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Determination of mometasone furoate solubility, using deep eutectic systems, and topical formulation- experimental and computational studies

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ABSTRACT

The low solubility of some drugs in aqueous medium, is currently a challenge for the pharmaceutical industry, affecting drug bioavailability and treatment efficacy, so there is the need to find new solutions for this challenge. In this work, the solubility of a glucocorticoid drug, mometasone furoate (MF), in different deep eutectic systems (DES) is studied. DES present the advantage of being sustainable solvents, which can be used directly in the final formulation, and establish a synergistic effect with the drug. The solubility of MF in different DES is increased, when compared to the solubility of this drug in an aqueous medium, particularly in DES composed by levulinic acid and terpenes such as menthol and thymol, where the solubility of MF was of 24.1 and 103.3 mgMF/gDES, respectively. Solubility was also assessed using the computational determination of the Hansen solubility parameters of MF in these DES, in particular the total solubility parameter (δ_T) and Relative Energy Difference (*RED*). The obtained results correlate well with the MF measured experimentally, showing that this computational tool can be further used to predict MF solubility in DES. Furthermore, oil-in-water emulsions containing DES with MF were developed, allowing more versatility compared to the drug in powdered form, and were prepared containing 1 and 5 % of DES with MF. This work highlights that DES can have an important role in drug solubilization and in the development of new formulation strategies for the pharmaceutical industries.

1. Introduction

The pharmaceutical industry, and drug development and discovery, has an undeniable social impact since it contributes to improve life conditions, population well-being, increases life expectancy and is set on finding cures for diseases that were once fatal. This is proved by the ever-growing value of this industry, which by 2022 had a market value of more than 1.48 trillion US dollars ("https://www.statista.com/topics/1764/global-pharmaceutical-industry/#editorsPicks," n. d.). Still, it is in constant development and is faced with several challenges, related with the high prices of the raw materials, the immense energy input that the operations in course require for production, the amount of waste generated during its manufacture and its related poor sustainability (Khan and Ali, 2022). This inevitably leads to increased costs and has negative environmental and social impact. There is a need to develop and im-

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prove drug production methods and processes, yielding effective and accessible products, obtained in a more sustainable manner (Becker et al., 2022; Milanesi et al., 2020).

Another challenging task of the pharmaceutical industry is related with the fact that some of the current drugs present limited or very low solubility in aqueous/physiological media, low systemic absorption and consequent low bioavailability (Bhalani et al., 2022). In this sense, for a drug to be effective in the human body, a higher amount is needed in the formulation for it to have its therapeutic effect. This has disadvantages in terms of production because a higher amount of drug needs to be produced, resulting in higher cost, and requiring more energy and materials. Also, this has negative consequences in drug-patient compliance since the intake of high doses of some drugs is normally accompanied with secondary adverse effects to the human health. Corticosteroids and glucocorticoids are a class of drugs that present such behavior (Bhalani et al., 2022). They are used in the treatment of various medical conditions such as inflammatory skin diseases such as psoriasis or atopic dermatitis, but also in asthma; they have anti-inflammatory properties and immunosuppressive and anti-proliferative and effects (Raposo et al., 2015). An example of a glucocorticoid is mometasone furoate (MF), that is widely prescribed as first line treatment for allergy related diseases, such as skin allergies or allergic rhinitis (Cowie et al., 2009; Faergemann et al., 2000; Lipworth and Jackson, 2000).

It is commercialized in the form of ointments or creams, but in the case of respiratory related diseases as inhalers or nasal sprays. Although it is effective in the prevention of the symptoms of the above-mentioned diseases, MF presents a solubility in DMSO and some alcohols, being much lower in aqueous medium (Raposo et al., 2015), which means that the formulation of effective products containing MF is a challenge.

There are strategies and techniques to improve aqueous solubility of poorly soluble pharmaceutical drugs, such as the use of carriers like polymers or fatty acids, micronization of the drug (through spray drying, for example), among others (Malamatari et al., 2020; Nair et al., 2020). These strategies rely on changing slightly the hydrophobic/hydrophilic affinity or the physical characteristics of the drug, that will allow improved absorption by the organism. Still, these strategies require the use of additional processes, compounds, or apparatus, that can make drug formulation more time consuming and expensive.

Nonetheless, even when administered or formulated in the above-mentioned ways, the low solubility MF in physiological media is still an issue. In recent years, a class of solvents that can improve drug solubility, its permeability and bioavailability, has emerged-deep eutectic systems and natural deep eutectic systems (DES and NADES) (Aroso et al., 2016; Bhalani et al., 2022; Paiva et al., 2014; Teng et al., 2003). DES are considered "green" and sustainable solvents, since they fully comply with the green chemistry metrics, and they are in most cases biodegradable and biocompatible. Because they result from the combination of two or more components, that can be tailored to a specific application, in what concerns drug solubility the DES can be designed to interact with the drug and increase its solubility. Another advantage of solubilizing drugs in DES, is that they can increase their stability, avoiding issues such as degradation or polymorphism, all due to the physico-chemical interactions established between the DES and drug (Liu et al., 2022).

The use of DES to improve drug solubility and efficacy has been explored in the last decades, as for example in the work of Stott et al. and Phaechamud et al. (Phaechamud et al., 2016; Stott et al., 1998) that describes the solubility enhancement of ibuprofen in eutectic mixtures composed of different terpenes. Other compounds with limited aqueous solubility have been studied, to assess its solubility in DES such as curcumin, caffeine or edravone (Huber et al., 2021b; Jeliński et al., 2024a; Lomba et al., 2023), which are widely used in drug development and have vast therapeutic uses. These works report on the solubilization ability and the influence of DES composition, on the drug-solvent interactions, and explore the choice of DES using computational screening methods such as COSMO-RS, which can predict some of the thermodynamic properties of a given DES. Of special interest is the study of the solubility of antibacterial drugs in DES, such as antibiotics. Antibiotics are the most effective treatment to treat bacterial infections, and some of the most prescribed medicines in the world (Hutchings et al., 2019). Still, their use is often prolonged and can cause severe adverse effects in the patients, mainly due to its limited solubility in aqueous/physiological medium. Solvents that can increase this aqueous solubility are needed and DES can have a role in this challenge. Cysewski and co-workers have studied solubility of antibiotics such as cefixime, dapsone sulfanilamide and sulfacetamide in DES (Jeliński et al., 2019, 2024b; Tajmir and Roosta, 2020), both using experimental and computational methods, showing that DES have a beneficial effect in these drugs' solubility and efficacy.

The reasons for this increase in drug aqueous solubility have been the subject of different studies, that suggest that DES-drug interactions rule drug solubility, which is of course related with the DES composition. Effects such as hydrotropy of DES, where it acts as a co-solvent to enhance the drug's aqueous solubility, have been discussed and proposed in different works (Huber et al., 2021a; Jeliński et al., 2024a; Sales et al., 2022). They suggest that the DES acts as a hydrotrope specie and forms an aggregate around the solute (drug), while also promoting interactions with the water, thus facilitating dissolution (Sales et al., 2022).

In this work, different DES composed of organic acids, secondary alcohols and sugars were prepared, and the solubility of MF was evaluated and compared with commercially available solvent ethoxydiglycol (Transcutol®P). Alongside with the solubility studies carried out experimentally, computational methods were also used to confirm and predict the MF solubility in DES and a commercial solvent. Furthermore, emulsions containing the MF dissolved in the DES were prepared and characterized. The results from this work can help in the development of new pharmaceutical formulations of MF, specifically for topical application, and present a strategy that combines experimental and computational data to determine solubility parameters of drugss in DES. The use of DES that enhance solubility, permeability and consequently the bioavailability of poorly water-soluble drugs is explored. This approach envisages new ways to drug formulation and production that are more sustainable and promote better patient compliance and more effective treatment.

2. Materials and methods

2.1. Materials

All the reagents used in this work were obtained with the maximum commercially available purity and are presented in Table 1.

2.2. DES preparation

DES were prepared by weighing the components onto glass vials according to their molar ratio and stirred at room temperature, or in some cases at 40 °C, for at least 2 h (Table 2). After that, clear homogeneous liquids were obtained, and no precipitation of any of the DES components was observed.

2.3. Water content determination

The water content of levulinic acid and levulinic acid-based DES was measured using a Karl-Fischer Coulometer without a diaphragm (MetroOhm), using Coulumat AG as an analyte. The obtained values are an average of at least three independent measurements for each sample.

Table 1
Information of the reagents used within this work, namely its purity, CAS and commercial brand. N.A. stands for not available and is used when there was not available information.

Reagent	Purity/wt%	CAS	Commercial brand
glycerol	≥99.5	56-81-5	Sigma-Aldrich
lauric acid	≥98	143-07-7	Sigma-Aldrich
levulinic acid	98	123-76-2	Sigma-Aldrich
thymol	≥98.5	89-83-8	Sigma-Aldrich
DL-menthol	≥95	111-90-0	Sigma-Aldrich
L-menthol	≥99	2216-51-5	Sigma-Aldrich
benzoic acid	n.a.	65-85-0	Sigma-Aldrich
carvacrol	99	499-75-2	Sigma-Aldrich
D-glucose monohydrate	N.A.	14,431-43-7	Sigma-Aldrich
hydroxypropylmethylcellulose- HPMC	N.A.	9004-65-3	Sigma-Aldrich
Nile red	≥ 97	7385-67-3	Sigma-Aldrich
DL-lactic acid	> 85	50-21-5	TCI
sodium acetate	N.A.	127-09-3	Riedel-de-Haën
hydranal coulomat AG	N.A.	67-56-1	Honeywell
mometasone furoate	99	83,919-23-7	Cristal Pharma
ethoxydiglicol (Transcutol®P)	N.A.	111-90-0	Kindly gifted by Gattefossé-France
Bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone and caprylic/capric triglyceride (Abil®Care 85)	N.A.	N.A.	Kindly gifted by Evonik Industries AG
Bis-PEG/PPG-20/5 dimethicone, methoxyPEG/PPG-25/4 dimethicone, caprylic/capric triglyceride (Abil®Care XL)	N.A.	68,411-27-8	Kindly gifted by Evonik Industries AG
C12-15 alkyl benzoate (Tegosoft®TN)	N.A.	68,411-27-8	Kindly gifted by Evonik Industries AG
PEG-20 glyceryl laurate (Tagat®L2)	N.A.	59,070-56-3	Kindly gifted by Evonik Industries AG
PEG-12 dimethicone (BRB 526)	N.A.	68,937-54-2	Kindly gifted by Evonik Industries AG
PEG-18 glyceryl oleate/cocoate (Antil®171)	N.A.	68,201-46-7	Kindly gifted by Evonik Industries AG
polyglyceryl-4-isostearate (Isolan®GI 34)	N.A.	091,824-88-3	Kindly gifted by Evonik Industries AG
cetrimide BP	N.A.	1119-97-7	Kindly gifted by Evonik Industries AG
Bis-PEG/PPG-20/5 dimethicone	N.A.	n.a.	Kindly gifted by Evonik Industries AG
methoxyPEG/PPG-25/4 dimethicone	N.A.	n.a.	Kindly gifted by Evonik Industries AG
Methylvinylether/maleic anhydride copolymer crosslinked with decadiene (PVM/MA-Stabileze®QM	N.A.	136,392-67-1	Kindly gifted by ISP
Isopropyl myristate (IPM)	98%	110-27-0	José Vaz Pereira, S.A.
Isopropyl alcohol	N.A.	67-63-0	José Vaz Pereira, S.A.
sorbitan oleate (Span®80)	N.A.	1338-43-8	José Vaz Pereira, S.A.
polysorbate 80 (Tween®80)	N.A.	9005-65-6	José Vaz Pereira, S.A.
propylene glycol	N.A.	57-55-6	José Vaz Pereira, S.A.
ethanol absolute anhydrous	N.A.	64-17-5	Carlo Erba

Table 2
Prepared DES and compositions.

Component 1	Component 2	Component 3	Molar ratio	Name
DL-lactic acid	D-glucose	Water	5:1:3	LA:G:W (5:1:3)
DL-lactic acid	sodium acetate	–	3:1	LA:SA (3:1)
Thymol	L-menthol	–	1:1	T:M (1:1)
Carvacrol	L-menthol	–	1:1	C:M (1:1)
benzoic acid	L-menthol	–	1:3	BA:M (1:3)
DL-lactic acid	DL-menthol	–	2:1	LA:M (2:1)
levulinic acid	DL-menthol	–	1:1	LevA:M (2:1)
levulinic acid	Thymol	–	1:1	LevA:T (1:1)

2.4. Solubility assays

In an initial screening, MF solubility in the prepared DES, levulinic acid and ethoxydiglycol was determined by successive additions of powdered MF to glass vials containing each of the DES or solvents. After each addition, the vials were stirred at room temperature, until no visible particles were observed, assuming complete solubility. This was repeated until saturation was achieved, and the amount of MF dissolved was determined. All measurements were performed in triplicate, and results were translated as the ratio mg_{MF}/g_{DES}. For the DES that presented highest MF content, the solubility values were confirmed via high performance liquid chromatography (HPLC). Analysis was carried out in an Agilent 1100 system, equipped with a C18 column from Thermo Keystone (250 × 4.6 mm). The isocratic method uses acetonitrile:water 70:30 as mobile phase, a flow rate of 0.5 mL/min and an injection volume of 25 μL, at 40 °C. Mometasone furoate was detected by UV at 248 nm. A standard stock solution of MF was prepared, from which different dilutions were obtained, to obtain a calibration curve that allowed accurate MF identification and quantification by HPLC. The obtained calibration curves obtained in the different prepared DES are as follows: LevA:M, $y = 60.36x + 124.62$ with $R^2 = 0.9865$; Leva:T, $y = 54.33x + 7.9769$ with $R^2 = 0.9998$.

2.5. Polarity determination

The relative polarity of the DES LevA:M (2:1) and LevA:T (1:1), and ethoxydiglycol, was determined following the method that uses Nile Red as a solvatochromic probe, and is reported in literature (Craveiro et al., 2016; Dai et al., 2013). Briefly, a Nile Red stock solution of 1 $g.L^{-1}$ is prepared in ethanol and stored at 4 °C. For each sample (DES and ethoxydiglycol) 1 mL was placed in a 1 × 1 cm cuvette and a blank spectrum was obtained (between 400 and 800 nm). To each of the samples, 5 μL of Nile Red stock solution were added to the cuvette and mixed thoroughly and placed under a gentle nitrogen stream to evaporate the ethanol. The spectra were immediately acquired, at room temperature. At least 3 different measurements for each sample were performed and the final E_{NR} parameter was obtained determining the maximum absorbance wavelength and using the following equation 1

$$E_{NR} = \frac{28,591}{\lambda_{max}} \quad \text{(eq. 1)}$$

with E_{NR} in $Kcal.mol^{-1}$ and λ_{max} in nm.

2.6. Hansen solubility parameters determination

The three Hansen solubility parameters (HSPs) were evaluated in this study, namely dispersion (δ_D), dipolar (δ_P), and hydrogen bonding (δ_H) ones, as well as the total solubility parameters (δ_T). They were predicted using the group-contribution methods established by Hoftyzer and van Krevelen (van Krevelen and te Nijenhuis, 2009), using the molar volume calculated using Fedor's model (Fedors, 1974) (*supplementary information, from* Table S.1 to S.5). For the DES LevA:M (2:1) and LevA:T (1:1), the solubility parameters were determined using the mixture rule described by Jaime Lara *et al.*(Lara et al. (2017).

Once the HSPs of both DES, ethoxydiglycol and solute MF are known, the solvent-solute degree affinity was assessed using two different approaches. The first one was consisted in a three dimensional evaluation, taking into consideration the relative distances between solute-solvent (R_a, equation (2)) between MF and the solvents regarding a hypothetic interaction radius/solubility sphere (R_0) of MF, which consequently allowed to study the affinity degree in terms of relativeness or also known as the *Relative Energy Difference* (R_{ED}, equation (3)), where the superscript "*MF*" represents the solute Mometasone Furoate and "*S*" the solvents/systems LevA:M (2:1), LevA:T (1:1) and ethoxydiglycol. According to the work of Hansen et al. (Hansen, 2007), if $R_{ED} > 1$ there is no good affinity between the solute and solvent, therefore it is expected a low solubility. However, if $R_{ED} < 1$ this means that the solute-solvent interaction is favourable to occur and therefore the molecules will dissolve. On the other hand, if $R_{ED} = 0$, the solubility of the solute is expected to be only partial.

$$R_a = \left(\sqrt{4\left(\delta_d^{MF} - \delta_d^{S}\right)^2 + \left(\delta_p^{MF} - \delta_p^{S}\right)^2 + \left(\delta_h^{MF} - \delta_h^{S}\right)^2} \quad \text{(eq. 2)}$$

$$RED = \frac{R_a}{R_0} \quad \text{(eq. 3)}$$

In the second approach, the affinity was assessed by determining the difference between the total solubility parameters ($\Delta\delta_t$) of the MF and each solvent/system, using equation (4):

$$\Delta\delta_t = \left|\delta_t^{MF} - \delta_t^{S}\right| \quad \text{(eq. 4)}$$

In this case and according to Hansen's assumption (Hansen, 2007), the two substances are only considered miscible if their $\Delta\delta_t < 3.7$ $MPa^{1/2}$.

2.7. Emulsion preparation

Oil in water (o/w) emulsions containing DES or ethoxydiglycol were prepared. The oil phase was prepared at room temperature (cold process), achieved by dispersing the surfactant (bis-PEG/PPG-16/16, PEG/PPG-16/16, dimethicone and caprylic/capric triglyceride) and the co-emulsifier (PEG-20 glyceryl laurate) in the oil (C12-15 alkyl benzoate) and mixing at 700 rpm (MR 3001, Heidolph, Germany) for about 15 min. Next, an aqueous phase was prepared at room temperature by dispersing the aqueous thickening agents (HPMC and PVM/MA) in water at 1000 rpm (MR 3001, Heidolph, Germany). The cetrimide (0.075 % w/w) and the ethoxydiglycol or DES, with or without MF at 0.1% (w/w), were added to the aqueous solution and the resulting mixture was homogenized until a clear homogeneous gel was achieved (described in Table 3).

The emulsification phase was performed at room temperature by slowly adding the oil phase to the aqueous phase, with high shear mixing at a rate of 12,800 rpm/min (IKA® T25 Ultra Turrax). This addition was performed at uniform rate over a period of 5 min. The final pH was adjusted to 4 with NaOH.

2.8. Rheological studies

Experimental procedures for assessing structure were conducted using a Kinexus Lab + Rheometer (NETZSCH, Wittelsbacherstraβe, Germany) with controlled stress capabilities.

2.8.1. Rotational viscosity analysis

The rotational viscosity was assessed utilizing a cone-and-plate setup. The measurements spanned a shear stress range from 1 to 100 Pa, with logarithmic increments from 0.1 to $100s^{-1}$. Additionally, a shear stress ramp test was conducted over the same stress range for a duration of 1 min. These measurements were all taken at a constant temperature of 25 °C in the 24 h following the emulsions preparation.

2.8.2. Oscillatory frequency assessment

Oscillatory frequency sweep tests were executed using a cone-plate configuration. The frequency range for these tests was set between 100 Hz and 0.01 Hz, applying a constant shear strain of 0.1%. These tests were also performed at a temperature of 25 °C, in the 24 h following the emulsions preparation.

2.9. Droplet size determination

The droplet size distribution of the emulsions was determined through light scattering techniques, utilizing a Malamatari et al., 2020 (Malvern Instruments, Worcestershire, UK) equipped with a Hydro S accessory. Approximately 0.1 g of each emulsion was dispersed in 5 mL of water to attain the desired level of turbidity, ensuring an obscuration degree in the range of 10%–20%. The emulsion sample was then introduced into the measurement chamber containing water, with stirring at 1750 rpm. The results were pre-

Table 3
Qualitative and quantitative formulation containing DES or ethoxydiglycol.

Excipients	Composition in % (w/w)			
	Emulsion Control 5% ethoydiglycol	Emulsion Control 1% ethoydiglycol	Emulsion Control 5% ethoydiglycol	Emulsion Control 1% ethoydiglycol
Oil phase				
bis-PEG/PPG-16/16, PEG/PPG-16/16, dimethicone and caprylic/capric triglyceride	5.0	5.0	5.0	5.0
PGL	4.0	4.0	4.0	4.0
C12-15 Alkyl benzoate	5.0	5.0	5.0	5.0
Water phase				
Cetrimide	0.075	0.075	0.075	0.075
HPMC	2.0	2.0	2.0	2.0
PVM/MA	0.30	0.30	0.30	0.30
MF	0.10	0.10	0.10	0.10
Ethoxydiglycol	5.0	1.0	–	–
DES	–	–	5.0	1.0
NaOH 1 N	pH 4	pH 4	pH 4	pH 4
Purified water	q.s to 100	q.s to 100	q.s to 100	q.s to 100

sented as the volume-based relative distribution of droplet sizes, with diameters corresponding to the 10th, 50th, and 90th percentiles (mean ± SD; n = 6). These measurements were conducted in the 24 h post-preparation of the emulsions.

3. Results and discussion

3.1. Determination of MF solubilities and DES polarities

The solubility of mometasone furoate (MF) was determined in the different DES and in commercially available ethoxydiglycol. This solvent is reported as having excellent solubilizing power towards poorly water-soluble drugs such as erythromycin (Hussain et al., 2022), tamoxifen, sulforaphane or rifampicin, for example (Hashemzadeh and Jouyban, 2022). It is also reported to be a permeation enhancer for topical application of drugs (Osborne and Musakhanian, 2018). Its solubilizing power is related to its composition, it is a diethylene glycol monoethyl ether (DEGEE) and a protic solvent (Osborne and Musakhanian, 2018). Nevertheless, this solvent still presents side effects such as skin and respiratory irritation, and its non-toxicity is dependent on its purity level.

An initial screening assay of MF solubilities was performed, to determine which of the studied DES would solubilize the highest amount of MF (Table 4). The presented results show that MF can have a higher solubility in the studied DES, when compared to its solubility in water. Between the different DES, the ones with menthol in its composition show the highest solubility values, especially when compared to the ones with a more polar and hydrophilic character, such as LA:G:W (5:1:3) and LA:SA (3:1). Also, DES with levulinic acid show the highest value of MF solubility, especially LevAc:T (1:1), showing a better performance than ethoxydiglycol. The solubilities of MF in DES composed by levulinic acid were also confirmed by HPLC, and the results were in good accordance.

Polarity is undoubtedly one of the best physicochemical properties to help understand the behaviour of different solvents towards a given solute and rationalize solubility results. The polarity of DES is usually studied using a solvatochromic probe, such as Reichardt's dye or Nile red is a dye (Craveiro et al., 2016; Dai et al., 2013; Deye et al., 1990; Farooq et al., 2020; Yablon and Schilowitz, 2004), and the obtained results are a qualitative polarity scale in regards to a given common solvent. In this work, polarity of DES LevA:M (2:1), LevA:T (1:1) and ethoxydiglycol was determined using Nile red (prepared in ethanol) and results are presented in Table 5. Using this method, the maximum absorbance (in the visible spectrum region) wavelength is determined for the samples under study. It is known that solvents with non-polar/hydrophobic character shift the maximum absorption wavelength to lower values, and polar/hydrophilic solvents to higher wavelengths. Considering equation (1), the higher the E_{NR} value, the lower the polarity, and the polarity order obtained in this work is the following.

LevA:T (1:1) > Levulinic acid > LevA:M (2:1) > ethoxydiglycol.

Following the basic principle that "like dissolves like", the high solubility of MF in LevA:T (1:1) can then be justified by the preference of MF to an apolar environment similar to the one of DES LevA:T (1:1). Results in Table 3 show that MF has low solubility in most of the hydrophilic/polar systems, although MF's molecular structure (Fig. 1). Being E_{NR} a simple relative scale, it is only possible to hypothesize that solvents with values similar to the obtained ones, specifically analogue to LevA:T (1:1), would be the most suitable for MF. Furthermore, the results show also that the DES LevA:M (2:1) is slightly more polar than ethoxydiglycol. The two DES have in its composition both polar and apolar species, which influence the shifts that occur in the Nile red's maximum absorption wavelength.

But, besides polarity, there are indeed a lot of other physicochemical factors that may affect most substantially the solubility of MF in the present solvents, which would complement and justify the higher solubility of MF in ethoxydiglycol than LevA:M (2:1), even when this last is more polar.

Table 4
Solubility of MF in the prepared DES, as well as in levulinic acid and ethoxydiglycol, determined by visual method and by HPLC.

DES/Solvent	MF solubility (mg_{MF}/g_{DES}) Visual	MF solubility (mg_{MF}/g_{DES}) HPLC	Water content (wt%)
LA:G:W (5:1:3)	< 1	–	–
LA:SA (3:1)	< 1	–	–
T:M (1:1)	32.2	–	–
C:M (1:1)	27.5	–	–
BA:M (1:3)	10.6	–	–
LA:M (2:1)	9.10	–	–
LevA:M (2:1)	25.2 ± 0.9	24.1 ± 0.5	0.82
LevA:T (1:1)	107.0 ± 2.8	103.3 ± 1.1	0.78
Levulinic acid	30.7	–	0.58
ethoxydiglycol	45.5	–	–

Table 5
Wavelength of the maximum absorption and Polarity of the studied solvents.

Solvent	λ_{max} (nm)	E_{NR} (kcal.mol^{-1})
LevA:M (2:1)	564.22 ± 0.38	50.67
LevA:T (1:1)	646.00 ± 0.00	44.26
ethoxydiglycol	551.33 ± 1.15	51.86
Levulinic acid	640.00 ± 0.00	44.67

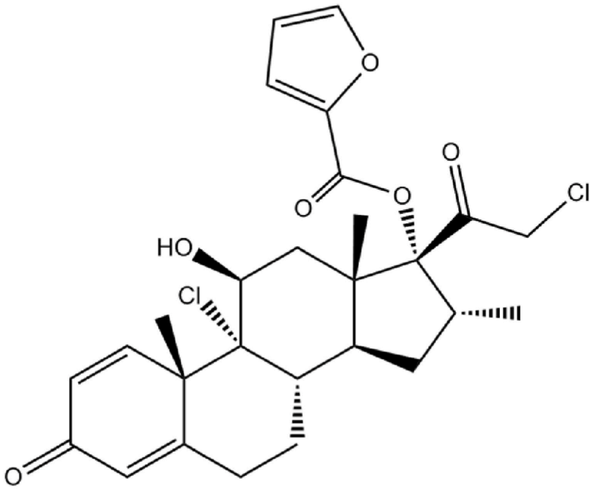

Fig. 1. Molecular structure of Mometasone Furoate (MF).

Taking these results into account, it is observed that DES containing levulinic acid and menthol or thymol were the ones that showed the best potential to be further prepared and tested. Previous work reported by Petitprez et al. showed that DES containing cyclodextrin and levulinic acid in its composition increased MF solubility (Petitprez et al., 2022) to 6.7 mg_{MF}/mL_{DES}, and Al-Akayleh et al. reported on the increased solubility of MF in hydrophobic DES composed of capric acid and menthol (Al-Akayleh et al., 2019), obtaining a value of 2.4 mg_{MF}/mL_{DES}. Increased solubility of corticosteroids can be achieved by in more acidic media, because this stabilizes MF molecules (Teng et al., 2003). This may explain why, according to Table 2, DES composed of both levulinic acid and hydrophobic terpenes solubilize higher amounts of MF. Also, levulinic acid has been used in the cosmetic industry and in topical formulas, mainly as a preservative (Papageorgiou et al., 2010), which means it is safe to be used in the envisaged MF formulations.

3.2. Hansen solubility parameters (HSPs)

The computational determination of Hansen solubility parameters (HSPs) is one of the most common computational methods used in the screening of solvents for a given solute. In the DES field, this has been reported as a valid and effective method to predict the solubility behaviour of compounds in DES (Fernandes et al., 2021), as well as explain the increase of solubility of poorly water-soluble active pharmaceutical ingredients (API)/drugs in different DES, such as acetaminophen, naproxen, or coumarin (Khorsandi et al., 2021; Makoni et al., 2020; Mokhtarpour et al., 2020). Therefore, such an approach was also assessed in this work, to understand better the solubility behaviour of MF in the studied DES.

Theoretically, these computational studies and predictions are based on the determination of the solubility parameters that measure intermolecular interactions between molecules that arise from dispersion (δ_D), dipole-permanent dipole forces (δ_P) and hydrogen bonding (δ_H) (Makoni et al., 2020). These, when combined, allow the calculation of the total solubility parameter (δ_T)shown in equation (6) (Hossin et al., 2016).

$$\delta_T = \sqrt{\delta_D^2 + \delta_P^2 + \delta_H^2} \quad \text{(eq. 6)}$$

In this work, the degree of affinity between MF and the studied solvents was evaluated according to the obtained HSPs, for DES LevA:M and LevA:T and ethoxydiglycol, to validate the previously obtained experimental data, and in order to understand in detail the MF solubilization behaviour towards in DES.

Considering the obtained HSPs of the DES individual components, MF and ethoxydiglycol and comparing with the results available in the literature (Table 4), it was possible to observe that, most of the experimental values are in accordance with the literature ones, but in the case of MF some differences are observed. This can be related on how, for this method, the structure of the molecules is fragmented; that is, the choice of functional groups that were used to calculate the Hansen parameters. Since there is not a standard way in using the group contribution method, different results are obtained if the selected groups differ. This occurs mainly in large molecules, such as in MF (Fig. 1).

Table 6 shows the HSPs obtained for the DES, MF and ethoxydiglycol, and from the presented results, we can see that DES LevA:T (1:1) presents a solubility behaviour very similar to MF, which indicates that there is a high affinity between them and consequently the reason that it would be expected a relatively higher solubility of MF in LevA:T (1:1), which is also observed in the solubility values obtained experimentally (Table 7).

In fact, by comparing the experimental solubilities data (Table 2), with the results from the two parameters used to evaluate the affinity degree, *RED* and $\Delta\delta_T$ in Tables 5 and it is possible to observe that in both cases LevA:T (1:1) appears as the best solvent for MF. Regarding the *Relative Energy Difference* (*RED*), a three-dimensional graphical representation of the results (Fig. 2), allows a simple screening of good and bad solvents for MF.

Table 6
Comparison between the HSPs and molar volume (V_m in cm^3/mol) of the listed compounds predicted in this work and the values reported in the literature.

Compound	This work					Literature					Ref.
	V_m	δ_D	δ_P	δ_H	δ_T	V_m	δ_D	δ_P	δ_H	δ_T	
LevA	105.00	16.95	8.35	10.69	21.71	N/A	N/A	N/A	N/A	N/A	N/A
M	170.80	18.56	2.93	10.82	21.68	175.60	16.60	4.70	10.60	20.25	Hansen (2007)
MF	271.60	22.72	5.75	11.32	26.02	N/A	19.60	9.40	3.60	22.10	Makoni et al. (2020)
T	142.90	19.73	3.58	11.83	23.29	166.90	19.00	4.50	10.80	22.31	Hansen (2007)
ethoxydiglycol	131.60	16.57	5.74	14.06	22.47	130.90	16.10	9.20	12.20	22.20	Hansen (2007)

Table 7
HSPs of DES and ethoxydiglycol and the study of their affinity degree with MF using RED and $\Delta_{\delta T}$ methods.

System	V_m	δ_D	δ_P	δ_H	R_a	*RED*	Class.[a]	$\Delta_{\delta T}$	Class.[a]
	($MPa^{1/2}$)								
LevA:M (2:1)	17.67	5.84	10.74	21.49	10.10	> 2.02	**S**	4.53	**NS**
LevA:T (1:1)	19.46	5.71	11.88	23.50	6.54	> 1.31	**S**	2.52	**S**
ethoxydiglycol	16.57	5.74	14.06	22.47	12.60	> 2.52	**NS**	3.56	**MS**
MF	22.72	5.75	11.32	26.02	–	–	–	–	–

∗ Calculated using a R_0 = 5.0 $MPa^{1/2}$.
[a] Classification: "S" – Soluble; "*NS*" – Not Soluble; "*MS*" – Moderately Soluble.

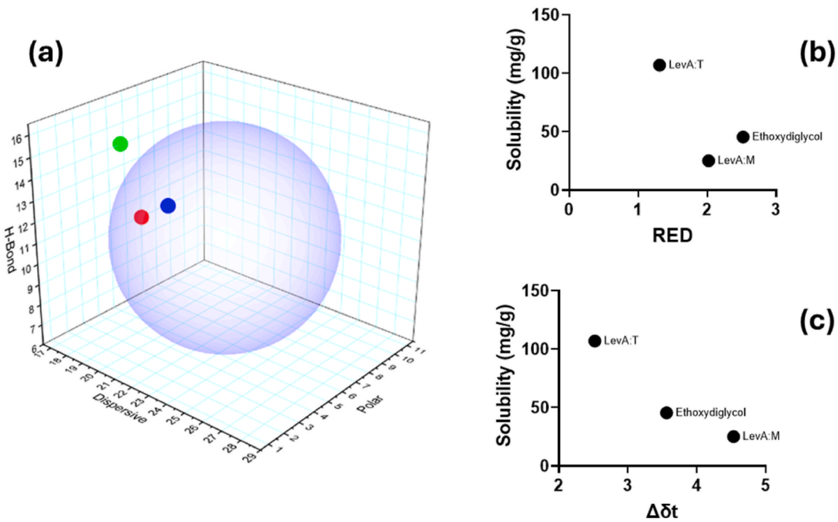

Fig. 2. 3D representation of the solubility sphere of MF and the position of each of the studied solvents (blue sphere – LevA:T (1:1); Red sphere – LevA:M (2:1); Green sphere – ethoxydiglycol), representing the obtained HSPs **(a)**. Relationship between experimental solubility (visual) of MF in the solvents LevA:T (1:1), LevA:M (2:1) and ethoxydiglycol), and their affinity degrees calculated using RED **(b)**, and $\Delta\delta_t$ **(c)** approaches. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

From Fig. 2, we can see that DES LevA:T (1:1) is the one closest to the centre of MF's solubility sphere, meaning that MF solubility in this DES is predicted to be higher, which once again is also observed in the experimental solubility determination.

It is important to mention that the radius of the solubility sphere used in this work (R_0 = 5.0 $MPa^{1/2}$) is not the real R_0 of MF, but a constant value that is commonly used for large-size molecules. According to Hansen (2007), there is an inverse relationship between the R_0 of a molecule and V_m, so a compound such as MF with a predicted V_m of 271.60 cm^3/m, has a R_0 slightly lower than 5.0 $MPa^{1/2}$.

This is why the *RED* values in Table 5 are expected to be higher than the ones listed in literature. Additionally, Fig. 2 shows that ethoxydiglycol is outside of the solubility sphere of MF while LevA:M (2:1) is inside, but from the experimental data MF has a higher solubility in ethoxydiglycol than LevA:M (2:1). In fact, by relating the experimental values of solubility with the affinity degrees, it is possible to confirm that *RED* (2 (b)) does not represent correctly the behaviour observed experimentally. On the other hand, despite the use of the $\Delta\delta_t$ parameter being more common for conventional solutions, it describes more accurately the solubility order (Fig. 2 (c)) compared with the results from Table 2. The lower $\Delta\delta_t$ value represents higher affinity to MF (the solute) and consequently, higher solubility.

Despite the limitations pointed out in the two methodologies (RED or $\Delta\delta_t$), HSPs are indeed a very powerful tool that can help predict and rationalize the solubility behaviour of known and novel drugs, screening the best solvents, or even improve their poor aqueous solubility (Lu et al., 2016; Petříková et al., 2021).

3.3. Emulsion preparation and characterization

Because the preparation of a topical product containing MF was intended, o/w emulsions were prepared, using MF dissolved either in ethoxydiglycol or DES and characterized (*see experimental*). Although the solubility of MF is higher for DES LevA:T, the presence of thymol, although safe, can potential result in a DES that is more prone to cause skin irritation. The preparation of o/w emulsions containing menthol-based DES has already been reported, and proved successful (Pillai et al., 2015; Van Osch et al., 2020). Therefore, and because menthol is used in topical formulations and acts as skin permeation enhancer, the emulsion development considered in this work, was carried out using LevA:M DES.

Rheological behaviour is important when developing products for topical and transdermal applications, influencing its efficacy and absorption and permeability through the skin.

Fig. 3 shows the flow curves obtained for the prepared emulsions, both with ethoxydiglycol or with DES LevA:M (1:1), in two different amounts of 1 and 5% each.

From Fig. 3, it can be observed that the prepared formulations exhibit a shear-thinning behaviour, which is usually required for skin application of topical formulations. Also, with the increased amount of glycol in the emulsions, there is a decrease in viscosity. Fig. 4 shows the rheology results obtained from oscillation mode measurements of the same emulsions, both the storage modulus (G′) and loss modulus (G″). From these results we can see that emulsions containing DES have lower G′ and G″ values, when compared with emulsions containing glycol, and that the emulsion containing 5% of DES has the lowest G′ and G″ values. This indicates that the structure of the emulsion with high concentration of DES is less robust than emulsions containing glycols. However, the emulsions prepared with 1 % of DES show a gel-like behaviour since its G′ is higher than G''which assured stability during the oscillation stress tests and shows the emulsion has long-term storage stability.

The prepared emulsions with ethoxydiglycol and DES were also characterized in terms of their droplet size, and results are presented in Fig. 5. This data can give us information regarding the stability of the prepared o/w emulsion, since small and uniform droplet size distributions indicate that an emulsion is physically stable (Bom et al., 2020). Droplet size can also have effects on the degradation and long-term stability of the emulsion, its texture and optical appearance, and viscosity (Jurado et al., 2007). From these results we can see that emulsions prepared with the 1% content of ethoxydiglycol and/or DES, present a uniform distribution in terms of droplet size, represented by a defined peak, and with ca. 90% of the droplets with a size of 5 μm. When the amount of both

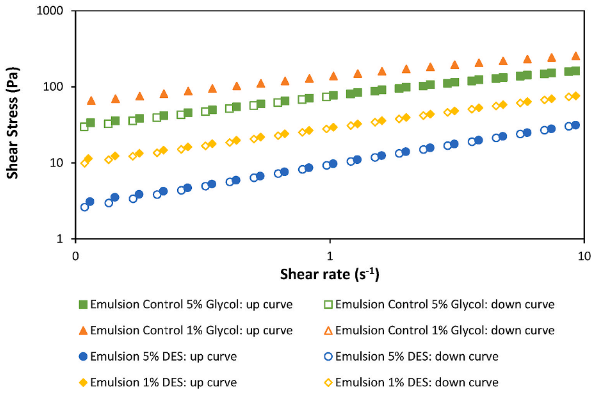

Fig. 3. Flow curves obtained for the prepared emulsions containing 1 and 5% of glycol and DES, as well as control samples.

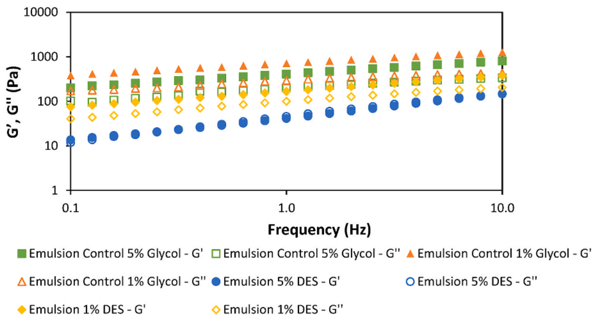

Fig. 4. Rheological measurements of storage and loss modulus variation with frequency, of the prepared emulsions containing 1 and 5% of glycol and DES, as well as control samples.

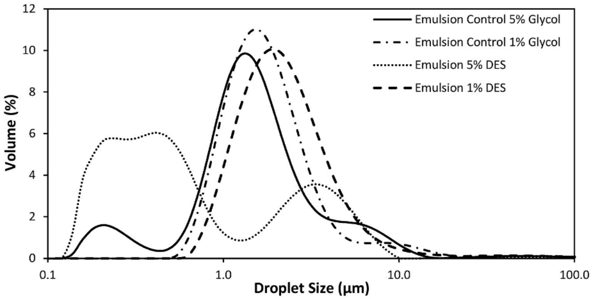

Fig. 5. Droplet size distribution of the different prepared emulsions, with and without DES Lev A:M (2:1).

glycol and DES is increased to 5%, a bimodal distribution of droplet size is observed, represented by two peaks; in the case of 5% of glycol droplets have 0.2 and 1.5 μm, and in the case of 5% of DES the emulsion droplets present sizes of 0.3 and 3.1 μm. This means that these emulsions have heterogeneous behaviour, and the ones containing 1% of DES are more suitable for the formulation of a topical product.

4. Conclusions

From this work, it becomes evident that DES are solvents that can have a significant impact in the solubility of poorly water-soluble drugs, as is the case of MF. DES composed by LevA:T and LevA:M are able to increase MF solubility by at least two orders of magnitude, when compared to MF solubility in water, and similar values of solubility are obtained when compared to commercial solvent ethoxidiglycol. This shows that DES can have an impact in the formulation of MF containing pharmaceuticals, allowing for the development of new products. The use of DES for drug solubilization and formulation presents some advantages, related with the fact that the DES results of a combination of individual compounds that besides increasing drug solubility, can have an effect in its permeability and availability. These DES, are composed of terpenes such as menthol and thymol, which are well known skin permeation enhancers, and so it is expected that formulations containing these DES will have an improved performance when used as topical emulsions.

Within this work, computational determination of Hansen solubility parameters was also carried out, to validate the experimentally obtained solubility results, but also to demonstrate the possibility to use this computational data in the prediction of DES as solvating systems for drugs. The obtained results from this methodology reveal that RED and $\Delta\delta_t$ parameters can be obtained, and despite some limitations in the calculation methods, the results correlate well with the ones obtained experimentally. This also demonstrates that LevA:T is able to dissolve MF in higher amounts, compared to the other studied DES.

Furthermore, the results obtained show that it is possible to incorporate DES containing MF, into o/w emulsions. The emulsions prepared with LevA:M containing MF, were prepared and characterized in terms of their rheological properties, exhibiting a sheer thinning behavior, usually required for emulsions for topical applications. The addition of DES, in 1 and 5% in the final formulation, affects the properties of the o/w emulsion, particularly a decreased viscosity, when compared to emulsions without DES. Still, emulsion stability is not affected by the presence of DES in the final formulation. The prepared emulsions were also characterized in terms of their droplet size behavior, and it is observed that emulsions containing 1% of DES present a homogeneous droplet size distribution.

Considering all the presented results, the use of DES for the development of emulsions for topical applications is proved possible, and to the best of our knowledge, the use of DES containing mometasone furoate and its formulation as o/w emulsions is presented for the first time. Furthermore, since the solubility of mometasone furoate in DES is greatly increased when compared toits water solubility, this can be a strategy that can be extended for the formulation of other poorly-water soluble drugs, and alternative drug-delivery methods.

CRediT authorship contribution statement

Rita Craveiro: Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Ângelo Rocha:** Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cláudio Fernandes:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Ana Rita C. Duarte:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Joana Marto:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation. **Alexandre Paiva:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2024.101783.

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