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Review Article

Ion-paired Drug Delivery: An Avenue for Bioavailability Improvement

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ABSTRACT

Ion-pairing is reported to improve the lipophilicity and subsequently the transport rate of polar drugs across lipid membranes. Lipophilisation of ionic drugs with high aqueous solubilities by ion-pair formation with appropriate counter-ion have proven to be promising for several applications. The aim of this review is to present the usefulness of ion-pair for improving the poor bioavailability of ionic drugs through various routes. The review covers an update on the applications of this strategy to improve drug delivery through various routes of administration including ocular, oral, parenteral and transdermal. It is discussed how ion-pair complexes assist in introducing functionality that would allow formation of a neutral molecule which can be subsequently encapsulated into delivery systems to be distributed by various routes of administration.

Keywords: Bioavailability, Counter-ion, Drug- delivery, Hydrophobic molecule, Ion-pair formation

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INTRODUCTION

Ion-pair is a pair of oppositely charged ions held together by Coulomb attraction without formation of a covalent bond. They behave like a single unit. Hydrophobic ion pairing technique has been used to increase the hydrophobicity of molecules containing ionizable groups by stoichiometric replacement of the polar counter ions with more hydrophobic ones (Choi and Park, 2000). Ion-paired delivery has emerged as a viable approach for enhancing solubility of ionic molecules in non-polar solvents, augmentation of protein and DNA transport and addressing the poor bioavailability issues of hydrophilic drugs (Neubert, 1989; Neubert and Dittrich, 1990; Van *et al.*, 1999; Kamal *et al.*, 2007; Chorny *et al.,* 2007; Rastogi *et al.*, 2009; Ma *et al.,* 2010; Hao *et al.*, 2010). In this review, the application of ion paired system to delivery of drugs through various routes of administration is discussed.

Transdermal Delivery

Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion-pairs can increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous microenvironment of the epidermis releasing the parent charged drug which can diffuse within the epidermal and dermal tissues (Megwa *et al.*, 2000; Valenta *et al.*, 2000).

Sarveiya *et al.* (2004) reported a 16-fold increase in the steady-state flux of ibuprofen ion-pairs across a lipophilic membrane. They determined the influence of pH and ion-pairing on the permeation of ibuprofen across polydimethylsiloxane (PDMS) membrane. Diffusion studies at different pH values (4.0, 5.0, 6.0, 7.0 and 8.0) indicated that ibuprofen sodium flux increased significantly with increasing pH from 4.0 to 7.0. Above pH 7.0, a decrease in diffusion was observed. The permeability coefficient increased with an increase in the amount of unionized acid.

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Some workers studied the possibility of improving the efficiency of transdermal delivery of salicylate through human epidermis by ion-pair formers (alkylamines and quaternary ammonium ions). The relationship between the physicochemical properties of the counter-ions and salicylate flux was examined. It was found that flux can be correlated to the conductivity associated with the penetrant solution, molecular size of the counter-ion and lipophilicity expressed as either octanol/water partition coefficient of the ion pairs or the carbon chain-length of the counter-ions. Mathematical models have been developed to predict salicylate flux from these physicochemical parameters (Megwa *et al.*, 2000).

Nash *et al.* (1992) tested the ion pair absorption hypothesis with respect to the topical route of drug delivery. The experiment consisted of preparing various lidocaine-n-alkanoate ion pairs, then characterizing them by proton magnetic resonance spectroscopy, elemental analysis and conductivity. Percutaneous absorption studies through excised hairless mouse skin were carried out using ethanolic solution of radiolabeled ^{14}C-lidocaine-octanoate, ^{14}C-lidocaine-decanoate and ^{14}C-lidocaine-dodecanoate. The difference between the flux values of lidocaine-1-^{14}C-dodecanoate and ^{14}C-lidocaine-dodecanoate infers that lidocaine-dodecanoate did not cross the excised, full-thickness, hairless mouse skin as an intact 1:1 ion pair.

To improve transdermal delivery of meloxicam, Zhang *et al.* (2009) studied ion-pair formation with six organic bases, diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, and N-(2'-hydroxyethanol)-piperidine. The authors proved the formation of a meloxicam/amine ion-pair in solution by (13) C-NMR (nuclear magnetic resonance). Their results suggested that the degree of enhancement possibly depends on the structure and hydrophilicity of the counter ions. The enhancing effect of ion-pairing on the skin permeation of Glipizide was studied by Tan *et al.* (2009). (13)C NMR spectroscopy was used to identify the ion-pairing formation between Glipizide and the respective counter-ion and the effect of an interaction with amines as counter-ions, including diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, N-(2-hydroxylethyl) piperidine with Glipizide was observed. All the amines investigated in the study exhibited enhancing effect on Glipizide flux, and triethylamine had the most potent enhancing effect. The study concluded that the formation of ion-pairs between Glipizide and counter ions is a useful method to promote the skin permeation of Glipizide.

Ocular Delivery

In 2000, Sznitowska and other workers prepared submicron emulsions containing pilocarpine as ion-pair with mono-dodecylphosphoric acid (Sznitowska *et al.*, 2000). Physical stability of these preparations was confirmed during 4 months of storage at 4^{o}C. Approximately 50% of the drug was found in the aqueous phase of emulsion separated using an ultrafiltration technique, while the rest was present in the oily phase and interphase. The miotic effect observed in rabbits after application of the ion-pair in aqueous solution or in submicron emulsion was the same; indicating that the drug distribution into the oily phase of the colloidal vehicle does not improve ocular bioavailability.

An exhaustive study carried out by Trotta *et al.* (2002) assessed the ion pairing of retinoic acid (R.A) using microemulsions as delivery vehicles to influence the topical permeation. Phenylalanine methyl ester, phenylalanine ethyl ester, histidine methyl ester, tryptophan methyl ester and valine methyl ester were used as counter ions. The results recommended that O/W microemulsions containing a counter-ion can be used to optimise drug targeting without a concomitant increase in systemic absorption. Aqueous dispersions of solid lipospheres containing up to 7.5% pilocarpine as lipophilic ion pairs were prepared by Cavalli *et al.* (1995). The lipospheres had a size range between 75-85 nm, consisted mainly of stearic acid and egg lecithin; pilocarpine base was incorporated as ion pair with mono-octylphosphate, mono-decylphosphate and mono-hexade-cylphosphate. The authors concluded a promising result for sustained ocular delivery of pilocarpine.

Oral Delivery

Antiviral drugs often suffer from poor intestinal permeability, preventing their delivery via the oral route. Miller *et al.* (2010) utilised an ion-pairing approach of the low-permeability antiviral agents zanamivir heptyl ester (ZHE) and guanidino oseltamivir (GO). The counterion 1-hydroxy-2-naphthoic acid (HNAP) was utilised to enhance the lipophilicity and permeability of the highly polar drugs.

HNAP enhanced the apparent permeability of both compounds across Caco-2 cell monolayers in a concentration-dependent manner. Consistent with a quasi-equilibrium transport model, a linear relationship with slope near 1 was obtained from a log-log plot of Caco-2 P (app) versus HNAP concentration, supporting the ion-pair mechanism behind the permeability enhancement.

The potential of ion-pair formation to improve the oral absorption was studied by Gelder *et al.* (1999) for two highly potent and selective antiretroviral agents viz., 9-(2-phosphonyomethoxypropyl) adenine (PMPA) and AMD3100. Transepithelial transport of these two agents is very poor as PMPA is negatively charged and AMD3100 is positively charged at physiological pH. Ion pair formation was carried out to solve this problem. Positively charged counter ions such as t-hexyl-, t-heptyl-, t-octylammonium bromide and dodecyl-, tetradecyl-, hexadecyltrimethylammonium bromide were used to form ion pairs with PMPA, while sodium taurodeoxycholate (*in vitro* experiments) and sodium taurocholate (*in vivo* experiments) were used as counter ions for AMD3100.

Results obtained from partitioning studies of the drugs in the presence or absence of counter ion revealed that competition by other ions was responsible for the absence of an effect: when pure water was used as the aqueous phase, a reduction of the initial aqueous concentration was observed for both the agents; however, as soon as other ions were present in the aqueous phase, the effect of the counter ion was diminished or completely abolished. The oral bioavailability in rabbits revealed that, AMD3100 in the presence of 4 equivalents of taurocholic acid remained very low and was only 3.2-fold better (i.e. 3.6%) in comparison to pure AMD3100. The authors concluded that the formation of ion pairs may not be very efficient as a strategy to enhance transepithelial transport of charged hydrophilic compounds, as competition by other ions may abolish the beneficial effect of counter ions.

Parenteral Route

A study compared the pharmacokinetics of doxorubicin incorporated as ion-pair into solid lipid nanospheres (SLN) with that of the commercial solution of the drug. Male albino rats (Wistar-derived strain) were treated i.v. with equivalent doses (6mg kg^{-1}) of two different doxorubicin formulations: an aqueous dispersion of SLN carrying doxorubicin and a commercial doxorubicin solution (Adriablastina). These formulations were injected, under general anaesthesia, through a cannula into the jugular vein and blood samples were collected at 1, 15, 30, 45, 60, 120 and 180 min after administration. After 180 min rats were killed and samples of liver, heart, lung, kidney, spleen and brain were collected. Blood and tissue samples were analysed by a spectrofluorimetric method. The anthracycline concentration in the blood was markedly higher at each point times with the SLN than with the commercial solution. The drug concentration was also higher in the lung, spleen and brain. SLN-treated rats showed a lower doxorubicin concentration in liver, heart and kidney. The results showed that SLN increased the area under the curve (0-180 min) of doxorubicin compared to conventional doxorubicin solution and led to a different body distribution profile (Zara *et al.*, 1999). The doxorubicin present as ion-pair complex has enhanced lipophilicity which resulted in an increment in apparent partition coefficient between lipid and water enabling higher drug payloads and bio-distribution.

Miscellaneous

Ion-pair drug delivery can also apply for inhalation therapy for infectious lung diseases like tuberculosis. Potent anti-tuberculosis drug, isoniazid was modified into an ionizable form suitable for hydrophobic ion pairing. The charged prodrug, sodium isoniazid methanesulfonate (Na-INHMS), was then ion paired with hydrophobic cations, such as alkyl-trimethylammonium or tetra-alkylammonium. The water solubility of the tetra-heptylammonium-INHMS complex is about 220-fold lower than that of Na-INHMS. The half-life of this HIP complex is on the order of 30 min, making the enhanced transport of the drug across biological barriers possible. This work represents use of a pro-drug approach to introduce functionality that would allow hydrophobic ion pairing complex formation for a neutral molecule (Zhou *et al.*, 2002).

Zimmer fabricated polyalkylcyanoacrylate nanoparticles by an emulsion polymerization process and antisense oligonucleotides were loaded on the particles by adsorption. A cationic polymer, DEAE-dextran, was incorporated into the particle matrix or a cationic hydrophobic detergent (CTAB) was used to form a lipophilic oligonucleotide ion pair. Enzymatic digestion of the oligonucleotide was

almost quantitatively inhibited by this nanoparticle complex and cellular uptake by different cell lines was significantly enhanced. *In vivo*, the bio-distribution of the oligonucleotide nanoparticle complex resulted in targeting of oligonucleotides to the liver. Improvements in antisense treatments with nanoparticles were demonstrated for tumor therapy as well as for antiviral applications (Zimmer, 1999).

Sineerat *et al.* (2008) investigated a water insoluble complex of cationic propranolol HCl with anionic sodium lauryl sulfate. They concluded that the 'propranolol-sodium lauryl sulfate complex' provided promising sustained drug delivery and were feasible to be encapsulated in microparticles for a more sustained drug release effect. Austin *et al.* (1998) studied the distribution of salmeterol and proxicromil between unilamellar vesicles of dioleoylphosphatidylcholine (DOPC) and aqueous buffer at pH 7.4, using an ultrafiltration method, as a function of compound concentration, DOPC concentration, and buffer ionic strength. The binding of these ionized lipophilic compounds to neutral DOPC vesicles induces a surface charge, which causes the observed membrane distribution coefficient D (mem)obs to vary significantly with bound compound to DOPC ratio and with ionic strength. This variability is shown to be well-described with use of the Gouy-Chapman theory of the ionic double layer and is contrasted with the ideal behavior shown by the neutral compound clofibrate.

Increasing ionic strength is also shown to increase the observed 1-octanol-buffer distribution coefficients D (o/w) obs of proxicromil but through a very different mechanism involving the extraction of ion pairs. This study highlights the experimental difficulty in determining concentration-independent liposome distribution coefficients of ionized lipophilic compounds and describes when deviations will be significant and how observed values may be corrected for such effects. The general effect of ionic strength on membrane-buffer distribution and 1-octanol-buffer distribution was discussed with particular reference to the very different propensity for ion pair formation shown by the two systems, and the most suitable experimental conditions that should be used with each system.

De Verdiere *et al.* (1997) reported that polyalkylcyanoacrylate (PACA) nanoparticles loaded with doxorubicin allowed multidrug resistance to be overcome *in vitro*. However, increased cytotoxicity is not always correlated with an increased level of intracellular drug. They observed that a direct interaction between nanoparticles and cells is a necessary requirement for overcoming resistance. In addition, the results showed that the degradation products of PACA (mainly polycyanoacrylic acid) in the presence of doxorubicin were able to increase both accumulation and cytotoxicity, thus suggesting the formation of a doxorubicin-polycyanoacrylic acid ion-pair. It was concluded that resistance was overcome as a result of both the adsorption of nanoparticles to the cell surface and increased doxorubicin diffusion by the accumulation of an ion pair at the plasma membrane.

Matschiner and colleagues developed a formulation with optimized penetration of the ion-pair between erythromycin and octadecansulfonate (Matschiner *et al.*, 1995). The lipophilicity erythromycin by ion pairing was improved and the determination of lipophilicity was based on partition coefficients and on the penetration of ERY into a modified multilayer membrane system. It was shown that the penetration of erythromycin into a lipophilic acceptor system was three times higher when ion pairing was used in comparison with the penetration of the erythromycin base alone. The optimized formulation was compared with formulations containing ethanol and with the commercial product Zineryt. It was concluded that the dosage of the antibiotic used can be markedly reduced by optimizing a vehicle for the ion pair.

The chemical reaction of vidarabine (VIDA) with isohexyl cyanoacrylate nanoparticles in a pH-dependent fashion occurs only in the presence of dioctylsulfosuccinate (DOSS). The formation of an ion pair with DOSS allows a better contact of VIDA with the monomer during the polymerization process taking place in micelles. On the basis of molecular weight profiles of the polymer, determined by gel permeation chromatography (GPC), Guise *et al.* (1990) proposed that VIDA induces the polymerization of cyanoacrylic monomers through a zwitterionic pathway. This mechanism allows the covalent linkage of the drug

with the polymer, which is consistent with NMR experiments. The study illustrated the need for physicochemical studies in the design of new colloidal drug delivery formulations.

Leuprolide acetate, an analogue of luteinizing hormone-releasing hormone (LH-RH), was hydrophobically ion paired with a long chain fatty acid, sodium oleate, in an aqueous solution (Choi and Park, 2000). It was found that with increasing the stoichiometric molar amounts of sodium oleate to leuprolide approached up to 2.5-3, the solution became gradually turbid with increasing particle sizes, indicating leuprolide precipitation as a result of hydrophobic ion pairing. On the other hand, beyond that critical molar ratio range, the solution turned clear with much reduced particle size, indicative of micelle formation. The hydrophobically modified leuprolide-oleate complex was lyophilized and directly encapsulated within biodegradable poly (D, L-lactic-co-glycolic acid) (PLGA) microspheres via a single oil-in-water (O/W) emulsion method. Microsphere morphology, leuprolide release behavior, and polymer mass erosion profiles were examined in comparison to the PLGA microspheres prepared with free leuprolide. The results indicated that ion-pairing rendered the protein more hydrophobic, increased its solubility in organic solvents and thereby improved its loading.

CONCLUSION

Ion-pairing can be a valuable tool for enhancing solubility and stability in an organic solvent. The complexes formed can be formulated into particulates with higher drug loading. This technique has found unique opportunities in delivery of polyelectrolytes (e.g. peptide, proteins, polynucleotide) by using them as hydrophobic ion-paired moieties for designing particulates and microemulsions that during formulation require direct solubilization in organic solvents. Additionally, this approach can also improve stability and permeability across biological membranes. Formation of ion pairs normally does not entail an alteration in the structure and function of drug. Thus, this approach can assist in designing better dosage forms for alternative routes of administration.

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