Expert Opinion on Drug Delivery

ISSN: 1742-5247 (Print) 1744-7593 (Online) Journal homepage: https://www.tandfonline.com/loi/iedd20

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To cite this article: Sónia N. Pedro, Mara G. Freire, Carmen S. R. Freire & Armando J. D. Silvestre (2019): Deep eutectic solvents comprising active pharmaceutical ingredients in the development of drug delivery systems, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2019.1604680

To link to this article: https://doi.org/10.1080/17425247.2019.1604680

Accepted author version posted online: 06 Apr 2019.
Published online: 30 Apr 2019.

EXPERT OPINION ON DRUG DELIVERY
https://doi.org/10.1080/17425247.2019.1604680

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REVIEW

Deep eutectic solvents comprising active pharmaceutical ingredients in the development of drug delivery systems

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ABSTRACT

Introduction: Deep eutectic solvents comprising or acting as solvents of active pharmaceutical ingredients (API-DES) emerged as promising alternatives to improve therapeutic efficiency, with the additional possibility to integrate them in (bio)polymer-based systems to enhance their delivery.

Areas covered: A critical review of the API-DES field evolution is herein presented, namely on the capacity of DES to integrate APIs in their composition and on the use of DES as solvents for APIs. These strategies avoid a current major concern related to drugs and APIs, *i.e.* polymorphism, and increase the solubility and bioavailability of the target API which leads to increased bioavailability. Owing to their composition versatility, polymerizable API-DES can also be prepared. Finally, the incorporation of API-DES in (bio)polymer-based systems to improve drug delivery is presented and discussed.

Expert opinion: The relatively easy preparation of API-DES and their capacity to tune the API's release profile when incorporated in (bio)polymer-based systems represent an effective alternative to improve the APIs therapeutic action and to develop controlled drug delivery systems. Given the potential and progress demonstrated so far, the authors foresee further research on novel API-DES and on their delivery routes, envisaging the development of alternative therapies and final approval as therapeutics.

ARTICLE HISTORY
Received 21 January 2019
Accepted 4 April 2019

KEYWORDS
Active pharmaceutical ingredients; deep eutectic solvents; biopolymer-based systems; drug delivery; drug solubility

1. Introduction

Improving the efficiency of the existing drugs is currently one of the major goals of pharmaceutical industries [1]. Rather than developing new drugs with higher bioavailability, which requires new clinical trials, there are undisputable assurances and profits in improving the already tried-and-tested therapies [2]. To improve their pharmacological action, drugs can suffer incremental changes, such as the modification of the drug's form and formulation, assessment of new combinations, and the use of different dosages or novel administration routes. One of the characteristics with great ceiling for improvement is hydrophilicity; approximately 40% of the approved drugs and nearly 90% of the drugs under development are poorly water-soluble, which leads to low bioavailability and permeation [3]. Especially for Biopharmaceutics Classification System II (BCS Class II) substances, with low solubility and high permeability, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids [4]. Although numerous approaches are reported in the literature [5], the improvement of the drugs' solubility and bioavailability remains one of the most challenging aspects of drug development, particularly for oral-drug delivery systems. In order to enhance oral bioavailability, solid dispersions have been used as one of the most successful approaches [6]. These are described as a family of dosage forms where the active pharmaceutical ingredient (API) is dispersed in a biologically inert matrix prepared by melting or solvent evaporation methods [6]. The first drug whose rate and extent of absorption was significantly enhanced using a solid dispersion technique dates back to the 1960s, when Sekiguchi and Obi [7] studied the absorption differences between sulfathiazole and its eutectic mixture with urea. After this pioneering work, and aiming to improve APIs solubility and dissolution profiles, other studies reported on eutectic mixtures and deep eutectic solvents (DES) comprising active pharmaceutical ingredients (APIs) [8,9].

Innovation in drug efficacy improvement has been constrained by the common use of solid forms of APIs, often associated with physical and chemical instability in their final dosage [10]. These concerns can be due to their polymorphism and dissolution and oral drug absorption in humans, thereby conditioning the drug's bioavailability [11]. An alternative to overcome these concerns is the APIs' conversion into liquids. Contrarily to solid forms, liquids display a higher solubility in water since the energy barrier associated with the enthalpy of fusion is overwhelmed, providing a higher therapeutic response [12]. However, the manufacturing of APIs in the liquid form must ensure safety, efficacy, and stability of the final drug product. One illustrative example of the development of liquid forms of APIs is their conversion into ionic liquids, constituted by anionic and/or cationic active ingredients (API-ILs) [13–15]. The first report on API-ILs described the synthesis of ranitidine docusate, a dark red liquid with a glass transition temperature of −12°C, capable of avoiding ranitidine's polymorphic conversion [16]. An additional API-IL, comprising lidocaine and docusate as ions, was also reported [17]. Due to their advantages, an increasing number of reports on

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Article highlights

- Eutectic mixtures and deep eutectic solvents comprising active pharmaceutical ingredients (API-DES) are here presented as a novel approach to develop liquid forms of APIs. The versatility in the design of these new liquid forms, by the proper selection of the hydrogen bond-donor (HBD) and hydrogen bond-acceptor (HBA) species, dictate their role in drug delivery and thus their pharmacological action.
- API-DES have vast applications in drug delivery and ability to overcome some drawbacks of solid drugs by increasing the drug's stability, solubility, permeation, bioavailability and therapeutic action.
- API-DES stand-out for their unique characteristics and applications; not only it is possible to incorporate them into (bio)polymer-based systems, but they can also be designed to present polymerizable moieties. Ultimately these mixtures can be applied in the development of controlled delivery systems, exerting a triple action: acting as monomers for polymers production, as polymerization media itself and by providing the API for controlled drug delivery.
- Even though DES hold great promise to be accepted by the pharmaceutical industry and commercialized as APIs' alternative solvents and as novel formulations capable of incorporating APIs, more complete and thorough studies are still required as the full chemical and biological evaluation is demanding.
- The authors encourage the development of (bio)polymer-based systems for API-DES delivery. New directions in the fabrication of these systems are expected in the near future. Biological assays are also still required to fully develop API-DES and novel drug delivery systems based on polymers with high therapeutic action and controlled drug release.

This box summarizes key points contained in the article.

API-ILs emerged in the past years, being described as a novel strategy to improve drugs therapeutic action and delivery [18,19]. However, the difficulty in using ILs as new solvents for APIs conveys in their mostly unknown toxicity profiles, which are mostly dependent on the IL's structure. This fact has delayed their acceptance in the pharmaceutical and biomedical areas [13]. Therefore, the development of alternative processes feasible to apply in the pharmaceutical industry must be pursued. In this field, eutectic mixtures and deep eutectic solvents (DES) have emerged as advantageous alternatives to incorporate APIs, being also able to produce new liquid forms of APIs and to enhance their bioavailability. DES are usually prepared by the combination of molecules whose toxicity profiles are already well established and whose use in pharmaceutical applications is already well accepted. These mixtures allow to overwhelm a series of *in vitro* and *in vivo* studies and ideally decrease the high E-factor associated with the pharmaceutical industry [13]. Furthermore, and contrarily to ILs, the preparation of DES only requires the mixing of at least two species, i.e. a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA), with no chemical reactions occurring.

DES are eutectic mixtures that deviate from the ideal thermodynamic solid-liquid phase behavior, i. e. a mixture of pure compounds for which the eutectic point temperature is below than that of an ideal liquid mixture (Figure 1) [20,21]. Strong hydrogen-bond interactions between the HBD and HBA species that form the DES are responsible for a decrease in the melting temperature to such a degree where the mixture can be liquid at room or human body's temperature [22]. DES, unlike ILs, are mixtures, and not pure compounds, and can be at best a solution of ions and not a fluid constituted solely by ionic species [21]. DES preparation usually involves the simple mixing of at least two components, generally under stirring and moderate heating [23]. Importantly, the temperature to which the mixture is subjected must be carefully controlled to prevent the decomposition of the individual components that make up the DES [24]. Since no chemical reaction is involved in the preparation process (it presents 100% of the atom economy and fits within one of the Green Chemistry principles), there is also no formation of by-products [25]. Thus, their purity is only dependent on the purity of the individual starting components and on the avoidance of degradation products. This being said, the toxicity of the final mixture must be carefully assessed since significant differences from the individual constituents might be observed [26–28]. To overcome some of the cytotoxicity

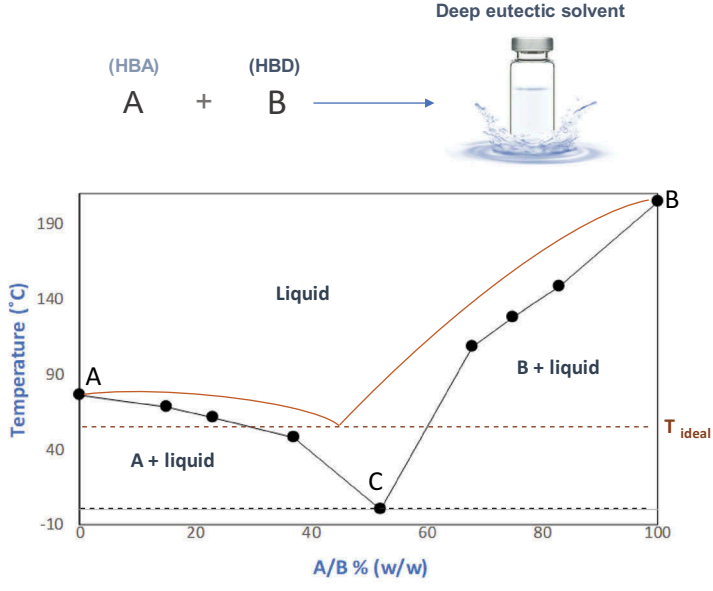

Figure 1. Phase diagram of a DES showing the depression of the freezing point of the mixture (T_E) compared with its ideal behavior (T_{ideal}).

concerns related with DES, especially when their human consumption is envisaged, the research on natural DES (NADES) has been recently expanded [29]. Furthermore, due to the possibility of combining an enormous number of HBDs and HBAs, NADES can be considered tailor-made solvents with high interest in biomedical and pharmaceutical applications [30,31]. As such, DES comprising the API as the HBD or HBA species or as solvents to improve the solubility of target APIs have been studied.

2. DES as new solvents for APIs

Pharmaceuticals require a solvent to assist in processing and in the transportation of materials [32]. Water is the most commonly used and most desirable solvent-vehicle for pharmaceutical products [33]. Nevertheless, improvements in the solubility of poorly water-soluble drugs usually require the use of organic solvents such as ethanol, acetone, or ethers. Therefore, improving the solubility of APIs, by a safer way still remains a challenge. A large increase in solubility can be achieved by the use of more benign co-solvents, such as sorbitol, glycerol, propylene glycol and polyethylene glycol, among others [34]. However, solubility enhancements achieved are not so promising as those observed with DES.

DES have been widely studied as alternative solvents for APIs' solubilization, particularly for topical formulations [23]. Promising results on the solubilization of poorly water-soluble drugs in DES have been reported, as summarized in Table 1. For example, ibuprofen solubility in aqueous solution can be increased by using propylene glycol and polyethylene glycol (PEG 300) as co-solvents achieving enhancements of 193-fold and 700-fold, respectively [34]. Nevertheless, ibuprofen's solubility can be increased more than 5,400-fold in DES, when compared with its solubility in water [35]. Other non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen and ketoprofen, and analgesics like acetaminophen, are additional examples of drugs that have been investigated in this regard [35,36]. Li and co-workers [37] demonstrated solubility enhancements for itraconazole, piroxicam, lidocaine, and posaconazole of 6700-, 430-, 28-, and 6400-fold, respectively, compared to their solubility in water, using a DES based on cholinium chloride (ChCl) and glycolic acid (molar ratio 1:2). A solubility enhancement for itraconazole of 53,600-fold by adding a third component, oxalic acid, into this DES, at a molar ratio of 1:1.6:0.4, has also been reported [37]. The NADES formed by menthol:camphor (1:1 molar ratio) also proved to be a promising biocompatible solvent for ibuprofen, allowing to achieve solubility of 40.4 ± 8.8 $\mu g.mL^{-1}$ (vs. 9.81 ± 2.71 $\mu g.mL^{-1}$ in water at the same temperature) [38].

A better understanding of the DES solvation ability was provided by a theoretical approach for the solubilization of lidocaine in ChCl:lactic acid and β-alanine:lactic acid (1:1) [39]. The reported results show the efficient lidocaine solvation by the referred solvents due to a combination of hydrogen bonding and non-specific Van der Waals interactions. The predicted solubility of lidocaine in these solvents was several orders of magnitude higher than in water and comparable with that obtained with ILs, hence being a competitive platform for APIs solubilization.

In addition to improvements in solubility, DES have also been reported as promising solvents to improve the chemical stability of APIs. It is known that many APIs decompose through a variety of pathways and are not stable in aqueous solution, for instance, many ester-containing pharmaceuticals, such as aspirin, undergo hydrolysis upon prolonged storage in water [40]. Recently, DES were highlighted for their stability improvement capability when used for APIs solubilization. In one study, the hydrolysis of aspirin into salicylic and acetic acids in the DES ChCl:1,2-propanediol was 8.2 times slower than in aqueous solution [35]. The betaine:urea mixture also increases the stability of β-lactam antibiotics, namely imipenem and clavulanic acid, by 7- and 2.5-fold, respectively, when compared with their aqueous solutions [41]. Therefore, DES may be designed to improve both the solubility and the stability of a target drug.

The described characteristics are crucial to increase the bioavailability of APIs. Accordingly, in a pioneering work in Balb/c mice by Farggian and co-workers [42], where pharmacokinetic studies of rutin solubilized in proline:glutamic acid DES were conducted; it was reported an enhancement of the oral absorption of the target drug. By comparing the administration of a rutin solution in water with the equivalent rutin formulation in a DES, a change in t_{max} (maximum time) was observed, namely 15 min *vs* 60 min, with no changes in the absorption rate. Surprisingly, a marked difference in C_{max} (maximum concentration) and AUC (area under the curve) was detected, revealing an increase in the relative bioavailability of rutin in the DES formulation of approximately 100% when compared with its behavior in aqueous solution. The proline:malic acid:lactic acid:water mixture, at molar ratio 1:0.2:0.3:0.5, also leads to an increase (12-fold) in the solubility of berberine, known for its anti-diabetic properties, while also

Table 1. Reported solubility improvements of APIs in DES solvents at room temperature.

API	Solubility in water ($mg.mL^{-1}$);	DES (molar ratio, HBA:HBD)	Solubility in DES ($mg.mL^{-1}$);	Reference
Aspirin	7.03 ± 0.03	ChCl:1,2-propanediol (1:2)	202.00 ± 3.15	[35]
Acetaminophen	19.95 ± 0.12	ChCl:1,2-propanediol (1:2)	324.00 ± 4.23	[35]
Ibuprofen	0.07 ± 0.00	Camphor:menthol (1:1)	282.11 ± 6.67	[38]
		Tetrapropylammonium bromide:1,2-propanediol	383.40 ± 4.03	[35]
Itraconazole	<0.001 ± 0.00	ChCl:glycolic acid:oxalic acid (1:1.6:0.4)	53.60 ± 1.20	[37]
Lidocaine	3.63 ± 0.00	ChCl:glycolic acid:oxalic acid (1:1.7:0.3)	295.40 ± 6.80	[37]
Ketoprofen	0.34 ± 0.00	ChCl:Levulinic acid (1:2)	329.10 ± 4.42	[35]
Naproxen	0.06 ± 0.00	ChCl:1,2-propanediol (1:2)	45.26 ± 1.24	[35]
Piroxicam	0.02 ± 0.00	ChCl:glycolic acid:oxalic acid (1:1.7:0.3)	3.10 ± 0.10	[37]
Posaconazole	0.01 ± 0.00	ChCl:glycolic acid:oxalic acid (1:1.7:0.3)	88.40 ± 2.40	[37]
Rutin	0.12 ± 0.05	ChCl:proline (3:1)	2.79 ± 0.10	[42]

leading to an eightfold increase of its concentration in blood [43].

Amongst the DES studied, ChCl-based mixtures have been the most explored to solubilize APIs. This trend is mainly associated with the fact that these DES are already well characterized in the literature, and ChCl is a strong HBA species and safe and low-cost compound [37]. Despite the remarkable results on solubility improvements, the use of ChCl with HBDs with non-negligible toxicity, like glycolic acid or oxalic acid (Table 1), can be a potential problem in the implementation of these mixtures as solvent media for pharmaceutical formulations. In this sense, the DES components must be carefully selected, and their cytotoxicity evaluated when addressing this purpose.

3. API-DES formulations

Unlike the previously described strategy, the enhancement of APIs' solubility may also occur when the API is converted into its liquid form, i.e. through the formation of deep eutectic solvents comprising the target active pharmaceutical ingredient (API-DES). Since these DES possess in their composition an API, and thereby exhibit therapeutic action, they belong to the previous proposed therapeutic deep eutectic solvents (THEDES), which comprised inactive pharmaceutical ingredients [44]. Most APIs may act as HBDs and/or HBAs, and thus be used as DES phase-forming constituents. However, the proper selection of both the HBA and HBD plays a critical role in API-DES formation, in the creation of a DES liquid at the body's temperature and on the resulting therapeutic properties. API-DES can be prepared from a large number of APIs, combined with a wide variety of other compounds, e.g. metabolites [45] or permeation enhancers [46,47]. DES can also be prepared from two different APIs, resulting in dual function liquid forms [17,45] (Figure 2). API-DES can additionally present a polymerizable character when comprising APIs with polymerizable moieties [48] further allowing the adequate tuning of the delivery profile. Despite all the possible combinations, and the fact that APIs can act as HBAs, most of the API-DES reported up to date are prepared using the API as the HBD species, since most of them present amine, carboxylic acid and alcohol groups [45]. Among API-DES, dual function is one of the most promising strategies since it allows the incorporation of two active ingredients in the same formulation, while avoiding the polymorphism of both APIs if a liquid form is obtained [45].

One of the oldest eutectic mixtures known is the anesthetic cream EMLA® (Eutectic Mixture of Local Anaesthetic; melting temperature = 16°C) used in transdermal delivery, composed of prilocaine (melting temperature = 38°C) and lidocaine (melting temperature = 68ºC) [49]. This eutectic mixture represents a landmark in drugs' solubilization enhancement strategies, and this was the first eutectic mixtures to be patented and commercialized [50]. However, EMLA®'s adverse side effects, mainly attributable to prilocaine, led to the creation of other dual function eutectic mixtures, such as lidocaine: procaine and lidocaine:tetracaine. The lidocaine:tetracaine mixture is also liquid at room temperature, presenting a melting temperature similar to lidocaine:prilocaine (ca. 18° C) [51]. More recently, the creation of a remarkable dual function API-DES based on ibuprofen and lidocaine was reported [17]. Moreover, *in vivo* tests indicated that the anesthetic effect of lidocaine in this eutectic mixtures is faster and stronger when compared with the commercial EMLA® and the lidocaine:tetracaine mixture, having a pharmacological effect in 10 min vs. 1 h and 30 min, respectively.

The facilitation of transport through the skin barrier brought by EMLA® motivated a broad spectrum of studies in this field. In addition to dual function DES, a new field of development emerged, with API-DES comprising permeation enhancers in their composition aimed for topical and transdermal delivery. In 1998, Stott and co-workers [46] described API-DES composed of ibuprofen, and several skin permeation enhancers, such as 1,8-cineole, L-menthol, thymol, D-limonene, cymene and L-menthone. From the investigated mixtures, the ibuprofen: thymol binary system should be highlighted due to its lower melting temperature (32ºC) and a remarkable solubility enhancement of 12.7-fold. Furthermore, the depression in the mixture melting temperature down to 32°C represents an additional advantage since the recrystallization of the API at lower temperatures can be used as an approach to improve the product stability under storage.

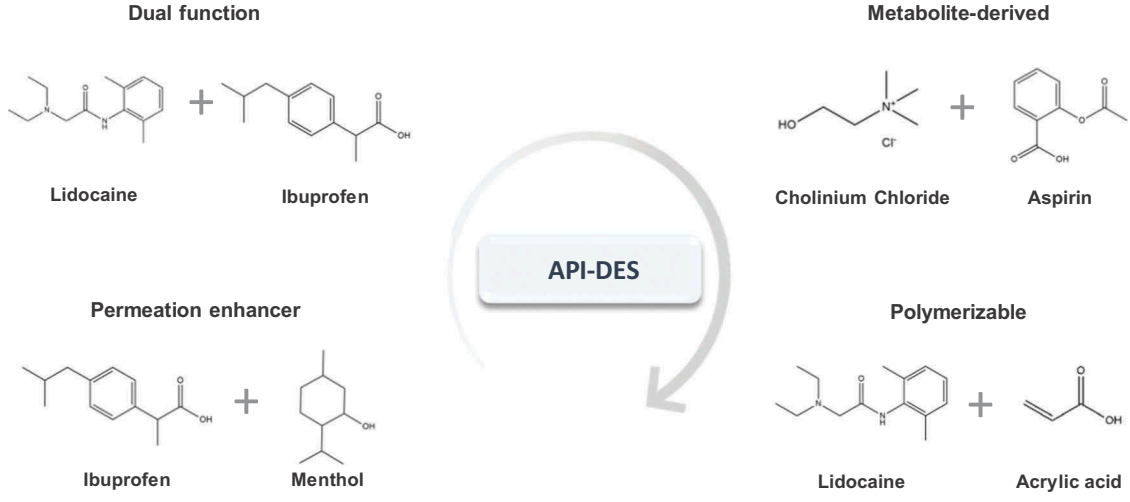

Figure 2. API-DES strategies using different HBAs/HBDs with distinct biological properties and functions.

Permeation enhancers like menthol have been widely used in API-DES formulations for transdermal delivery. Menthol has been combined with coenzyme Q_{10} (CoQ_{10}) [52], paeonol [53], ibuprofen [54] and aspirin [55], always resulting in liquid API-DES at body's temperature (melting temperature = 32-37ºC). The permeation behavior in isotonic solution of the menthol: ibuprofen formulation has also been studied [54]. Such studies, conducted on Franz cells compared the API-DES permeation capability to the pure API, and a threefold increase was observed with the API-DES form. Unfortunately, this is one of the few works where skin permeation studies have been conducted and published.

Fatty acids have also been successfully used in the development of promising API-DES formulations. One example of this utilization was first reported for transdermal delivery purposes and comprised the combination of lauric and palmitic acids with ibuprofen and lidocaine, resulting in mixtures with melting temperatures near the human skins temperature [52,56]. More recently, lauric acid was used in the preparation of an API-DES with CoQ10 envisaging its use in oral delivery, resulting in a DES with a melting temperature of 37.93 °C [47]. Most of the reported API-DES display melting temperatures near or below the human body's temperature; however, for future applications, other fundamental parameters, such as drug solubility, dissolution rate, and bioavailability need to be evaluated.

API-DES can be used not only to improve the drug's oral bioavailability but also to develop alternative delivery systems to avoid cases of erratic absorption and inadequate plasma concentrations of drugs like itraconazole. Different drug carriers have been investigated for itraconazole delivery, such as solid dispersions [57], inclusion complexes with cyclodextrin [58], and mixed polymeric micelles [59]. However, to avoid the systemic effects, topical formulations have demonstrated to be advantageous since they provide local treatment of fungal infections, fast drug delivery to the target site, and higher drug levels in tissues [60]. With this purpose, API-DES alternatives with itraconazole and phenol have been reported for topical application [60]. This liquid form of the antifungal allows not only the increase in the drug concentration for topical use but also avoids its recrystallization [61]. However, screening of less toxic permeation enhancers, studies of chemical stability, skin irritancy and *in vitro* and *in vivo* antifungal effects of this type of API-DES are essential for further developments.

Significant solubility improvements using API-DES have already been verified for several APIs, such as paeonol, with an increase up to 60 µg/mL [53], and ibuprofen [54] with a 12-fold increase in solubility when in the API-DES form. Another example of the API-DES capacity to enable the solubilization of poorly water-soluble APIs is the development of 'liquid aspirin', formed by acetylsalicylic acid and ChCl [45]. The resulting mixture proved to be miscible with water and stable up to 3 days at room temperature without presenting any signs of recrystallization (Figure 3).

Table 2 summarizes the successful development of liquid forms of APIs using the API-DES approach, with emphasis on the decrease of melting temperatures. The evidences given by API-DES throughout the years undoubtedly boosted their research for the improvement of existing therapeutics. Therefore, different drugs from different pharmacological classes and with different drug delivery purposes have been successfully reported. Nevertheless, for their administration, these liquid drugs require proper vehicles, allowing them to accurately reach their target and to modulate their release profiles. To this end, the last section of this review focuses on the use of API-DES in (bio)polymer-based systems for drug delivery purposes.

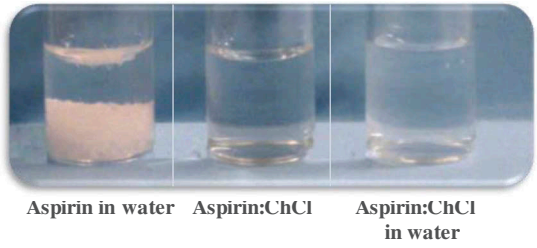

Figure 3. Visual representation of aspirin:ChCl liquid form using the API-DES strategy and subsequently improved solubility in water (Reproduced with permission from [45]).

Table 2. Examples of API-DES reported in the literature, molar ratio, melting temperature, and envisioned route of administration.

API-DES	Molar ratio	Melting temperature (°C)	Route of administration	Reference
CoQ10:Menthol	–	37	Oral	[52]
CoQ10:Lauric acid	1:2	37	Topical	[47]
Ibuprofen:Lauric acid	2:5	35	Topical	[56]
Ibuprofen:Lidocaine	–	–27	Transdermal	[17]
Ibuprofen:Thymol	1:2	32	Transdermal	[46]
Itraconazole:Phenol	3:20	0	Topical	[60]
Lidocaine:Lauric acid	–	6	Topical	[62]
Lidocaine:Camphor	1:1	33	Topical	[63]
Paeonol:Menthol	4:6	32	Transdermal	[53]
Resorcinol:ChCl	1:1	6	Oral**	[45]
Apirin:ChCl	2:1	–67*	Oral**	[45]
Ranitidine:Glycerol	2:1	–87*	Oral**	[45]
Phenformin:Glycerol	2:1	–69*	Oral**	[45]
Ranitidine:Urea	2:1	–31*	Oral**	[45]
Adiphenine:Urea	2:1	–45*	Oral**	[45]
Adiphenine:Aspirin	2:1	–23*	Oral**	[45]
Ranitidine:Aspirin	2:1	–37*	Oral**	[45]

(*) Glass transition temperatures of the respective mixtures.
(**) Although not described in the original manuscript, it was considered the original API application.

4. DES incorporation in (bio)polymers for drug delivery

In recent years a notorious evolution of drug delivery strategies has been observed, involving both modifications to conventional methods and design of new devices [64]. Polymers have played an important role in this evolution, by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and tuneable (or stimuli-responsive) release of both hydrophilic and hydrophobic drugs.

In addition to API-DES comprising APIs to improve therapeutic efficacy, API-DES can also be used for the development of controlled delivery systems as monomers for polymer production. Their use in polymer-based systems was initially introduced with the synthesis of poly(octanediol-co-citrate) elastomers using a mixture composed of 1,8-octanediol and lidocaine and citric acid as the second polymer precursor [65].

The drug delivery system preparation allowed the authors to conclude that the DES exerts a triple action, providing the API for drug release, acting as the monomer required for the elastomers preparation, and acting itself as the synthetic media for polymerization. However, this approach is still controversial, since upon DES' polymerization the DES concept is compromised due to the condensation of 1,8-octanediol with citric acid. Still, by taking advantage of the DES capacity to polymerize, novel systems have been proposed using frontal polymerization (FP) strategies involving acrylic acids and lidocaine [48]. Acrylic acid:lidocaine and methacrylic acid:lidocaine have been reported as API-DES with a triple role, which after polymerization are able to offer a controlled release of lidocaine. Even though the referred API-DES present reactive monomers, the polymerizing monomer co-former does not chemically react with the API. These mixtures are initially liquid at room temperature and possess all qualities of conventional DES; however, upon polymerization of the same, the DES concept is lost due to the development of a polymer-based delivery system with an API incorporated in the polymeric matrix. The advantage of the creation of drug delivery systems in one step is that the chance of decreasing or losing the drug activity by processing is minimized. Moreover, the relatively easy tailoring of the viscosities of the monomer and the densities of the DES by the manipulation of the HBD and the mixture's molar ratio favored the accomplishment of the FPs with high conversion monomers conversion (90–100%) [48]. Despite the potential of FP, in future studies, improving polymerization efficiency to nearly 100% is essential in order to avoid the presence of residual free monomer.

In addition to their application in the development of polymer-based drug delivery systems, DES have proven to be advantageous in biopolymer's processing and dissolution, as shown with agar [66], chitin [67] and cellulose [68]. Given their biocompatible and versatile character after the biopolymers dissolution, the mixtures with DES can be directly applied as delivery systems [69]. The oldest studied system for API-DES delivery is associated with EMLA®, commercialized either as a cream or in a patch form [70]. In the latter case, a single-dose unit of EMLA® is incorporated in a cellulose absorbent disc. Although EMLA® patches have been developed and highlighted for their easy application, they seem to exert the same effect as the cream form in cutaneous pain relief [71]. Substantial improvements in the level of analgesia.

The lidocaine and prilocaine mixture used in EMLA® has been studied in the development of a local delivery system to the periodontal pocket [72]. Cellulose derivatives such as ethyl-(hydroxyethyl)cellulose (EHEC) and a hydrophobically modified EHEC have been tested as potential carrier systems for the anesthesia mixture's delivery, demonstrating a sustained drug release over a minimum of 1 h [72]. Interactions between the modified cellulose polymers and cationic and ionic surfactants, namely myristoyl-choline bromide and sodium dodecyl sulfate (SDS), were determined in the absence and presence of the API-DES. One of the most interesting features of mixed surfactant/EHEC systems is the increase in viscosity upon increasing the temperature. This behavior allows to administrate an API in a low-viscous polymer system that thickens in contact with the body. The obtained data indicated the possibility of formulating a temperature-sensitive system where small amounts of the API-DES can be incorporated without severely affecting the gelation behavior of the polymer. However, even if a temperature-induced increase in viscosity is an advantage, the use of these surfactants has associated toxicological and carcinogenic effect [73].

API-DES can be used in biopolymer-based systems not only for their therapeutic action and polymerizable character but also as porosity enhancers in supercritical fluid sintering. An example has been demonstrated with the anti-inflammatory API-DES menthol:ibuprofen (3:1 molar ratio) [44]. This delivery system was developed by the impregnation of a polymeric blend (composed of starch and poly-ε-caprolactone (SPCL)) with the API-DES, after supercritical CO_2 ($scCO_2$) sintering. This foaming process with the API-DES allows to obtain a porous matrix impregnated with the intended API. The liquid API-DES contributes to a significant modification in the aggregation of the polymer particles, leading to a higher porosity and interconnectivity (Figure 4). *In vitro* dissolution studies demonstrated similar dissolution profiles between pure ibuprofen and its liquid form with menthol; however, ibuprofen presented a faster release rate from the polymeric carrier impregnated

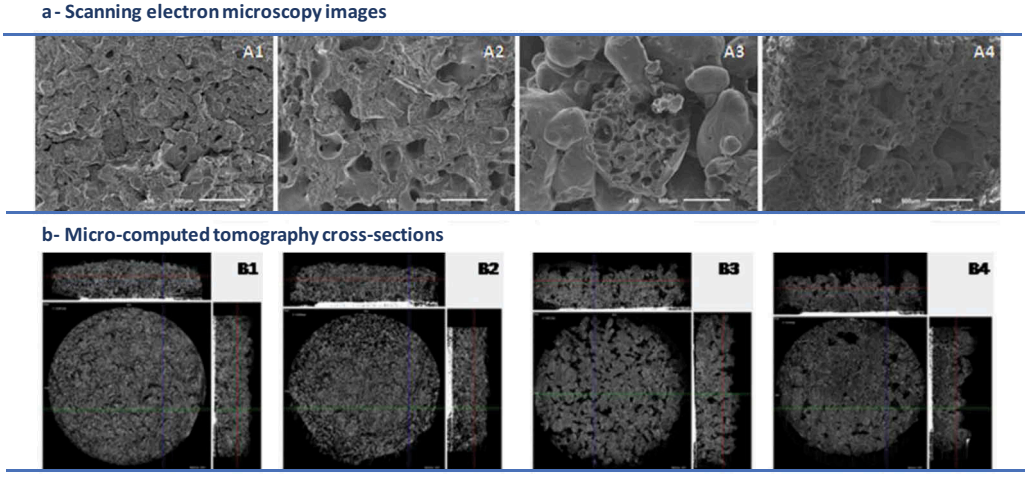

Figure 4. SEM images and micro-CT images of SPCL (B1), SPCL + ibuprofen (B2); SPCL + 10% API-DES (B3), and SPCL + 20% API-DES (B4) (Reproduced with permission from [44]).

with API-DES than in its pristine form. Such a fact highlights the advantage of using API-DES and biopolymer-based systems to change/tune the APIs release profile. Despite this fact, a full application of this strategy must be further developed. More recently, using the same polymeric blend and the same approach based on $scCO_2$ sintering, it was possible to develop a controlled drug delivery system with a DES-based on ChCl and ascorbic acid, in which the dexamethasone solubility increased by several orders of magnitude [74].

Recently, a fast-dissolving gelatine-based system was studied for API-DES delivery. Contrarily to previous studies in this area, aiming topical and transdermal delivery, the work of Mano and co-workers [75] focused on the development of an oral drug delivery system. Fast-dissolving delivery systems dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. These systems usually enable a rapid onset of action with a significant increase in the drug's bioavailability when compared to common oral administration systems. With this purpose in mind, the ChCl:mandelic acid mixture was used as an API-DES model to evaluate the capacity of these mixtures to be encapsulated in gelatine nanofibers produced by electrospinning. The produced nanofibers, of low cost, biodegradable nature and with antibacterial activity, presented a fast drug release profile. Cytotoxicity studies showed that the gelatine fibbers with DES do not display negative influence on cell proliferation, being suitable for oral administration. Despite the demonstrated fast dissolution of the model drug and the existing evidences of the electrospinning nanofibers capacity to enhance oral bioavailability, this must be assessed in more detail, addressing the pharmacokinetic parameters in order to verify the advantages of these systems over systems comprising solid forms of APIs.

Figure 5 summarizes different API-DES applications in (bio) polymer-based systems, demonstrating the potential of using these formulations in the development of novel therapeutic delivery systems, while at the same time addressing the delivery of drugs in their liquid forms in a biocompatible way.

5. Conclusions

Despite the fact that many drugs exhibit multiple crystalline forms (polymorphs), the reliance of the pharmaceutical industry on solid-state drugs remains. However, solid-state drugs and their polymorphs have a profound effect on the chemical properties and therapeutic efficacy of a specific drug. Furthermore, solid drugs display a lower solubility in water, and thus lower bioavailability, than similar liquid forms. To overcome these drawbacks, novel liquid forms of APIs in the form of API-DES have been proposed and investigated and represent a new approach that must be considered by pharmaceutical industries. API-DES, formed by APIs as constituents of the DES itself or the use of DES to solubilize the APIs, have been described. DES do not require to be formed only by two species, and both approaches are in fact connected since the dissolution of a target API in a DES leads to the incorporation of the API in the DES itself. Nevertheless, both approaches may lead to enhanced solubility, therapeutic action, and stability of the target API, while avoiding the polymorphism of the original drug. Furthermore, API-DES can be created with a wide variety of compounds, and thus designed to have a specific and enhanced therapeutic action, including those with dual function effect, and by the incorporation of penetration enhancers.

Some advances in (bio)polymer-based systems were here revised for the delivery of API-DES, emphasizing the potential and innovation brought by API-DES with polymerizable character. This particular type of API-DES is capable of exerting a triple action, i.e. by providing the API for drug release, acting as the monomer itself and as the synthetic media for polymerization. These systems provide new drug delivery options and represent a step forward in the development of novel drug delivery systems. Despite the existence of initial promising results with this strategy and examples of its potential applications, more profound research is still required to enable the full comprehension and manipulation of these drug delivery systems.

6. Expert opinion

Eutectic mixtures and DES represent a competitive platform to improve the therapeutic action and delivery of APIs. They do not only display a high potential to act as alternative solvents for APIs but are also able to incorporate APIs in their formulation. Both approaches lead to improved solubility and bioavailability, as well as the stability of the drugs. Even though ILs have also been proposed as a way to circumvent the polymorphism of drugs by converting them into the liquid state, DES do not need the reaction steps required in the synthesis of

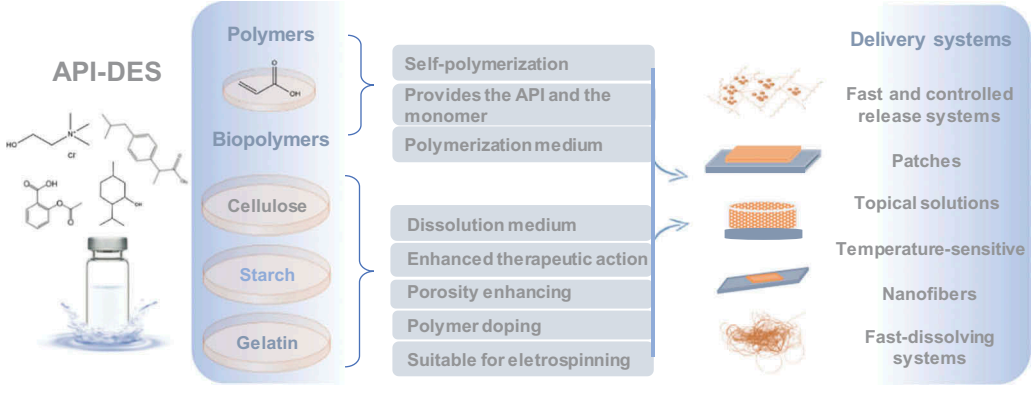

Figure 5. Comprehensive assembly of different API-DES applications and functions in (bio)polymer-based systems.

ILs. DES are prepared by the mixing of at least two compounds able to establish strong hydrogen-bonds, thus leading to a significant decrease in the melting temperature of the mixture when compared to their individual components. Their relatively high viscosity can be manipulated in a non-toxic way, by manipulating the mixture ratio or by addition of water or polyols, such as glycerol [76]. Furthermore, their remarkable enhancement of solubility for different APIs and the improvement in pharmacokinetics demonstrate the possibility of using DES in several drug delivery applications as alternatives to conventional solvents and other enhancement techniques. Even though some DES comprising non-negligible toxicity components have been reported in the literature, a more careful choice of the DES components should be carried out.

Contrarily to ILs [77], there is still a profound lack of information on the molecular-level mechanisms responsible for the high solubilization capacity of DES. Therefore, strong efforts must be made to fill this gap. Results on this field will allow the proper design of DES for target applications, avoiding trial-and-error approaches. In the same line, it has been a challenge to predict which mixtures and which molar ratios will originate API-DES. A significant collection of their solid-liquid phase diagrams and data correlating compositions and properties is still required, particularly to allow to easily distinguish DES of others eutectic mixtures. Equally, for their study, the development of predictive models to appraise their phase and solubility behavior is mandatory.

Most studies reporting API-DES formulations have topical and transdermal delivery as their main objectives; nevertheless, API-DES applications go far beyond, and oral delivery purposes have also been proposed. The studies reported in the literature regarding API-DES are mostly focused on determining their phase diagrams, with insufficient information on the mixtures stability with temperature changes over time. Furthermore, there is a lack of information on drug release, cytotoxicity and therapeutic action of API-DES. Future progress should include bioavailability, dissolution, skin permeation and irritancy tests, as well as the screening of different permeation enhancers. More than *in vitro* studies, *in vivo* applications of API-DES formulations must be carried out, passing from non-clinical to clinical assays, to evaluate their safety and efficacy.

In the near future, different combinations of compounds to create DES are expected, leading to unlimited options of design. Novel studies will allow to understand the role of the API as HBD or HBA in the overall efficacy of the DES. These mixtures must be evaluated in further detail, allowing to have more promising therapeutic options and to compare the performance of different pharmacological classes. To this end, not only cholinium-derivatives but also other primary metabolites and other permeation enhancers should be studied.

Even though there is a long path to follow, the example of the patented and commercial EMLA® product containing the eutectic mixture formed by lidocaine and prilocaine represent a promising example in this field. API-DES, supported with appropriate studies, have a tremendous potential to be accepted by the pharmaceutical industry and, in the end, to be commercialized. Within the API-DES studies so far reported, (bio)polymer-based systems have been studied to improve the API-DES therapeutic action and delivery in a controlled way. Given their versatility in terms of functionalization and properties, more efficient therapeutic delivery systems with novel liquid forms of APIs combined with biopolymers hold great promise for the development of novel and effective biocompatible approaches.

In addition to the use of biopolymers to incorporate API-DES for controlled delivery purposes, the possibility of using API-DES with polymerizable character stands out. In this field, DES exert a triple action: (i) provide the API for drug release; (ii) act as the monomer; and (iii) act itself as the solvent media for polymerization. However, more profound research is still required to enable the full comprehension and characterization of these drug delivery systems. In the coming years, new directions for the preparation of API-DES delivery systems are expected, both by exploring different biopolymers and different API-DES. In particular, the conjugation of API-DES with macromolecular carriers may present interesting characteristics when orally administrated if the systems are able to prevent rapid renal excretion of the API and restrict the drug entry into cells, thus prolonging their plasma circulation time and improving their pharmacokinetic profiles, thus offering new indications for drug use [78,79]. However, pharmacokinetic studies are required to evaluate the performance of these novel delivery systems. Despite the few existing studies which show promising results in this field, data on the therapeutic efficacy on the intended target is still insufficient and the immunogenicity of the (bio)polymer-based materials used must be addressed. The existing investigations on this field are usually focused on the preparation of the drug delivery systems and in proof of concept tests, without addressing *in vitro* release experiments and *in vitro* biological studies.

Other types of systems must be considered in the future for API-DES delivery, as is the example of nanocarriers capable of enhancing drug's bioavailability and solubility. Stimulus-sensitive preparations comprising API-DES, such as pH and temperature-driven delivery systems, must also be explored. Despite still being in its infancy, if the innumerous possibilities of designing API-DES and delivery systems are considered, the results herein revised support a new direction for liquid formulations containing APIs, with promising potential for implementation in the market.

Funding

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, FCT Ref. UID/CTM/50011/2019, financed by national funds through the FCT/MCTES, as presented in the manuscript in the funding section and the project DeepBiorefinery (PTDC/AGR-TEC/1191/2014).

Declaration of interest

SN Pedro has been supported by the PhD grant (SFRH/BD/132584/2017) financed by FCT, Fundação para a Ciência e a Tecnologia. CSR Freire has a FCT research contract under Stimulus of Scientific Employment 2017 (CEECIND/00464/2017). MG Freire was supported by the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 337753. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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