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Formulation of a eugenol-based O/W emulsion for application as a topical and oral anesthetic by low-energy emulsification

Formulación de una emulsión O/W a base de eugenol para su aplicación como anestésico tópico y oral por emulsionacion de baja energía

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Abstract

Emulsions are systems formed by two immiscible liquids, one of which is dispersed in the other as droplets with relative stability. These have multiple applications, among them, in the formulation of pharmaceutical and cosmetic products. Its preparation requires generating a large interfacial area, which is usually attained by using the physicochemical formulation know-how on surfactant-oil-water (SOW) systems. Among the applications in the pharmaceutical industry, topical creams, and emulsions for intravenous and for oral administration can be found. Eugenol can be extracted from cloves (Syzygium aromaticum) by various methods, including steam distillation, hydrodistillation and Soxhlet extraction. Furthermore, emulsions based on eugenol can be obtained for a variety of applications, including as topical and oral anesthetic. Nanoemulsions can be formulated with a mixture of nonionic surfactants Span 20/Tween 80 at an HLB of 11 to 13 and a total surfactant concentration of 4%, using the dilution phase transition method (so-called spontaneous emulsification) to attain stable O/W eugenol-based emulsions. Paraffin oil/eugenol ratio of 4/1 can be used to reach a final emulsion internal oil phase content of 10% with 4% surfactant and 86% aqueous phase. Different polymers are used as viscosifying agents, including carboxymethylcellulose. Under these conditions, eugenol-based emulsions with an average droplet size of less than 2 μm can be attained, with topical and oral anesthetic characteristics.

Keywords: Eugenol, emulsion, formulation, nonionic surfactant, low energy, HLB

Resumen

Las emulsiones son sistemas formados por dos fases, una de las cuales se encuentra dispersa en la otra en forma de gotas. Éstas tienen múltiples aplicaciones, entre ellas, en la formulación de productos farmacéuticos y cosméticos. Su preparación requiere la generación de una gran área interfacial, la cual se obtiene haciendo uso del saber-hacer de formulación fisicoquímica de sistemas surfactante-aceite-agua. Entre las aplicaciones en la industria farmacéutica resaltan: cremas tópicas para la aplicación de fármacos, emulsiones para administración intravenosa y emulsiones para administración de medicamentos vía oral. En este trabajo se obtienen emulsiones a base de eugenol para ser utilizadas como anestésico tópico y bucal. El eugenol fue extraído del clavo de olor (Syzygium aromaticum) por diversos métodos, entre ellos, destilación por arrastre con vapor, hidrodestilación y extracción Soxhlet. Las emulsiones fueron preparadas con una mezcla de surfactantes no iónicos Span 20/Tween 80 a un HLB de 11 a 13 y a una concentración total de surfactante de 4%, utilizando el método de transición de fases por dilución. Este método es generalmente usado para obtener nanoemulsiones. La relación aceite de parafina/eugenol fue de 4/1 para alcanzar un contenido de fase interna final de la emulsión de 10% con un 4% de surfactante y 86% de fase acuosa. El polímero utilizado como viscosante fue carboximetilcelulosa. En estas condiciones, se logró obtener una emulsión con tamaño de gota promedio menor a 2 μm, con características de anestésico local tópico y bucal, utilizando un componente activo natura, el eugenol.

Palabras clave: Eugenol, emulsión, formulación, surfactante no iónico, baja energía, HLB

1 Introduction

Nanoemulsions are non-equilibrated dispersed systems of two immiscible liquids with submicron droplet size (Forgiarini et al., 2001b, Komaiko y McClements 2015). Most of the systems formulated to produce nanoemulsions are multicomponent systems (Bullón et al., 2007, 2021, Salager et al., 2020). Therefore, due to the partitioning phenomenon of surfactant species, it is possible to modify the interfacial composition during the emulsification process through the change of water and oil ratios (Márquez et al., 2002, Márquez et al., 2008, Salager, et al., 2000, Salager et al., 2004). This is the principle of the emulsification method initially called emulsion inversion point (EIP) described by Marszall (1976), used by Lin (1978), and improved by Sagitani (1981). The method to obtain nanoemulsions of the oil-in-water (O/W) type consists of adding water to a dispersion formed by the oil and the surfactant mixture until the final submicron emulsion is attained. The importance of microemulsions and/or lamellar liquid crystals phases for nanoemulsions formation through a phase-dilution inversion method (also called spontaneous emulsification) has been discussed in previous work (Forgiarini et al., 2001a, López-Montilla et al., 2002, Márquez et al., 2008). The generation of these structures, such as microemulsions or liquid crystals in surfactant-oil-water (SOW) systems, depends on the physicochemical formulation, and mainly, on the surfactant formulation parameter, which can be expressed as HLB or also as SCP or sigma (Forgiarini et al., 2021, Salager et al., 2020).

Bullón et al. (2007) and Marquez et al. (2008) obtained soybean oil emulsions in water stabilized by emulsifiers such as ethoxylated and non-ethoxylated sorbitan esters and lecithin using the dilution phase transition method. In both cases, the presence of lamellar liquid crystals was observed. These microstructures make it possible to obtain emulsions of submicron droplet sizes after phase transitions during dilution (Forgiarini et al., 2001a, Márquez et al., 2008).

The elaboration of micro or nanostructured products in the pharmaceutical field is crucial because they have a large interfacial area and can be used to control active ingredients, such as those present in natural oils (Bullón et al., 2021, McClements y Rao 2011, Ostertag et al., 2012). Eugenol is an essential oil present in cloves *(Syzygium aromaticum).* About 80.7% of clove essential oil is composed of eugenol. In addition, it contains other compounds such as eugenol acetate (14.8%), ß-caryophyllene (4.1%), and oleanolic triterpene acid (3.2%). The extraction of eugenol is carried out through different separation methods. Among them, the most used are steam distillation, hydrodistillation, and Soxhlet extraction (Just et al., 2016, Khalil et al., 2017). This is used clinically as a local anesthetic and antiseptic, specifically in treating periodontal diseases, due to its antiseptic and anti-inflammatory action (Ahmad et al., 2019, Pramod et al., 2016). It has proven antimicrobial properties against a wide spectrum of bacteria (Ali et al., 2005, Marchese et al., 2017). Although its application is common, eugenol can cause causing caustic injuries or superficial burns when placed directly and in high concentrations in the soft tissues. Pure Eugenol at concentrations greater than 10^{-4} mmol/mL (> 600 mg/ml) inhibits cell migration. It modifies the synthesis of prostaglandins, which affects cellular respiration, mitochondrial activity, and produces severe changes in the enzymatic activity of the cell membrane (Aburel et al., 2021, Gerosa et al., 1996). For this reason, various vehicles have been used for their application (Ahmad et al., 2019).

In this study, eugenol is used as an active ingredient in the formulation of an emulsion with topical antiseptic and anesthetic action, composed of paraffin oil, eugenol, water and a mixture of nonionic surfactants, using a low-energy phase transition emulsification method. Droplet size and rheology of the emulsions are evaluated, as well as its anesthetic action in sensory tests.

2 Methodology

2.1 Substances

The surfactants used in this work are a mixture of two nonionic surfactants of the type non-ethoxylated and ethoxylated sorbitan esters, known commercially as Span 20 and Tween 80, respectively. Span 20 is a mixture of sorbitan esters of the monolaurate type with an average molecular weight of 346 g/mol, a density of 0.95 g/ml at 25º C, and an HLB of 8.6. Tween 80, also known as polysorbate 80, consists of a monooleate-type sorbitan ring and ethylene polyoxide with an average molecular weight of 1,310g/mol and an HLB of 15. Both surfactants were obtained from Sigma (Spain). The oily phase was liquid paraffin and the viscosifying polymer carboxymethylcellulose, both provided by Cientifica Andina (Venezuela). The electrolyte was sodium chloride (JT Baker, Mexico, analytical grade). The active component eugenol was extracted from cloves (Syzygium aromaticum) through steam distillation, hydrodistillation, and Soxhlet extraction. Figure 1 presents the molecular structures of eugenol, Span 20, and Tween 80 schematically.

2.2 Extraction of eugenol

Eugenol extraction was performed through three methods:

- Steam distillation: This process consists of co-distillation of the essential oil with water vapor in simple distillation equipment. Thus, the vegetable sample is placed in an inert chamber and subjected to a stream of superheated water vapor, where essential oils that have high boiling points are distilled and then condensed, collected, and separated from the aqueous fraction.

- Hydrodistillation: This is a variant of the simple steam distillation method. The vegetable raw material is loaded into a hydrodistillation unit to form a compacted bed. The water vapor is injected with enough pressure to overcome the hydraulic resistance of the bed. The steam encounters the clove bed to heat it and release the contained essential oil, which, in turn, evaporates. In this equipment, a trap is placed at the end of the coolant, separating the oil from the condensed water, which improves and facilitates the essential oil extraction.

- Soxhlet extraction: In this method, the solid to be extracted is placed in a cartridge made of filter paper, which is inserted in the center of the chamber. A low boiling point solvent is placed in the balloon and heated to maintain constant reflux. The vapors rise into the condenser, and the condensed liquid falls into the cartridge containing the solid. The solvent fills the chamber and extracts the desired compound from the plant material. Once the cartridge is filled with the solvent, a smaller diameter tube generates a vacuum that drags the solvent with the oil to the distillation balloon.

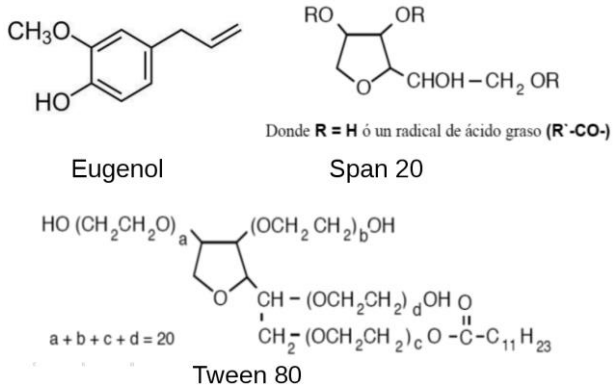

Fig. 1. Molecular structures of eugenol, Span 20 and Tween 80.

2.3 Emulsion formation

The emulsification procedure was carried out as follows: the mixture of surfactants Span 20 and Tween 80 was first dissolved in the oil phase, with a paraffin oil/eugenol ratio of 4/1 and an oil/surfactant phase ratio of 2.5/1. Next, the aqueous phase (0.06% NaCl) was gradually added to the dispersion of surfactant and oil (0.7 ml/min), maintaining a constant mixing speed (250 rpm) and temperature (30ºC). The mixer used was an IKA agitator, Eurostar model. Then, the viscous phase was diluted in the remaining water necessary to obtain 50 g of the final emulsion composed of 4% surfactant, 10% oil phase (paraffin + eugenol), and 86% water.

2.4 Droplet size

The mean droplet size and droplet size distribution were determined using an LS 13320 laser light diffraction particle size analyzer (Beckman Coulter), measuring 0.04 to 2000 μm. The measurements were carried out by diluting the samples with the aqueous phase used to prepare the emulsion. The average droplet size reported is the Sauter diameter d[3,2]. In addition**,** the d(0,9) is presented, which is the diameter below 90% by volume of the droplets of the distribution.

2.5 Rheological behavior

A rotational rheometer (TA instruments), model ARG2, was used to perform the viscosity measurements of the emulsions formed. Data were obtained on the stress vs. shear rate for a cone-plate geometry or concentric cylinders, according to the flow behavior of the emulsions.

2.6 Sensory analysis

The anesthetic effect of emulsions with the active component eugenol was studied through sensory analysis tests, applying the emulsion topically on the skin and inside the mouth, and determining the time of anesthetic effect on the area.

3 Results and Discussion

The eugenol extraction methods were analyzed, considering the yields. The eugenol extraction procedure by steam distillation was carried out in approximately four hours, obtaining a yield of 37.5%. The technique by hydrodistillation was performed in two hours, attaining a yield of 9.3%. Finally, the Soxhlet extraction was completed in approximately three days, with a yield of 36.3%. Soxhlet being an extraction of the liquid-solid type, solid particles and pigments and other unwanted compounds were in the final sample. On the other hand, it was not possible to successfully separate eugenol from other compounds as they have very similar boiling points. As a consequence of the parameters studied, such as time, yield, and oil purity, the methods selected for the extraction of eugenol from cloves were steam distillation and hydrodistillation (Khalil et al., 2017).

An HLB formulation scan from 11 to 13 was performed and the systems were composed of 4% of the surfactant mixture Span 20 and Tween 80, 8% paraffin oil, 2% eugenol, and 86% aqueous phase were emulsified. The emulsion's droplet size was measured for the different formulations (Figure 2). At HLB = 12.5, a minimum droplet size of the emulsion is observed, which is the characteristic behavior of SOW systems at some distance from the optimal formulation (Salager, Nielloud, et al., 2000, Tolosa et al., 2006). At HLB = 12.5 d[3,2] and d(0,9) are similar, indicating that this emulsion

is the least polydisperse (Bullón et al., 2007). This generates greater stability of the emulsions, which is improved by the following factors: 1) a smaller droplet size due to an increase in the interfacial area and an increase in electrostatic and steric repulsion interactions; 2) a less polydisperse droplet size distribution; and 3) the viscosity of the external phase, which can be increased with a viscous agent.

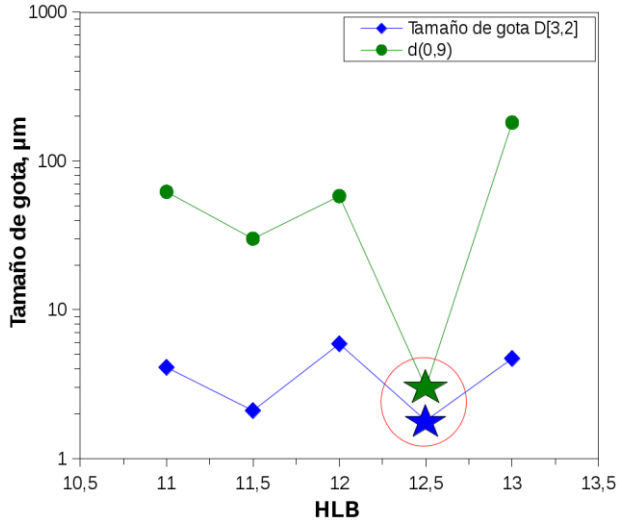

Fig. 2. Average droplet size d[3,2] (◆) and d(0,9) (●) of paraffin oil/eugenol/Span 20-Tween 80/aqueous phase emulsions as a function of HLB. T = 30 C.

Eugenol is a polar oil, making its emulsification difficult due to its low solubilization in SOW systems (Bouton et al., 2009, Márquez et al., 2008, Ontiveros et al., 2015). The blend of surfactants Span 20 and Tween 80 has been shown to be suitable for the emulsification of polar oils, such as triglyceride oils (Bullón et al., 2007). In addition, the droplet diameter of less than 2 µm obtained from the emulsions at an HLB = 12.5 demonstrates that this formulation allows eugenol to be encapsulated in the emulsion. Therefore, this emulsion was a suitable vehicle for application. Furthermore, it is better than eugenol oil in its pure state, which can be toxic and generate irritation when applied directly to the skin or in the mouth for local anesthesia, particularly in dentistry (Gerosa et al., 1996).

At HLB = 11, an opaque unstable emulsion was obtained due to the proximity of the phase inversion point (Salager, et al., 2000). For this reason, the HLB of 12, 12.5 and 13 were selected to study the relationship between rheological behavior and droplet size of the emulsions formed.

Figure 3 shows the rheological behavior of emulsions formed at HLB 12, 12.5 and 13. Emulsions present a shear-thinning behavior. Thus, a suitable formulation of an anesthetic emulsion for a topical application requires (Gallegos y Franco 1999, Pons et al., 2007, Tadros et al., 2004, Tadros 1994):

- High viscosity at low shear for better application.

- Low viscosity at high shear to spread the cream on the skin.

- Wettability and anesthetic effect for several minutes.

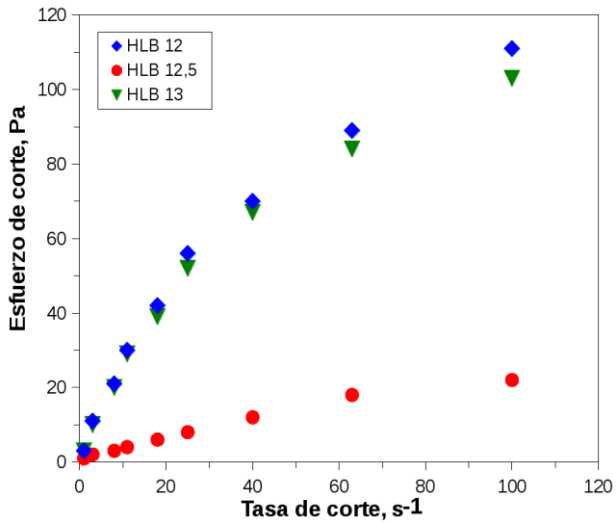

Fig. 3. Rheological behavior of emulsions of the paraffin oil/eugenol/Span 20-Tween 80/aqueous phase system, as a function of HLB. T = 30 C.

The first two characteristics were improved for the three emulsions shown in Figure 3, using the polymer carboxymethylcellulose as a viscosifying agent at 3% in the total system. Moreover, this polymer can be used in O/W emulsions, modifying the rheological behavior and increasing the stability of the emulsions formed (Celis et al., 2008). The third, the anesthetic effect, was studied through a sensory analysis of the emulsion applied topically on the skin and mouth. It was found that the emulsion has an effect on sensory properties after 2 min of being applied, with a duration of 20±1 min from its application until the skin surface obtains sensitivity again.

4 Conclusions

In this work, a formulation for eugenol use as a topical and oral anesthetic was attained, respecting the limits of toxicity, using an emulsion as a vehicle. A low energy emulsification method, also called spontaneous emulsification was used to obtain submicrometer emulsions. It was found that the most appropriate methods for extracting eugenol from cloves (*Syzygium aromaticum)* are steam distillation and hydrodistillation. Moreover, the emulsion's stability, droplet size, and rheological properties allow the application of eugenol as an active ingredient for use as a topical and oral anesthetic.

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