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Lipid nanoparticles for the transport of drugs like dopamine through the blood-brain barrier

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1. Introduction

Diseases and disorders of the nervous system, like Parkinson disease (PD) and others neurodegenerative pathologies are widespread in our society. The arsenal of treatments against these pathologies continues to increase, but in many cases its use is limited. This is due to the blood-brain barrier (BBB), which acts by limiting the penetration of drugs into the brain.

Based on this background, this study consists of the design and development of solid lipid nanoparticles (SLNPs) capable of transporting different therapeutic molecules to the cerebral parenchyma affected by neurodegenerative diseases. In addition, due to the prevalence of PD, one of the best drugs that could be used to treat this pathology would be dopamine (DP); however, due to its nature DP is unable to reach its therapeutic targets. So, we have encapsulated the DP inside of these SLNPs and we have studied them to ascertain if this SLNPs loaded with DP retain the same physicochemical properties as the empty ones. Finally, the SLNPs were marked and injected systemically into control animals to demonstrate its ability to cross the BBB and reaching the brain cells successfully.

2. Material and methods

2.1. Synthesis of SLNPs

SLNPs were prepared according to a sonication method followed by the use of the high-speed homogenizer. In a first step, an aqueous phase and an oily phase were mixed. On the one hand, the aqueous phase was composed of 7.5 ml of Tween® 80 solution (0.20 % w/v), 7.5 ml of chitosan solution (0.05 % w/v). In the case of NPs loaded with DP, it was used different concentrations of DP. On the other hand, the oily phase was composed of tripalmitin (0.35 % w/v), octadecylamine (0.134 % w/v), and 1 ml of dichloromethane. The union of both phases is subjected to sonication during 6 min. Subsequently, it was subjected to agitation on a Silent Crusher M stirrer at 5500 rpm for 10 min.

2.2. Microphotographic analysis

The devices used for this study have been transmission electron microscope (TEM) and Scanning Electron Microscope (SEM).

2.3. Experimental animals

The in vivo experimental procedures to assess the penetration of the SLNPs in the brain have been developed in adult male Wistar rats (Charles River).

2.3.1. Histology and microscopy

To assess the efficiency of uptake of SLNPs into the brain parenchyma, rhodamine-123-fluorescence-labeled-SLNPs, prepared following the sonication method previously described, were injected in the animals throughout the radial tail vein. After 2h from the systemic NPs injection, animals were sacrificed; the brains were removed and cut into slices of 20 μm with a cryostat.

3. Results and discussion

3.1. Physicochemical characterization of NPs: particles size, PDI, and particle zeta potential

Figure 1a shows the SLNPs in SEM microscopy. Large clusters formed by the accumulation of SLNPs are visible. These aggregates may be due both to the treatment for visualization by microscopy and to the high concentration of SLNPs [1], since the polydispersity and size measurements show a high stability parameter. These SLNPs have a spherical and slightly oval shape, with a smooth surface. Homogeneity in sizes is evident. Figure 1b focuses on a single SLNP by TEM microscopy. It has a spherical shape and an approximate equivalent size to the data of the previous Zetasizer, 200-300 nm.

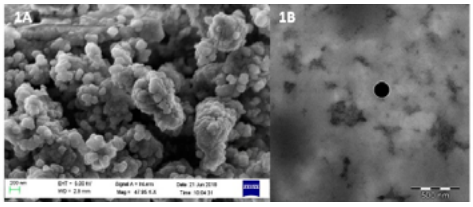

Fig. 1. Empty NPs. a SEM. b TEM

3.2. Estimation of rhodamine fluorescence of e-SPNPs in the cerebral parenchyma

As observed under confocal microscope (Fig. 2), the empty SLNPs are able to cross the BBB; they appear as red vesicles due to the rhodamine fluorescence within the cerebral parenchyma. Despite the short time elapsed since the injection of the SLNPs (2 h), they can be observed inside cytoplasm of the nervous cells, probably associated with the endomembrane cellular system (Fig. 2a); however, some of them are still detected in the lumen of the vessels and inside the vascular wall (Fig. 2b). Different receptors in endothelial cells could be involved in the mechanisms responsible for the capture of the SLNPs to be transported through the BBB to the brain parenchyma [2, 3]. Nevertheless, these mechanisms are not yet fully known, so more research in this field will be require in the future [3].

4. Conclusions

The SLNPs loaded with concentrations of DP between 0.2 and 0.05 % have sizes below 300nm being suitable for penetration through the blood-brain barrier.

SLNPs show a spherical shape, and the DP release is sustained over time resulting adequate to be used as pharmaceutical preparation. SLNPs labeled and administered systemically to adult male Wistar rats demonstrate their penetration ability into the brain parenchyma.

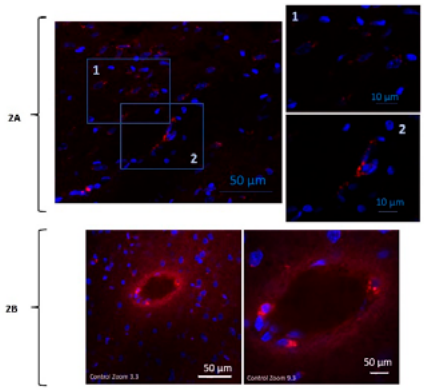

Fig. 2. Confocal microphotographs of a brain sections showing the rhodamine fluorescent SLNPs in the cerebral parenchyma. a The SLNPs as red vesicles inside the nervous cells (probably neurons) (1) and in the vasculature (2). b SLNPs inside the vascular wall and also in nervous cells

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References

1. Chantaburanan T, Teeranachaideekul V, Chantasart D, Jintapattanakit A, Junyaprasert VB. Effect of binary solid lipid matrix of wax and triglyceride on lipid crystallinity, drug-lipid interaction and drug release of ibuprofenloaded solid lipid nanoparticles (SLN) for dermal delivery. J Colloid Interface Sci. 2017;504:247–56.

2. Alyautdin R, Khalin I, Nafeeza MI, Haron MH, Kuznetsov D. Nanoscale drug delivery systems and the blood–brain barrier. Int J Nanomedicine. 2014;9:795–811.

3. Trapani A, De Glio E, Cafagna D, Denora N, Agrimi G, Cassano T, Gaetani S, Cuomo V, Trapani G. Characterization and evaluation of chitosan nanoparticles for dopamine brain delivery. Int J Pharm. 2011;419(1):296–307.

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