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DEVELOPMENT AND OPTIMIZATION OF POLYMERIC NANOCAPSULES INTENDED FOR OPHTHALMIC ADMINISTRATION

Katzer T.[1*];Pohlmann, A. R.[2]; Guterres, S. S.[1]; Beck, R. C. R.[1]
[1]Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, UFRGS.
[2]Departamento de Química Orgânica, Instituto de Química, UFRGS.
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Introduction: Nanocapsules are nanocarriers characterized by a polymeric wall surrounding an oily core, which particle diameters range from 10 to 1000 nm. The oily component can have a great influence on the particle size and polydispersity index (PDI) due to the difference in its viscosity, hydrophobic characteristic and interfacial tension. Castor oil (CO) consists of up to 90% of ricinoleic acid, which presents anti-inflammatory effects, produces a more stable tear film and a significant decrease in ocular dry eye symptoms. The medium-chain triglycerides (capric/caprylic acids [CCM]) present good compatibility, solvent properties and are non-irritating to the eyes. In the same way, mineral oil (MO) is used in ophthalmic formulations due to its lubricant properties.
Objective: The aim of this work was to develop and optimize polymeric nanocapsules intended for ophthalmic administration (drug delivery), evaluating the employing of different polymers and oily components, such as CO, CCM and MO and their mixtures.
Materials and Methods: Nanocapsules were prepared by interfacial deposition of preformed polymer. The particle size of all formulations was firstly determined by laser light diffraction to verify the presence of microparticles. Formulations presenting only particles at the nanoscale were selected for further studies. They were prepared in duplicate, had their pH values measured and were also analyzed by photon correlation spectroscopy to determine their mean particle size, PDI and the ζ-potential. The quantitative composition of the formulations is described in Table 1. The swelling/dissolution test of polymeric films were carried out in triplicate for the different oils. The films were weighed after 2 minutes, 2, 5 and 15 days. Statistical analysis was performed (Student's *t*-test for two groups, $\alpha = 0.05$) to analyze the particle size.
Results and Discussion: Firstly, it was proposed to use separately the same amount of each oil. However, the formulations prepared with PCL and EUD using MO showed, besides nanoparticles, particles at the micrometric scale (F3, F8), as well as the formulation prepared with PCL using CO and even with the mixture CO/CCM (F7 and F10, respectively). Thus we tried to mix them with other oils in study. All the other formulations (F1, F2, F4, F5, F6, F9, F11) presented only nanometric particles right after preparation. Among these formulations, the nanocapsules prepared with EUD presented size in the range of 120 - 194 nm, PDI below 0.16, positive ζ-potential and pH in the acid range (pH 4.9 - 5.7). On the other hand, nanocapsules prepared with PCL showed higher ($p<0.05$) mean particle size (198 - 237 nm), PDI below 0.16, negative ζ-potential and pH between 6.2 and 7.2. Except the formulation F4 all others formulations remained stable for at least 15 days. The polymeric films used in the swelling/dissolution test had a change lower than 6% in their weights over 15 days, demonstrating that these oils do not swell or dissolve the polymer of the nanocapsule wall.
Conclusions: It was possible to optimize polymeric nanocapsule formulations using different polymers and oils intended to ophthalmic drug delivery systems, obtaining them with appropriate physicochemical characteristics, regarding mainly their particle size control at the nanoscale.

Table 1. Composition of different nanocapsule formulations (v/v)

	Organic Phase							Organic Phase					
	CCM	MO	CO	EUD	PCL	Span 60®		CCM	MO	CO	EUD	PCL	Span 60®
F1[a]	3.30%	-	-	1%	-	-	F7	-	-	3.30%	-	1%	0.77%
F2[a]	-	-	3.30%	1%	-	-	F8	-	3.30%	-	-	1%	0.77%
F3	-	3.30%	-	1%	-	-	F9[a]	1.65%	1.65%	-	-	1%	0.77%
F4[a]	1.65%	1.65%	-	1%	-	-	F10	1.65%	-	1.65%	-	1%	0.77%
F5[a]	-	1.65%	1.65%	1%	-	-	F11[a]	-	1.65%	1.65%	-	1%	0.77%
F6[a]	3.30%	-	-	-	1%	0.77%							

All the aqueous phases contained 0.77% of polysorbate 80. All the organic phases contained acetone as organic solvent.
[a]: formulations that presented size distribution only at nanoscale.

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