1. Introduction

Silicone polymers (e.g. poly(dimethyl siloxane) and derivatives) are the only class of hybrid organic/inorganic polymers having wide range of applications in pharmaceutical and cosmetic products due to their unique properties such as high lubricity, non-toxicity, excessive spreading, and film formation. Because most of silicone compounds are water-insoluble, they are delivered in aqueous disperse systems such as conventional emulsions, microemulsions, nanoemulsions, etc.

Until now silicone emulsions are prepared by different methods like homogenization, ultrasonication, and mechanical agitation. Silicone emulsions obtained by these methods show broad size distributions which cause large drops and a fast phase separation during storage [1].

In order to increase the stability of the silicone emulsions, diverse emulsifiers have been used: nonionic [2], ionic [3], silicone type [4], polymers [5], biopolymers [6], stabilizers [7], electrolyte suspensions [8], etc. However, it still remains the stability problem. On the other hand, in several cases high amounts of emulsifiers [9] or emulsifying alkyl derivatives are used [10] which is not recommended for personal care applications. Thus they can produce dryness in hair and skin, irritation, inflammation and allergic reactions [11], furthermore to its significant impact on environmental pollution [12].

The emulsification-diffusion method to prepare nanoparticles or nanoemulsions was proposed by Quintanar-Guerrero et al [13]. This process involves the emulsification of a partially water-miscible solvent (previously saturated with water), containing an oil (for nanoemulsions), in an aqueous phase (previously saturated with the solvent), containing a stabilizer. The subsequent organic solvent distillation (from the oil-in-water emulsion formed) leads to the formation of nanodroplets in the aqueous phase. This method presents several advantages, such as the use of cosmetically acceptable organic solvents, high reproducibility and easy to scale up [14-15].

The main aim of this investigation is the optimization of the emulsification diffusion method by direct solvent displacement to prepare stable silicone oil nanoemulsions and physicochemical evaluation during storage (mean droplet size, polydispersity index, zeta potential, pH, etc.).
2. Materials and methods

2.1. Materials

Dimethicone 100 cSt (Dimethyl silicone oil®) and Amodimethicone 3500 cSt (Amino silicone oil®) were obtained from KCC (Seul, Korea). Phenyltrimeticone 22.5 cSt and cyclopentasiloxane/Dimethiconol 6000 cSt were purchased from Droguería Cosmopolita (Mexico City, Mexico). Poloxamer 188 (Pluronic® F-68) was obtained from Sigma-Aldrich (St Louis, USA). Ethyl acetate of analytical grade was purchased from Fermont (Monterrey, Mexico). Distilled water was of Milli-Q® quality from Millipore® (Massachusetts, USA). All the other reagents were at least of analytical grade and were used with no additional purification.

2.2. Preparation of silicone oil nanoemulsions

Silicone oil nanoemulsions were prepared using the emulsification-diffusion method involving the direct displacement of solvent by distillation described by Quintanar-Guerrero et al [13]. The organic solvent (ethyl acetate) and distilled water were mutually saturated for 1 min before use, in order to achieve thermodynamic equilibrium of both liquids. Then, 10 g of silicone oil was dissolved in 60 mL of organic solvent (saturated with water), and this organic solution was emulsified with 120 mL of an aqueous solution (saturated with organic solvent) of Pluronic F-68 (1-5 % w/v) using a high-shear stirrer (Ultraturrax®, IKA Labortechnik, T18 Basic, USA) at 3500-15500 rpm for 10 minutes. The oil-in-water emulsion formed was directly placed into a rotavapor (Heidolph Laborota® 4000, Germany) at 70 mm Hg, 30 rpm and 40 °C during 45 minutes. A multilevel factorial experiment design 3² was performed, where stirring rate (3500, 9500 and 15500 rpm) and percentage of emulsifier (1, 3 and 5%) were the evaluated factors.

2.3. Measurement of mean droplet size and droplet size distributions

Mean size and the polydispersity index of silicone oil nanoemulsions were determined by laser light scattering technique (Coulter N4 Plus, USA). Laser light wavelength was 678 nm (He/Ne 10 mW). Measurements were obtained at a 90° fixed-angle for 180 s at 25° C. 50 µL of each system was diluted in 25 mL of deionized water. Measurements were performed three times for all prepared batches.

2.4. Measurement of Zeta Potential (ζ)

Zeta potential was determined using Laser Doppler micro-electrophoresis and phase analysis of light scattering in a Zetasizer® (Malvern Instruments, UK) which employs a He/Ne laser with 633 nm of wavelength and 4mW. An average of 50 runs using ultrapure water as solvent at 25 °C of temperature were executed. Measurements were performed three times for all prepared batches.

2.5. Measurement of pH

The pH of optimized diluted systems (1:10) was measured with a potentiometer (Corning® 340 pH-meter, USA). Measurements were performed three times for all prepared batches.
2.6. Accelerated stability test

Stability studies of optimized silicone oil nanoemulsions were performed by keeping samples at 40 ± 2 °C and 75 ± 5 % of relative humidity. These studies were performed for the period of 3 months. Droplet size and polydispersity index were determined at 0, 1, 2, 3, 4, 8, and 12 weeks. Measurements were performed three times for all prepared batches.

3. Results and discussion

3.1. Preparation of silicone oil nanoemulsions

3.1.1. Optimization of silicone oil nanoemulsions prepared by emulsification-diffusion method

Experiment designs have been widely used in the pharmaceutical and cosmetic industry, in process optimization [16]. In this investigation the experimental design was factorial $3^2 = 9$ individual treatments, with two replicas for a total of 27 treatments. Stirring rate (3500, 9500 and 15500 rpm) and emulsifier percentage (1 to 5 % w/v) were the factors evaluated. Stirring time was kept constant (10 minutes). Table 1 shows the characteristics of prepared silicone systems. Formation of nanoemulsions was explained by Quintanar-Guerrero et al. the method of emulsification-diffusion solvent displacement [14-15].

The droplet size analysis showed that prepared batches in experimental design were in a range of 179.7 ± 2.7 nm to 2673.7 ± 277.7 nm, while polydispersity index values ranged from 0.04 ± 0.01 to 1.04 ± 0.2. Factor’s effects in studied variables were negative, because an increase in the agitation rate or in emulsifier concentration leads to a decreased in droplet size and polydispersity index (variance analysis [ANOVA] $P<0.05$) Figure 1. This behavior can be explained by the fact that the stirring rate is a critical parameter for nanoemulsions formation. It has been reported that emulsification at high stirring rates using a rotor-stator homogenizer can reduce the average droplet size to submicron scale. On the other hand, Poloxamer 188 being a nonionic emulsifier, provides a steric stabilizer effect that avoids aggregation of fine droplets of these nanosystems. Poloxamer hydrophilicity enables it to form oil-in-water emulsions (O/W) and in this case, silicone-in-water emulsions (Si/W) [17-18]. The influence of stirring rate and emulsifier concentration in silicone emulsions was investigated by Mehta et al. and Saadevandi et al [19-20]. They showed that increasing stirring rate, emulsions with narrow size distributions were obtained due to the breaking of large to small droplets, it consequently improves emulsions stability. Also, droplet size and polydispersity index of the emulsions decreases with increasing the emulsifier concentration. However, an excessive increase in emulsifier concentration does not produce significant reduction in droplet diameter [20]. Based on these results, preparation conditions of silicone oil nanoemulsions were chosen as follows: stirring rate: 15500 rpm, stirring time: 10 minutes and percentage of Poloxamer 188: 3% (w/v).
3.1.2. Application of the method of preparation with different silicone oils

Dimethicone 100 cSt emulsions were prepared under preparation conditions established in experimental design but emulsification was conducted by conventional homogenization method in the absence of organic phase and it was compared with dimethicone 100 cSt nanoemulsion obtained by the emulsification-diffusion method at the same preparation conditions. The droplet size distribution of the obtained system by conventional method exhibited broad droplet distribution reflected in polydispersity index of 0.97 ± 0.15 and an average droplet size of 1128.8 ± 467.7 nm. Phase separation was observed after 24 h. In contrast, the obtained system by the emulsification-diffusion method exhibited narrow distribution with polydispersity index of 0.06 ± 0.05 and an average droplet size of 213.4 ± 4.3 nm. The preparation of silicone-in-water emulsions (Si/W) by homogenization with rotor-stator homogenizer was performed by Jasinska et al. obtaining droplet size distributions in the range of 2000 to 10000 nm [21]. These results agree with those we obtained in this work. The formation of nanoemulsions by emulsification-diffusion
method was explained above. With this in mind, it was decided to prepare nanoemulsions with different silicones (dimethicone 100 cSt, amodimethicone 3500 cSt, phenyltrimethicone 22.5 cSt and Dimethiconol 6000 cSt) by the emulsification-diffusion method at set conditions in experimental design.

3.2. Characterization of silicone oil nanoemulsions

Table 1. Physicochemical characterization of silicone oil nanoemulsions.

<table>
<thead>
<tr>
<th>Systems</th>
<th>Mean Droplet Size (nm)</th>
<th>Polydispersity Index</th>
<th>Potential Zeta (mV)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM Dimethicone*</td>
<td>1128.8 ± 467.7</td>
<td>0.97 ± 0.15</td>
<td>**</td>
<td>5.61 ± 0.18</td>
</tr>
<tr>
<td>NE Dimethicone</td>
<td>213.4 ± 4.3</td>
<td>0.06 ± 0.05</td>
<td>-19.4 ± 1.6</td>
<td>5.56 ± 0.09</td>
</tr>
<tr>
<td>NE Amodimethicone</td>
<td>205.2 ± 16.5</td>
<td>0.05 ± 0.06</td>
<td>+40.8 ± 6.1</td>
<td>7.57 ± 0.07</td>
</tr>
<tr>
<td>NE Phenyltrimethicone</td>
<td>215.9 ± 6.6</td>
<td>0.06 ± 0.04</td>
<td>-21.8 ± 2.7</td>
<td>5.88 ± 0.15</td>
</tr>
<tr>
<td>NE Dimethiconol</td>
<td>302.1 ± 15.3</td>
<td>0.16 ± 0.12</td>
<td>-32.4 ± 3.0</td>
<td>5.63 ± 0.14</td>
</tr>
</tbody>
</table>

* Unstable: Phase separation after 24 hours of preparation.
** We can’t determine Zeta Potential.

Figure 2. Droplet size distribution of silicone oil nanoemulsions.

3.2.1. Mean droplet size and droplet size distribution

The average droplet size is a very important control process parameter and particularly in insurance quality, because physical stability of nanoemulsions depends on the average droplet size and distribution [22]. The nanoemulsions of dimethicone, amodimethicone, phenyl trimethicone and dimethiconol showed average droplet sizes of 213.4 ± 4.3 nm, 205.2 ± 16.5 nm, 215.9 ± 6.6 nm and 302.1 ± 15.3 nm respectively. The polydispersity index of the nanoemulsions were; 0.06 ±
0.05, 0.05 ± 0.06, 0.06 ± 0.04 and 0.16 ± 0.12 respectively (Table 1). The highest droplet size and polydispersion index of dimethiconol nanoemulsion can be explained by its higher viscosity compared with the other silicone oils. YoeKura and Kawagauchi et al. investigated the influence of silicone oils viscosity in average droplet size emulsion. Their results showed that the average droplet size increases with increasing of oils viscosities, at higher viscosity is more difficult to break droplets and reduce its size. Therefore silicone oils with high viscosities result in the formation of emulsions with large sized droplets and broad distributions [23-24]. In Figure 2, droplet size distributions of silicone nanoemulsions are observed. These results evidence that nanoemulsions had droplets sizes between 80-500 nm., so that it can be shown that silicone nanoemulsions prepared had nanometric droplet sizes and unimodal monodisperse populations, since their polydispersity index is between 0 and 0.2 [25].

3.2.2. Zeta Potential (\(\zeta\))

The zeta potential is used as an important parameter for characterize the electrostatic interaction between particles in a dispersed system, so the physical stability of the system is determined by the balance between repulsive and attractive forces. Thus, zeta potential is a measure of the magnitude of the repulsive interaction between colloidal particles and therefore an indicator of nanoemulsion stability. Silicone oils droplets get their electrostatic charge through the emulsification process. Nanoemulsions had zeta potential in a range of \([19.4 ± 1.6 - 40.8 ± 6.1]\), this suggests good stability since it is associated to the small size of silicone droplets and to the steric stabilization of the nonionic emulsifier. On the other hand, zeta potential also indicates the nature of the charge gotten by particles in dispersion. Amodimethicone nanoemulsion is the only system that has a positive zeta potential. The amine group in its structure is the responsible for conferring positive charge to the droplet surface. These results agree with those reported by Li et al. and Dussaud et al. who studied the zeta potential of silicone emulsions [26-27].

3.2.3. pH

The pH value of nanoemulsions must be between 5 - 8.0, in order to ensure the correct application over the skin and hair without produce irritation. It was found that the average pH values of all prepared nanoemulsions were in the range of 5.61 - 7.57 which is acceptable for cosmetics products [28].

3.3. Stability of silicone oil nanoemulsions

Emulsions and nanoemulsions are thermodynamically unstable dispersed systems composed by at least two immiscible liquids. These are systems out of equilibrium, so they are stabilized with emulsifiers and their properties depend on many factors (nature of components, preparation methods, temperature, etc.). The accelerated stability aims to provide data to predict product stability, lifetime and formulation compatibility with packaging material [29]. This study is important to check if the nanoemulsions prepared are able to endure high temperatures to determine their physical stability. The integrity of nanoemulsions was studied after being submitted to accelerated stability study at conditions described in experimental section. The
obtained results are shown in Figure 3, where it shows that nanoemulsions do not have a statistically significant modification in droplet size and polydispersity index (ANOVA, P>0.05). What we can conclude is that the prepared silicone oil nanoemulsions are kinetically stable showing no significant changes after being submitted to stability study.

Figure 3. Influence of set storage conditions in accelerated stability study: on the average droplet size a) and polydispersity index b) of the prepared silicone oil nanoemulsions.
4. Conclusions

In this investigation, it was possible to obtain silicone emulsions of different kind of poly (dimethyl siloxane) and its derivatives by emulsification-diffusion method by direct displacement with nanometer droplet size and narrow distributions, as well as they was kinetically stable, due to their physical properties and excellent stability, this method can have important Implications in the development of skin care and hair care products.

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Disclosure

The authors report no conflicts of interest in this work.

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