Polymeric nanoparticles, prepared from nano-emulsion templating, as novel advanced drug delivery systems crossing the Blood-Brain Barrier

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Abstract

Introduction

The administration of drugs to the Central Nervous System (CNS) is a key issue for the treatment of neural diseases. The intravenous administration, compared to the highly invasive intracranial administration, represents a promising alternative. However, due to the presence of the **Blood-Brain Barrier** (BBB), most drugs do no reach the CNS, thus producing low therapeutic efficiencies[1].
In this context, the need for effective drug delivery systems to the CNS is still a challenge. **Polymeric nanoparticles** constitute a promising strategy to target drugs through the BBB using the intravenous route. Diverse types of molecules have been previously used for the nanoparticle functionalization to **target the BBB**, such as permeabilization agents to achieve a passive targeting or monoclonal antibodies against receptors in the BBB to achieve an active targeting[2]. However, current approaches are not sufficiently efficient on the BBB crossing[3].
Therefore, to develop polymeric nanoparticles that efficiently cross the BBB, non-toxic, biocompatible and biodegradable materials are required, together with a safety method of preparation[3]. The use of a preformed polymer instead of the *in situ* polymerization and the **nano-emulsion templating** technology constitutes an interesting and versatile strategy[4]. Nano-emulsions are fine emulsions with droplet sizes typically between 20 – 200 nm, showing high kinetic stability against sedimentation / creaming and a transparent to translucent appearance[5]. Their preparation by low-energy emulsification methods represents an alternative to high-energy methods not only for obtaining nano-emulsions with smaller and less polydisperse droplets, with an energy and cost efficient procedure, but also due to the high versatility of achieving nano-emulsions with the desired characteristics. Among low-energy methods, the **phase inversion composition (PIC) method** is advantageous for the pharmaceutical industry[5] because it can be performed under mild conditions (e.g. mild temperatures). Once nano-emulsions are prepared, the formation of nanoparticles is achieved by solvent evaporation (schematic representation of nanoparticle production methodology on Figure 1).

Objectives

The **aim** of this work was to design polymeric nanoparticles from nano-emulsions templating that efficiently cross the BBB, once administered by the intravenous route.

Results

Poly-(lactic-co-glycolic acid) (PLGA) nanoparticles were designed by the PIC nano-emulsification method followed by solvent evaporation. Nano-emulsions were stabilized with the polysorbate 80 surfactant, since previous studies reported its ability to enhance BBB permeability. Loperamide was incorporated into nanoparticles, prior to nano-emulsion formation, with the aim to study the BBB nanoparticles crossing via *in vivo* analgesia measurements, since the drug loperamide hydrochloride (LOP) produces a central analgesia, but it does not cross the BBB by itself. Nanoparticle surface was further functionalized with the anti-transferrin receptor monoclonal antibody (anti-TfR mAb), overexpressed in the BBB.

Polymeric nano-emulsions were obtained in the electrolyte solution (W) / polysorbate 80 (O) / [4wt% PLGA + 0.1wt% LOP in 20/80 ethanol/ethyl acetate] system, at 25ºC. Nano-emulsions with 90wt % of water content, with an O/S ratio of 70/30 were chosen due to the compromise between the low surfactant content and sizes appropriate for the intravenous administration (around 120 nm). Polymeric nanoparticles, formed by solvent evaporation from template nano-emulsions, showed hydrodynamic radii of around 100 nm and negative surface charges. Loperamide encapsulation efficiency was found

to be very high (>99wt%) and the *in vitro* release profile from nanoparticles was sustained, as compared with the drug in aqueous solution. The covalent binding of the anti-TfR mAb to the nanoparticle surface was successfully achieved by means of the carbodiimide reaction. A concentration step was required to achieve therapeutic loperamide concentrations. *In vitro* toxicity determinations demonstrated that nanoparticles were non-hemolytic neither non-toxic at the *in vivo* required concentrations. Central analgesia was measured *in vivo* by means of the hot plate test. The passive targeting of the BBB by non-functionalized nanoparticles produced slight analgesic effects, while the active BBB targeting by the anti-TfR mAb produced a marked analgesia (50% more than the basal level). Therefore, it could be **concluded** that the formulated nanoparticles, functionalized with the anti-TfR mAb constitute a promising alternative to deliver drugs to the CNS by the intravenous route of administration.

References

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Figures

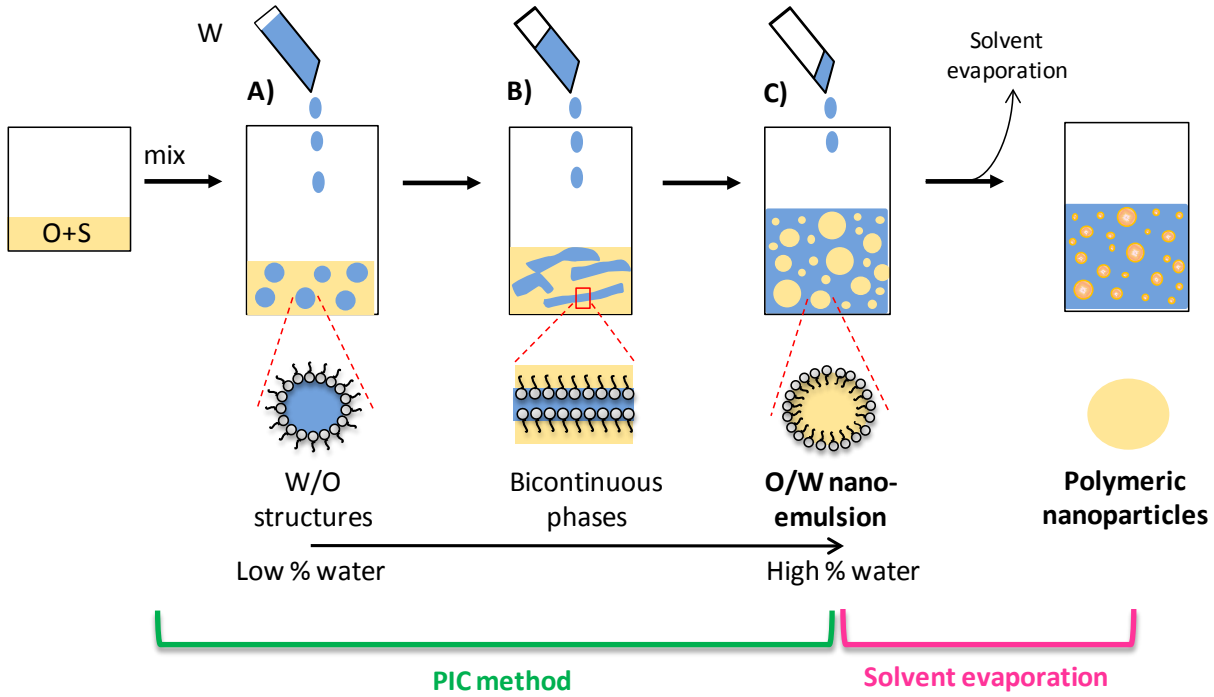

Figure 1: Schematic representation of the whole process for the nanoparticles production.