, several studies showed contradictory results for the same parameter-property relationship, requiring the optimization of the process parameters for each new formulation [19,20]. The lack of robustness and reproducibility during the nano formulation of PLA at laboratory scale hampers the successful transfer from research to the clinical application [21,22]. Novel formulation approaches focusing on a deeper understanding of the nanoparticles formation mechanism as well as its final thermodynamical state depending on the processing conditions were aimed to control the drug delivery process such as the initial burst release [22,23].

Furthermore, the scale-up process of nanoparticles conveys additional complexity to the control of the pharmacokinetic and pharmacodynamic mechanisms to the standardised conventional drug products studies, preventing its clinical translation. The control of each technical parameter of the scaling up production process is required as even slight differences can be found between different batches of the same nanoproduct due to dependence on the nanoparticles physicochemical properties [24]. Currently, only one formulation based on PLA nanoparticles (Genexol © PM) is in Phase III of clinical trials in the EU as well as in the US after the successful market launch in South Korea, India and Indonesia. Common methods to nanoparticle manufacturing (such as nanoprecipitation) involve several steps that usually lack reproducibility, controllability, and exhibit a low production rate [25]. However, recently discovered technologies such as microfluidics could improve the reproducibility of nanoparticles batch-to-batch, increasing the clinical translation of nanomedicines [26]. Likewise, the therapeutic endpoints should be aimed from the conceptual design of the nanoparticle to attain the potential clinical benefit and commercial viability. Clinical drug development programs require large investments that are only worthy if both clinical and economic benefits entail a considerable improvement over the existing treatment [27]. Overall, PLA is characterised by thermomechanical properties that have promoted its use in the biomedical field. However, the current gap between material research, preclinical test, clinical requirements and regulatory aspects hampers the translation of PLA nanoparticles research to the clinical level. New formulations by interdisciplinary approaches should be developed aiming at the end-user requirements from the genesis of PLA-based nanoparticles to reach the pharmaceutical market.

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