doi:10.20396/revpibic262018509

XXVI Congresso de Iniciação Científica Unicamp
17 a 19 de outubro Campinas | Brasil

Bupivacaine-loaded nanostructured lipid carriers prepared with beeswax, lavender or melaleuca oil: characterization and physico-chemical stability

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Abstract
Although bupivacaine (BVC) is one of the most widely used anesthetics worldwide, improving its therapeutic efficacy without increasing the clinical doses may open possibilities for new applications for this drug. In this study, we prepared innovative formulations: nanostructured lipid carriers (NLC) functionalized with beeswax, lavender or melaleuca oil in order to increase the anesthetic efficiency of BVC. For this, after preparation and characterization of the NLC by dynamic light scattering and determination of the encapsulation efficiency (% EE), stability was monitored during 12 months. The NLC showed appropriate physical-chemical features, with high %EE and stability. The developed formulations proved to be good candidates to increase the therapeutic efficacy of BVC so that further in vitro and in vivo tests are under course to evaluate their advantages, in comparison to the commercial BVC formulation.

Key words:
bupivacaine, nanostructured lipid carriers, drug-delivery.

Introduction

Local anesthetics (LA) are small molecules which quick clearance from the site of injection limits the duration of analgesia to a few hours. Bupivacaine S75:R25 (Novabupi® or BVC) is widely used in surgical procedures, with a time of action of 4-6 h[1]. To prolong BVC action and to avoid the need of repeated administration, it becomes interesting to encapsulate it in NLC. These lipid-based drug-delivery systems are able to prolong drug release, reduce drug toxicity and increase the time of analgesia, thus optimizing the pharmacological activity of anesthetics[2].
The results shown here refer to the stability studies (12 months storage at room temperature), of NLCs prepared with natural lipids, for the delivery of BVC. The optimized formulations and their controls were followed regarding the size, polidispersion and zeta potential of the nanoparticles.

Results and Discussion

NLC formulations were prepared by the emulsification-ultrasonication method[1]. They were composed by 10% beeswax (BW), 4.5% lavender (LO) or melaleuca (MO) oil, 5% Pluronic F-68 and 1% BVC, w/w. The formulations with (NLC_{BVC}) and without BVC (NLC_{FREE}) were characterized by dynamic light scattering (DLS) and encapsulation efficiency (%EE) (Table 1).

Table 1. Physical-chemical characterization of the optimized NLC_{BVC} formulations, and controls.

Systems	Size (nm)	PDI	Zeta (mV)	%EE
NLC_{BVC} BW+LO	209.3±2.1	0.148±0.01	- 45.6±1.6	54.2±2.4
NLC BW+LO	229.6±3.4	0.115±0.02	- 24.7±0.2	-
NLC_{BVC} BW+MO	252.5±1.8	0.154±0.01	- 48.6±1.5	61.3±3.6
NLC BW+MO	240.2±2.6	0.132±0.03	- 32.8±0.4	-

The physico-chemical stability study is justified by the tendency of other lipid-based nanosystems (liposomes, solid lipid nanoparticles) to destabilize over time, due to the instability of colloidal systems. The stability results obtained with the NLC are shown in Figure 1 and they shown no significant differences over one year storage.

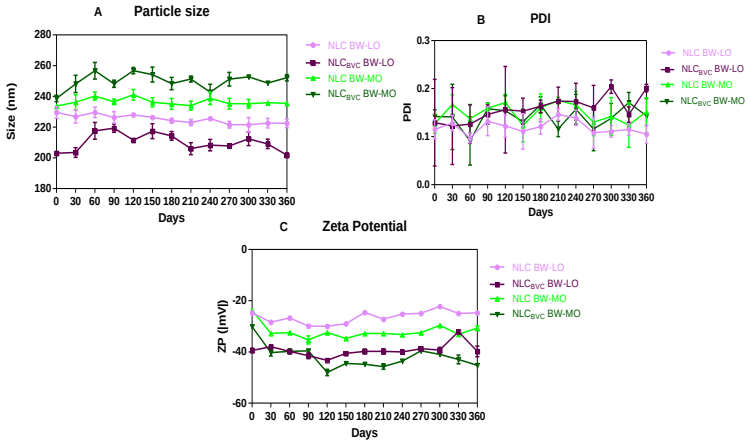

Figure 1. Stability tests: Changes in Size (A); PDI (B) and zeta potential (C) during 12 months, as measured by DLS.

Conclusions

The stability study proved that the opmized nanosystems containing BVC kept the size (*ca.* 250nm), low polidispersity (<0.20) and negative zeta potential (ca. |20-40| mV) of the particles. Due to the good physical-chemical stability, future studies will be carried on to evaluate the possible improvement in anesthesia attained with this novel pharmaceutical forms.

Acknowledgement

The authors thanks CNPq (G.G.), FAPESP (#14/14457-5) and Cristália Prod. Quim. Farm.Ltda for kindly providing Novabupi®.

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