Development of polymeric colloidal nanocarrier based on maltodextrin

Desenvolvimento de nanocarreadores poliméricos coloidais de maltodextrina

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nanocarrier; polymeric nanoparticle; drug delivery; maltodextrin; physical stability; silicone surfactant.

Palavras-chave:
nanocarreador; nanopartícula polimérica; maltodextrina; estabilidade física; surfactante de silicone.

Abstract

The development of nanocarriers has been the focus of many studies designed to produce novel drug delivery systems. Thus, this study describes the development and characterization of a novel delivery system denominated as polymeric colloidal nanocarriers (PCN) made up of a maltodextrin core dispersed in a continuous phase of silicone. The developed PCN were prepared following two main consecutive steps: generation of a water-in-oil nanoemulsion using a high pressure homogenizer followed by extraction of the water present in the internal phase to obtain the maltodextrin PCN dispersed in an anhydrous nanosuspension. The obtained dispersion was analyzed by dynamic turbidimetry, dynamic light scattering and scanning electron microscopy (SEM) to respectively register results related to the physical stability, the average diameter and the morphological aspect. Based on the results of the characterizations, it was possible to evidence that the use of a surfactant concentration equal or higher than solid contents improves the nanosuspension physical stability and diminishes the PCN particle size.

Resumo

Muitos estudos têm sido realizados na área de desenvolvimento de nanocarreadores como sistemas carreadores de fármacos. Nessa mesma linha, este estudo descreve o desenvolvimento e a caracterização de um novo sistema carreador denominado nanocarreadores poliméricos coloidais (NPC) constituído de uma matriz coloidal de maltodextrina dispersa em uma fase contínua de silicone. Os NPC desenvolvidos foram preparados em duas etapas: obtenção de uma nanoemulsão água em óleo usando homogeneizador de alta pressão seguido da extração da água da fase interna da nanoemulsão para obter NPC de maltodextrina dispersos

em uma nanosuspensão anidra. Os sistemas obtidos foram analisados por turdimetria dinâmina, espalhamento de luz dinâmico e microscopia eletrônica de varredura (MEV) para obter resultados, respectivamente, de estabilidade física, diâmetro médio de partícula e morfologia. A partir desses resultados, foi possível evidenciar que o uso de uma concentração de emulsificantes igual ou maior que a porcentagem de sólidos do sistema melhora a estabilidade física da nanosuspensão e diminui o tamanho das partículas.

1 Introduction

Nanocarriers are nanometric particles used to deliver drugs or biomolecules, generally comprising sub-micro particles with a size below 1,000 nm and with spherical morphology. Over the years, drug delivery systems based on nanoparticles have shown huge potential in biological, medical and pharmaceutical applications.

These systems have the potential to improve the therapeutic index of currently used drugs and may increase their efficacy, may reduce their toxicity or may enhance their bioavailability (GRALLERT et al., 2012). They can also modify the solubility and the stability of drugs, allowing the development of novel chemical entities which were formerly rejected in pre-clinical or clinical phases due to their inappropriate pharmacokinetics or biochemical profile (GRALLERT et al., 2012). Moreover, nanocarrier systems can facilitate the development of multifunctional polymeric systems for targeted drug delivery (NASONGKLA et al., 2006), combination therapy (LARINA, 2005) or systems for usage in theranostics (ALEXIS et al., 2008).

*However, most nanocarriers reported in the literature are more suitable for delivering hydrophobic drugs because they are produced using mainly lipophilic materials to build the matrix of the nanoparticles, for example: poly(lactic acid), poly(**ε**-caprolactone), poly(**β**-hydroxybutyrate), poly(methylmethacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate) which demand organic solvents to solubilize them (GRABNAR; KRISTL, 2011; REIS, 2006). Thus, molecules to be encapsulated must have a good compatibility with the lipophilic matrix, wherefore just poorly water-soluble active pharmaceutical ingredients are able to be encapsulated by this process (MÜLLER et al., 2007; AL HAJ; RASEDEE, 2009; PARDEIKE, 2009).*

Therefore, an alternative for hydrophilic drugs delivery has been required to improve or to allow their application through lipophilic routes such as the skin. Then, this work focused on the development of an innovative strategy to produce systems capable of encapsulating hydrophilic molecules, patented in "Colloidal Nanoscale Carriers for Active Hydrophilic Substances and Method for Producing Same" (CERIZE et al, 2013). This strategy involves the combination of two technologies to build nanocarriers: the first is the use of high shear homogenization technique for producing water-in-oil nanoemulsions; the second is based on solvent extraction to consolidate the formation of the polymeric nanoparticles themselves. These two combined techniques enabled the generation of polymeric colloidal nanocarriers dispersed in an anhydrous nanosuspension (CERIZE et al., 2013).

In order to evaluate some formulation aspects which might be affect these PCN nanosuspension physical stability, this work reports a study concerning about surfactant concentration impact on physical stability.

2 Materials

Maltodextrin (Malto) was purchased from Givaudan. Dimethicone with viscosity of 100 cSt was obtained from Daltomare (São Paulo, Brazil). Silicone Surfactants – Cyclopentasiloxane and PEG/PPG 20/15 dimethicone (SF1540®) were purchased from Momentive (São Paulo, Brazil). Poloxamer 188 (Polox) was purchased from Sigma-Aldrich. Analytical grade sodium chloride was used.

3 Methods

3.1 Production Process of the maltodextrin polymeric colloidal nanocarriers (PCN)

The PCN were prepared as described in **Figure 1** *by a nanoemulsification method followed by water extraction from the internal phase of the preformed nanoemulsion.*

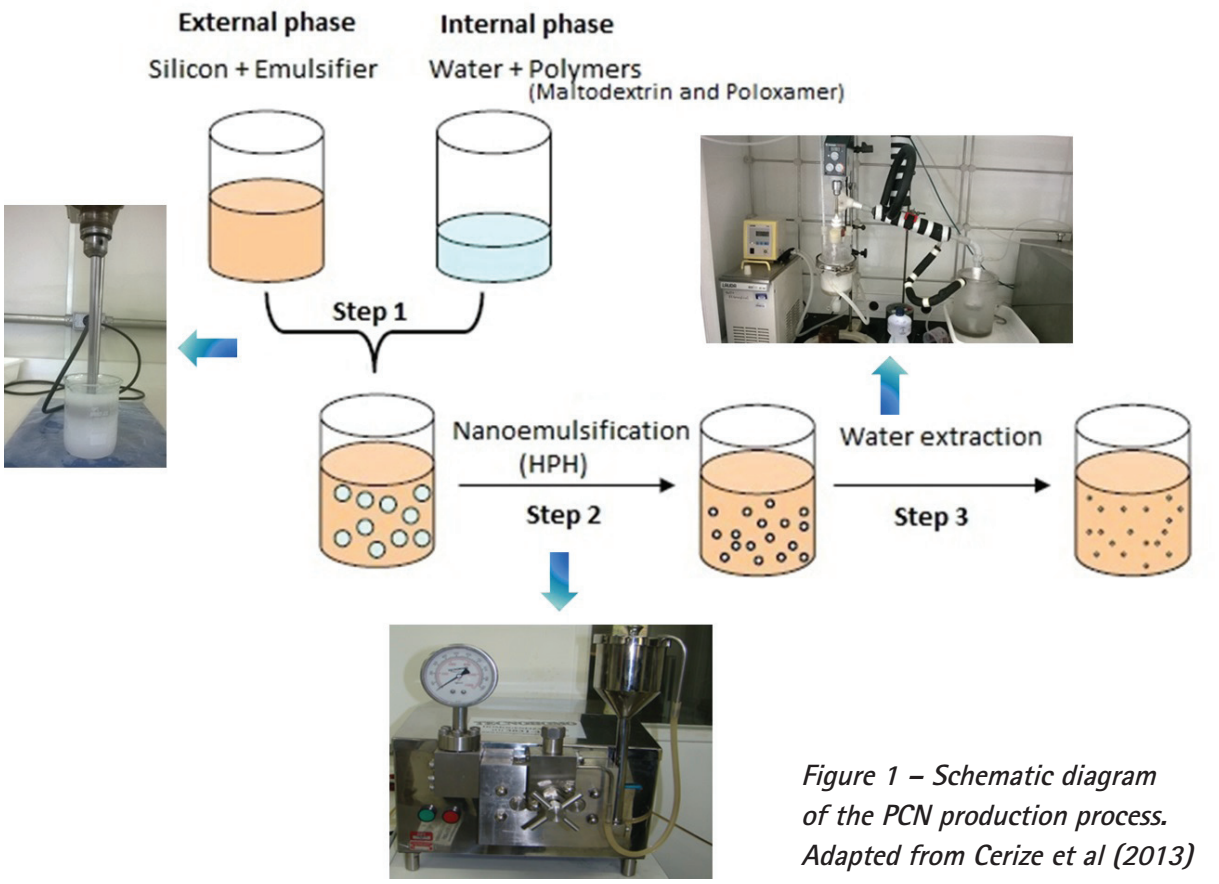

Figure 1 – Schematic diagram of the PCN production process. Adapted from Cerize et al (2013)

The internal phase of the nanoemulsion was prepared by dissolving maltodextrin into an aqueous solution containing NaCl. Silicone (dimethicone) with surfactant SF1540 was used as the external phase of the nanoemulsion. A pre-emulsion was firstly obtained by mixing the two phases by means of a mechanical agitation (Mechanical Homogenizer, IKA model RW 20 digital) for 5 min at 1,000 rpm prior to the process using a high pressure homogenizer (Homogenizer Invensys APV, Model APV-2000) operating at 1,000 bar (6 cycles).

Afterwards, the obtained nanoemulsion was transferred to a vacuum reactor and was gently shaken at 50 °C to remove the water. The system was monitored by removing aliquots of emulsion at predetermined time intervals.

Following this fabrication protocol, three experiments were performed with different formulation conditions.

3.2 Physical Stability

The physical stability of the obtained nanocarriers was evaluated during a three-day period (1 h interval between consecutive scans) using a dynamic turbidimeter (Turbiscan® Lab, model MA 2000, France). The backscatterring and transmission profiles were used to calculate the Turbiscan Stability Index (TSI) and to compare the performance of the different samples tested within the scope of the present work.

3.3 Particle Size

The particle size measurement was carried out by the dynamic light scattering technique (Zetasizer, Malvern). The sample preparation protocol consisted in adding approximately 10 mg of the suspension containing the PCN to 1 g of silicone (SF-1202) with 2 % of Silform60-A. The measurements were performed in triplicate and the average results concerning particle size ($Z_{average}$) and Polidispersity Index (PI) were reported herein.

3.4 Morphological Characterization

The morphology was evaluated by using the Field Emission Gun Scanning Electron Microscopy technique (microscope FEG-SEM, Model Quanta 3D, FEI).

The sample preparation protocol consisted of vacuum-assisted membrane filtration using 0.22 µm cellulose-esther membranes followed by rinsing with cyclohexane to remove the silicone excess still present in the sample. The membrane with the harvested particles was dried on a desiccator under vacuum during at least 24 h. Afterwards, the membrane with particles was sputter-coated to deposit a thin layer of Au-Pd.

The operating procedure of the microscope considered the use of the high-vacuum mode and the accelerating voltage of 20 kV.

4 Results and Discussion

The formulation and physical-chemical characterization of performed experiments are presented in ***Table 1****.*

Table 1 – Formulation and Characterization Results of Maltodextrin PCN.

Batch	*Internal phase*				*External phase*		*Physical-Chemical Characterization*	
	Malto % w/w	*Polox* % w/w	*Salt* % w/w	*Water* % w/w	*SF1540* % w/w	*Silicone* nm	*Particle Size* PI*	*Physical Stability* TSI
1a	5	4	0.4	21	10	279	0.19	15.9
1b	5	4	0.4	21	10	281	0.07	11.7
2	5	4	0.4	21	5	393	0.14	16.6

*PI = Polydispersity Index;

The samples generated by using the production process protocol were classified as nanosuspensions and, because of the presence of sub-micron particles suspended in an organic medium, they all presented a white opaque fluid aspect as can be seen in ***Figure 2.***

Figure 2 – Visual aspect of maltodextrin nanoparticles dispersed in silicone.

*The physical stability values expressed by Turbiscan Stability Index (TSI) showed in **Table 1**, as well as the destabilisation kinectic graphic showed in **Figure 3**, allow evaluating the influence of the concentration of emulsifier in the stabilization of nanocarrier suspensions. Comparing the physical stability of batch 1a (TSI 15.9) and 1b (TSI 11.7), which contained 5 % of SF1540, with the batch 2 (TSI 16.6) formulation containing 10 % of the same emulsifier, we can found that the SF1540 at a concentration of 10 % was more efficient to stabilize the suspended nanocarriers in silicone medium.*

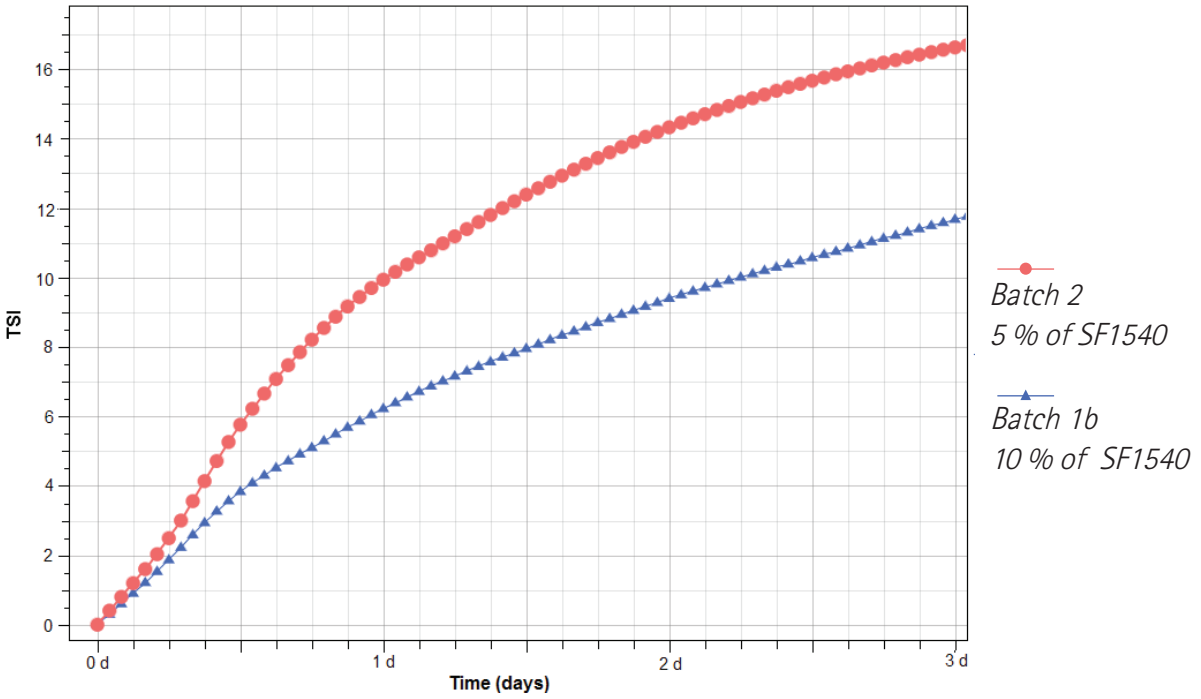

Figure 3 – Destabilisation kinectic profiles of batch 2 containing 5 % of SF1540 (red curve) and of batch 1b containing 10 % of SF1540 (blue curve)

*This demonstrates that to maintain stable maltodextrin nanoparticles in silicone medium, it is necessary to work with equal or higher concentrations of solids. Therefore, it enabled to identify that the most stable formulation to produce the maltodextrin polymeric colloidal nanocarriers dispersed in silicone correspond to batch 2 showed in **Table 1** which contains the proportions: 5 % of maltodextrin (w/w), 4 % (w/w) of Poloxamer, 0.4 % (w/w) of NaCl and 10 % (w/w) of emulsifier.*

*In turn, the system with 10 % of SF1540 (batch 1a and batch 1b) showed an uniform size distribution of particles smaller than the system with 5 % of SF1540 (batch 2). The particle size distribution of batch 1b has been shown in **Figure 4** with a mean diameter of 281 nm and polidispersity index of 0.07.*

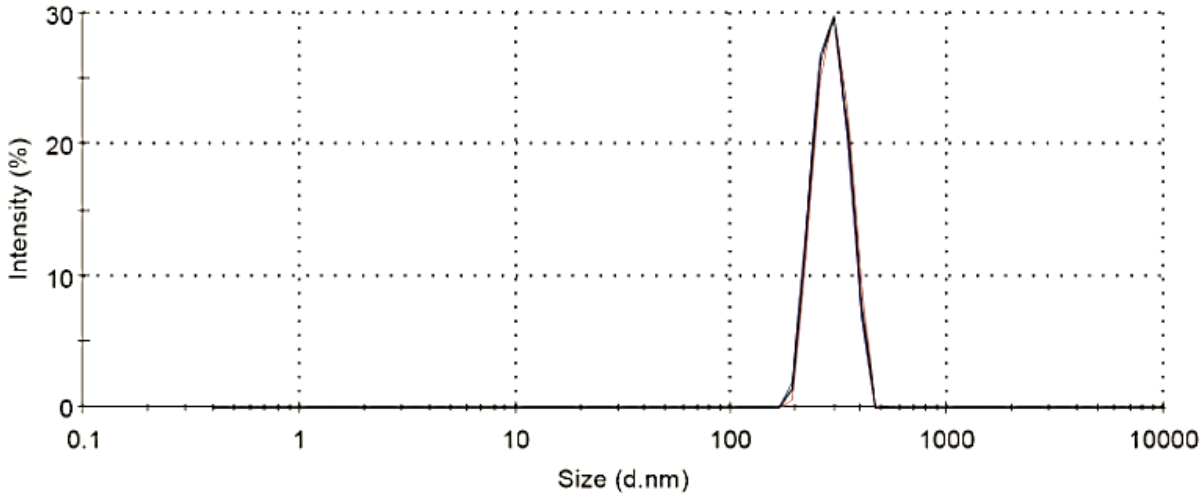

Figure 4 – Particle size distribution of maltodextrin PCN (sample corresponding to batch 1b shown in Table 1).

The batch-1b photomicrograph shown in ***Figure 5*** *indicates that the PCN are represented by nearly spherical nanostructures with smooth and regular surfaces. The image also depicts that the particle size distribution is homogeneous and the average size operates in the sub-micron range.*

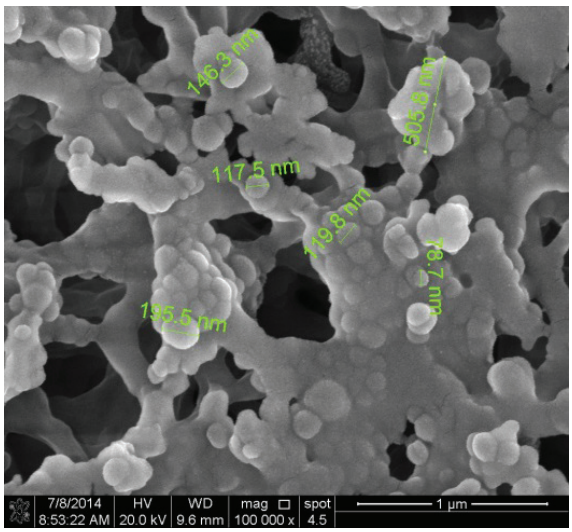

Figure 5 – SEM-FEG image of maltodextrin PCN demonstrating the spherical morphology.

5 Conclusion

This study demonstrated that it is possible to obtain polymeric colloidal nanocarrier systems based on maltodextrin dispersed in silicone with improved physical stability using a surfactant concentration equal or higher than solid contents.

Moreover this work showed that a formulation containing 5 % of maltodextrin, 4 % of Poloxamer, 0.4 % of salt and 10 % of SF1540 was suitable for obtaining maltodextrin polymeric colloidal nanocarriers dispersed in silicone with particle size smaller than 300 nm and polidispersity index less than 0.2.

These nanocarriers emerge as a versatile system to encapsulate different hydrosoluble drugs. Furthermore, an important point to emphasize is that the technique does not require organic solvents as the previously described techniques. Moreover, the proposal of using silicone as the external phase seems to be advantageous because this material has interesting properties as low surface tension and low adherence which confer high spreadability over substrates, for example, the skin. Furthermore, silicone is physiologically inert making it an alternative material to be used as an external phase in the anhydrous nanosuspensions which can be used to develop novel oral or topical drug delivery systems.

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