Lipid and polymeric nanoparticles designed for the treatment of corneal vascularization

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ABSTRACT SUMMARY
Three distinct nanostructured drug delivery systems were prepared (liposomes, solid lipid nanoparticles and polymeric nanospheres) containing sunitinib, an anti-angiogenic drug, for the treatment of corneal vascularization. Solid lipid nanoparticles resulted in higher drug release in a suitable period and promoted greater corneal retention of the drug when compared to the other formulations tested.

INTRODUCTION
Transparency and refraction properties of a healthy cornea are predominantly mediated by the absence of blood vessels in the corneal tissue. However, several pathological processes affecting the cornea may induce corneal vascularization, usually leading to vision impairment. Sunitinib (SUB) is an antiangiogenic drug that has demonstrated a significant reduction of corneal vascularization in rabbits1, 2, 3. Incorporation of SUB in nanosystems may increase its corneal retention, decrease drug resistance mediated by P-glycoprotein and the conversion of the drug to its inactive isomer E (trans) when exposed to light.

The aim of this work was to develop liposomes, solid lipid nanoparticles (SLN) and polymeric nanospheres loaded with sunitinib, compare release profile and corneal retention of this drug from polymeric and lipidic nanostructured systems.

EXPERIMENTAL METHODS
Nanospheres and solid lipid nanoparticles were obtained by solvent emulsification / evaporation method. Emulsion was obtained by mixing the organic phase, containing dissolved lipids or polymers, with the aqueous phase. Organic solvent was removed by a rotary evaporator, which promoted precipitation of either lipid or polymer and the formation of nanoparticles. Glycerol monostearate was used to produce SLN and poly-$\varepsilon$-caprolactone to prepare nanospheres. Liposomes were prepared with soybean phosphatidylcholine by thin lipid film hydration method followed by extrusion through polycarbonate membranes.

The nanoparticles formulations were characterized for their encapsulation efficiency, size and polydispersity index (PdI). Comparative corneal retention studies were performed using porcine corneas in a modified Franz diffusion cell. Drug release profile was determined in Franz diffusion cells equipped with dialysis membrane. Quantitative determination of the drug was performed by a validated HPLC method and for the corneal retention experiments, a bioanalytical method was developed and validated.

Statistical analyses were performed by analysis of variance (ANOVA) with Tukey’s test.

RESULTS AND DISCUSSION
Liposomes were approximately 80 nm in diameter, nanospheres were 140 nm while SLN were 180 nm, all particles were monodisperse (PdI < 0,2). Encapsulation efficiency was above 83% for liposomes, 97% to SLN and about 89% for nanospheres corresponding, respectively, to a concentration of 625 µg/mL, 320 µg/mL and 420 µg/mL of sunitinib in the dispersion.

Release profile of sunitinib varied for each formulation. Liposomes were able to sustain drug release by a greater period than that observed for polymer nanospheres and solid lipid nanoparticles (Figure 1).
Figure 1. Comparison of in vitro release profile of sunitinib in simulated tear fluid from liposomes (LIPO), solid lipid nanoparticles (SLN) and nanospheres (NE). * p < 0.05.

SLN showed higher corneal retention of SUB when compared to other systems. Within thirty minutes corneal retention of SUB from NLS (15 μg/cm²) was over 2-fold the concentration observed for liposomes (6.8 μg/cm²). Nanospheres also showed corneal retention of SUB superior to liposomes. Thirty minutes after applying nanospheres, corneal retention of SUB (12.74 μg/cm²) was almost twice that observed for liposomes in the same period (6.8 μg/cm²) (Figure 2).

Figure 2. Sunitinib retained in the corneas following thirty minutes and one hour after application of formulations: liposomes (LIPO), nanospheres (NE) and solid lipid nanoparticles (SLN).

* p < 0.05 comparing formulations in the same period of study.
# p < 0.05 comparing the same formulation in another study period.

Nanospheres and NLS showed higher SUB corneal retention when compared to liposomes (p <0.05). A striking difference between these two nanosystems and liposomes is the presence of surfactants in the formulation. In this study, the surfactants used in the preparation of nanospheres and SLN were nonionic surfactants. Apparently, these surfactants helped increase the corneal permeability of the drug by interfering with cell membrane properties, which might have become more permeable.

CONCLUSION
In this work, SLN exhibited a better performance in promoting corneal retention of SUB in comparison with liposomes and polymeric nanospheres. SLN also released the drug faster than the other systems which can be considered advantageous for the topical ocular pathway. SLN demonstrated potential applications as delivery systems to improve clinical response associated with the administration of antiangiogenic drugs to the cornea.

REFERENCES

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