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Short communication

Design and optimization of a chitosan coated nanostructured lipid carriers of paliperidone

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Introduction

Schizophrenia is a chronic, severe psychiatric disease characterized by delusions and hallucinations, disorganized speech and behavior, social withdrawal, affective flattening and amotivation, and cognitive dysfunction (Lewis and Lieberman, 2000). Paliperidone (9-hydroxyrisperidone) (PAL), which is the main active metabolite of risperidone, belongs to the class of second-generation antipsychotics as a benzisoxazole derivative. In 2006, it was approved by the U.S. Food and Drug Administration for the acute and maintenance treatment of schizophrenia. Like other atypical antipsychotics, paliperidone acts by inhibiting serotonergic type 2 receptors (5-HT2A) and dopamine type 2 (D2) receptors in the brain (Chue and Chue, 2012).

The brain, which is the most vital organ in our body, is protected by the Blood-Brain Barrier (BBB), a highly sophisticated brain support system. The BBB acts as a barrier that prevents the entry of unwanted substances from the bloodstream into the brain (Dong, 2018). As the BBB is also the primary obstacle to drug delivery to the brain, various approaches have been attempted to overcome this barrier (Bourganis et al., 2018). Intranasal administration, which is among the non-invasive strategies, offers a safe means of drug targeting to the brain, allowing direct passage to the central nervous system (CNS) without encountering the BBB and hepatic first-pass effect associated with oral administration (Keller et al., 2022).

Numerous approaches have been investigated for nose-to-brain delivery of nanostructured lipid carriers (NLCs) which are composed of a mixture of solid and liquid lipids to form a matrix and stabilized with surfactants.

The major disadvantage of intranasal administration is the mucociliary clearance, which reduces the residence time and consequently the drug absorption in the nasal cavity. This condition can be resolved through the surface modification of lipid nanoparticles using a cationic polymer such as chitosan (CH). Recent studies have reported that CH has mucoadhesive, penetration-enhancing properties across epithelial mucus and increases the duration of nasal retention (Bruinsmann et al., 2019).

In light of above discussion, it was proposed to develop and evaluate CH-coated PAL loaded NLCs for brain delivery after intranasal administration to overcome the limitations. In this context, in vitro characterization studies were carried out by coating PAL-loaded NLC formulations with low molecular weight CH. The effect of different surfactants on CH coating was investigated.

Materials and methods

The high-pressure homogenizer (Microfluidics Inc., USA) was operated for the preparation of NLCs. Tripalmitin (Sigma Aldrich, Japan) and oleic acid (Sigma Aldrich, Italy) were chosen to form lipid matrix while Na-cholate (Alfa Aesar, Germany) (NLC-N) or Tween® 80 (Loba Chemie, India) (NLC-T) were used as surfactants. The coating process was carried out by mixing equal volumes of NLC formulation and CH (Sigma Aldrich, LMW: 50,000-190,000 Da, Germany) solution at different concentrations (0.25% and 0.5%). Before and after coating process, the particle size, PDI (polydispersity index) and surface charge of the nanoparticles were determined. The particle size and PDI of NLCs were determined by dynamic light scattering technique (Nano ZS, Malvern, UK). The zeta potential values were also determined from

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the electrophoretic mobility (Zetasizer Nano ZS, Malvern, UK). In order to obtain the suitable scattering intensity, all samples were diluted with ultrapurified water (n=6).

Results and discussion

The aim of this study was to develop and evaluate CH-coated PAL-loaded NLCs for brain delivery by intranasal administration. Particle size, PDI and zeta potential of PAL-loaded NLCs with/without coating of CH are presented in Table 1.

Table 1. Particle size, PDI values of coated/uncoated formulations

Code	CH (%w/v)	PS ± SD (nm)	PDI ± SD
NLC-N	-	110.8±2.22	0.161±0.005
NLC-T	-	123.1±1.01	0.243±0.004
CH-NLC-N1	0.25	600.1±23.8	0.308±0.042
CH-NLC-T1	0.25	209.6±1.86	0.314±0.003
CH-NLC-N2	0.5	874.5±31.6	0.366±0.030
CH-NLC-T2	0.5	323.9±5.52	0.436±0.047

As shown in Table 1, NLCs prepared using Na-cholate and Tween 80 as surfactant exhibited particle sizes of 110.8 ± 2.22 nm and 123.1 ± 1.01 nm. Besides, corresponding zeta potential values were -66.4 ± 0.87 mV and -45.3 ± 1.76 mV respectively as seen in Fig. 1. Additionally, the prepared formulations confirmed the homogeneity of particle size distribution by exhibiting a PDI value lower than 0.3. After the coating of NLC-N and NLC-T with CH, the zeta potential values turned positive, and the particle size significantly increased confirming the accumulation of CH on the surface of the nanoparticles. In the coating process it was observed that the particle size was 600.1 nm for CH-NLC-N1 and 874.5 nm for CH-NLC-N2 coded formulations. On the other hand, the particle size of CH-NLC-T1 was found to be 209.6 nm while, an increase was observed for CH-NLC-T2 which was prepared by 0.5% CH. It can be emphasized that, while higher ionic interaction between Na-cholate and chitosan may enhance the polymer deposition on the surface of particles, the lower surface charge of Tween 80 stabilized NLCs attributes a thinner polymer layer around the nanoparticles. It can be concluded that the CH coating process was affected by the type of surfactants. Besides, the particle sizes of CH-NLC-T1 and CH-NLC-T1 were observed to be 209.6 nm and 323.9 nm when coated with 0.25% and 0.5% w/v CH respectively. It indicates the effect of the concentration of polymer on the coating process.

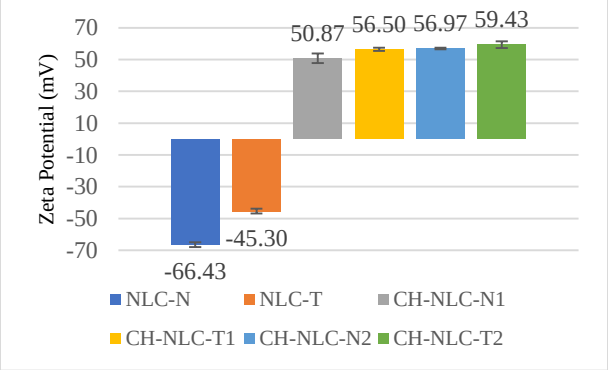

Fig. 1. Zeta potential values of coated/uncoated formulations

Conclusion

The coating of nanoparticles with polymers has an important advantage for preventing mucociliary clearance in intranasal application. In our study, NLC formulations were successfully coated by chitosan which has the excellent mucoadhesive properties. Finally, although these results seem promising, further investigations on the effect of surfactant type will be carried out to optimize coating processing.

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