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Short communication

A study on the compatibility of Ibuprofen with some essential oils used for formulation of semi-solid pharmaceutical dosage forms for topical use

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Introduction

Ibuprofen represents one of the most popular non-steroidal anti-inflammatory drugs which is widely used in treatment of acute pain and fever, as well as some chronical conditions. Thanks to its excellent analgesic and anti-inflammatory properties, ibuprofen is used as an active pharmaceutical ingredient (API) in many different pharmaceutical dosage forms, for oral and topical administration, such as tablets, oral suspensions and gels (Maswadeh, 2016). Due to the close contact of the API with one or more excipients in the formulation, any kind of interaction may result with a negative impact on the stability, physical or performance attributes of the product (Gupta et al., 2019). Therefore, for a rational selection of excipients, screening of API-excipient compatibility is a crucial aspect of the formulation development process for ensuring a safe and robust product development (Chadha & Bhandari, 2014).

Taking into consideration that ibuprofen is a highly reactive compound (contains carboxylic functional group) and the essential oils are known to have a complex chemical composition (Turek & Stintzing, 2013), the aim of this study was to investigate the solid-state compatibility of ibuprofen with Orange oil and Lavender oil which are commonly used essential oils for formulation of Ibuprofen gel for topical use.

Materials and methods

Materials

The non-steroidal anti-inflammatory drug ibuprofen was supplied by Solara Active Pharma Sciences (India), whereas the Orange oil and Lavender oil were supplied by IREKS Aroma d.o.o. (Croatia). Potassium dihydrogen phosphate (Merck), Orto-phosphoric acid 75% (Merck) and Acetonitrile (Merck) were also used.

Methods

Fourier-Transform Infrared (FTIR) spectroscopy: Varian 660 FTIR spectrometer (Varian Inc.) was employed for collection of the FTIR spectra of the binary mixtures. Attenuated total reflectance (ATR) spectra (resolution 4 cm^{-1}, 16 scans per spectrum) were obtained by MIRAcle ZnSe ATR module (PIKE technologies) with low-pressure micrometer clamp, in the 4000-550 cm^{-1-} region. The temperature-controlled FTIR ATR spectra were collected using GladiATR module with diamond crystal (PIKE technologies), coupled with variable temperature module and high-pressure micrometer clamp, in the 4000-400 cm^{-1} region.

Differential scanning calorimetry (DSC):
The DSC measurements were performed on a NETZSCH DSC 204 F1 Phoenix instrument, in aluminium pans with a perforated lid (sample mass 3 mg), from 25 – 100 °C, at heating rate of 10 K/min under dynamic nitrogen atmosphere (30 mL/min).

High performance liquid chromatography (HPLC): The related and degradation products were analyzed

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according to HPLC in-house method, using Thermo Ultimate 3000 HPLC system with diode array detector (214 nm, 220 nm, 240 nm and 260 nm) and Zorbax Eclipse XDB C18 (150 mm x 4.6 mm i.d; 5 µm) column (Agilent).

Results and discussion

The solid-state analysis of the binary mixtures of ibuprofen with the analyzed essential oils, has shown a possible solid-state interaction in the binary mixture of ibuprofen with Orange oil, in 1:1 ratio, exposed at 40 °C/75% RH. Namely, the FTIR spectrum of this binary mixture exhibits some vibrational bands in the region 1250 – 950 cm^{-1} which cannot be related neither to API, nor to the essential oil. Additionally, an appearance of new vibrational bands around 840 cm^{-1}, characteristic for the structure of limonene oxide (Pisarenko et al., 2008), were observed. Knowing that the main component of the Orange oil is limonene, which according to the literature data is unstable when exposed at elevated temperature and relative humidity, this might be an indication that the observed changes might be a result of some degradation process of the essential oil. On the other hand, changes were not observed in the binary mixture of ibuprofen and Lavender oil, neither in the initial, nor in the stressed binary mixture. However, in the DSC curves of both binary mixtures, the melting endotherm of ibuprofen was completely disappeared. This can be explained with its dissolving in the liquid essential oil at higher temperature. HPLC analysis was also performed and the results showed a continuous increase of the related impurities, with 8.25% increase of total impurities in the binary mixture of ibuprofen and Orange oil, exposed at 40 °C/75% RH, compared to 1.79% increase of total impurities in the binary mixture of ibuprofen with Lavender oil, exposed at the same stress conditions.

Based on the hypothesis that the increased impurities might originate as a result of some degradation process of the oil, the Orange oil itself was exposed to the same stress conditions for 30 days. However, no changes in the FTIR spectrum of the stressed essential oil were observed after this time. This shows that the observed changes were not due to the degradation of the oil, but as a result of an interaction that is taking place between ibuprofen and Orange oil, under certain conditions. To inspect the temperature influence on the possible interaction, temperature-controlled FTIR ATR spectra were collected from 25 – 40 °C (1 °C/minute), at constant relative humidity, for the binary mixture of ibuprofen and Orange oil in 1:1 ratio. However, the obtained spectra did not exhibit any changes. This result points out that the interaction is taking place only under certain combination of temperature and relative humidity.

To simulate storage temperature of the finished product, the same binary mixture was exposed for 30 days at 30 °C/75% RH and no changes in the FTIR spectra were observed under these conditions.

Since the ratio 1:1 is considered as worst-case scenario, the binary mixtures with both essential oils were prepared in formulation ratio 10:1, stressed under same conditions and analyzed with the same techniques. The FTIR spectra of the stressed binary mixtures, after 30 days exhibited no changes. Additionally, the HPLC analysis showed significant decrease of the total related impurities to 0.37% and 0.13% in the binary mixtures of ibuprofen with Orange oil and Lavender oil, exposed at 40°C/75% RH, respectively.

Conclusion

Summarizing the obtained results, it is evident that due to the complex nature of essential oils, some of them could easily interact with ibuprofen when used as excipients in formulations for topical administration. However, when Orange oil is used in formulation ratio and the product is properly stored, it is stable and do not interact with the API, confirming its safe application in the formulation. Therefore, detailed evaluation and careful choice of excipients is of crucial importance during formulation stage of the development in order to ensure a stable and safe finished product.

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