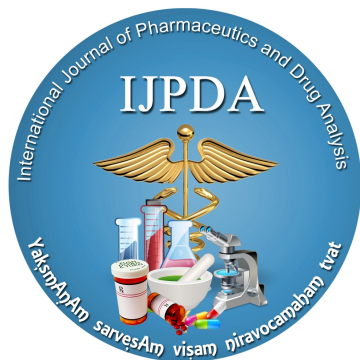


Current Trends: Ion Exchange Resinates in Controlled Drug Delivery



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Abstract:

Ion exchange resins (IER) recently used in the controlled release drug delivery due to its properties, more efficient, accurate drug loading, control release and better stability. IER are the attractive carriers for the controlled drug delivery systems which suitable for drug-delivery technologies, including oral controlled release, reduction of toxicity, site specific, fast dissolving, iontophoretically assisted transdermal, nasal, ophthalmic, and taste masked systems. The present review is to focus, current technological developments like the factors affecting the nature and strength of the binding/loading of drug-sized model compounds into the ion-exchange resins. Also the practicability of ion exchange resins for delivery of drugs loading and IER applications and future potential.

Keywords: Ion exchange resins, Resinates, Controlled drug delivery

Introduction

Recently the ion exchange resins (IER) carriers attracted pharmaceutical researchers due to its vast applications in controlling the drug release. Ion-exchange resins have been widely studied in medical and pharmaceutical applications, including controlled drug delivery, leading to some commercial resin based formulations. Ion-exchangers provide an efficient means to adjust and control drug delivery, as the electrostatic interactions enable precise control of the ion-exchange process and, thus more uniform and accurate control of drug release compared to systems that are based only on physical interactions. However, the ion-exchange resins have many advantageous properties compared to other carriers, such as more efficient drug loading,

enhanced control release, better mechanical, chemical and thermal stability, and good formulation properties, which make the IER attractive carrier for controlled drug delivery systems.

Adams and Holmes synthesized the first ion-exchange resins in 1935 [1] and from 1950's to the present the complexation of drugs with ion-exchange resins has been studied extensively. The advantage of ion-exchange materials for controlled drug delivery is their ability to bind and exchange charged drug molecules. Several peroral ion-exchange products have been developed for sustained and controlled drug release.

Research over the past few years has revealed that IER are equally suitable for drug-delivery technologies, including oral controlled release, reduction of toxicity, site specific, fast dissolving, iontophoretically assisted transdermal, nasal, ophthalmic, and taste masked systems [2-7]. The present review is to focus, the factors affecting the nature and strength of the binding/loading of drug-sized model compounds into the ion-exchange resins. Also the feasibility of ion exchange resins for delivery of drugs loading and IER applications.

Structure and properties of ion-exchange materials:

Ion-exchange materials, such as macroreticular resins, gels, membranes and fibers, contain two components: a water insoluble structural component consisting of a polymer framework, and a functional component consisting of fixed acidic or basic ion-exchange groups [8-12]. Ion exchangers can be classified according to the nature of these structural and functional components. The ion-exchangers can hence be divided into cation-exchangers and anion-exchangers on the basis of the functional groups. The ionisable acidic/basic groups, such as $-\text{SO}_3^-$, $-\text{COO}^-$ (cation-exchangers) or $-\text{N}^+(\text{CH}_3)_3$, $-\text{NH}_3^+$, $-\text{NH}_2^+$ and $-\text{NH}^+$ (anion-exchangers), are covalently attached to the framework of the ion-exchanger, and their charge compensated for by mobile counter-ions. Thus, the exchangeable mobile counter-ions are cations in the case of cationexchangers and anions in the case of anion-exchangers. IER may also contain different types of ionic groups of the same charge (bifunctional/polyfunctional exchangers) or opposite charges (amphoteric exchangers). Ion-exchangers can be characterized in a quantitative manner by their capacity, which is defined as the number of ion-exchange groups in a specified amount of ion-exchanger [8, 11]. Depending on the acid or base character of the ionic groups, the IER can be classified into strong and weak ion-exchangers (Table 1.). The weakly basic groups ($-\text{NH}_3^+$, $-\text{NH}_2^+$, $-\text{NH}^+$) are ionized only under low pH conditions, and the effective capacity of compound binding by these groups is progressively decreased by an increase in pH. Similarly, the weakly acidic groups ($-\text{COO}^-$) are ionized only under high pH

conditions. In contrast, strongly basic/acidic groups ($-\text{N}^+(\text{CH}_3)_3$ / $-\text{SO}_3^-$, $-\text{PO}_3^{2-}$) remain ionized over the entire pH-scale and, thus, the effective capacity of the ion exchanger is practically pH independent.

Mechanisms of ion-exchange:

The ion-exchange reaction is a reversible, selective and stoichiometric interchange of mobile ions of like charges between the ion-exchanger and the external liquid phases [11]. Each counter-ion that is released from the ion-exchanger is replaced by an equivalent amount of another ionic species of same sign and valence due to the electroneutrality requirement. Based on the nature of the ionic species being exchanged, the ion-exchange process is either anionic or cationic (Equation 1 and 2).

Preparation of ion exchange Resinates:

The important step in the preparation of drug resinates is to purify the resins. Purification of resin can be achieved by washing with absolute ethanol, ethanol and water mixture. Final washing with water removes all the impurities. Purification is generally done by cycling repeatedly between the sodium and hydrogen forms with a cation exchanger (or) between the chloride and hydroxide forms with anion exchanges. The conversion can be achieved by soaking the resins with acid or alkali solutions, respectively. After changing the ionic form, the resin is subjected to washing with distilled water until elute becomes neutral in reaction, and finally is dried at 50°C . Loading of drugs is generally done by two processes:

1. Batch process – The resin particles are agitated with a large volume of concentrated drug solution until equilibrium is established. Subsequently the resin is to be washed to remove free and un-associated drug and thereafter it is air dried.
2. Column process – A highly concentrated drugs solution is eluted through a bed or packed column of the resin, until effluent concentration is same as that of eluent.

The loading of drug onto the ion exchanger and release kinetics from the complex is depend upon the characteristics of ion exchanger, drug properties and the external conditions (Table 2).

Table 1. Classification of ion exchange resins

Resin Type	Polymer Backbone	Functionality	Examples
Strong cation exchanger	Polystyrene divinyl benzene	-SO ₃ ⁻	Amberlite IRP 69, Indion-244, Amberlite-120, Dowex 50, Amberlite IRP09
Weak cation exchanger	Acrylic - divinyl benzene	-COO ⁻	Indion-204, Indion-264, Amberlite IRP 88, Amberlite IRC50, Diaion WK100
Strong anion exchanger	Polystyrene and divinylbenzene	N ⁺ -R ₃	Amberlite IR-400, Dowex-1, Duolite AP145
Weak anion exchanger	Polystyrene and divinyl benzene	N ⁺ R ₂	Amberlite IR 4B, Dowex

Table 2. Factors affecting the loading and release of drugs from the ion-exchangers:

Factor	Effect	Reference
Ion-exchanger dependent		
Ion-exchange capacity	Drug binding affinity and release	[13,14]
Nature of fixed ionic groups	Ionization and selectivity	[15,16]
Particle size	surface area, adsorption efficiency and drug release	[17-21]
Degree of cross-linking	pore size of ion-exchanger, drug diffusion	[22,23]
Drug dependent		
Lipophilicity	binding affinity	[24-27]
pKa	Ionization	[28,29]
Sterical properties	binding affinity	[25]
Molecular size	diffusion coefficient, binding affinity	[8,23]
External condition		
Concentration of solution	Drug release	[11,17,22,23]
Valence of surrounding ions	Drug release	[30,31]
pH	Ionization of drug and ion-exchanger	[29]
Temperature	porosity of ion-exchanger, drug loading and diffusion	[21,32]
Agitation/ stirring speed	Drug diffusion	[21-23,32]

Table 3. Some recent applications of IER in controlled drug delivery systems.

IER	Drug	Effect on drug release/delivery	Ref.
Dowex 50WX series	Betahistine dihydrochloride	Once-daily extended-release	[33]
Brominated poly(2,6-dimethyl-1,4-phenylene oxide)-methacryloxypropyl trimethoxysilane	Sodium salicylate	Scaffolding material for controlled release delivery.	[34]
Indion 254	Diltiazem hydrochloride	Ionically cross-linked microcapsules; extended release up to 15 h.	[35]
acrylic copolymers	Cefotaxime sodium	higher adsorption	[36]
Indion 234	Ranitidine HCl, Domperidone	<i>In-vitro</i> and <i>ex vivo</i> retardation in release	[37]
Sulfonated Styrene–Divinylbenzene Cross-linked Copolymer	Chlorpheniramine	increased drug binding and release	[38]
Indion 234 and Tulsion 343	Diphenhydramine Hydrochloride	for effervescent and dispersible tablets	[39]
[poly(ethylene-g-styrenetrimethyl-ammonium-chloride)]	Riboflavin-5-phosphate	Mucoadhesive properties <i>in vivo</i>	[40]
Dowex WX2-400	dextromethorphan hydrobromide	Fast disintegrating tablets with Sustained drug release	[41]
Dowex 50Wx4 and Dowex 50Wx8	Diltiazem	Sustained release suspensions, stability	[42]
Cholestyramine	Potassium diclofenac	utility for enteric drug delivery	[43]
poly(propylene-g-vinylbenzyltrimethylammonium-chloride)	Ketoprofen	iontophoretically assisted transport across rat skin favored	[44]
Dowex 50Wx2 and x4 Dowex 50Wx8	dextromethorphan hydrobromide and diphenhydramine hydrochloride	extended delivery of two combined drugs with the equivalent therapeutic dose	[45]
Carboxyalkyl methacrylates	Propranolol·HCl, diltiazem·HCl and verapamil·HCl	release kinetics with the suitable hydrophobicity	[46]
SP-Sephadex	Tetracycline	Self propelled drug release achieved	[47]
Aminex 50W-X4	adenovirus conjugated to liposomes	reduce the toxicity of the AL complexes	[48]
Amberlite-IRA900	Diclofenac	oral floating drug delivery	[49]

Pharmaceutical Applications of the IER in controlled release systems:

Ion-exchangers, primarily resins, have been studied as controlled release formulations at least in oral, transdermal, nasal and ocular drug delivery (Table 3). Numerous drug therapies benefit when the active ingredients are released at a controlled rate so that constant, sustained, site-specific or pulsatile action is obtained. Formulation of drugs as constant or sustained release products, using ion-exchangers,

has been utilized to improve drug safety and efficacy, enhance patient compliance, reduce dosing intervals and increase drug stability.

Modified release oral drug delivery:

The use of ion exchange resins into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. Prolonged drug release in

simulated gastric and intestinal fluid independent of the pH of the dissolution media can be achieved with sustained release Formulations of diltiazem [42] resins using strong cation exchange resins for the preparation of microcapsules. The release of salicylates from the strong anion exchange fiber, Smopex DS-218v molar ratios of the external chloride-ions versus the salicylate bound in the fiber [28]. Ion exchange resins and the effects of coating by various aqueous polymeric dispersions on the complexes for developing new sustained-release fast disintegrating tablets of dextromethorphan. Higher coating level decreased the release rate [41,50] further Jeong et al. developed a comprehensive mathematical model using a mechanistic approach by considering diffusion, swelling, and ion exchange processes solved by numerical techniques involved in polymer (poly vinyl acetate) coated dextromethorphan- resin complexes for studying release characteristics[51].

A sigmoidal-release system rapidly releases the drug from a multiple-unit device after a predetermined lag time, and can achieve both time-controlled and rhythmic release. IER were studied in the development of sigmoidal-release systems. Eudragit RS (Röhm, Darmstadt, Germany), an AER with limited quaternary ammonium groups, is coated over beads with a sugar core surrounded by organic acid and drug mixture. The ionic environment, induced by the addition of an organic acid to the system, was found to be responsible for pulsatile release [52, 53]. A controlled release resin beads of betahistine dihydrochloride, a short half-life freely water soluble drug, was developed to allow once-daily administration to improve patient compliance and eliminate the risk of intolerance of the drug, that a promising once-daily extended-release microcapsules of the highly water soluble drug, was successfully designed [33] The ionically cross-linked microcapsules were capable of releasing Diltiazem hydrochloride up to 9 h, and that from dual crosslinked microcapsules was extended up to 15 h [35, 42]. Microparticles with complex architectures based on the polyelectrolyte complexes between an acrylic ion exchange resin and two polysaccharides: gellan and xanthan gum were prepared and used for the adsorption of antibiotic cefotaxime sodium as a new drug delivery systems [36].

Gastric retentive:

IER beads with bicarbonate and coated with a semipermeable membrane. These beads exhibit prolonged gastric residence due to release of carbon dioxide which is trapped inside the coating of the beads. In addition to the bicarbonate, a model drug, theophylline, diclofenac sodium has also been loaded onto the coated resin based on Dowex. This system gives a controlled release of drug, mediated by the coating, and has potential applications as a controlled release gastric retentive system [49, 54]. The application of low-density ion exchange resin (IER) Tulsion 344, for floating drug delivery system (FDDS), and study the effect of its particle size on rate of complexation, water uptake, drug release, and in situ complex formation [55].

Mucoadhesive drug delivery:

Drugs whose target is the stomach, such as antibiotics against *Helicobacter pylori* for local treatment of gastric ulcer, the development of oral drug delivery systems meets with physiological obstacles such as limited residence time and inefficient drug uptake by the gastric mucosa. microparticles consisting of amoxicillin-loaded ion-exchange resin encapsulated in mucoadhesive polymers (polycarbophil and Carbopol 934) were prepared with the aim of increasing the efficacy of amoxicillin in the treatment of peptic ulcers by achieving targeted delivery to the gastric mucosa and prolonged drug release [56] Cholestyramine microcapsules [57] a novel gastro-mucoadhesive delivery system based on ion-exchange fiber has been developed for Riboflavin-5-phosphate sodium salt, which is site-specifically absorbed from the upper gastrointestinal tract [40].

Taste masking

Many therapeutically useful drugs have quite a bitter taste, which limits their utility in oral formulations. The drug release from ion-exchange materials is highly dependent on the physiological pH and electrolyte concentration within the GI tract. This can be applied for taste masking of drugs. Efficient taste protection by ion-exchange resins has been demonstrated with a variety of drugs, such as Diphenhydramine Hydrochloride, Fexofenadine Hydrochloride, Rizatriptan

Benzoate, Levamisole Hydrochloride, Chloroquine Phosphate, dextromethorphan, ephedrine, pseudoephedrine, ranitidine, ciprofloxacin, erythromycin and clarithromycin [9, 10, 58, 59]. Unlike with many other approaches used in taste masking, ion-exchange materials are applicable also for suspensions, which are the preferred formulations in e.g. pediatric and geriatric medications [60, 61].

Transdermal:

Ion exchange resin could be considered as concentrated electrolytes with one immobile ionic species. The addition of ion exchange resin to get or other composites vehicles complicates the process of passive drug release. The drug release was measured as a function of current density and NaCl concentration using a novel an iontophoretic cells. Ion-exchange resins have also been used in topical products for local application to the skin, including those where drug flux is controlled by a differential electrical current (iontophoretic delivery).

In a study which employed resins of cationic drugs ambroxal and chlorpheniramine, the amount of drug released from the resinate prepared by simultaneous loading of (dual resinate) ambroxal and chlorpheniramine was not significantly different from that from the classical ambroxal resinate or chlorpheniramine resinate, but was considerably higher than that from the concurrent administration of two classical resins. These results indicated that the concurrent administration of resins affected drug release and the dual-drug resinate can be used as an alternative carrier for an ion-exchange delivery system [62]. An ion-exchange membrane to enhance transdermal iontophoretic transport of a model permeant salicylate and an antiviral agent Acyclovir has demonstrated the potential of a new approach using a positively charged ion-exchange membrane to enhance transdermal iontophoretic transport of negatively charged drugs [63]. The fluctuation of the release rate of ketoprofen [44], sodium salicylate [24], levodopa and metaraminol [29] from the vehicles was much lower compared with that of simple gels for transdermal delivery using ion-exchange fibers as controlling device.

Nasal:

A novel nasal formulation, in the form of a nicotine-Amberlite resin complex powder, has been developed that provided an optimal combined pulsatile and sustained plasma nicotine profile for smoking cessation. Amberlite IRP69 and Amberlite IR120 are similar cationic exchange materials with the same ion exchange capacity but due to a smaller particle size range (10-150 μm). Amberlite IRP69 had a better flow property and a better adsorptive capacity than Amberlite IR120. The nicotine plasma profiles demonstrated that an initial rapid peak plasma level of nicotine followed by a sustained elevated level could be achieved by adjusting the ratio of free to bound nicotine in the Amberlite powder formulation [64].

Ophthalmic delivery

Novel delivery system for ophthalmic drugs was developed using an antiglaucoma agent Betaxolol Hydrochloride as a model. The new delivery system involved both the binding and release of drug from ion exchange resin particles. Betaxolol was studied in-vitro via a release model analysis. The ocular comfort of Betaxolol was greatly enhanced by reducing the availability of free drug molecules in the precorneal tear film. The amount of resin concentration was selected to obtain optimum binding of the drug. The zeta potential of suspended particles was adjusted to produce flocculated suspension [6]. levobetaxolol hydrochloride [65] based on an ionic complex of partially neutralized poly(acrylic acid) (PAA) solid inserts could be useful mucoadhesive ophthalmic drug delivery system, ciprofloxacin hydrochloride complexed with ion exchange resin to avoid incompatibility between drug and polyacrylic acid. The developed formulation was stable and nonirritant to rabbit eyes and in vitro drug release was found to be around 98% over a period of 24 hours [66].

A sustained release ocular drug delivery composition and a method of making same are provided which comprises microspheres containing a pharmaceutically active agent, a core of an ion-exchange resin and a polymeric coating completely surrounding the core wherein the coating is

water-insoluble and hydrolytically stable in physiological environments. The coating is non-erodible in physiological environments and is characterized by a diffusion constant suitable for the pharmaceutical agent to diffuse from the core to an aqueous environment at a predetermined release rate [67].

Conclusion:

The extensive literature review has shown the potential of the ion exchange resins as carrier for the novel drug delivery systems. From many

decades the ion exchange resins are used for various purposes, but it can be still used in the modern drug delivery application such as taste masking, controlled release, sustained release, gastroretentive etc. thus the ion exchange drug delivery systems can be utilized to improve drug safety and efficacy, enhance patient compliance, reduce dosing intervals and increase drug stability. This may help the pharmaceutical researcher formulate the controlled release drug delivery more effectively.

Table -4 Some important patents on ion exchange resins:

US patent number	Issue date	Type of system	Model drug(s)	Remarks	Ref.
8062667	Nov. 22, 2011	Coated resin complex	Morphine sulfate, oxycodone HCl	PVA coated resin complexes retard the drug release	[68]
7871645	Jan. 18, 2011	Resin complex	Phenylephrine Hydrochloride, hydrocodone	Controlled swelling	[69]
7147845	12/12/2006	Silver ion resinsates.	Silver thiosulfate	Antimicrobial treatment and prevention of infections	[70]
20050181050	08/18/2005	coated dextromethorphan-resin particles	Dextromethorphan (HBr salt)	controlled release	[71]
6514492	02/04/2003	Resin beads	Quinolone	Effective Taste masking	[72]
6254883	March. 7, 2001	Ionexchanger group grafted to a carrier	Sodium salicylate, tacrine	control release	[73]
6193962	02/27/2001	cross-linked carboxylic acid resin	2-aminoacetamide	Taste masking	[74]
6268368	07/31/2001	Resinsates	Buspirone	Targeted therapeutic effect	[75]

Authors' Contributions

Authors contributed equally to all aspects of the study.

Conflicts of Interest

The authors declare that they have no competing interests.

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