Patent Review

For reprint orders, please contact: reprints@future-science.com

Pharmaceutical Patent Analyst

Ionic liquid-based transdermal delivery of propranolol: a patent evaluation of US2018/0169033A1

Hitesh Chopra[1], Pradeep Kumar[2] & Inderbir Singh*,[1]

[1]Chitkara College of Pharmacy, Chitkara University, Punjab, India

[2]Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng 2193, South Africa

*Author for correspondence: inderbir.singh@chitkara.edu.in

Ionic liquids (ILs) are organic salts of asymmetric organic cations and inorganic/organic anions and are considered green alternative to organic solvents. ILs have high thermal stability, low volatility, low toxicity and high biodegradability. ILs are frequently used for enhancing the solubility and stability of active pharmaceutical ingredients. This study describes an invention related to the preparation of amorphous melts of propranolol incorporated into transdermal patches for infantile hemangioma intervention. Reduction in skin irritation and a significant increase in transdermal permeability of propranolol from its amorphous melts was reported. However, toxicity and stability issues of the IL-based active pharmaceutical ingredients and their drug delivery systems are yet to be established from regulatory perspective before exploiting commercial viability of these forms.

First draft submitted: 30 July 2019; Accepted for publication: 12 September 2019; Published online: 15 October 2019

Keywords: amorphous melts • ionic liquids • irritation • propranolol • toxicity • transdermal drug delivery

Topical route for the delivery of therapeutic agents is preferred over other routes due to better patient compliance, avoidance of first-pass metabolism, significant accumulation in skin lesions, reduced systemic side effects and sustained therapeutic action. However, potential challenges for topic delivery such as particle size limitation, inappropriate aqueous/lipid solubility of active pharmaceutical ingredients (APIs), variable transdermal permeability and skin irritation require innovative approaches [1]. Ionic liquids (ILs), defined as organic salts of asymmetric organic cations and inorganic/organic anions, have been considered as a green alternative to volatile organic solvents for a wide variety of applications [2,3]. These complex compounds are liquid at room temperature and have a melting point generally below 100°C [4]. As a solvent, ILs have unique properties such as almost zero vapor pressure at room temperature, high thermal, chemical and electrochemical stability, easily miscible with most of the solvents and ability to dissolve organic and inorganic material [5].

Recently, ILs have been employed for several pharmaceutical applications [6]. The most common among these applications being solubility enhancement of poorly soluble drugs [7–10] and synthesizing novel active pharmaceutical ingredients [11,12] with modified properties like increased solubility and increased thermal stability. Furthermore, the inherent antimicrobial activity of ILs makes them useful therapeutic agents and formulation preservatives. For transdermal drug delivery, ILs have been proposed as formulation additives, substitute for oil or water, transdermal penetration enhancers and solubilizers. Although the safety profile of ILs has not yet been fully established, cytotoxicity of the ILs in human dermal fibroblasts has been found to be safer compared with the corresponding precursors. Caparica *et al.* studied the influence of two choline-amino acid ILs, 2-hydroxyethyl-trimethylammonium-L-phenylalaninate and 2-hydroxyethyl-trimethylammonium-L-glutaminate, on solubility enhancement of poorly soluble ferulic acid and rutin [13]. Aoyagi *et al.* formulated amorphous melts of propranolol using ILs. The melts exhibited increased permeability of propranolol along with significantly reduced skin irritation [14]. The above discussion evidenced ILs to be green nontoxic excipients for enhancing solubility and loading alongside ensuring the safety and stability of the delivery systems.

newlands press

Chemistry of ILs

ILs are molten salts and exist in liquid state at temperatures below 100°C due to bulky, asymmetric cations and weakly coordinating anions that cause destabilization in a lattice. Due to their destabilization, they can afford profound applications. It has been estimated that there are possibly 10^{18} combinations possible through ILs and any of the molecules can be combined with the ILs for any desirable property. Recent studies have elucidated the structure of ILs using NMR, mass spectroscopy, thermal techniques and other analytical properties [15]. The ILs have been classified into three generations depending on their journey (Figure 1) [16]. The first generation consists of the use of ILs as solvents because of their physicochemical properties such as low vapor pressure and thermal and chemical stability. The main drawback of this generation was that they were sensitive toward atmospheric oxygen requiring inert gas atmosphere [17]. The second generation focused mainly on the tuning of ILs for specific reactions such as media and catalysts, for extractions, as electrolytes for electrochemistry, nanotechnology, biotechnology, engineering, lubricants, magnetic fluids, propellants or hydraulic fluids and a wider liquid range as compared with molecular solvents. However, third generation ILs have defined physical and chemical behavior with significant biological activity [18]. Due to the increasing inclination toward the use of green solvents for the API synthesis, the ILs have replaced them all to a larger extent [19]. The IL-assisted API synthesis leads to the formation of API–IL complexes that have applicability in replacing the dissolution media for most of the APIs [20]. The ILs have also found use as solvents for proteins poorly soluble drugs [21,22] or as an additive for microemulsions [23,24].

ILs & drug delivery across the skin

The main aim of the drug delivery system is to protect the drug from getting metabolized before reaching the target site at a deliverable rate. However, things are not as easy as they seem to be. There is no doubt that transdermal and topical delivery provides alternative routes from oral and intravenous but the main stratum corneum proves to be a barrier to the main delivery [25]. Many chemical and natural enhancers have been tried to cross the drugs. Nowadays, ILs are fetching attention and are deeply investigated for their role in transcellular and paracellular drug transport mechanism [26]. Additionally, the data from computational and experimental studies showed that there is a wide scope of using ILs as drug penetration enhancers [27]. Lim *et al.* had investigated to insert the 1-octyl-3-methylimidazolium cations ($OMIM^+$) from a diluted aqueous ILs solution into a model of a bacterial cell membrane [28]. It has been found that the permeability coefficient of ammonia increases by factor 7. Further continuing, Moniruzzaman *et al.* developed ionic liquid-in-oil microemulsions to increase the solubility of a sparingly soluble drug, acyclovir, to enhance its topical and transdermal delivery [29]. Dobler *et al.* investigated the effect of imidazolium-based ILs on the properties and stability of o/w and w/o emulsions wherein low toxicity and better drug penetration into deeper skin layers were reported with the use of ILs [30]. Zhang *et al.* studied the transdermal permeation enhancement property of 20 imidazolium ILs employing testosterone as a model drug [31]. The ILs were reported to act by altering the surface properties of stratum corneum and by disruption of a compact regular/compact arrangement of the corneocytes. This provided evidence of the biological activity of ILs. The other types of cations have also been investigated like aromatic pyridinium and imidazolium cations, for instance, Monti *et al.* investigated the use of alicyclic pyrrolidinium-, morpholinium- and 1,4-diazabicyclo[2.2.2]octane-based ILs for skin retention and transdermal permeation enhancement of diltiazem. The IL used, N-methyl-N-decylmorpholinium bromide, exhibited significant enhancement in transdermal permeability of the selected drug along with reduced toxicity [32]. Many other findings also suggest the use of ILs in permeability enhancement in the case of biological membranes [33–35].

Solubility enhancement by ILs

Poor solubility is the most common issue the pharmaceutical industry is encountering in recent years. As a result, many of the drugs that perform superbly may not be able to enter mainstream [36]. Such molecules generally have polar groups on molecular structure and are difficult to dissolve, which apparently gives them poor solubility nature in apolar liquids or lipid-high mixtures. But to overcome this issue there has been suggestive evidence that ILs can act as a solubilizer for such types of drugs [37,38]. However, it has been found that solubility also depends on the type of ILs used. For instance, cationic ILs are less effective in enhancing solubility as compared with their anionic counterparts. In a typical solubility enhancement study, Williams and co-workers evaluated pyridinium-based ILs paired with $[NTf_2]$ and $[NIJCN_2]$ anions for drugs such as Danazol and Itraconazole. It was observed that the solubility capability increased with an increase in the alkyl chain length of pyridinium cation. The solubility of the above-mentioned drug was found to be the highest with the use of 1-hexyl-3-hexyloxycarbonylpyridinium cation

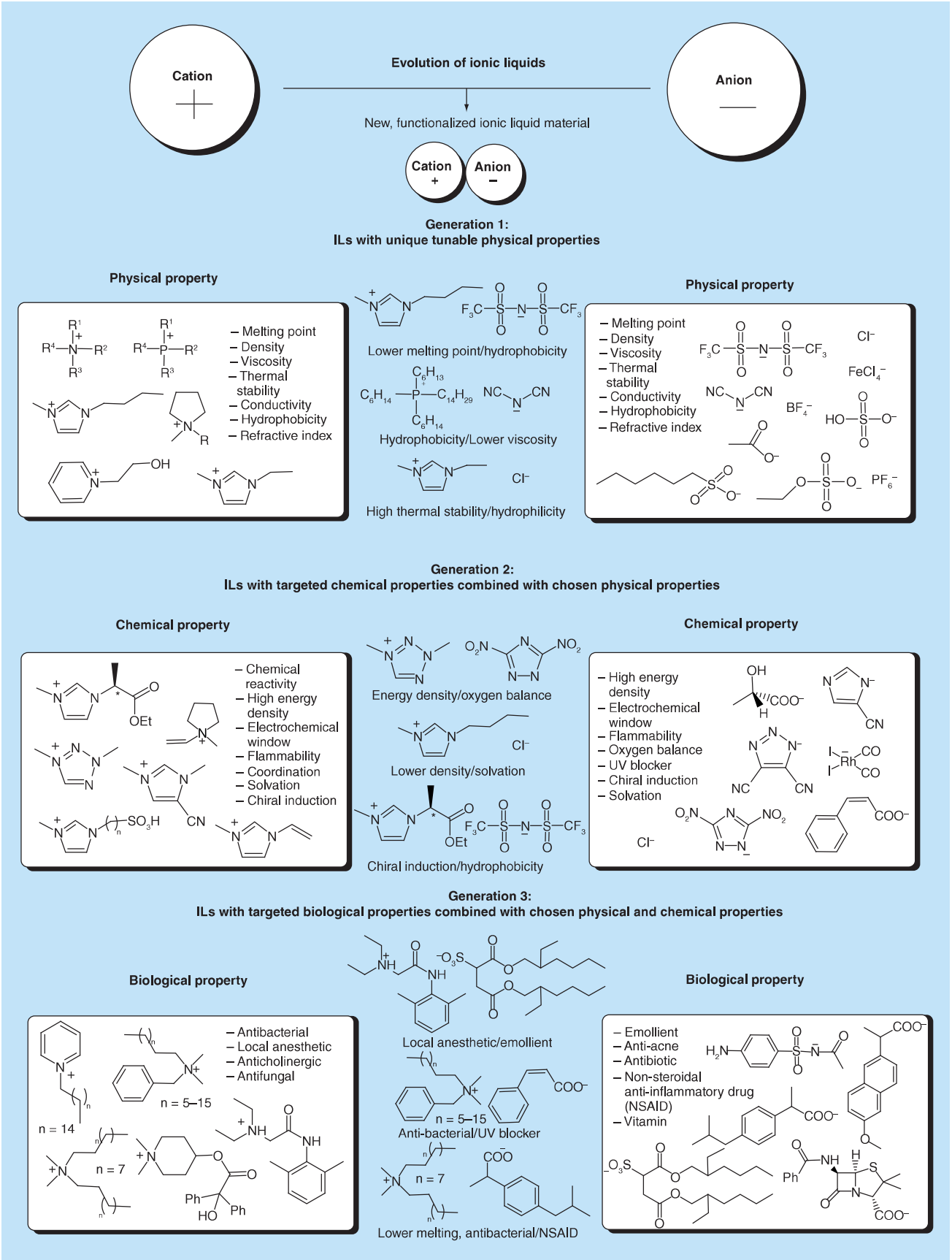

Figure 1. Classification of ionic liquids based on their evolution.
IL: Ionic liquid.
Reproduced with permission from [16] © the Centre National de la Recherche Scientifique (CNRS), France and The Royal Society of Chemistry, Great Britain (2007).

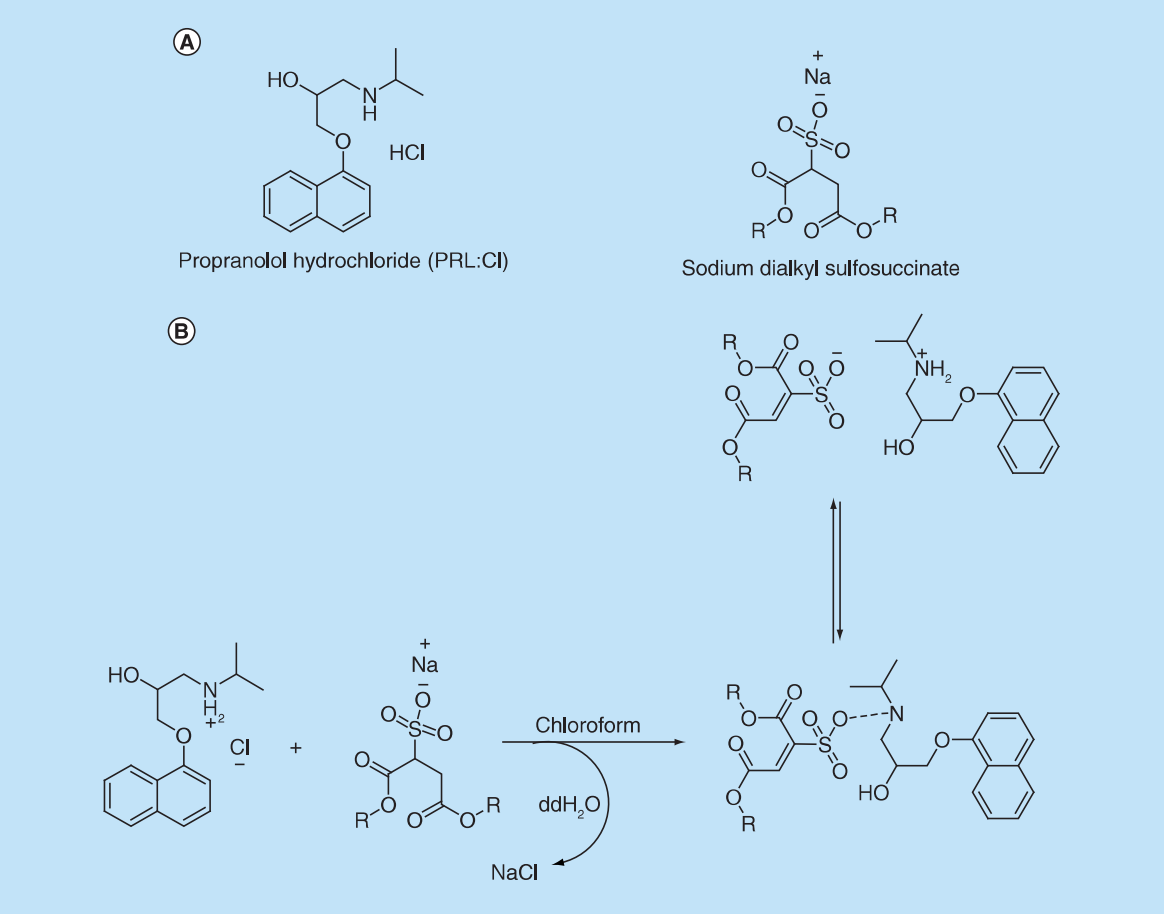

Figure 2. Schematic representation of preparation of amorphous melts of propranolol hydrochloride using sodium dialkyl sulfosuccinate.

[hhcpy] and the [NTf_2] anion [39]. Most recently, Jesus *et al.* employed N-acetyl amino acid N-alkyl cholinium-based ILs as co-solvents for enhancing (two- to fourfold) the aqueous solubility of paracetamol and diclofenac sodium [40].

Evaluation of patent application: US2018/0169033A1

The focus of this evaluation report is a US patent application filed by K Aoyagi, M Zakrewsky and S Mitragotri in 2017. The patent application describes a unique method for the transdermal delivery of propranolol by the formation of amorphous melts that can be delivered by applying on the skin without the use of organic solvents [41]. The rationale behind the invention was to address various limitations and side effects of propranolol such as significantly higher first-pass metabolism, poor accumulation in the skin and causes diarrhea, gastric reflux and hypoglycemic conditions. Propranolol has been considered as the first-line drug for *infantile hemangiomas* – a form of infantile tumor which, if left untreated, may result in physical disfigurement, scarring and ulceration of skin lesions. The topical application of propranolol offers targeted delivery to the site of skin lesions while minimizing saturation in the systemic circulation. The invention discussed here addresses the dose-dependent, inflammatory skin irritation observed with topical application of propranolol. Instead of harsh organic solvents, amorphous melts of propranolol were prepared followed by formulation of transdermal patches. Amorphous melts of propranolol were prepared with sulfosuccinates (Figure 2) and physicochemical analyses (NMR, FTIR, TGA, DSC) were performed.

The alkyl part of the four sodium dialkyl sulfosuccinates was isobutyl (C4), amyl (C5), hexyl (C6) and octyl (C8) that are part of four further different formulations such as propranolol diisobutyl sulfosuccinate (PRL:C4), propranolol diamyl sulfosuccinate (PRL:C5), propranolol dihexyl sulfosuccinate (PRL:C6) and propranolol dioctyl

sulfosuccinate (PRL:C8). The IL dialkyl sulfosuccinates were used more frequently due to their GRAS status by the US FDA. Moreover, it is relatively cheap, easily available and form melts with other species for transdermal application. The simple salt metathesis reaction takes place in which the sodium salt and hydrochloride salt are mixed in the molar ration of 1:1 in double-distilled water. After this step, the extraction was carried out with chloroform and washed with double-distilled water to remove chloroform. The Quantofix chloride test and silver nitrate precipitate test were used for the monitoring of chloride content. The final formulation was placed in a vacuum to dry for about 36 h at 60°C.

The main advantage of this delivery system for the treatment of IH was topical delivery of propranolol with lowered side effects of systemic saturation and to target the drug easily. Till date several researchers have reported the transdermal delivery of propranolol but the dose-dependent skin irritation still persisted. To counteract these issues, amorphous melts were chosen as a strategy. In an earlier study by the research group, choline and geranic acid formulations as deep eutectic mixtures exhibited reduced skin irritation. The same method was applied for propranolol to form the melts. After removing the residual water, the transparency and fluidity were retained for the melts. The melts thus formed were found to have low viscosity and required no solvent for the topical application. The PFB was found to be more soluble in ethanol as compared with the IPM. The permeation study across the porcine skin demonstrated ≈30-times increase in the flux across the skin barrier with formulation of PRL: C8 showing higher permeability compared with the PFB-EtOH.

The mechanism of irritation reduction was elucidated by the measuring the molar conductivities of PRL:C8 and PRL:C5 at various concentrations in both water (to simulate aqueous environments like the epidermis, dermis and systemically) and octanol (to simulate the stratum corneum [SC]). The association of the melt was found to be stronger for the subcutaneous lipids, due to the lower dielectric constant. It was found that the propranolol melts in octanol have 100-times fewer molar conductivity than the melts in water – proving that the molecular species permeated the skin as a pair. The skin irritation was evaluated on the MatTek Epiderm FTTM human skin equivalent tissues (MatTek Corporation, MA, USA) by measuring the interleukin IL-1α release. For this, the new media were applied before the application of the new formulation, then after 4 h the 200 µl was collected and evaluated by using Human Interleukin-1α ELISA Kit (Pierce Biotechnology Inc., IL, USA). The different formulations such as 0.1 and 0.2 M PFB EtOH formulations, positive control (5% SDS in phosphate-buffered saline [PBS]), negative control (PBS) and EtOH solvent control were also evaluated. Among the prepared amorphous melts, PRL:C5 and PRL:C8 showed low viscosities and ease of handling. Although PRL:C8 showed no enhanced or reduced drug transport efficiency as compared with PRL-EtOH, a marked reduction in skin irritation (≈40-fold) and significant increase in transdermal permeability of propranolol from PRL:C8 was reported. Skin irritation, an adverse effect of propranolol, was reduced in case of propranolol amorphous melts possibly due to shielding of electrostatic interactions between propranolol and the cell membrane.

In summary, the invention elucidates the method for preparing amorphous melts of propranolol with proposed reduced skin irritation and enhanced transdermal permeation capability. The amorphous melts of the drug may be incorporated onto different transdermal drug delivery systems viz. films, gel, creams, ointment, etc. for the treatment of skin disorders. However, toxicity and stability issues of the IL-based amorphous melts are required to be addressed closely for exploring commercial viability of these forms.

Future perspective

The ILs have recently been regarded as green solvents for improving physicochemical properties of drug molecules at nontoxic concentrations. At nanoscale and microscale levels, ILs exhibit tunable intrinsic structural organization with diverse biological activities and applications. The molecular structure and hence definitions and nomenclature of ILs may still be considered as 'under construction'. In addition, the mechanism of action of biologically active ILs requires further exploration as with such solvent properties, ILs may pose safety challenges similar to nanomaterials. The studies defining the relation between molecular structure/organization of ILs and their properties/applications are still at early stages of development. Chemical, biological, material, pharmaceutical and medical scientists need to explore the applications of ILs for developing future medicines taking into account the regulatory, mechanistic and toxicological issues.

Executive summary

- Topical drug delivery system has been considered as a patient biddable system.
- Ionic liquids are organic salts that are liquid in their pure state near ambient conditions.
- Ionic liquids are highly viscous, frequently exhibit low vapor pressure, low combustibility, are thermally stable.
- Infantile hemangioma is the most common form of infantile tumor and if untreated can result in significant physical disfigurement due to ulceration and scarring of skin lesions.
- The drug delivery formulation explained herein contains a sufficient amount of the amorphous propranolol to deliver a therapeutically effective amount of the amorphous propranolol to the patient in need of treatment, such as for the treatment or amelioration of infantile hemangioma.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Singhal M, Lapteva M, Kalia YN. Formulation challenges for 21st century topical and transdermal delivery systems. *Expert Opin. Drug Deliv.* 14, 705–708 (2017).
2. Messali M. An efficient and green sonochemical synthesis of some new eco-friendly functionalized ionic liquids. *Arabian J. Chem.* 7(1), 63–70 (2014).
3. Ratti R. Ionic liquids: synthesis and applications in catalysis. *Adv. Chem.* 2014, 729842 (2014).
4. Zhu Y, Hosmane NS. Ionic liquids: recent advances and applications in boron chemistry. *Eur. J. Inorg. Chem.* 38–39 (2017). 4369–4377
5. Koel M. Ionic liquids in chemical analysis. *Crit. Rev. Anal. Chem.* 35(3), 177–192 (2005).
6. Marrucho IM, Branco LC, Rebelo LP. Ionic liquids in pharmaceutical applications. *Annual Rev. Chem. Biomol. Engg.* 5, 527–546 (2014).
7. Sintra TE, Shimizu K, Ventura SP, Shimizu S, Lopes JC, Coutinho JA. Enhanced dissolution of ibuprofen using ionic liquids as catanionic hydrotropes. *Physical Chem. Chemical Phy.* 20(3), 2094–2103 (2018).
8. Jesus AR, Soromenho MR, Raposo LR *et al.* Enhancement of water solubility of poorly water-soluble drugs by new biocompatible N-acetyl amino acid N-alkyl cholinium-based ionic liquids. *Eur. J. Pharm. Biopharm.* 137, 227–232 (2019).
9. Kumar V, Parmar VS, Malhotra SV. Enhanced solubility and selective benzoylation of nucleosides in novel ionic liquid. *Tetrahed. Lett.* 48(5), 809–812 (2007).
10. Zheng Y, Xuan X, Wang J, Fan M. The enhanced dissolution of β-cyclodextrin in some hydrophilic ionic liquids. *J. Phys. Chem. A* 114(11), 39260–39331 (2009).
11. Frizzo CP, Wust K, Tier AZ *et al.* Novel ibuprofenate-and docusate-based ionic liquids: emergence of antimicrobial activity. *RSC Adv.* 6(102), 100476–100486 (2016).
12. Ferraz R, Branco LC, Marrucho IM *et al.* Development of novel ionic liquids based on ampicillin. *MedChemComm.* 3(4), 494–497 (2012).
13. Caparica R, Júlio A, Baby A *et al.* Choline-amino acid ionic liquids as green functional excipients to enhance drug solubility. *Pharmaceutics* 10(4), 288 (2018).
14. Aoyagi K, Zakrewsky M, Mitragotri S. Formulating propranolol as an amorphous melt affords reduced skin irritation potential for transdermal drug delivery. *Technology* 3(04), 214–238 (2015).
15. Hapiot P, Lagrost C. Electrochemical reactivity in room-temperature ionic liquids. *Chem. Rev.* 108(7), 2238–2264 (2008).
16. Hough WL, Smiglak M, Rodríguez H *et al.* The third evolution of ionic liquids: active pharmaceutical ingredients. *N. J. Chem.* 31(8), 1429–1436 (2007).
17. Moustafa EM, Abedin SZ, Shkurankov A *et al.* Electrodeposition of Al in 1-Butyl-1-methylpyrrolidinium Bis(trifluoromethylsulfon- yl) amide and 1-Ethyl-3-methylimidazolium Bis(trifluoromethylsulfonyl)amide Ionic Liquids: *In Situ* STM and EQCM Studies. *J. Phys. Chem. B* 111, 4693–4704 (2007).
18. Balk A, Holzgrabe U, Meinel L. 'Pro et contra'ionic liquid drugs – challenges and opportunities for pharmaceutical translation. *Eur. J. Pharm. Biopharm.* 94, 291–304 (2015).
19. Dyson PJ, Geldbach TJ. Applications of ionic liquids in synthesis and catalysis. *Electrochem. Soc. Interface* 16(1), 50–53 (2007).
20. Bioni T, Arêas E, Couto L, Favarin G, El Seoud O. Dissolution of cellulose in mixtures of ionic liquid and molecular solvents: relevance of solvent-solvent and cellulose-solvent interactions. *Nordic Pulp Paper Res. J.* 30(1), 105–111 (2015).

21. Balk A, Wiest J, Widmer T, Galli B, Holzgrabe U, Meinel L. Transformation of acidic poorly water soluble drugs into ionic liquids. *Eur. J. Pharm. Biopharm.* 94, 73–82 (2015).
22. Sahbaz Y, Williams HD, Nguyen TH *et al.* Transformation of poorly water-soluble drugs into lipophilic ionic liquids enhances oral drug exposure from lipid based formulations. *Mol. Pharm.* 12(6), 1980–1991 (2015).
23. Qiu Z, Texter J. Ionic liquids in microemulsions. *Curr. Opin. Colloid Interface Sci.* 13(4), 252–262 (2008).
24. Kuchlyan J, Kundu N. Ionic liquids in microemulsions: formulation and characterization. *Curr. Opin. Colloid Interface Sci.* 25, 27–38 (2016).
25. Prausnitz MR, Langer R. Transdermal drug delivery. *Nature Biotech.* 26(11), 1261 (2008).
26. Sidat Z, Marimuthu T, Kumar P *et al.* Ionic liquids as potential and synergistic permeation enhancers for transdermal drug delivery. *Pharmaceutics* 11(2), 96 (2019).
27. Lim GS, Jaenicke S, Klähn M. How the spontaneous insertion of amphiphilic imidazolium-based cations changes biological membranes: a molecular simulation study. *Physical Chem. Chemical Phys.* 17, 29171–29183 (2015).
28. Lim GS, Zidar J, Cheong DW, Jaenicke S, Klähn M. Impact of ionic liquids in aqueous solution on bacterial plasma membranes studied with molecular dynamics simulations. *J. Phys. Chem. B* 118(35), 10444–10459 (2014).
29. Moniruzzaman M, Tamura M, Tahara Y, Kamiya N, Goto M. Ionic liquid-in-oil microemulsion as a potential carrier of sparingly soluble drug: characterization and cytotoxicity evaluation. *Int. J. Pharm.* 400(1–2), 243–250 (2010).
30. Dobler D, Schmidts T, Klingenhöfer I, Runkel F. Ionic liquids as ingredients in topical drug delivery systems. *Int. J. Pharm.* 441(1–2), 620–627 (2013).
31. Zhang D, Wang HJ, Cui XM, Wang CX. Evaluations of imidazolium ionic liquids as novel skin permeation enhancers for drug transdermal delivery. *Pharm. Dev. Technol.* 22(4), 511–520 (2017).
32. Monti D, Egiziano E, Burgalassi S *et al.* Ionic liquids as potential enhancers for transdermal drug delivery. *Int. J. Pharm.* 516(1–2), 45–51 (2017).
33. Stoimenovski J, MacFarlane DR. Enhanced membrane transport of pharmaceutically active protic ionic liquids. *Chem. Comm.* 47(41), 11429–11431 (2011).
34. Zakrewsky M, Lovejoy KS, Kern TL *et al.* Ionic liquids as a class of materials for transdermal delivery and pathogen neutralization. *Proc. Natl Acad. Sci. USA* 111(37), 13313–13318 (2014).
35. Kubota K, Shibata A, Yamaguchi T. The molecular assembly of the ionic liquid/aliphatic carboxylic acid/aliphatic amine as effective and safety transdermal permeation enhancers. *Eur. J. Pharm. Sci.* 86, 75–83 (2016).
36. Di L, Fish PV, Mano T. Bridging solubility between drug discovery and development. *Drug Discov. Today* 17(9-10), 486–495 (2012).
37. Alawi MA, Hamdan II, Sallam AA, Heshmeh NA. Solubility enhancement of glibenclamide in choline–tryptophan ionic liquid: preparation, characterization and mechanism of solubilization. *J. Mol. Liquids* 212, 629–634 (2015).
38. Shamshina JL, Cojocaru OA, Kelley SP *et al.* Acyclovir as an ionic liquid cation or anion can improve aqueous solubility. *ACS Omega* 2(7), 3483–3493 (2017).
39. Williams HD, Sahbaz Y, Ford L, Nguyen TH, Scammells PJ, Porter CJ. Ionic liquids provide unique opportunities for oral drug delivery: structure optimization and *in vivo* evidence of utility. *Chem. Comm.* 50(14), 1688–1690 (2014).
40. Jesus AR, Soromenho MR, Raposo LR *et al.* Enhancement of water solubility of poorly water-soluble drugs by new biocompatible N-acetyl amino acid N-alkyl cholinium-based ionic liquids. *Eur. J. Pharm. Biopharm.* 137, 227–232 (2019).
41. Aoyagi K, Zakrewsky M, Mitragotri S. US15/837420 (2018).