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Note

Influence of a lipophilic drug on the stability of emulsions: An important approach on the development of lipidic carriers

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Abstract

The aim of this work was to investigate the influence of a lipophilic drug, Ibuprofen, on the stability of o/w emulsions. Five formulations were prepared by the phase inversion temperature (PIT) method, and Ibuprofen was incorporated into their oil phase. Emulsion stability was evaluated by short- and long-term studies. Concerning the former, stability under centrifugation showed an improved profile for Ibuprofen-loaded emulsions. The latter confirmed such findings. In conclusion, a rather resistant interfacial film may take place when Ibuprofen was incorporated into the emulsions. Therefore, the critical hydrophilic–lipophilic-balance (HLB) of o/w emulsions can be affected by a lipophilic drug into their oil phase. Such approach is of great importance on the development of lipid carriers for therapeutic drug targeting.

Keywords: Emulsions; HLB; Stability; Lipophilic drugs; Ibuprofen

Emulsion formulation requires thorough studies in order to check the most important parameters to prepare stable emulsified products. A parameter of utmost importance in the development of pharmaceutical emulsions is their HLB. The presence of an additional component in the emulsion can considerably damage its behavior (Washington, 1996). Therefore, the aim of this work was to investigate the influence of a lipophilic drug, using Ibuprofen as model, on the stability of o/w emulsions and, consequently, on its critical HLB.

Five formulations (Table 1) were prepared by PIT method (Morales et al., 2003) using Tween 20 and Span 80 (Sigma, USA), Miglyol 812 (Condea, USA), and Ibuprofen (Euresian, India). This drug was dissolved in Miglyol 812 by ultrasonication for 15 min. Span 80 was melted into this mixture to produce the oil phase and Tween 20 was melted in distilled water, resulting in the water phase. Both phases were heated separately to 70 °C and then inter-dispersed. Final emulsions were obtained after homogenization with an IKA Ultra-Turrax T-25 at 16,000 rpm for 10 min.

Visual aspect was evaluated under two storage conditions (25 °C ± 2 and 4 °C ± 2). The creaming was followed by the measurement of the creaming index (CI) (Onunkwo and Adikwu, 1997). Particle size distributions of emulsions were examined using a laser scattering analyzer. The results were reported as X_{10}, X_{50} and X_{90}, being the droplet diameter for the 10th, 50th and 90th cumulative volume percentiles. The pH and the viscosity of the formulations were also analyzed. Accelerated stability test was performed as previously reported (Formiga et al., 2006).

The critical HLB of the Miglyol 812 is 15.367 (Macedo et al., 2006). The influence of Ibuprofen on such oil phase was evaluated in order to determine changes on the stability profile.

All systems were fluid emulsions with milky white appearance and with no indication of instability. This visual aspect did not present remarkable changes along 120 storage days, and the effect of the drug on the CI of the formulations was not considerable (results not shown).

The pH curves were very similar for all formulations (Fig. 1). A reasonable explanation for the tendency of pH dropping values

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Table 1
Composition of the emulsions (amounts in g)

Components	F0	F1	F2	F3	F4	F5
Oil phase						
Miglyol 812	5.0	5.0	5.0	5.0	5.0	5.0
Span 80	0.215	0.215	0.215	0.215	0.215	0.215
Ibuprofen	–	0.1	0.2	0.3	0.4	0.5
Water phase						
Tween 20	1.785	1.785	1.785	1.785	1.785	1.785
Distilled water q. s. ad	100.0	100.0	100.0	100.0	100.0	100.0

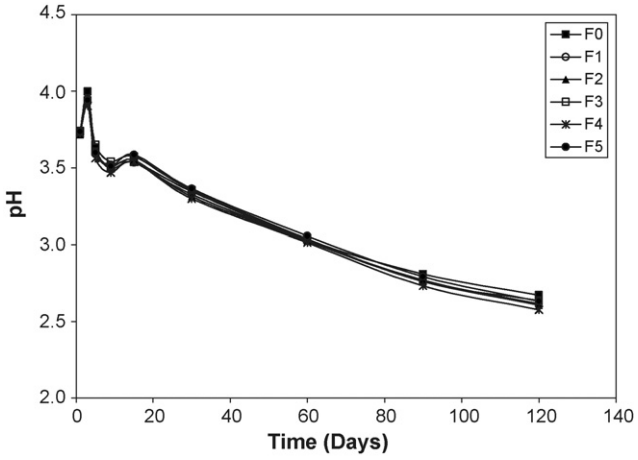

Fig. 1. pH evolution of the formulations stored at 25 °C ± 2 for 120 days.

would be a possible degradation of the capric and caprylic acids, components of Miglyol 812. This is very common in emulsified systems containing emulsified agent, and can be attributed to their degradation, which generate fatty acids by partial hydrolysis (Tabosa do Egito et al., 1994).

According to the droplet size results, it was smaller in F4 and F5 (Table 2). Since it is determined by the surfactant-to-oil weight ratio (Fernandez et al., 2004), these results suggest a surfactant property of Ibuprofen on the o/w interface, regarding the amphiphilic character of its molecular structure (Fig. 2) and its accumulation at the o/w interface (Ridell et al., 1999). Thereby, the Ibuprofen incorporation into the oil phase led to an additional input of surfactant at the o/w interface, resulting in breaking the droplets into smaller ones. Although the influence of Ibuprofen on droplet size was quite important, its effect on CI was less than expected considering non-accelerated studies. This is a contradictory effect taking into account the low viscosity of the emulsion. However, centrifugation data, which is more accurate (Tadros, 2004), clearly demonstrated the effect of the drug in reducing the CI.

Table 2
Results of the droplet size analysis and viscosity measurements

	F0	F1	F2	F3	F4	F5
Droplet size analysis (μm)						
X_{10}[a]	1.12	1.03	0.92	0.97	0.75	0.74
X_{50}[a]	2.66	2.45	2.15	2.29	1.72	1.77
X_{90}[a]	5.69	5.41	4.56	4.91	3.69	3.93
Viscosity for 100 s^{-1} (mPas)	1.37	1.22	1.30	1.38	1.37	1.43

[a] X_{10}, X_{50} and X_{90} droplet diameter for the 10th, 50th and 90th cumulative volume percentiles.

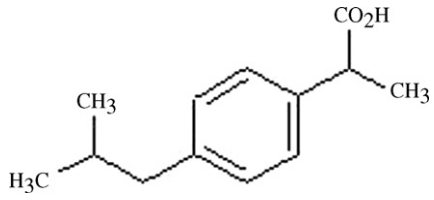

Fig. 2. Molecular structure of Ibuprofen.

The centrifugal stress was used in order to investigate the resistance of Ibuprofen-loaded emulsions to different speeds of rotation (Fig. 3). At all speeds, F4 and F5 showed the lowest creaming rates. This indicates that when Ibuprofen is added into emulsions, not only the droplet size is reduced, but also their resistance to centrifugation is enhanced. The reason for this behavior could be the influence of Ibuprofen in the molecular association between Span 80 and Tween 20. It was reported that Ibuprofen presents a terminal carboxyl group that may interact by hydrogen bonds with the nonionic surfactants head groups (Rangel-Yagui et al., 2005). As the nonpolar region of the drug lies into oil droplet, Ibuprofen would enhance the van der Waals forces between the hydrocarbon chains of Span 80 and Tween 20. Therefore, the drug could work as an additional surfactant, and a close-packed film composed by Span 80, Tween 20 and Ibuprofen would take place. An optimization of the critical HLB is expected.

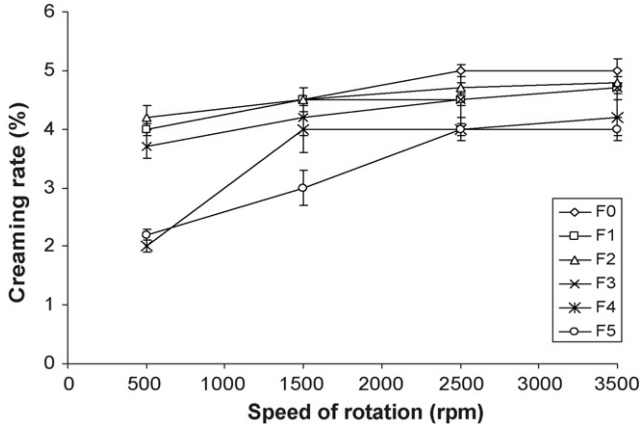

Fig. 3. Stability under centrifugation.

The addition of a lipophilic or amphiphilic agent in a submicronic emulsion can lead to an important physicochemical change on its behavior. Sometimes, this procedure can induce an increase on the stability of the emulsion, as observed in this study. In conclusion, the incorporation of active agents into such carrier demands a careful evaluation of physicochemical parameters, which play an important role in its bioavailability.

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