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DoE studies for obtaining a self-assembling nanostructured system based on citronellol homopolymers: a brand-new application for a green lipophilic material

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Introduction:

Self-assembling drug delivery systems represent a great interest in the field of nanocarriers development since the supramolecular devices obtained are capable to load actives molecules for different uses such as cosmetics, drugs and foods [1]. These systems constituted by one or more materials have as feature the ability to get spontaneously a level of organization, structuring isolated and stable particles, fibers, gels, among others, able to convey and delivery interest molecules [1], [2]. In this work we seek developing a nanocarrier based on a self-assembling emulsified system focusing on the use of a new lipophilic compound, citronellol homopolymer, a terpene present in several kinds of plants worldwide. Here, we use two marketed types of citronellol homopolymers [3], one with low viscosity (CL) and another with high viscosity (CH), to obtain lipid nanoparticles using citronellol homopolymer as constituent of lipid matrix, in a simple process of emulsification. DoE (design of experiments) was used to evaluate proportions of CL ou CH, blend of surfactants and amount of co-surfactant (glycol propylene) able to provide the lowest size and more homogeneous system after emulsification. The aim of this work was to study the ability of citronellol homopolymers in forming self-assembling nanostructured lipid carriers using regular emulsification processes with non-ionic surfactants.

Materials & Methods:

Four 2^3 DoE (Design of Experiments) were used, where percentages of surfactants 1:1 (polysorbate 80 (Tw80) added of ethoxylated oleic alcohol (EOA) or poloxamer 188 (P188) - 4 and 8% w/w), propylene glycol (PPG) (5 and 15% w/w), and content of citronellol homopolymer (low or high viscosity, CL or CH, respectively) in the oily phase (13 and 87% w/w) were factors and levels studied. Besides, two intermediate levels were included with regard to the content of citronellol homopolymer in the oily phase (25 and 75% w/w), resulting in 16 formulations for each DoE (DoE1: EOA-CL; DoE2: P188-CH; DoE3: EOA-CL; DoE4: P188-CH) as presenting in Table 01. All the formulations were produced by emulsification.

Table 01. Sequence of four DoEs executed with factors and levels used. Oil Phase and Aqueous Phase show amounts of materials used to prepare 10 g formulation. Each formulation was analysed in triplicate by laser diffraction.

DoEs (DoE1: EOA-CL; DoE2: P188-CH; DoE3: EOA-CL; DoE4: P188-CH)					Compounds grouping						
					Oil Phase				Aqueous Phase		
Formu-lation	Tested order	[%sur-factants]	[%CL or %CH] in oil phase	[%Propy-lene glycol]	CL or CH (g)	GMS (g)	Propy-lene glycol (g)	EOA or P188 (g)	Tw80 (g)	PVPK30 2% dispersion (g)	Purified Water (g)
13	1	8	25	5	0.063	0.188	0.500	0.400	0.400	5.000	3.450
5	2	4	25	5	0.063	0.188	0.500	0.200	0.200	5.000	3.850
2	3	4	87	15	0.218	0.033	1.500	0.200	0.200	5.000	2.850
15	4	8	13	5	0.033	0.218	0.500	0.400	0.400	5.000	3.450
8	5	4	13	15	0.033	0.218	1.500	0.200	0.200	5.000	2.850
4	6	4	75	15	0.188	0.063	1.500	0.200	0.200	5.000	2.850
7	7	4	13	5	0.033	0.218	0.500	0.200	0.200	5.000	3.850
10	8	8	87	15	0.218	0.033	1.500	0.400	0.400	5.000	2.450
6	9	4	25	15	0.063	0.188	1.500	0.200	0.200	5.000	2.850
9	10	8	87	5	0.218	0.033	0.500	0.400	0.400	5.000	3.450
11	11	8	75	5	0.188	0.063	0.500	0.400	0.400	5.000	3.450
1	12	4	87	5	0.218	0.033	0.500	0.200	0.200	5.000	3.850
3	13	4	75	5	0.188	0.063	0.500	0.200	0.200	5.000	3.850
12	14	8	75	15	0.188	0.063	1.500	0.400	0.400	5.000	2.450
14	15	8	25	15	0.063	0.188	1.500	0.400	0.400	5.000	2.450
16	16	8	13	15	0.033	0.218	1.500	0.400	0.400	5.000	2.450

Results & Discussion:

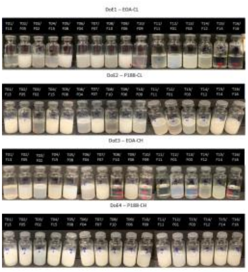

Figure 1. Pictures of sixteen formulation from DoE 1–4. T01-T16 refer to the tested order which the formulations were executed and F01-F16 refers to formulations tested with different factors and levels.

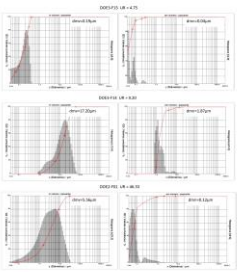

Figure 2. Histograms obtained by laser diffraction analysis from formulations with different UR depicting the uniformity of size distribution.

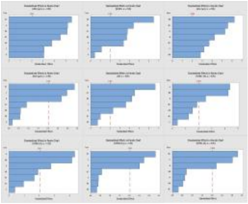

Figure 3. Standardized effects in Pareto Chart from DoE3 analysis using Response Surface Regression model. Factors A: [EOA+Tw80]; B: [CH in oil phase]; C: [Propylene glycol]..

Two optimization studies were done for each DoE, considering parameters that had presented significance for the models in RSR and R2 > 0,6. The desirability obtained was higher for those studies where size parameters (dmn, dmn, d50v) and uniformity parameter (SPAMv and UR) were minimized and parameter related to percentage of particles (%500v, %300v, %300n, and %100n) were maximized, D > 0,83 for all DoEs, whereas the indication of targets for size resulted in a lower desirability index, with D = 0.75 for DoE2, as an example. Concerning the optimization study, the formulation suggested for reaching the parameters in DoE3, which allowed to obtain two formulations with features of a monodispersed nanoparticles, was 8% of surfactants (EOA+Tw80), 13% of CH in oil phase, and 9% of propylene glycol..

Conclusions:

It was possible to obtain self-assembling formulations using citronellol homopolymer as part of the oily phase in lipid nanoparticles and ordinary surfactants as polysorbate 80 and EOA. The citronellol homopolymer has shown an interesting feature as solvent for lipophilic actives what might be interesting to carrier them in cosmetic and pharmaceutical formulations in a sustainable and ecological way.

Parameters used in DoE study unveiled that it is important monitoring the size of particles depict in different ways since measures of size just in passing number is not able to demonstrate the real yield of process to provide in a specific range. Thus, the uniformity ratio might be used to point the process and formulation more capable to provide size range and yield specified.

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