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Emulsified systems based on glyceryl monostearate and potassium cetyl phosphate: Scale-up and characterization of physical properties

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ABSTRACT

Introducing a pharmaceutical product on the market involves several stages of research. The scale-up stage comprises the integration of previous phases of development and their integration. This phase is extremely important since many process limitations which do not appear on the small scale become significant on the transposition to a large one. Since scientific literature presents only a few reports about the characterization of emulsified systems involving their scaling-up, this research work aimed at evaluating physical properties of non-ionic and anionic emulsions during their manufacturing phases: laboratory stage and scale-up. Prototype non-ionic (glyceryl monostearate) and anionic (potassium cetyl phosphate) emulsified systems had the physical properties by the determination of the droplet size ($D[4,3]$, μm) and rheology profile. Transposition occurred from a batch of 500–50,000 g. Semi-industrial manufacturing involved distinct conditions: intensity of agitation and homogenization. Comparing the non-ionic and anionic systems, it was observed that anionic emulsifiers generated systems with smaller droplet size and higher viscosity in laboratory scale. Besides that, for the concentrations tested, augmentation of the glyceryl monostearate emulsifier content provided formulations with better physical characteristics. For systems with potassium cetyl phosphate, droplet size increased with the elevation of the emulsifier concentration, suggesting inadequate stability. The scale-up provoked more significant alterations on the rheological profile and droplet size on the anionic systems than the non-ionic.

1. Introduction

Introducing a pharmaceutical product on the market involves several stages of research. During the development, a series of refinements in the formulation is achieved progressively, including manufacturing processes. The scale-up stage comprises the integration of previous phases of development and their integration, as well as the transfer of technology to fabricate a given product. This phase is extremely important since many process limitations which do not appear on the small scale become significant on the transposition to a large one. In practice, the transition from a laboratory to a plant system is not direct, and the product is usually manufactured on intermediate scales (Galindo-Rodríguez et al., 2005). Among the aspects that should be studied to obtain a successful scale-up, the following ones deserve particular attention: definition of the critical parameters of the process; identification of the requirement of high temperatures, pressure or any other exceptional condition; level of the process innovation; operational difficulties; and identification of differentiated equipment necessity (Santoro, 2006).

Although emulsified systems have been extensively used as pharmaceutical dosage forms, their introduction into the market is likely to be delayed because of their property to possess a case-by-case profile due to the intrinsic instability as a vehicle (Galindo-Rodríguez et al., 2005; Baby et al., 2007).

Emulsions are thermodynamically unstable systems formed by a mixture of two immiscible liquid phases and a third phase named emulsifier (Gennaro, 2000; Ansel et al., 2000; Lou et al., 2001). These emulsifiers can be classified according to their predominant chemical charge as: non-ionic, anionic, cationic and amphoteric. Independently on the molecule charge in water dispersion, each

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emulsifier has particular mechanisms to stabilize emulsion systems (Korhonen, 2004).

The main reason for using emulsified systems is to improve patient's compliance to a given therapy. Topical emulsions are easily applied over the skin, they may be simply washed, and, as a vehicle, emulsions are able to reduce intrinsic irritancy of several active substances. In addition, sensorial and viscosity properties are conveniently adjusted (Ansel et al., 2000; Lachman et al., 2001). Emulsified systems are of great potential to the development of systems capable of protecting actives sensible to light and/or hydrolysis and to provide controlled release of such actives (Gennaro, 2000).

The stability of emulsions depends on their physicochemical characteristics, such as droplet size, rheological characteristics, conductibility, interlamellar and free water distribution, behavior under centrifugation and different temperatures, amongst others (Welin and Bergenstahl, 2000; Tadros, 2004).

Since scientific literature presents only a few reports about the characterization of emulsified systems involving their scaling-up, this research work aimed at evaluating physical properties of non-ionic and anionic emulsions by determination of droplet size distribution and rheology during their manufacturing phases: laboratory stage and scale-up.

2. Experimental

2.1. Materials

Formulations were developed with the following raw materials: dibutyl adipate (Henkel/Cognis), glyceryl monostearate (Cognis), purified water, cetyl alcohol (Sasol), xantham gum (Jungbuzlauer), methylparaben (San Fu Chemical), propylparaben (San Fu Chemical), mineral oil (EMCA), potassium cetyl phosphate (BASF), glycerin (Brenntag), isopropyl palmitate (Croda) and, caprylic/capric triglyceride (Cognis). Raw materials were of pharmaceutical grade and they were obtained from commercial sources, used without any further purification.

2.2. Prototype formulations

The prototype formulations possessed identical qualitative and quantitative compositions, presented in Tables 1 and 2, except the emulsifiers and their concentrations. All other raw materials were maintained unaltered in order to minimize possible interferences during the processes and were used as received without any further purification.

2.3. Laboratory production stage

Formulations were prepared heating both aqueous and oil phases up to 75 °C. At 75 °C, the oil phase was transferred to the aqueous phase under continuous agitation (1000 rpm–mechanical agitator IKA® RW 20 D2W equipped with dissolver stirrer/propeller). After 10 min of mixing, emulsions were cooled down until reach room temperature of 25 ± 1 °C at the speed of 850 rpm. The batches were 500.0 g each, using always the same capacity beaker.

Table 1
Non-ionic prototype formulations (N)

Component	N3 (w/w%)	N5 (w/w%)	N7 (w/w%)
Xantham gum	0.50	0.50	0.50
Glycerin	10.00	10.00	10.00
Cetyl alcohol	3.00	3.00	3.00
Glyceryl monostearate	3.00	5.00	7.00
Caprylic/capric triglyceride	10.00	10.00	10.00
Methylparaben	0.20	0.20	0.20
Propylparaben	0.10	0.10	0.10
Purified water	73.20	71.20	69.20

Table 2
Anionic prototype formulations (A)

Component	A3 (w/w%)	A5 (w/w%)	A7 (w/w%)
Xantham gum	0.50	0.50	0.50
Glycerin	10.00	10.00	10.00
Cetyl alcohol	3.00	3.00	3.00
Potassium cetyl phosphate	3.00	5.00	7.00
Caprylic/capric triglyceride	10.00	10.00	10.00
Methylparaben	0.20	0.20	0.20
Propylparaben	0.10	0.10	0.10
Purified water	73.20	71.20	69.20

2.4. Transposition stage: scale-up

Batches of 50,000 g were obtained with Becomix® RW 60CD industrial reactor equipped with anchor-type propeller. The process variables were the agitation intensity of emulsification and the homogenization during cooling down, as described: (1) agitation during emulsification and cooling down—1.0 and 2.0 mm/s; (2) homogenization during emulsification and cooling down—8.0 and 21.0 m/s. The prototype formulations selected to scaling-up were those obtained with 5.0% glyceryl monostearate (non-ionic, N5) and 3.0% potassium cetyl phosphate (anionic, A3), in agreement with the results. Conditions of heating and time are described in Section 2.3.

2.5. Droplet size

For the droplet size evaluation, a laser diffraction Mastersizer Microplus (Malvern Instruments) equipment was used. For the measurement, 500 mL of purified water was added to a 600 mL beaker. The probe speed was set 2000 rpm and sample was slowly added until the obscuration achievement of 10–30%. After reaching obscuration level, sample was analyzed and the values recorded. All measurements were performed twice and the mean values of $D[4,3]$ (μm), mean size in function of sample volume, were statically analyzed (ANOVA) to verify meaningful changes among formulations and processes.

2.6. Rheology

Rheology measurements were performed using a Rheometer® AR 550 (TA Instruments), with stainless steel cone geometry with 60 mm of diameter and angulations of 1:59:19. For the non-ionic systems, the equipment was set with a shear stress of 1–22 Pa, in a flow model, and 22 sampling points during 2 min at 25 ± 1 °C and, after reaching a shear stress of 22 Pa, it was reduced up to 1 Pa in 2 min with another 22 points of sampling.

For the anionic systems, the equipment was set with a shear stress of 4–100 Pa, in a flow model, and 22 sampling points during 2 min at 25 ± 1 °C and, after reaching shear stress of 100 Pa, it was reduced to 4 Pa in 2 min with another 22 points of sampling.

Enough sample was used so that the whole cone was filled. The shear rate and apparent viscosity were measured in duplicate. The viscosity values were analyzed for meaningful changes using variance analysis (ANOVA).

Table 3
Droplet size distribution of non-ionic emulsions (N) 48 h after preparation

Formulations	10% of the droplets (μm)	50% of the droplets (μm)	90% of the droplets (μm)	Average *D*[4,3] (μm)
N3	1.89	41.10	92.66	44.95
N5	0.74	16.38	50.28	21.45*
N7	0.59	14.70	38.80	17.47*

*Values with $P < 0.05$ when compared to standard formulation by ANOVA. Average *D*[4,3] (μm) = average diameter based on the average volume of the droplets distribution. N3–N7 are the emulsified non-ionic systems.

Table 4
Droplet size distribution of anionic emulsions (A) 48 h after preparation

Formulations	10% of the droplets (μm)	50% of the droplets (μm)	90% of the droplets (μm)	Average *D*[4,3] (μm)
A3	0.89	1.65	3.85	2.06
A5	0.82	1.60	4.89	2.28*
A7	0.74	6.64	63.57	22.95*

*Values with $P < 0.05$ when compared to standard formulation by ANOVA. Average *D*[4,3] (μm) = average diameter calculated based on the average volume of the droplets distribution. A3–A7 are the emulsified anionic systems.

Table 5
Mean viscosity ($n = 2$) and standard deviation of non-ionic anionic emulsions calculated by Herschel-Buckley model

Formulation	Mean viscosity (Pa s)
N3	2.493
N5	3.329*
N7	3.668

*Values with $P < 0.05$ mean statistical difference (ANOVA). N3–N7 are the emulsified non-ionic systems.

Table 6
Mean viscosity ($n = 2$) and standard deviation of anionic emulsions (A) calculated by Herschel-Buckley model

Formulation	Mean viscosity (Pa s)
A3	6.614
A5	7.665*
A7	5.529*

*Values with $P < 0.05$ mean statistical deference (ANOVA). A3–A7 are the emulsified anionic systems.

3. Results and discussion

It is known that problems associated with costs and time consuming of industrial processes may be avoided if key-parameters are previously studied. Industrial processes are usually designed through gradual increase of the manufactured batch size. Basically, the idea is to simulate production as much as possible and to optimize the operating parameters before large-volume work is performed. Scale-up might be translated as the production planning of a new process where it is demonstrated in smaller scale, through experimental tests, how the satisfactory final product could be achieved (Galindo-Rodríguez et al., 2005; Santoro, 2006).

Measuring assessments to determine droplet size in disperse systems, as emulsions, may be performed by several techniques. Experimental limitations should be carefully examined prior to the selection of a method. Uncertain results could be obtained when methodology requires sample dilution or inferior/superior detection limits are not taken into consideration (Washington, 1992; Alba et al., 1999). For the non-ionic systems, the formulations with high emulsifier concentration produced emulsions with statistically smaller droplet size. On the other hand, the anionic formulations behaved differently. Tables 3 and 4 show the distribution results of the droplet size.

The average *D*[4,3] (μm) droplet size distribution for the non-ionic formulations were respectively 44.95, 21.45 and 17.47 μm for N3, N5 and N7. In the case of anionic emulsions (potassium cetyl phosphate), the values were different, being respectively 2.06, 2.28 and 22.95 μm for A3, A5 and A7 systems.

Droplet size of non-ionic emulsions had a significant decrease when the concentration of emulsifier was increased (Table 3). This result was related to what was found by Chanana and Sheth (1995). These authors had observed that the increase of emulsi-

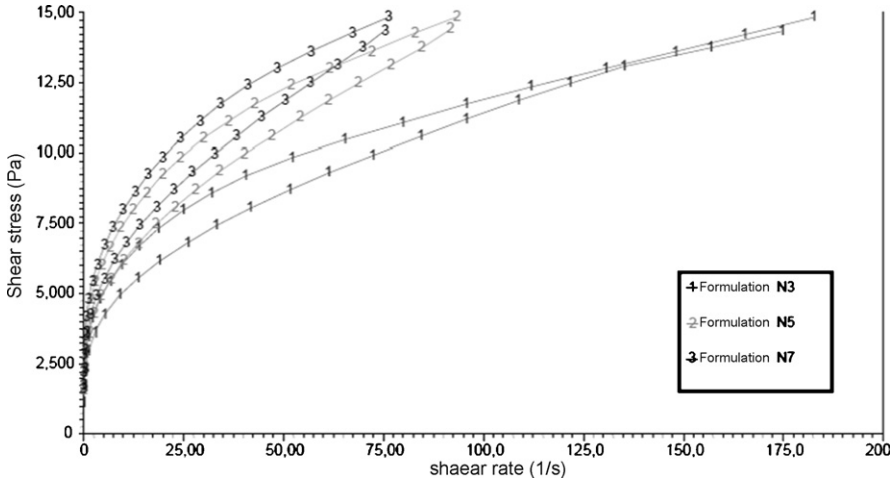

Fig. 1. Rheological behavior of non-ionic emulsions (N) with different emulsifier concentration (glyceryl monostearate) 48 h after preparation.

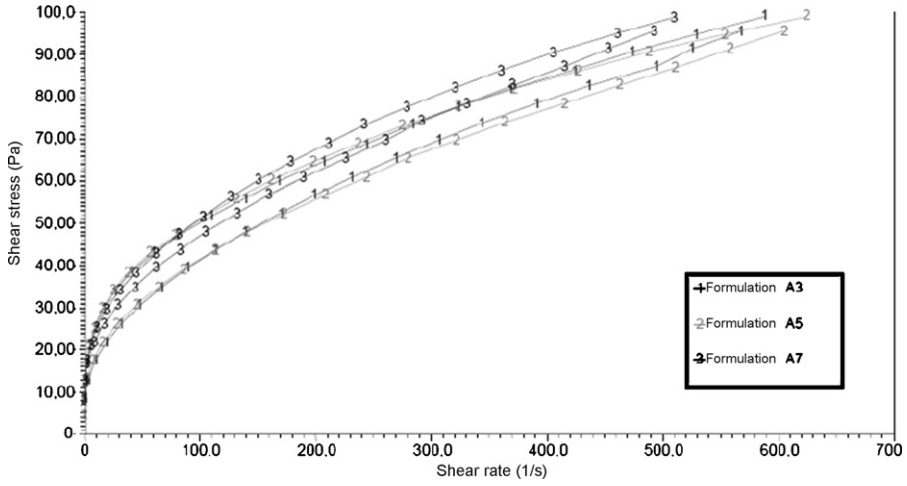

Fig. 2. Rheological behavior of anionic emulsions (A) with different emulsifier concentration (potassium cetyl phosphate) 48 h after preparation.

fier concentration produced decrease in the droplet size of the emulsions constituted of water, glycerin, propylene glycol, soy oil and non-ionic emulsifiers (Tween® 80 and Span® 80). Such results demonstrated that the formulation with the highest concentration of emulsifiers presented better physical stability since smaller values of droplet size suggest and infer better stability (Roland et al., 2003).

The mean viscosity values are presented in Tables 5 and 6. Both systems, anionic and non-ionic, had shear thinning flow behavior as showed in Figs. 1 and 2. Formulation N7 presented the highest mean viscosity value using Herschel-Buckley model (Tadros, 2004). The highest viscosity is related to superior resistance to shear stress, benefiting the stability of the system. The results were in agreement with those obtained by Korhonen et al. (2000). Comparing the non-ionic and anionic systems, it was verified that anionic emulsifiers produce, in general, systems with smaller size of droplets, thus, with high viscosity which is considered as an important result to obtain the desired final product attributes.

The increase of emulsifier concentration for anionic systems changed the droplet size distribution from monomodal to multimodal forms. This can be verified analyzing the two separate peaks formed with the highest emulsifier concentration. According to Thanasukarn et al. (2004), the presence of a separate peak at a higher droplet size region could mean partial coalescence, influencing negatively on the stability of the systems.

Rheological assessment allows the identification of instability signs related to the physical stress proportioned over emulsified systems and it is also able to establish a correlation of shear exposure and destabilization of emulsions (Tadros, 2004; Santoro, 2006; Fischer et al., 2007). The rheology data showed that the increase in droplet size caused the decrease of mean viscosity, interfering with the stability of the systems.

The influences of scaling-up and agitation velocity were also evaluated by means of physical properties of the systems. When comparing the semi-industrial produced emulsions (50,000 g) with those obtained in laboratory scale, formulations N5 and A3 were selected. Concerning agitation, its design must be considerate as a critical point. Several kinds of flux systems are obtained depending of the agitation system shape (Realdon et al., 2002).

Regarding the rheological analysis of the non-ionic systems, it was verified that agitation velocity and homogenization at low intensities permitted the production of emulsions with rheological characteristics similar to those produced in laboratory scale. In contrast, the increase in agitation velocity and homogenization caused an augment of, approximately, 206% on the mean viscosity of the non-ionic formulations obtained after the scale-up. The increase in viscosity was related with the droplet size that usually decreases when the elevation of the agitation velocity and homogenization occurs during the process (Roland et al., 2003). In addition, higher viscosity values may be explained as a result of mutually bind of the hydrophilic portions of the emulsifiers at the droplet surface that would hold together the coarse droplets in a structure in which their movement could be hindered by the same volume (Realdon et al., 2002).

For the anionic systems after scaling-up, the parameters evaluated were statistically significant. An alteration on the rheological profile was observed, thus obtaining viscosity mean values higher than those anionic emulsions prepared in laboratory scale. With the increase in agitation velocity and homogenization there was a decrease in viscosity. In relation to droplet size, the scale-up caused a size increase, suggesting a loss of physical stability (Lashmar et al., 1995). According to the mentioned reference, the main factor that interferes on physicochemical properties of emulsions obtained in semi-industrial scale is the homogenization power, since mechanical manufacturing conditions give rise to different viscosities (Realdon et al., 2002).

4. Conclusion

Comparing the non-ionic and anionic systems, it was noticed that anionic emulsifiers generated systems with smaller droplet size and higher viscosity on the laboratory scale. Besides that, for the concentrations tested, the augmentation of the glyceryl monostearate emulsifier content provided formulations with better physical characteristics. For systems with potassium cetyl phosphate, the droplet size increased with the elevation of the emulsifier concentration, that points toward inadequate stability. Transposition allowed revealing how technological process of preparation of emulsions could have quite a significant influence on physical characteristics of the product (Realdon et al., 2002). The scale-up provoked more significant alterations on the rheological profile and droplet size on the anionic systems than the non-ionic. Moreover, it was observed that a scale-up procedure must be designed in relation to a well prepared technical transfer to assure product quality, overall reduction of costs and timely accomplishment of market readiness (Galindo-Rodríguez et al., 2005).

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