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Delivery of ionizable hydrophilic drugs based on pharmaceutical formulation of ion pairs and ionic liquids

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ABSTRACT

New therapeutics such as antisense oligonucleotides, small interfering RNA and peptide-drug conjugates are taking great relevance in the pharmaceutical industry due to their specificity of action and their improved safety profile. However, they could present bioavailability issues due to their hydrophilic nature, such as BCS class III drugs. Therefore, the formation of ion pairs of these type of molecules allows modifying their physicochemical characteristics such as polarity and lipophilicity leading to improved permeability. By carrying out a tailored synthesis, it is possible to obtain complexes with greater stability and better performance *in vitro* and *in vivo*, where their correlation with physicochemical properties continues to be a growing field of research. Moreover, ionic liquids (IL), which are substances that melt below 100 °C, have enabled modifying various drug properties, showing promising results *in vitro-in vivo*, especially when they are included in suitable drug delivery systems, such as nanoparticles, microparticles, self-emulsifying drug delivery systems, and transdermal patches, among others. The drug-IL is formed from the therapeutic agent and a counterion, mainly by ionic interactions, and resulting in a wide variety of derivatives with different properties. However, the pharmaceutical field is limited to the use of some excipients or GRAS (generally recognized as safe) substances, so the search for new counterions is of great interest. In this article, we have compiled key indexes that can be obtained from databases to guide the search for suitable counterions, together with different drug delivery system strategies to choose the most appropriate formulation according to the non-parenteral route of administration selected. Intellectual property advancements in the field are also presented and analyzed.

1. Introduction

Since the early 1980s, combinatorial chemistry and high throughput screenings have identified an increasing number of efficacious drug candidates with undesired physicochemical properties, such as low permeability across physiological membranes or low aqueous solubility [1]. Permeability and solubility of a drug are key parameters in determining the rate and extent of drug absorption and are therefore directly related to the compound's bioavailability [2], which is why both parameters are reflected within the biopharmaceutical classification system (BCS). BCS categorizes pharmaceutical compounds into four different groups (class I – IV) [3–5]. Drugs with high solubility (*i.e.* the highest dose strength is soluble in <250 mL of aqueous media over the pH range of 1–6.8 [6] in combination with low permeability (*i.e.* the extent of absorption in humans is determined to be <85% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose [6] are classified into BCS class III. The often hydrophilic or ionic nature of BCS class III compounds is responsible for their favorable aqueous solubility but potentially jeopardizes their transport across lipophilic biological membranes [7]. This situation has become more relevant due to the appearance of new hydrophilic entities, such as antisense oligonucleotides [8], small interfering RNA [9],

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peptide-drug conjugates [10] and antibiotic and anticancer new drug candidates of natural sources [11–12]. Then, strategies addressing these challenges are needed to open or improve therapies with hydrophilic compounds [13–15]. The literature reports several successful approaches for increasing the permeability of an ionizable hydrophilic drug (IHD), such as chemical modifications by synthesizing prodrugs [16–18], resulting in novel chemical entities driving a train of complex and costly activities including novel safety assessments and clinical trials for efficacy. Other studies focus on technological strategies through which the drug structure is maintained and uptake is facilitated by the use of absorption enhancers [19–21]. Another focus is on impacting influx and efflux transporters [22–23] or enzymes [24] for the improvement of gastrointestinal absorption.

Along these lines, "ion pairing" of IHDs with hydrophobic counterions has been attracting interest for more than four decades in pharmaceutical sciences [25–28]. The term "hydrophobic ion pairing" was introduced in 1998 by Meyer and Manning [29] and describes complexes of oppositely charged ions, *i.e.* a positively or negatively charged IHD coupled to a (often bulky) hydrophobic counterion of opposite charge. Drug and counterion are associated by hydrophobic and electrostatic interactions. To the outside, the ion pair acts as a neutral or nearly neutral entity with increased lipophilicity as compared to the free drug molecule, which is easily assessed *in vitro* by the determination of partitioning coefficients between an aqueous and a lipid phase [30–33] or in cell culture permeability assays [34–35]. These investigations serve as predictive data for drug transport across natural barriers including eukaryotic cell membranes or bacterial surfaces. In addition, ionic liquids (IL) have emerged as a new strategy to improve drug permeability based on ionic pairing [36]. ILs are substances formed only by ions and that have a melting point below 100 °C [37]. Its use has extended to different technological branches, such as synthesis, catalysis, electrochemistry, biomass conversion, fuel production, among others [38]. The pharmaceutical industry has not been oblivious to its applications, and its use has been described as a solvent in the synthesis of drugs, as a means of recrystallization, in purification techniques - analytical separations, as a vehicle for drug delivery, and properly as drugs [39]. This last application is very interesting, due to the large number of derivatives that can be obtained from a drug with different counterions to form a drug-ionic liquid (drug-IL) [40] Additionally, dual drug ionic liquids (dual drug-IL) can be synthetized, where the complex is formed from two therapeutic entities [41–42].

There is a wide variety of substances that can serve as counterions for drug-IL, resulting in compounds that can be designed according to the required physicochemical goal [38,40]. Nonetheless, the pharmaceutical field is limited to some excipients and GRAS substances that can be used, to facilitate regulatory approval [43–44].

This review reports on ion pair formation relating to poorly permeable hydrophilic substances and the synthesis of ionic liquids, critically discusses the advantages and drawbacks of these formulation strategies with a focus on the oral/enteral, buccal, nasal, ocular, and transdermal routes of administration. There also is a focus on consolidating ion-pairing concepts by presenting simple physicochemical properties to guide the reader in the choice of counterions for synthesis and the delivery system of the complex depending on the route of administration desired.

2. Physicochemical properties of an ionizable hydrophilic drug (IHD)

The ability of a molecule to solubilize itself in a substance of a fatty nature, known as lipophilia, is widely understood, versus the hydrophilic term that corresponds to the ability of an entity to dissolve in water [45]. On the other hand, we have the term hydrophobic that indicates a compound that dissolves in apolar solvents and that in this review we will use in the same sense as lipophilic [45]. The partition coefficient octanol-water (Log P) has been used to define the hydrophilic-lipophilic character of a drug. Based on this, we can establish that an IHD will be those drugs that have a Log P value below 2.0 [46] and that also have an ionizable chemical group (see Table 1 and 2).

The first parameter can be obtained experimentally or by computer simulation, where there are good reviews about this topic [47–49]. The second concept is associated with chemical functionalities present in the molecule and whose strength in terms of acid-base is represented by its pKa. This parameter can be obtained experimentally and there are also several computational approaches that have been used for its simulation [49–51].

Another important characteristic of some drugs is their amphiphilic character [52–53]. This concept indicates a substance that has in its structure a hydrophilic and lipophilic region [53]. Fig. 1 shows two examples, where the hydrophilic or polar region can be visualized in blue and polar surface area (PSA) can be calculated for characterization. In these cases, the PSA values for otilonium and ibandronic acid are 64.6 $Å^2$ and 139 $Å^2$, respectively.

3. General outlook of ion pairing formulations for IHD

Systemic absorption of a compound is a prerequisite for its systemic effects. Many drugs, however, have poor membrane permeability at physiological pH frequently attributed to their charged nature and/or high polarity [54–55]. An example is alendronate, which has a bioavailability of less than 1% and a Log P of −1.3, showing an apparent permeability of 0.091 cm/s × 10^{-6} versus the positive control (Verapamil: 38.2 cm/s × 10^{-6}) in a PAMPA model (Parallel Artificial Membrane Permeability Assay) [56]. The negative partition coefficient, in this and other cases, reflects the poor ability of a compound to cross a biological lipid membrane, however, this condition cannot be generalized, where a carrier-mediated active transport for Lisinopril (Log P: −2.86) has been observed [55]. The usefulness of Log P as an indicator of drug lipophilicity has been demonstrated in several studies and it has been established that passive diffusion predominates with Log P values above 0.5 [55]. Additionally, the distribution coefficient (Log D) at a specific pH can be calculated or determined. This indicator takes into account both the non-ionized and the charged form of the drug in a system octanol-buffer considering a biorelevant pH such as saliva (6.0–7.0), stomach (1.0–3.5), small intestine (7.5–8.0), large intestine (5.5–7.0) or Blood (7.4) [57]. Other important values are skin pH 4.5–5.5 [58], nasal pH 5.5–6.0 [59] and ocular pH 7.4 [60]. In this way, IHDs with Log $D_{(pH\ 5.5)}$ or Log $D_{(pH\ 7.4)}$ less or equal than 0.5 will be good candidates for the preparation of ionic pairs that improve their permeability in the mentioned administration routes.

To date, numerous studies have demonstrated the usefulness of lipophilicity enhancement for the purpose of higher drug transport across biological membranes [61] *in vitro* and *in vivo* as well for eukaryotic [62–65] and for prokaryotic cells [66–67]. It turned out that efficiently designed ion pairs of IHDs and counterions can increase the drug concentration at the site of action, but overall, it must be critically stated that promising *in vitro* results do not necessarily reflect successful *in vivo* outcomes. Moreover, the impact of successful ion pairing is beyond uptake considerations, where drug release can be modulated [65], or *in vivo* enterohepatic circulation is affected in some cases [68].

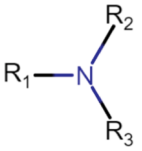
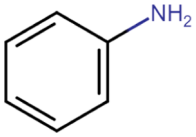
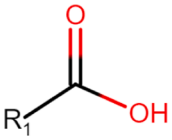
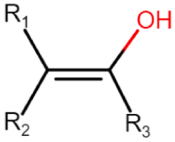
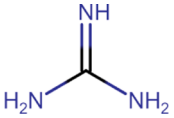
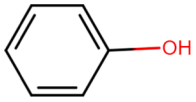
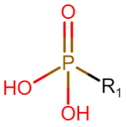
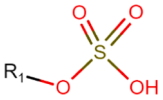
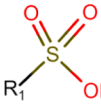
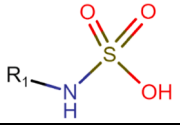
Interestingly, other studies reported systemic effects of ion pairing in reducing the binding of drugs to plasma lipoproteins suggesting,

Table 1
Criteria for the classification of drugs based on their partition coefficient.

Classification[a]	Log P (oct/water)
Hydrophilic	<2.0
Hydrophilic to Hydrophobic	2.0–4.0
Hydrophobic	>4.0

[a] http://chimactiv.agroparistech.fr/en/methodologie/extraction/savoir-plus/10.

Table 2
Principal ionizable chemical groups of selected molecules.

Ionizable chemical group	Structure	Molecule example[a]	pKa[a]
Alkylamine R = H or Alkyl group		Lidocaine	8.01
Arylamine		Benzocaine	1.86
Carboxylic acid		Ibuprofen	3.97
Enol		Teriflunomide	5.20
Guanidinium		Metformin	12.4
Phenol		Estriol	10.54
Phosphate		Alendronate	1.66
Sulphate		Chondroitin sulfate	< 0
Sulphone		Docusate	−0.75
Sulfamic		Cyclamic acid	1.71

[a] PubChem https://pubchem.ncbi.nlm.nih.gov/.

incomplete dissociation even in circulation [62]. For example, an improvement of pharmacokinetic (PK) parameters was demonstrated after intravenous administration in mice for doxorubicin-cholesteryl hemisuccinate ion pairs incorporated into liposomes [62] as well as for doxorubicin-oleic acid nanoparticles [63].

The incorporation of IHDs into lipid drug delivery systems is challenged by their hydrophilic nature and low solubility in the lipid layer resulting in low drug loading, stability challenges during manufacture and/or storage and uncontrolled release after administration [14,69]. The amphiphilic or neutral surface of ion pairs, however, may facilitate the formulation of polar drugs into liposomes [62], nanoparticles [68,70–75], nanoemulsions [63], microparticles [76] or self-emulsifying drug delivery systems (SEDDS) [31,69]. Consequently, drug loading and entrapment efficiency of formerly IHDs are optimized for their hydrophobic ion pairs into lipid formulations [65,67,77–78].

As the chemical structure of the drug is not altered by the ion pairing approach, it may be expected that toxicity remains unchanged. It was reported, however, that the possibility of embedding ion pairs into lipid drug delivery systems indeed affected their toxicological profile. For example, doxorubicin accumulation within the heart, kidney and lung following intravenous injection of ion pair complexes was higher as compared to the free drug [63,73].

One exciting emerging field for hydrophobic ion pairing are biologics-based ion pairs in an effort to open the oral route for their delivery by deploying protecting formulations with selected hydrophobic counterions [79–83]. For example, insulin ion pairs were incorporated into nanoparticles and self-nanoemulsifying drug delivery systems, thereby protecting the peptide from degradation [68,70,84] The incorporation of the hydrophobic ion pair of desmopressin/sodium docusate into SEDDS successfully preserved desmopressin from degradation in the presence of glutathione and displayed protective effects against α-chymotrypsin [31]. Similarly, the acylation of octreotide under acidic conditions was less than 7% after 55 days due to the masking of the amine groups with dextran sulfate A and B and subsequent embedding into PLGA nanoparticles as compared to about 60% acylated octreotide for the marketed Sandostatin LAR® depot [76]. In conclusion, hydrophobic ion pairing is a beneficial strategy to retain protein stability during delivery from formulations. Moreover, the ion pairing approach offers an uncomplicated and cost-effective strategy for the lipophilicity enhancement of IHD substances. The properties and the formation efficacy are tunable through the counterion structure, e.g. by its aliphatic chain length (whereas longer chains lead to higher lipophilicity), or its polar/apolar characteristics and by the drug/counterion ratio [31–32,54,85–86].

Aside these advantages, ion pairing comes along with some challenges one of which is decreased aqueous solubility [32,54,65–66,68]. Moreover, the altered physicochemical features can influence the stability or pharmacokinetics (plasma protein binding, distribution, elimination) of a drug and ultimately its bioequivalence. Occasionally, ion pair complexes fail to facilitate permeability resulting in loss of activity. This has been attributed to the (often bulky) structure of the counterions and increased hydrodynamic diameter of the resulting ion pairs. Thereby, the increase in lipophilicity is over-compensated by the increase in size leading to a decrease of the ion pair's bioavailability. Similarly, it was hypothesized that large counterions, such as quaternary ammonium cations for instance, are sterically or thermodynamically hindered and thus lower attractive forces are present between the drug and the counterion [86–87]. Possibly, suboptimal counterion concentrations are responsible for the observed lack of absorption [88]. Nevertheless, these disadvantageous features are tunable by tailored counterion design [89] and has been recently demonstrated for ionic liquids [40]. These examples illustrate the need for tailored counterion design for hydrophobic ion pairing with the goal to improve bioavailability.

Safety is another reason for careful counterion selection [90]. The list of GRAS substances provided by the FDA may guide formulation scientists in selection, as introducing novel structures triggers regulatory constraints. In general, naturally derived oils and triglycerides are suitable as non-toxic ion pairing reagents whereas surfactants like sodium dodecyl sulfate (SDS) can cause detrimental effects due to various membrane interactions [35]. In this regard, the viability of Caco-2 cells was significantly reduced after one and four hours of incubation with enoxaparin-dodecylamine, which was linked to counterion toxicity [69] and counterions' dose dependent toxicity as reported in [31,91]. Ultimately, the intended administration route of the final formulation has to be taken into account as certain counterions are not qualified for some administration routes [92].

4. Formation of stable ion pairing complex with IHD

Interaction of IHDs with ion pairing agents can be carried out *in situ*

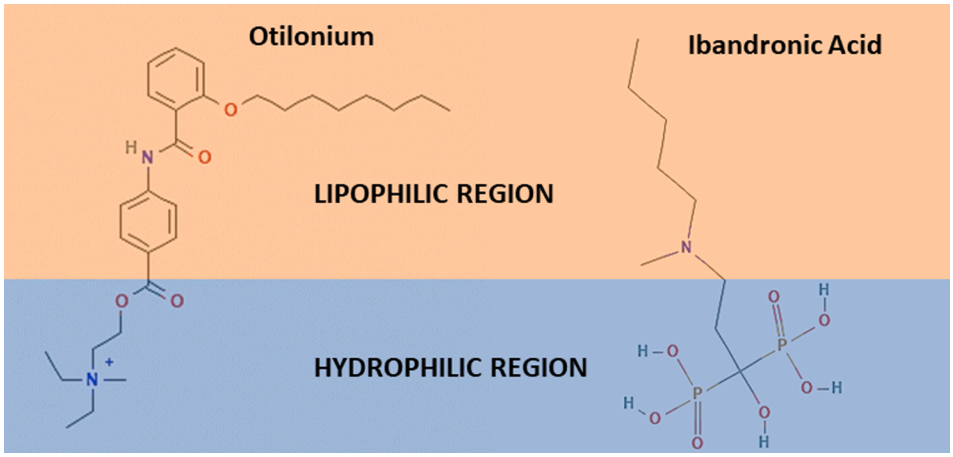


Fig. 1. Amphiphilic drug examples: otilonium and ibandronic acid.

(without the isolation of the complex) to study its permeability [28,56,93–95]. It has been established that for effective formation of the complex, the ΔpKa between the base and the acid must be ≥2.5, according to the proton-transfer model of Huyskens and Zeegers-Huyskens [94,96–97]. Table 3 shows the pKa of drugs and their counterions and other important properties to form ion pairs. The presence of strong functional groups such as phosphate (alendronic acid), sulfate (sodium lauryl sulfate) or sulfonates (benzenesulfonic acid) with low pKa and quaternary amine (hyoscine) or guanidinium group (phenformin) with high pKa in drugs or counterions, are recommended to form stable pairs, considering that coulombic interaction is the main force in the formation of these complexes [28,98]. For phenformin, the ΔpKa with its 1-hydroxy-2-naphthoic acid (carboxylic acid) versus 2-naphthalenesulfonic acid (sulfonic acid) counterions were 9.48 and 12.23 respectively, which resulted in a 5 times greater aqueous affinity constant for the last complex [99]. ΔpKa for amines such bisoprolol (secondary) and escitalopram (tertiary) ranges from 4.71 to 11.47 with different carboxylic acids (see Table 3). A special case corresponds to teriflunomide, a weak acid with pKa 5.2 (enol group), in which the ΔpKa was 2.5 with triethanolamine as counterion (pKa 7.77) and where the complex obtained was defined as an "hydrogen-bonded ion pair", which was confirmed by infrared spectroscopy [94].

On the other hand, peptide drugs have several ionizable groups and different acid-base character, so we cannot use the pKa of their residues as input, but rather their isoelectric point (pI). As observed in Table 3, insulin has a pI of 5.35 and at pH 7.4 (about two units above its pI), it presents a net negative charge. Then in a Hanks balanced salt solution (HBSS) with pH 7.4, the peptide could form ion pairs with basic amino acids such as arginine, lysine and histidine, which are positively charged below their pKa [91]. The same phenomenon was observed with acidic amino acids (aspartic and glutamic) at low concentrations, due to the presence also of the protonated alpha amino group, however, at high concentrations of these amino acids, the pH decreased and consequently the charge of the peptide, affecting the formation of the complex [91]. For basic peptide derivatives such as leuprolide (pI: 10.07) and octreotide (pI: 10.97), the formation of ion pairs can be performed in an aqueous medium with counter ions of pKa less than 7, such as sodium oleate (pKa 5.02), sodium deoxycholate (pKa 6.58), sodium docusate (pKa −0.75) or sodium decanoate (pKa 4.9) [100–101]. Likewise, we recommend carrying out the complexation with a buffer, for example phosphate pH 7.4 or other, due to the variability of the quality of water from different sources. DNA and RNA and their derivatives are other molecules that can be paired to optimize their encapsulation in a drug delivery system [102–105]. The presence of the phosphate group with a pKa of about 1.0 in these molecules, enables them to form complexes with cationic counterions [106].

The information described for the mentioned complexes is only qualitative and the application of quasi-equilibrium transport models in an immiscible system octanol: Buffer pH 6.5 was developed to study the partitioning of ionic pairs and obtain the affinity constants of the complexes. Based on this information, it is possible to identify other characteristics of the counterions to modulate the ion pair stability [99,110]. An example is zanamivir heptyl ester (ZHE)-1-hydroxy-2-naphthoic acid (HNAP) ion pair, which aqueous affinity constant was 388 M^{-1} versus 2.91 M^{-1} of the complex guanidino oseltamivir (GO)-HNAP. Both drugs have a guanidinium group with pKa 12.80 for GO and 11.26 for ZHE, and it was postulated that hydrogen bond (HB) interactions would be responsible for the highest affinity constant, where ZHE has 20 interactions (HB donor + HB acceptor) versus 13 for GO. Another case is the arginine-alendronate complex (pKa base: 13.2 and HB donor + HB acceptor: 13) that had a 1.3 affinity constant higher than the phenazopyridine-alendronate complex (pKa base: 5.05 and HB donor + HB acceptor: 9) in aqueous medium [56]. However, in non-aqueous medium (octanol), the affinity constant of phenazopyridine-alendronate pair was 9 times greater than the arginine-alendronate pair. Therefore, the partition coefficient of the counterion (Log P 2.62) contributed additionally to the ionic bond. Finally, non-aqueous affinity constant was fiver-order of magnitude greater than the aqueous constant. Therefore, apolar media is recommended in the synthesis of a biphasic system or SEDDS formulation, for example [31,69]. Additionally, solvents such as dichloromethane, isopropyl palmitate, acetone all of them with low dielectric constant, less than 40 (see Table 4), according Bjerrum's ion-pair theory can be used [54,93,96]. These solvents are able to minimize solvation effects, polarization of ions and hydrogen bonding on the complex [28,115]. Also, immiscible organic-aqueous mixtures can be employed to aid the solubility of ion pairing agents [54].

In many cases, the ion pairs are isolated to formulate these agents in drug delivery systems or for characterization, which will be described in a later section. Solvent removal [65,96,116], liquid-liquid extraction, centrifugation and drying with nitrogen gas [54], precipitation-filtration-oven drying [117] and precipitation-centrifugation-freeze-drying [100–101] are the most common methods used (see Table 4).

5. Ionic liquids with IHD

The development of pharmaceutical formulations requires reproducible and well-characterized processes to obtain consistent quality results according to quality by design (QbD) principles [118]. In this sense, it is necessary to isolate the ionic pair and control its purity and other physicochemical properties, so that it can be used as an active pharmaceutical ingredient or intermediary in the elaboration of a drug

Table 3
Properties of drugs and counterions of different pharmaceutical ionic pairs.

Drug	Counterion Name = pKa[a]	MW[a] (g/mol)	HA[a]	HD[a]	PSA[a] (Å^2)	Log P[b]	Ref.
Alendronic acid	Cation						[56]
pKa: 1.66 Acid[a]	Arginine = 13,2 sidechain[b]	174.20	6	7	125	−4.2	
MW (g/mol): 249.10[a]	Phenazopyridine = 5.05[b]	213.24	5	4	89.7	2.62	
LogD (pH 5.5): −8.02[c]	Pyridostigmine bromide = 9.5 [56]	261.1[c]	3[c]	0[c]	33[c]	−4.31[c]	
LogD (pH 7.4): −8.80[c]	Hyoscine butylbromide = 12 [56]	440.4 [c]	4[c]	1[c]	62[c]	0.76[c]	
Bisoprolol	Anion						[107]
pKa: 13.86 Base[a]	Fumaric acid = 3.15	116.07	4	2	74.6	0.46	
MW (g/mol): 325.44[a]	Maleic acid = 2.39	116.07	4	2	74.6	−0.48	
LogD (pH 5.5): −0.84[c]	Tartaric acid = 3.07	150.09	6	4	115	−1.35	
LogD (pH 7.4): 0.12[c]	Benzenesulfonic acid = -0.60	158.18	3	1	62.8	−1.2	
Breviscapine	Cation						
pKa: 2.75 Acid [108]	Octadecylamine = 10.67	269.5[b]	1[b]	1[b]	26[b]	8.5	[109]
MW (g/mol): 462.36							
LogD (pH 5.5): −3.26[c]							
LogD (pH 7.4): −4.84[c]							
DNA (Salmon)	Cation						
pKa: ~1.0 phosphate [106]	1-Ethyl-3-methylimidazolium = 23[d]	111.2[b]	1[b]	0[b]	8.8[b]	0.4[b]	[102]
MW (g/mol): 300.000							
LogD (pH 5.5): ≪ 0							
LogD (pH 7.4): ≪ 0							
Escitalopram	Anion						−96
pKa:9.57 Base[a]	Benzoic acid = 4.20	122.12[c]	2[c]	1[c]	37[c]	1.89[c]	
MW (g/mol): 324.39[a]	Ibuprofen = 4.41	206.28	2	1	37.3	3.97	
LogD (pH 5.5): 0.34[c]	Salicylic acid = 3.01	138.12	3	2	57.5	2.26	
LogD (pH 7.4): 1.27[c]	*p*-aminobenzoic acid = 4.86	137.14	3	3	63.3	0.8	
	Benzenesulfonic acid = − 0.60	158.18	3	1	62.8	−1.2	
Guanidino Oseltamivir	Anion						[110]
pKa:12.8 Base [110]	1-hydroxy-2-naphthoic acid = 3.02	188.18	3	2	57.5	3.196	
MW (g/mol): 326.39							
LogD (pH 6,5): −1,17 [110]							
Irinotecan	Anion						−112
pKa: 11.20 Base[a]	Sodium tripolyphosphate = 0.89 [111]	367.9[b]	1077[b]	0[b]	171[b]	−4.3	
MW (g/mol): 586.68[a]	Sodium docusate = -0.75 [111]	445.6[b]	4[b]	0[b] 0[b]	115[b] 74.8[b]	5.1	
LogD (pH 5.5): 0.68[c]	Sodium lauryl sulfate = -1.5 [111]	288.38[b]				1.6	
LogD (pH 7.4): 2.14[c]							
Insulin	Cation						−91
Isoelectric point: 5.35 [91]	Arginine = 13.2 sidechain[b]	174.20[b]	6[b]	4[b]	125[b]	−4.2	
MW (g/mol): 5,800 [91]	Histidine = 8.97 sidechain[b]	155.15[b]	5[b]	4[b]	92[b]	−3.2	
	Lysine = 10.53 sidechain[b]	146.19[b]	4[b]	3[b]	89.3[b]	−3	
	Anion						
	Glutamic acid = 2.19 sidechain[b]	147.13[b]	5[b]	3[b]	101[b]	−3.7	
	Aspartic acid = 1.92 sidechain[b]	133.1[b]	5[b]	3[b]	10[b]	−2.8	
	Sodium deoxycholate = 6.58 [91]	193.3[b]	2[b]	0[b]	40.1 [b]	4.7	
Memantine	Anion						−113
pKa: 10.27 Base[b]	Pamoic acid = 2.67	388.4[b]	6[b]	4[b]	115[b]	5.8	
MW (g/mol): 179.30[c]							
LogD (pH 5.5): 0.38[c]							
LogD (pH 7.4): 0.56[c]							
Leuprolide	Anion						
Isoelectric point: 10.07 [80]	Sodium oleate = 5.02[b]	304.4[b]	2[b]	0[b]	40.1[b]	6.5	[100]
MW (g/mol): 1209.4 [80]							
Octreotide	Anion						[101]
Isoelectric point: 10.97 [80]	Sodium deoxycholate = 6.58 [91]	414.6[b]	4[b]	2[b]	80.6[b]	4.9	
MW (g/mol): 1019.2 [80]	Sodium docusate = -0.75 [111]	445.6[b]	7[b]	0[b]	115[b]	5.1	
	Sodium decanoate = 4.9[b]	193.3[b]	2[b]	0[b]	40.1 [b]	4.7	
Phenformin	Anion						−99
pKa: 12.15 Base	1-hydroxy-2-naphthoic acid = 3.02	188.18	3	2	57.5	3.196[a]	
MW (g/mol): 205.26	2-naphthalenesulfonic acid = 0.27	208.23	3	1	62.8	0.63[a]	
LogD (pH 5.5): −2.22[c]	*p*-toluenesulfonic acid = -0.43	172.20	3	1	62.8	0.93[a]	
LogD (pH 7.4): −2.20[c]							
Teriflunomide	Cation						−94
pKa: 5.20 Acid[c]	Triethylamine = 10.62	101.19	1	0	3.24	1.45	
MW (g/mol): 270.21[c]	Diethylamine = 10.76	73.14	1	1	12.0	0.58	
LogD (pH 5.5): 1.38[c]	N-(2-Hydroxyethyl)piperidine = 8.96	129.2	2	1	23.5	0.96	
LogD (pH 7.4): −0.37[c]	Diethanolamine = 8.71	105.14	3	3	52.5	−1.43	
	Triethanolamine = 7.77	149.19	4	3	63.9	−1.59	
Vincristine	Anion						−65
pKa: 7.4 Base[a]	Oleic acid = 5.02[b]	282.5[b]	2[b]	1[b]	37.3[b]	6.5	
MW (g/mol): 824.96[c]							
LogD (pH 5.5): 0.55[c]							
LogD (pH 7.4): 2.60[c]							
Zaltoprofen	Cation						−93

(*continued on next page*)

Table 3 (*continued*)

Drug	Counterion Name = pKa[a]	MW[a] (g/mol)	HA[a]	HD[a]	PSA[a] (Å^2)	Log P[b]	Ref.
pKa: 4.79 Acid[a]	Triethylamine = 10.62	101.19	1	0	3.24	1.45	
MW (g/mol): 298.36[c]	Diethylamine = 10.76	73.14	1	1	12.0	0.58	
LogD (pH 5.5): 2.28[c]	N-(2-Hydroxyethyl)piperidine = 8.96	129.2	2	1	23.5	0.96	
LogD (pH 7.4): 0.50[c]	N-(2–hydroxyethyl)pyrrolidine = 9.79	115.17	2	1	23.5	0.60	
	Ethanolamine = 9.16	61.08	2	3	46.3	−1.31	
	Diethanolamine = 8.71	105.14	3	3	52.5	−1.43	
	Triethanolamine = 7.77	149.19	4	3	63.9	−1.59	
Zanamivir Heptyl Ester	Anion						
pKa:11.26 Base [110]	1-hydroxy-2-naphthoic acid = 3.02	188.18	3	2	57.5	3.196	[110]
MW (g/mol): 430.5							
LogD (pH 6,5): −1.31 [110]							

HA: Hydrogen bonding acceptors; HD: Hydrogen bonding donors; PSA: Polar surface area.

[a] SciFinder database.

[b] PubChem https://pubchem.ncbi.nlm.nih.gov/.

[c] Chemspider http://www.chemspider.com/.

[d] Based on 1,3-dimethylimidazolium [114].

Table 4
Method details of ionic pairs production.

Ionic pair	Solvent or mix	Dielectric constant (ε)	Purification methods	Ref
Alendronate-tetraheptylammonium bromide Alendronate-tetrabutylammonium iodide	Phosphate buffer (pH 2.2, 6.3 and 10.9): dichloromethane (DCM)	DCM: 8.93	Liquid-liquid extraction, centrifugation and drying with nitrogen gas	[54]
Zaltoprofen-Triethylamine Zaltoprofen-Diethylamine	Isopropyl palmitate	3.18	None	[93]
Escitalopram-Benzoic acid Escitalopram-Ibuprofen Escitalopram-Salicylic acid	Acetone	19.5	Solvent removal	[96]
Bisoprolol-Caproic acid Bisoprolol-Caprylic acid	Acetone	19.5	Solvent removal	[116]
Vincristine-Oleic acid	Ethanol (EtOH)/dichloromethane (DCM) 3:1	DCM: 8.93 EtOH: 24.5	Solvent removal	[65]
Donepezil-Embonate	Milli Q water (pH 6.28)	80.1	Precipitation-filtration-oven drying	[117]
Leuprolide-sodium oleate	Deionized water	80.1	Precipitation-centrifugation-freeze-drying	[100]
Octreotide-Deoxycholate, Octreotide-Decanoate Octreotide-Docusate	Demineralized water	80.1	Precipitation-centrifugation-freeze-drying	[101]

delivery system [39]. Depending on the characteristics of the drug, the counterion, the synthesis and the purification procedure, the product obtained can be an amorphous powder, a crystalline salt or an IL [43]. This last strategy in the pharmaceutical area has deepened the search for new IL counterions, where several excellent reviews describe aspects such as synthesis [119–121], applications in drug delivery [36,122–123], and effects on biological [38] or biopharmaceutical [124–125] properties. This section will focus then on relating simple physicochemical properties with different types of ion-pairing complexes, mainly drug-ILs with pharmaceutical excipients and GRAS substances, according to Table 5.

As mentioned, some complexes of ion pairings appear as crystalline salts with melting points greater than 100 °C, examples shown in Table 5 are: choline phenytoin, propantheline saccharinate, propantheline cyclamate, mepenzolate saccharinate and mepenzolate acesulfamate, where molecular modeling has allowed to describe the effect of different types of interaction on the formation of these substances and not their respective IL [43]. In order to present the information in a simplified way for pharmaceutical researchers unfamiliar with advanced simulation tools, rotatable bond count (RBC), the number of hydrogen bonding acceptors-donors, the polar surface area (PSA) and the complexity index (CI) were introduced. This last concept is an estimate of molecular structure heterogeneity based on type of bond, non-hydrogen elements and asymmetry, where a higher value represent more complexity. CI can be obtained from the PubMed database and it is calculated using the Bertz/Hendrickson/Ihlenfeldt formula [126].

In the choline phenytoin for example, CI for counterion (46.5) is the lowest among the five mentioned compounds and it has hydrogen bond donors and acceptors resulting the largest melting point of the group (215–217 °C) [43]. On the other hand, propantheline acesulfamate has the lower glass transition temperature (Tg) in the IL group, due high RBC [7], high PSA counterion (80.8), absence of hydrogen bonding donors (both base and counterion) and high IC for the base (474) and counterion (282). All of these factors reflect in a simplified way, electrostatic interactions, asymmetry, rotational freedom, and molecular shape of the complex, that have been reported and modeled as important features to obtain ILs [127]. For its part, the cyclamate anion has a hydrogen bond donor, which enables them to form a crystalline complex (melting point: 133–137 °C) with propantheline. The importance of this type of interaction also includes drugs, where tetrabutylphosphonium formed an IL with ketroprofen and a crystalline solid with diclofenac [128]. The main difference between the two molecules lies in the presence of an additional hydrogen bond donor in diclofenac.

Another important characteristic that has been considered in the design of IL is the choice of a bulky counterion, where docusate and didecyldimethylammonium are examples of them [123]. Dodecylsulfate with lower RBC and IC than docusate is less recommended, where the formation of a crystalline complex (melting point: 120–128 °C) with lumefantrine has been observed. Interestingly, some IL counterions can be used to complex with nucleotide and amino acid oligomers or macromolecules [76,129–130]. An example is benzyl dimethyl alkyl ammonium cation with anionic siRNA [131].

The first generation of ILs began in 1914 with the synthesis of ethylammonium nitrate. This was presented as a viscous liquid, nonvolatile,

Table 5
Properties of drugs and counterions of different ionic complexes.

Entity name	Product obtained			Drug				Counterion				Ref
	Type	MP (°C)	*Tg* (°C)	RBC	HB A-D	PSA (Å^2)	CI	RBC	HB A-D	PSA (Å^2)	CI	
Choline Phenytoin	CS	215–217	ND	2	4–1	58.2	350	2	1–1	20.2	46.5	[43]
Pyridostigmine saccharinate	LMS	94–96	4	2	3–0	33.4	183	0	4–0	77.9	314	[43]
Benzethonium saccharinate	IL	ND	−4	12	2–0	18.5	466	0	4–0	77.9	314	[43]
Propantheline saccharinate	CS	133–135	18	7	3–0	35.5	474	0	4–0	77.9	314	[43]
Propantheline acesulfamate	IL	ND	−20	7	3–0	35.5	474	0	5–0	80.8	283	[43]
Propantheline cyclamate	CS	133–137	20	7	3–0	35.5	474	2	4–1	74.8	200	[43]
Propantheline *p*-toluenesulfonate	IL	ND	7	7	3–0	35.5	474	1	3–0	62.8	206	[43]
Mepenzolate saccharinate	CS	187–189	53	5	3–1	46.5	432	0	4–0	77.9	314	[43]
Mepenzolate acesulfamate	CS	135–137	34	5	3–1	46.5	432	0	5–0	80.8	283	[43]
Lidocaine Docusate	IL	ND	−29	5	3–1	32.3	228	18	7–1	115	539	[123]
Didecyldimethyl-ammonium ibuprofenate	IL	ND	−73	4	2–0	37.3	203	18	0–0	0	200	[123]
TetrabutylphosphoniumKetoprofen	IL	ND	> 0	4	3–0	54.4	331	12	0–0	0	116	[128]
TetrabutylphosphoniumDiclofenac	CS	> 100	NA	4	3–1	49.3	301	12	0–0	0	116	[128]
Primaquine Cinnamate	IL	NR	NR	6	4–3	60.2	262	1	2–0	40.1	149	[132]
Lumefantrine Docusate	IL	52–60	ND	10	2–1	23.5	671	18	7–1	115	539	[133]
Lumefantrine Dodecylsulfate	CS	120–128	ND	10	2–1	23.5	671	12	4–0	72	244	[133]

ND: No detected; NR: No reported; LMS: Low melting solid; CS: Crystalline solid; IL: Ionic liquid.
RCB: Rotatable bond count; HB A-D: Number of of hydrogen bonding acceptors-donors, PSA: polar surface area; CI: complexity index was obtained from PubChem https://pubchem.ncbi.nlm.nih.gov/.

transparent and with high conductivity [134]. The second generation of IL was introduced with alkylpyridinium cations, which allowed the expansion of the use of these substances as solvents in different areas of chemistry [125]. However, some were unstable to humidity. This was addressed, with the synthesis of IL based on imidazolium and tetrafluoroborate, which started the third generation of IL. At this stage, drugs were introduced as counterions, initiating new biologically active substances [38]. Among IL synthesis procedures, the methathesis reaction is the most used for pharmaceutical ILs. In this method, a halide salt of the base reacts with an acid in its free form or salt of metals such as sodium, potassium, lithium, silver or also ammonium. Silver salts generate water miscible IL while those with sodium, potassium and lithium metals produce water immiscible IL [121]. The reaction can be carried out with or without the aid of temperature, in aqueous medium or organic solvents and also in suspension [128]. The obtained product can be purified by extraction with solvents and removing the remaining ions with successive washes. Another method to produce IL is based on the use of ion exchange resins to convert the halide salt to its hydroxyl form and the alkali metal salt to its acid form. Then, equimolar amounts of both species are combined in the neutralization reaction to produce drug IL [40,131]. Interestingly, polymer-drug IL complex were synthesized from ILs and L-lactide monomer by polymerization reaction to produce poly(L-lactide) drug-IL. In one procedure, the drug mefenamic acid was included in the initial IL and the polymerization was carried out to obtain the complex [135], and in the second, metathesis reaction was carried out between the polylactide-ammonium polymer and the silver mefenamate [136]. Both materials were used to produce drug delivery systems (see section 6).

6. Permeability of ion pairs and ionic liquids

Biological membranes are lipophilic in nature but not entirely. Phospholipids and cholesterol, which are some constituents of the cell membrane, are amphiphilic and lipophilic, respectively. Thus, in order to overcome this barrier by passive diffusion, the drugs must have an adequate balance lipophilic, size, hydrophilic character for their absorption, based on Lipinski's Rule [137–138]. For metoprolol (cationic drug) the effect of different lipids was studied in a PAMPA model, where the use of an anionic type PS18: 1 (1,2-dioleoyl-*sn*-glycero-3-[phospho-L-serine), increased the permeability of the drug versus a cationic and neutral lipids, mediated by ion pairing mechanism, demonstrating the feasibility of the lipophilic strategy [95]. Taking these aspects into account, an ion pair of an IHD can be custom designed, changing the polar nature of the compound and generating a new entity with adequate amphiphilicity and solubility. Although there are no definite rules for this purpose, some physicochemical properties of the ionic pair have been evaluated to correlate them with permeability according to Table 6. So, the increase in the transdermal permeability of escitalopram with different synthesized ion pairs was positively correlated with the apparent partition coefficient and pKa of the acidic counterion, and inversely with the molecular weight of the complex in a multiple correlation model [96]. Subsequently, the same investigation group found that the interaction of the hydrogen bond of the drug with the vehicle was reinforced with other hydrogen bond of the polar group present in the acidic counterion, which delayed permeability [139]. This effect was also previously investigated in the transdermal permeability of zaltoprofen (acid drug) ion pairs with various types of organic cations, finding an inverse relationship between the number of hydrogen bond-forming groups and drug permeability, which has been explained in terms of the interaction of the corneum stratum with the molecules. Recently, this approach was used to prepare hydrophobic H-bond pairing improving membrane permeability of leuprolide [140]. Polar

Table 6
Physicochemical properties of counterions and complexes and their impact on permeability.

Variable	Permeability	Ref
Apparent partition coefficient of the complex	Positively correlated	[96,141]
pKa counterion[a]	Positively correlated	[96]
Number of hydrogen bonding groups in counterion	Negatively correlated	[93]
Molecular weight counterion and complex	Negatively correlated	[96,107]
Polar surface area counterion	Negatively correlated	[93]

[a]Carboxylic acid counterions.

surface area (PSA) is another important parameter, obtaining a negative correlation (r = 0.929) between this variable and the rate of permeation for zaltoprofen-amine complexes, where the triethylamine ionic pair shows the highest permeability, with the lowest PSA value (3.24 $Å^2$) [93]. However, a study describing a series of ion pairs keeping the PSA constant found an inverse relationship between the apparent partition coefficient and bisoprolol permeability [116]. Therefore, new studies are required to better understand the absorption process of ion pairs from different biological barriers.

In the case of IL, there is less data about the influence of these properties in permeability of drug-IL complex and the use of these substances has focused on the search for new excipients with different functions in the drug delivery system [36,122]. IL has been synthesized as solvents to increase drug solubility, where we can highlight the IL based on N-alkyl cholinium-based cations and N-acetyl amino acid-based anions, with less cytotoxicity than its precursors and more than double the increase in drug solubility. The alanine-based anion in combination of the cation with 5-carbon alkylic chain (series 2–5) showed the best results for acetaminophen [142]. For increasing permeability, choline-malate IL was synthesized showing a double increase in dermal penetration for dextran compared to the control solution [143]. In this same line, drug-IL were prepared with amino acid esters and salicylic acid, where salicylate-aspartic diethyl ester showed the highest *in vitro* pig skin permeability associated with its highest Log P, among the synthesized derivatives [144]. The chain length has been shown to improve permeability in alkylimidazole derivatives, however, an increase in cytotoxicity was also observed [122]. In a dual drug-IL etodolac-lidocaine, an increase in skin permeability was observed only in the first drug, suggesting a disruption of the complex. The increase obtained for etodolac was 9.3 with respect to the drug alone, and there were no changes for lidocaine [42]. In another system, a liquid co-crystal was made from ibuprofen and lidocaine and applied in skin as a cream. A higher systemic concentration of ibuprofen versus lidocaine was observed at a concentration of 5% in the vehicle [41]. This phenomena was presumably due to the complex interaction with the biomolecules present in the skin, where previously a simultaneous transport of both drugs was demonstrated in a synthetic membrane [145]. For lidocaine a faster and higher systemic concentration was observed for the liquid co-crystal (lidocaine-ibuprofen) compared to the crystalline salt (hydrochloride) and an IL (docusate). This last complex presents a greater hydrophobicity and molecular weight, which would affect its retention in the skin [41].

For oral administration, a cation library was created as a guide for the synthesis of IL derived from selurampanel, which had higher dissolution rates and greater bioavailability than the free acid [40]. Structural descriptors of the counterions such as charges, number of hydrophobic atoms and theoretical diameter were correlated with flux (dissolution rate) and supersaturation time, where less hydrophobic derivatives showed higher fluxes and shorter supersaturation times than long hydrophobic chain counterions [40]. On the other hand, primaquine cinnamate derivatives showed an increasing in the cell permeability versus the covalent analogue or drug base [146].

In some cases, contact with fluids and biological barriers reduces the performance of these agents. Problems that may present include instability of the complex or precipitation due to reduced solubility [147–148]. These limitations can be improved by formulating these agents in different drug delivery systems, according to the description in the following section.

7. Drug delivery systems of IHD based on ion pairing and ionic liquids

The formulation of ion pairs prepared *in situ* or synthesized ILs in drug delivery systems, may bring several improvements on its performance, including better compatibility with biological fluids [133], increased bioavailability [69–70], and reduction of adverse effects [63,65,75], among others. Table 7 summarizes different types of formulations, their characteristics, and their performance in terms of permeability, bioavailability or pharmacokinetics.

7.1. Nanoparticles

The formation of ionic pairs allows the elaboration of nanoparticles (NP) by various procedures, improving the encapsulation capacity of the system in relation to the use of free drug [75,112,130,136]. For AZD2811 using polylactic acid–polyethyleneglycol (PLA-PEG) NPs produced by emulsification solvent extraction, it was obtained a drug loading of 3.2% with an efficiency of 15%, instead, the AZD2811-pamoate pair had a loading of 17% with an efficiency of 71% [75]. Other counterions were investigated in this study, such as HNAP, docusate, cholic acid, deoxycholic acid and oleic acid and a higher drug loading with the increase of hydrophobicity (Log P) was correlated. In addition, the molar volume of the complexes was calculated, obtaining an inverse relationship between this parameter and *in vitro* drug release, where the maximum T_{50} was for AZD2811-pamoate with 120 h. NPs showed minimal bone marrow toxicity and allowed more prolonged circulating drug levels with a longer half-life in relation to the free AZD2811.

High drug loading can also be obtained by precipitation and high-pressure homogenization with ion-pairing nanocrystals [113,117]. In this procedure, a hydrophobic counterion is recommended, where pamoic acid (log P 2.67) has been used with memantine [113] and donepezil [117], obtaining drug loading of 50% and 66% respectively. *In vitro* release of both complexes was sustained over time with T_{50} of 60 h and 7.47 h respectively and total drug exposure expressed in area under the curve (AUC) was 2-fold for the donepezil pair versus drug free solution. AUC was also improved with a nanostructured lipid carrier (NLC), with a 32-fold AUC for breviscapine complex versus the free drug solution. Breviscapine is highly hydrophilic ($LogD_{pH\ 7.4}$: −4.84) and presents fast metabolization rate, so the formation of an ion pairing with highly hydrophobic octadecylamine (Log P: 8.5), allowed its encapsulation in NLC and improved its pharmacokinetics [109]. An alternative approach is the use of polymer-drug IL to prepare polymeric NPs [135–136]. In this strategy, preformed polylactide-ammonium-mefenamate was employed for NPs preparation by emulsion-solvent evaporation technique with polyvinyl alcohol as surfactant. The highest drug loading obtained was 6.8% with an efficiency of 82.3% and about 70% mefenamate was released at 24 h for this formulation [136].

Another polymer-ion pairing complex was prepared with dextran sulfate and an antibody (human IgG-Fab fragment), and then poly (DL-lactide-co-glycolide) (PLGA) NPs were obtained by nanoprecipitation and emulsion solvent evaporation [130]. Nanoprecipitation led to a 70.76% efficiency versus the emulsion solvent evaporation method where 85.25% efficiency was observed. Moreover, the synthesized ion pair was completely dissociated in simulated body fluid and phosphate buffered saline [130].

7.2. Microparticles

In the same way as NPs, encapsulation of an ionic pair in microparticles improves drug loading [70,76,100]. An example is leuprolide which improved the loading from 9.4% to 11% in the oleate form when PLGA microspheres were manufactured [100]. The encapsulation efficiency of insulin increased two-fold in PLGA NPs, when the deoxycholate counterion was used [70]. Interestingly, NPs were incorporated into microcapsules manufactured with hydroxypropylmethylcellulose (HPMC) phthalate (HP55) as enteric coating. The relative bioavailability of insulin was 16.1% when the microcapsules were administered intragastrically in diabetic rats versus subcutaneous drug solution. It was postulated that deoxycholate may induce the opening of epithelial tight junctions improving insulin absorption [70]. In another peptide drug, the formation of a dextran ionic pair and its encapsulation in PLGA

Table 7
Types of drug delivery system to formulate ionic pairs or ILs.

Ionic pair or drug-IL	Drug delivery system					
	Type	L (%)[a]	E (%)[b]	Control release	Permeability, BA[c] or pharmacokinetic data	Ref
AZD2811 pamoate	PLA-PEG nanoparticle (NP)	17.0	71.0	50% – 120 h	half-life 18.2 h NP vs drug solution <1 h	[75]
Irinotecan lauryl sulfate	PEG-PLGA nanoparticle (NP)	3.7	71.6	50% – 12 h	AUC_{inf} 19,2-fold NP vs drug solution	[112]
Donepezil Embonate	Nanocrystal (NC)	66.0	99.0	50% – 7.47 h	$AUC_{(0-\alpha)}$ 2-fold NC vs drug solution	[117]
Breviscapine octadecylamine	Nanostructured lipid carrier (NLC)	NR	88.9	50% – 48 h	AUC_{0-t} 32-fold NLC vs drug solution	[109]
Leuprolide oleate	PLGA microspheres	11.7	96.3	~90% – 10 days	ND	[100]
Insulin deoxycholate	PLGA NP in HPMC phthalate microcapsules	4.54%	94.2%	55.8% – 6 h	Relative BA ~ 16.1% vs subcutaneous drug solution	[70]
Octreotide dextran sulfate	PLGA microparticles	7.9	81.7	~70% – 10 days	ND	[76]
Doxorubicin oleic acid	Nanoemulsion (NE)	7.4	93.7	~60% – 40 h	AUC 3.6-fold NE vs drug solution	[63]
Vincristine oleic acid	Nanoemulsion (NE)	0.48	78.6	~50% – 24 h	$AUC_{(0-\infty)}$ 1.5-fold NE vs drug solution	[65]
Lumefantrine Docusate	SEDDS	NR	NA	ND	AUC 35-fold SEDDS vs drug suspension	[133]
Peroxidase docusate	SEDDS	0.1	NA	ND	P^{d}_{app} 2.5-fold SEDDS vs drug solution	[151]
Insulin docusate	SEDDS	7.31	NA	ND	ND	[152]
Octreotide deoxycholate	SEDDS	0.5	NA	~80% – 2 h	Relative BA 5.21% vs intravenous drug solution	[101]
Enoxaparin dodecylamine	SEDDS	2.0%	NA	~33% – 6 h	2.25% of absolute bioavailability	[69]
Zaltoprofen triethylamine	Transdermal Patch (TP)	10%	NA	NR	Absolute bioavailability 42.53%	[154]
Felbinac triethylamine	Transdermal Patch (TP)	5.0%	NA	NA	AUC_{0-t} 2.0-fold TP vs Seltouch® reference	[155]
Lidocaine etodolac	Lidocaine etodolac patch (LEP)	4.4%	NA	NA	Steady-state flux 9.3-fold LEP vs Etodolac patch	[42]
Lidocaine diclofenac	Bilayer membrane	14.4%	NA	~65% – 20 h	ND	[156]
Doxorubicin-CHEMS[e]	Liposome	6.4%	99.29%	~70% – 24 h	AUC_{0-t} 11.48-fold liposome vs drug solution	[62]
ODN-DODAP[f]	Liposome	NR	80%	NR	half-live ~ 12 h	[104]
Choline salicylate graft copolymer	poly(ionic liquid) graft copolymer	40%	NR	~70% – 80 h	ND	[159]
Imidazolium ibuprofenate	Ionogel	50%	NR	~80% – 40 h	ND	[162]

NR: No reported; ND: No determined; No applicable: NA; [a] Loading of drug; [b] Efficiency; [c] Bioavailability; [d] Apparent permeability coefficient; [e] Cholesteryl hemisuccinate [f] Oligodeoxynucleotide-1,2-dioleoyl-3-dimethylammonium propane.

microparticles allowed the extended release of octreotide (>95% over 55 days) with minimal peptide degradation (<7%) [76].

7.3. Nanoemulsions

Ionic pairing of drugs with highly lipophilic counterions with long carbon chains have been used to prepare nanoemulsions [63,65]. We can highlight the use of oleic acid with a structure of 18 carbons and a log P of 6.5, which has been complexed with doxorubicin and vincristine, reaching encapsulation efficiency of 93.7% and 78.6%, respectively. In these cases, the nanoemulsion achieved greater exposure of the drug compared to solutions, reaching 3.6-fold and 1.5-fold AUC increase for doxorubicin and vincristine, respectively.

7.4. Self-emulsifying drug delivery systems

Drugs, peptides and proteins formulated in ionic pairs have been successfully included in SEDDS. Lipophilic counterions with high Log P such as deoxycholate (log P: 4.9) and docusate (log P: 5.1) are suitable. Docusate was used in the synthesis of an IL with lumefantrine and incorporated in different SEDDS formulations [133]. The lipid product consisting of glyceryl monolinoleate, poloxyl 40 hydrogenated castor oil and ethanol (25:50:25) - lumefantrine docusate, showed a 35-fold increase in AUC versus the drug suspension. An improvement in the bioavailability of itraconazole [149] and cabozantinib [150] was also achieved by using docusate in lipid formulations. Peroxidase as a protein model, was complexed with docusate and formulated in SEEDS. About 61% of the enzyme activity was maintained and the final product achieved a 2.5-fold increase in the apparent permeability coefficient (Papp), compared to protein solution [151]. In the case of peptides, the same strategy has been used with insulin docusate [152] and octreotide deoxycholate [101], where the latter complex achieved an oral bioavailability of 5.21% versus intravenous peptide solution. Dodecylamine, other positively charged lipophilic counterion (log P: 4.76), was paired with enoxaparin, a N-sulfated polysaccharide [69]. The incorporation of this complex in SEEDS led to a 2.25% of absolute bioavailability.

7.5. Patches

The use of non-bulky counterions such as triethylamine and maleic acid, among others, have been preferred for the formulation of transdermal patches [93,107,153]. In the case of anions used for the drug bisoprolol, the increase in the size of the complex was associated with a reduction in permeability, where bisoprolol besilate (MW: 501 g/mol) and bisoprolol mealeate (MW: 383 g/mol) had the lowest and highest value respectively [107]. For zaltoprofen different alkylamine were used and an inverse relationship between PSA and complex permeability was found, where triethanolamine (63.9 $Å^2$) and triethylamine (3.24 $Å^2$) had the lowest and highest permeability respectively [154]. The absolute bioavailability for the transdermal patch formulated with zaltoprofen-triethylamine was 42.53%. Felbinac has also been successfully paired with triethylamine, achieving an 2.0-fold increase in AUC versus Seltouch® reference transdermal patch [155]. In the case of ILs, several anti-inflammatory drugs have been converted to dual drug-IL with lidocaine as a counterion [42,156]. Of note, the lidocaine etodolac resulted in an increase of 9.3-fold in the steady-state flux versus an etodolac patch [42]. This formulation has advanced to clinical trials.

7.6. Liposomes

The anionic nature of oligo and polynucleotides has been the basis for formulating lipidic systems with cationic lipids [103–105]. Oligodeoxynucleotides (ODN) were encapsulated with efficiency over 70% using 1,2-dioleoyl-3-dimethylammonium propane (DODAP). The lipid vesicles obtained showed extended plasma circulation times with a half-life of about 12 h [104]. Recently, the procedure known as hydration-of-freeze-dried-matrix (HMDF), allows stable lipoplexes to be obtained with 12 months of storage stability at room temperature for siRNA encapsulation [157]. Dioleoyl trimethylammonium propane (DOTAP) was used as cationic lipid and siRNA entrapment efficiency was over 90%. The cell uptake and gene knockdown ability of the stored lipoplexes did not change significantly in relation to fresh preparations [157]. On the other hand, cationic drug doxorubicin has been complexed with anionic lipids such as cholesteryl hemisuccinate (CHEMS) to prepare liposomes [62]. Drug loading increased from 1.4% to 6.4% after the drug was paired with CHEMS and the liposomes showed a sustained drug release profile at pH 7.0 with about 70% at 24 h. The AUC for doxorubicin increased 11.48-fold in liposomes versus drug solution [62].

7.7. Other systems

Polymer drug-ILs form self-assembled nanoparticles that can deliver an ionically bound drug in a controlled manner [158–159]. Salicylate was complexed to a choline graft copolymer reaching a drug loading of 40% for the optimized product. Drug release was approximately 70% at 80 h and a reduction in proinflammatory cytokine expression was reported [159]. Another system is an ionogel, consisting of silica particles in whose pores an IL has been immobilized [160–161]. An example is imidazolium ibuprofenate, which was incorporated into a monolithic ionogel with a drug loading of approximately 50%. The system showed a controlled delivery of the drug with approximately 80% ibuprofen released in 40 h [162].

8. Non-invasive administration of ion pairing formulations for IHD

Parenteral dosage forms are widely used for IHD, due to the inherent high solubility of these molecules in the aqueous phase. However, this route of administration represents a challenge to patients and can lead to poor adherence to treatments. The formation of ionic pairs offers an alternative to achieve enhanced absorption of IHD by different routes of administration, where we highlight the research on the oral, buccal, nasal, ocular and transdermal routes.

8.1. Oral/enteral drug administration

The oral route is the most common route for drug administration and preferred by patients. As mentioned above, promising results were reported after oral administration of an insulin-sodium deoxycholate ion pair [68,70]. The subsequent encapsulation of the NPs into HPMC phthalate (HP55) microcapsules further lowered the blood glucose level and raised the relative bioavailability, which was attributed to the absorption enhancing features of the ion pair [70]. Similarly, the enoxaparin dodecylamine ion pair incorporated into SEDDS reached the blood compartment after oral administration in rats, whereas the aqueous enoxaparin solution failed. Firstly, the N-sulfated polysaccharide was prevented from degradation in the stomach and secondly, it successfully crossed the gastrointestinal barrier [69]. Recently, two ion pairs consisting of atenolol/brilliant blue and atenolol/bromophenol blue were studied for colon permeability in rats. Both formulations had improved permeability values (P_{app}) as compared to atenolol alone [33]. In another study, the effect of ion pair formation between trospium chloride and the counterions glycochenodeoxycholate (GCDC) and taurodeoxycholate (TDOC) was investigated *ex vivo* using rat jejunum in the Ussing chamber system. It was demonstrated that bile salt concentrations of 0.5 M lead to a permeation increase of the drug (factor 1.5 and 1.25, respectively), suggesting higher passive diffusion due to the ion pair formation. However, higher concentrations of GCDC and TDOC (2 mM to 8 mM) did not further improve the permeation of trospium chloride, which was explained by the almost complete masking of drug charges by the counterions at the concentration 0.5 M already [30]. The poorly permeable antiviral agents GO and ZHE were ion paired with HNAP and investigated in the rat jejunum perfusion assay. No significant improvement of P_{eff} was observed for the GO ion pair, whereas the ZHE ion pair resulted in significantly higher P_{eff} for 4 mM and 10 mM HNAP [110]. These findings were attributed to the higher association constant of ZHE-HNAP as compared to GO-HNAP, which makes the ion pair more resistant towards dissociation. A PK/PD study investigating an insulin-deoxycholyl-L-lysyl-methylester ion pair revealed equal PK profiles after intrajejunal administration in rats as compared to the subcutaneous administration of insulin, advancing further investigations towards the oral delivery of insulin [163].

8.2. Buccal drug administration

Buccal administration is an emergent alternative to intravenous injection as well as to the oral route, especially for peptides and proteins or other drugs that undergo degradation or suffer from hepatic first pass effects [164–166]. This stratified epithelium does not present tight junctions and thus ion pair permeability would be largely dependent in its physicochemical properties and interactions through the lipid-rich interstitium and lipid cell membranes [167]. To date, however, limited data is available on the buccal administration of ion pairs of IHD. Only one study reports the ion pairing of insulin with basic amino acids (arginine, histidine, lysine), acidic amino acids (glutamic acid, aspartic acid) and sodium deoxycholate (SDC) [91]. Besides arginine, any amino acid (concentration 10 μg/ml) significantly enhanced insulin permeability across TR146 buccal cells while simultaneously being non-toxic as assessed by TEER values and MTT assay. At 200 μg/ml, histidine and lysine ion pairs induced disruptive effects on the cell layer, whereas the acidic amino acids maintained cell integrity. Contrary to these findings, none of the SDC concentrations was effective and safe at the same time. Additionally, the authors confirmed the active transport for the neutral insulin-glutamic acid ion pair.

8.3. Nasal drug administration

Due to the high porosity of the nasal membrane and the low enzymatic concentrations [59,168] the nasal cavity is particularly suitable for the delivery of peptides and proteins. An example is insulin that was paired with trimethyl chitosan derivatives to form nanocomplexes [169]. The formulations showed a relative pharmacodynamic bioavailability from 9.1% to 12.3% and trimethyl chitosan pegylated nanocomplexes were less toxic to the nasal epithelium. On the other hand, polyethylenimine (PEI) of 25 kDa, 750 kDa and 1000 kDa were used to shield negative groups in the highly charged enoxaparin, enhancing its nasal absorption [89]. Comparably, the $AUC_{0\text{-}480\ min}$ and the absolute bioavailability were higher for all ion pair formulations as compared to the administration of pure enoxaparin. In fact, there was no

concentration dependent increase in the absorption rate of drug with increasing PEI concentrations, possibly due to self-aggregation of the counterion resulting in greater particle sizes or related to unfavorable drug/counterion ratios. Similar results were reported for ion pairs of methotrexate with increasing ratios of L-arginine after *in vitro* permeation experiments through freshly excised nasal mucosa from rabbits [170]. The authors attributed the absorption plateau for arginine ratios ≥1:3 to low thermodynamic driving forces in the permeation system. Methotrexate is classified into BCS class III [3], however, it is important to mention that active transport mechanisms contribute to its absorption, which might influence the results of the ion pairing study.

8.4. Ocular drug administration

Due to the physiological structure of the eye, drugs should exhibit both, hydrophilic as well as lipophilic properties [60,171]. Therefore, ion pairing approaches have been considered for ocular drug administration of IHD [172–173]. Given the amphiphilic nature drug and counterion there is a potential to reach the anterior and posterior segments of the eye to elicit therapeutic responses. For example, ocular administration of tobramycin-hexadecylphosphate ion pair (1:2) embedded in solid lipid nanoparticles, permitted the penetration of tobramycin into both vitreous and aqueous humor in rabbits [174]. In contrast, tobramycin was detected in the vitreous humor after ocular administration of the reference product Tobral® eye drops, with a fivefold lower concentration in the aqueous humor after three hours. Comparable observations were made in the vitreous and aqueous humor after intravenous administration of the ion pair as compared to Tobramycin solution. The ocular administration of carteolol ion paired with sorbate caused a 2.6 times higher AUC in the aqueous humor as compared to an equally concentrated solution of the pure compound [85]. In contrast, there was no difference in the plasma levels, suggesting no systemic absorption improvement by the ion pair.

8.5. Transdermal drug administration

Human skin acts as a selective barrier towards the permeation of substances. The intrinsic lipophilicity of the outer skin layers exceedingly reduces the penetration of charged and polar compounds like IHD. Instead, the skin mainly permits the absorption of uncharged molecules exhibiting favorable hydrophilic/lipophilic balance, meaning aqueous as well as lipid solubility [175–176] and requires a molecular weight <500 Da [177–178]. Ion pair complexes partition into the lipid stratum corneum as neutral entities and subsequently dissociate into charged species in aqueous environment [179]. Accordingly, salicylate complexed with different alkylamines (5–9C-atoms) was administered on rat and snake skin and data suggested the existence of ion pairs as explanation for the successful permeation increase [180]. This was contrary to the observations made by another *in vitro* study investigating salicylate complexed with alkylamines (1–12C-atoms) through human epidermis, as slightly lower permeability coefficients compared to the pure salicylate were found [88]. The later epidermal application of the respective ion pairs in rats, however, clearly increased the recovery of salicylate in dermis, subcutaneous tissue and top muscles as compared to pure salicylate and the respective sodium salt, which was attributed to lower clearance rates of the more lipophilic pairs from these tissues [88]. Likewise, corresponding plasma concentration levels increased more rapidly after ion pair administration and remained constant over 8 h, suggesting equilibrium between plasma and tissue concentrations.

An investigation studying ion pairs of lignocaine with different counterions showed an increased apparent partition coefficient, however, the steady state flux through a polydimethylsiloxane (PDMS) membrane model as well as through human epidermis was not significantly improved [141]. In this study, mainly small counterions (bromide, nitrate, sulfonate, and benzoate) with low lipophilicity were investigated, suggesting only weak ability to promote the absorption of lignocaine. Another interesting application, is the use of an IL counterion to administer a siRNA in the dermis [131,181]. For this, benzyl dimethyl alkyl ammonium cation was complexed with anionic siRNA and its local delivery was shown through transport studies in excised porcine skin and cell internalization. This system, termed robed-siRNA, was efficacious in limiting breakdown of elastin following UVB exposure, and demonstrating the therapeutic potential of this platform to treat skin diseases [131].

9. Intellectual property

In the patent space related to ion pairing strategies, various methods have been proposed for developing transdermal formulations with improved drug absorbability based on IHD (see Table 8). First, ion pair formation has been attempted for improving the transdermal delivery of a drug itself. For instance, a patch containing a hydroxyethylpyrrolidine salt of diclofenac was marketed in the US as Flector® Patch [182]. On the other hand, the transdermal delivery of an IHD has also been made by the addition of a transdermal absorption accelerator. WO00/61120 [183] and WO01/007018 [184] have reported that the addition of an organic acid salt (e.g., sodium acetate) together with a basic drug improves the transdermal absorption for a matrix-type patch. Moreover, WO01/005381 [185], reported improvement in the transdermal absorption for a matrix preparation with the addition of an ammonium salt (e.g., diethylamine hydrochloride) together with an acidic drug.

In US8,623,387, Medrx Co Ltd. reported that the use of an IL under nonaqueous conditions can enhance the stability of a drug in solution, and the use of a fatty acid-based IL having 5–20 carbon atoms as a solvent can improve the transdermal permeability of the drug by

Table 8
Description of patent applications of ionic pairs or ILs.

Title	Ionic pairing example	Application ID	Ref
Anti-inflammatory analgesic external patch	Hydroxyethylpyrrolidine diclofenac	JP11924693	[182]
Preparations for percutaneous absorption	Oxyptinin acetate	WO00/61120	[183]
Patches for external use	Tizanidine acetate	WO01/007018	[184]
Percutaneously absorbable preparations	Diethylamine diclofenac	WO01/005381	[185]
External preparation composition comprising fatty acid-based ionic liquid as active ingredient	Diisopropanolamine isostearate - indomethacin	US8623387	[186]
Patch preparation containing an acid scavenger	Diisopropanolamine Oleate - oxycodone	EP3342412	[187]
Composition for patch preparation comprising drug, organic solvent, lipophilic mass base, and powder	Diisopropanolamine isostearate - Brilliant blue	CA2875454	[188]
Transmucosal ketamine delivery composition	Nicotine oleic acid	US10172810	[189]
Formulations of propranolol and analogs as an amorphous melt or ionic liquid for transdermal drug delivery	Propranolol - dioctyl sulfosuccinate	US2018/0169033	[190]
Ionic liquids for transdermal drug delivery	Choline Sodium Geranate - Cefadroxil	US10449254	[191]

dissolving the drug or a salt thereof in the solvent to form a cluster ion composition [186]. In a further protection 8 years later, Medrx Co Ltd. describes a patch preparation for transdermal delivery comprised of acidic salt of basic drugs (as hydrochlorides) with a fatty acid-based IL and a potassium salt [187]. Then the IL is comprised of an organic amine and a fatty acid. This mixture is further admixed with the material for the patch development (rubber like, a silicone-based, or a vinyl ether like polymer). They show the result of several patch formulations of hydrochloride of oxycodone, hydromorphone and tizanidine, to possess better permeability when a potassium generating compound was used instead of sodium salt generating compound. Also, the permeability was better when a mixture of fatty acid and organic amine was used, than when amine was not used (and hence, no ionic liquid was formed).

Medrx Co Ltd. further describes a liphophilic system for transdermal drug delivery [188]. It consists on a lipophilic mass base (a lipophilic elastomer + tackifier + softening agent), a drug solution, using as solvent an IL or a mixture of solvent plus IL and an insoluble powder (insoluble on both solution and mass base). The drugs can be a wide spectrum including acidic drugs (ketoprofen, tranilast, phenobarbital, dantrolene, etc), basic drugs (lidocaine, diphenhydramine, diphenhydramine, tolperisone, etc), proteins (insulin, human growth hormone, elcatonin, calcitonin, EGF, VEGF, GLP-1, etc) and antigen peptides including WT-1, human papillomavirus, and nucleic acid derivative (DNA vaccines, antisense, ribozyme, aptamer, and siRNA).

Pharmaceutical Productions, Inc. describes translingual delivery system for IHDs, by forming hydrogen bonds to lipophilic species, thus forming a lipophilic association [189]. For acidic drugs, basic lipophilic species are used as amines or carboxylic acid amides (cetrimide, oleamidopropyl dimethylamine, dodecyldimethyl ammonium chloride, a quaternary surfactant, cetylpyridinium chloride, amides of caproic, caprylic, capric, lauric, myristic, palmitic or others acids). If the drug is basic, acid species are used as fatty acid, a long-chain alkyl sulfonic acid, or a long-chain alkyl sulfuric acid (caproic, caprylic, capric, lauric, myristic, palmitic, stearic among other acids). Other species can be present as excipients as long as they are less polar than water (sugar, polyol, alcohol, saccharide, polysaccharide, glycerin, propylene glycol, etc.) and a carrier (silica, silicified microcrystalline cellulose, etc). Their method can be used as buccal, sublingual and oral tablet; oral capsule; nasal, buccal or vaginal spray; liquid/semisolid, aerosol for nasal, buccal or pulmonary delivery; patch, lozenge, gum, film, strip, paper, suppository, pessary, etc. In their examples they used nicotine, associated with oleic acid at 1:1 ratio for sublingual administration at physiological pH 5.5–7.5. They achieved good absorption even when nicotine is in its ionized form. Besides the good absorption at physiological pH, this was achieved with low opposite charge species ratio (1:1). The formulation prepared showed fast absorption compared to commercially existing products (90% in 10 mins compared to COMMIT™ at 35% after 60 min and MICROTAB™ at 90% in 30 mins), however, acidic conditions are required for microtab and were not assessed as it can cause buccal ulcers. Other examples include epinephrine, fentanyl, alendronic acid and clorazepic acid. While they describe preparation of sublingual tablets, they do not discuss absorption yields for these compounds.

The University of California proposed a topical (transdermal) delivery for amorphous propranolol as a melt or IL for treating infantile hemangioma [190]. Topical administration is preferred to avoid systemic secondary effects and limited bioavailability at lesions location. With proper formulation of the ILs, they can be directly applied on the skin without adding organic solvents. It was found that the IL prepared with sodium dioctyl sulfosuccinates was the optimal carbon length of the succinate, achieving the highest penetration of propranolol through the skin while causing the least irritation compared with other lengths, or to propranolol hydrochloride solution in ethanol and isopropyl myristate.

On a further patent US10449254, the University of California generalizes their system, describing the use of ILs in a broader sense, also including deep eutectic solvents (DEP) which can act similarly to ILs if its constituents have enough polar moieties [191]. They describe therapeutic utility on ILs just as solvents for drug delivery, but also themselves as protection layers for injuries or burns for example and for their bactericidal activity, as previously reported by Grinstaff on patent WO2011/056545 [192]. They also mention the ability to deliver a broad range of drugs, proteins and other therapeutic substances, and the ability to control to which layer of the skin it can be preferably delivered through the proper formulation of the cationic and anionic species that form the IL or the DEP. As examples, they show how the mixtures can behave as a bactericidal by removing resistant biofilm and inhibits bacteria growth on them. They also shown that it was possible to retain a drug in the IL by enhancing the localization of the drug to certain layers of the skin and enhance transdermal penetration through all the layers of the skin. They show that mannitol preferably stays on the outer skin layers rather than diffusing through for the so-called mixture's LAN-6, LAN-13, LAN14, LAN-19 and LAN-21. On the other hand, when using cefadroxil with the LANL-21 mixture, it diffuses through the skin concentrating mostly on the dermis and the acceptor solution.

10. Perspective/Future opportunities

Since its introduction, the use of ionic pairs has increased rapidly in different areas of chemistry and pharmaceutical research [38,83]. The IL application in this last field has been possible due to the appearance of third generation ILs, where the safety profile has been improved using counterions with low toxicity [125]. Amino acid-based counterions and pharmaceutical excipients have been used with good results [144,193]. Recently, the search for new substances to synthesize new ILs has introduced a naturally occurring cinnamate anion and derivatives to prepare ILs with primaquine [132]. Also, naturally occurring carboxylic acids were used to prepare protic IL from papaverine [194]. This concept can be further extended to other natural organic acids and bases obtained from different extracts of vegetal origin. However, new toxicological studies are required to better understand the interaction of this new substance with biological systems, where some of them presumably disrupt the cell membrane [195]. Wiest et al [40], created a counterion library to synthesize selurampanel ILs, where hydroxyl, di and tri-series derivatives were non-toxic *in vitro*. Also, there is contradictory data about the permeability of these substances, where some reports have established an increase based on the apparent partition coefficient [145,196–197], while others have only found an increase in solubility and supersaturation time [40,198].

Regarding biological barriers, new opportunities open up for ion pairs through buccal, nasal and transdermal administration, where they could increase the absorption of new biological entities, such as antisense oligonucleotides, small interfering RNA and peptide-drug conjugates, commonly unstable after conventional oral administration.

11. Conclusion

The number of pharmaceutical compounds with unfavorable properties, such as poor intestinal absorption, has risen in recent decades and has challenged formulation scientists to date. Traditional formulation approaches often fail to transport these drugs to the target site in a suitable concentration or require uncomfortable administration routes. Therefore, the development of novel drug delivery options is of crucial importance to overcome the bioavailability limitations of pharmacologically effective agents. The ion pairing of new drug candidates or marketed drugs with hydrophobic counterions is widely used in pharmaceutical technology. To date, numerous studies reported the beneficial effects of the ion pairing approach, rendering this strategy a valuable tool to optimize physicochemical, biopharmaceutical, pharmacokinetic and toxicological properties of IHD. Embedding of the ion pairs into lipid drug delivery systems further supports the optimization of bioavailability and enhances therapeutic efficacy by protecting the drugs against enzymatic or hydrolytic degradation and offering

controlled release kinetics. As pointed out, ion pairing is a versatile drug development strategy that should be considered when formulating IHD for oral/enteral buccal, nasal, ocular, or transdermal application.

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