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Research paper

Radar charts based on particle sizing as an approach to establish the fingerprints of polymeric nanoparticles in aqueous formulations

Mariana D. Bianchin [a], Irene C. Külkamp-Guerreiro [a], Catiuscia P. de Oliveira [a], Renata Vidor Contri [a], Sílvia S. Guterres [a], Adriana R. Pohlmann [a, b, *]

[a] Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Av. Ipiranga 2752, 90610-000, Porto Alegre, RS, Brazil
[b] Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio Grande do Sul, CP 15003, 91501-970, Porto Alegre, RS, Brazil

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ABSTRACT

Pre-formulation studies are conducted each time new nanoparticulate formulations are in development to the selection of a satisfactory drug delivery system. We hypothesized that laser diffraction technique could be used as an initial screening, being an excellent tool to save time and reduce the number of necessary tests to select formulations. We built radar charts based on laser diffraction data as a new approach to determine the fingerprints of nanocarrier formulations in order to select promising drug delivery systems. To validate our approach different lipophilic dispersions of poly(epsilon-caprolactone) and polysorbate 80, combined with 4 solid materials: sorbitan monostearate (I), cetyl palmitate (II), stearic acid (III) or cholesterol (IV), and 4 oils: capric/caprylic triglycerides (A), mineral oil (B), octyl methoxycinnamate (C) or oleic acid (D), were prepared. Formulations were analyzed by laser diffraction, as well as considering the visual appearance, pH, organic phase viscosity, hydrodynamic diameter, polydispersity index, zeta potential and *in vitro* drug release. Specific fingerprints were determined for formulations having unimodal particle size distributions with low polydispersity. On the other hand, formulations showing multimodal particle size distributions were rapidly identified in the radar charts and classified as noncompliance products.

1. Introduction

In the recent years, nanotechnology has shown applications in distinct areas. Diverse nanoparticulated systems have been developed over the past 20 years, classified as hard and soft nanoparticles. Among the soft nanoparticles, solid lipid nanoparticles, nanostructured lipid nanocarriers, polymer micelles, polymeric nanospheres and polymeric nanocapsules have received much attention as drug delivery systems due to their advantages as biocompatible and/or biodegradable nanocarriers [1–4].

The polymeric nanoparticles have shown a wide range of possible applications due to their high intracellular uptake and drug active targeting, since their size distributions have average diameters between 100 and 500 nm [4]. Those nanoparticles can be named nanocapsules or nanospheres depending on their chemical composition and supramolecular structures. The nanocapsules are composed of an oily core and a polymer wall, stabilized by surfactants in aqueous dispersions, while the nanospheres are matrices of polymer dispersed in water, stabilized by surfactants [4]. The nanocapsules are easily prepared by interfacial deposition of pre-formed polymer (nanoprecipitation method), solvent displacement and self-assembling. Different polymeric nanocapsules prepared elsewhere showed mean hydrodynamic diameters between 200 and 500 nm [5–8].

In the past 15 years, our research group developed different polymeric nanocapsules varying oil, polymer and surfactant system [9–12] to encapsulate diverse drugs and other lipophilic substances [12–23] in order to control their release rates, to stabilize them against UV radiation, to modify their mechanical properties, or to improve their pharmacological effects [24]. After pre-formulation studies performed in each case, the average diameters of the nanocapsules ranged from about 200 to 400 nm regardless of their supramolecular structures (Table 1).

* Corresponding author. Instituto de Quimica, UFRGS, Av. Bento Gonçalves, 9500, Porto Alegre, 91501-970, RS, Brazil.
E-mail address: adriana.pohlmann@ufrgs.br (A.R. Pohlmann).

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Table 1
Formulations containing different compositions of oil, polymer, surfactant system containing or not drug and their average diameters in nanometers (nm).

Formulation	Oil	Polymer	Surfactant system	Drug	Diameter (nm)	Ref.
1	Bn benzoate	PLA	SM/P80	–	178	[9]
				IndOH	236	
2	Bn benzoate	PCL	SM/P80	–	221	[9]
				IndOH	256	
				DicOH	276	[10]
3	CCT	PCL	Epi170/SynF68	DicOH	182	[11]
4	CCT	EudS90	Epi170/SynF68	DicOH	190	[11]
5	CCT	EudS90	Epi170/SynF68	–	198	[12]
				Ethionamide	218	
6	CCT	PCL	SM/P80	DicOH	<400	[13]
				DicOH	327	[10]
				IndOEt	297	[14]
				Quercetin	285	[15]
				IndOH	240	[16]
				Lipoic acid	320	[17]
7	Mineral oil	PLA	SM/P80	IndOH	197	[18]
8	Mineral oil	PCL	SM/P80	IndOH	239	[18]
9	Bn benzoate	EudS90	SM/P80	DicOH	202	[10]
10	CCT	EudS90	SM/P80	DicOH	225	[10]
11	CCT	PMMA-f	SM/P80	–	210–260	[19]
					215	[20]
12	OMC	PCL	SM/P80	–	245	[15]
				Quercetin	265	
13	OMC	PCL	Epi170	–	255	[15]
				Quercetin	210	
14	CCT	PCL	Epi170	Quercetin	194	[15]
15	CCT/OMC	PCL	SM/P80	–	211	[21]
16	CCT/OMC	PCL	P80	–	220	[21]
17	CCT	PCL	SM/P80	–	201	[22]
18	CCT/OMC	PCL	Lip100/SM/P80	–	206	[23]
19	CCT/OMC	PCL	SM/P80	–	217	[23]
20	CCT/OMC	PCL	Lip100/P80	–	237	[23]
21	CCT/OMC	PCL	P80	–	216	[23]

Bn benzoate: benzyl benzoate; PLA: poly(lactide); SM: sorbitan monostearate; P80: polysorbate 80; IndOH: indomethacin; DicOH: diclofenac; CCT: capric/caprylic triglyceride; Epi170: Epikuron 170®; SynF68: Synperonic PE/F68®; EudS90: Eudragit S90®; PMMA-f: poly(methyl methacrylate)-benzazole conjugate; OMC: octyl methoxycinnamate; Lip100: Lipoid 100®.

One of the developed polymeric nanocapsules are the lipid-core nanocapsules, which supramolecular structure have been stablished after an extensive physico-chemical characterization using differential scanning calorimetry [25], small angle x-ray scattering [14], and viscosimetry [26]. The core is composed by a dispersion of sorbitan monostearate in capric/caprylic triglyceride, the polymer wall is composed of poly(ε-caprolactone) and the surface is coated with polysorbate 80 micelles [22]. The high viscosity of the internal lipophilic phase, the rigidity of those nanocapsules and their polymer wall are consequence of the presence sorbitan monostearate in their core [24]. Thereby, the lipid-core nanocapsules can be classified as a hybrid nanocarrier between the polymeric nanocapsules [4] and the nanostructured lipid carriers. The latter are dispersions of solid and liquid lipids in aqueous phase [27].

The lipid-core nanocapsules are advantageous since the control of the drug release is dependent on the lipid-core viscosity characteristics, besides the barrier effect of the polymeric wall [26]. The polymer and oily contents in the nanocapsule formulation can *i*) influence the release profile of different substances and improve the activity of the drug entrapped in the core [14,28], *ii*) improve the *in vitro* release kinetics [29] and *iii*) protect drugs against degradation [30].

Pre-formulation studies are conducted each time new nanocarriers are in development. A comprehensive physico-chemical analysis is mandatory to select appropriate formulations prior to further *in vitro* and *in vivo* biological evaluations. The main particle sizing characterization method is the dynamic light scattering. However, this technique is not able to determine if the nanoparticulate system has any microscopic contamination. Additionally, the dispersed systems are thermodynamically unstable and their tendency to aggregation is difficult to access. In general, multiple light scattering technique can furnish the kinetic parameters of sedimentation, creaming, flocculation and coalescence, as well as an estimative of the relative thermodynamic stability [23]. We hypothesized that laser diffraction technique could be used as an initial screening, being an excellent tool to save time and reduce the number of necessary tests to select formulations.

Radar charts are a useful graphical display method for multivariate data [31]. This approach is used in several fields, such as clinical epidemiology [31,32], development of sensors chips [33], and screening of elemental impurities [34], among others. In the pharmaceutical field, the radar charts using solvent data from the literature were proposed as a tool in the early stages of pharmaceutical process development [35].

Considering the exposed, we propose to build radar charts based on laser diffraction analysis as a new approach to determine the fingerprints of nanocarrier formulations in order to select promising drug delivery systems. Considering that cetyl palmitate, stearic acid, cholesterol and oleic acid are widely used as materials in lipid nanoparticles [36,37], and that sorbitan monostearate, capric/caprylic triglycerides, octyl methoxycinnamate and mineral oil [24] are used to formulate polymeric nanocapsules, we selected them to construct a matrix to validate our approach. Then, our objective was to evaluate different lipophilic dispersions of PCL and polysorbate 80 combined with 4 solid materials: sorbitan monostearate (I), cetyl palmitate (II), stearic acid (III) or cholesterol (IV), and 4 oils: capric/caprylic triglycerides (A), mineral oil (B), octyl methoxycinnamate (C) or oleic acid (D) as a strategy to establish radar charts for each formulation, as well as to define an appropriate fingerprint for promising drug delivery systems.