ION EXCHANGE RESINS AND APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY

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ABSTRACT

Ion exchange resins (IER) are cross-linked, water insoluble polymers carrying ionizable functional groups on their repeating positions. They are considered as safe materials due to their insoluble and nonabsorbable nature. This advantage made IER subject of several research in different areas of pharmaceutical technology such as oral sustained release, taste masking, rapid dissolution, stability enhancement and also they are used for their therapeutic activity since the middle of 20th century. This review discussed the general properties of IER and their novel applications in the area of pharmaceutical technology.

Key words: Ion exchange resins; Resin-drug complex; Resonates; Controlled release; Pennkinetic system; Taste masking.

INTRODUCTION

Ion exchange resins (IER) are water insoluble cross-linked polymers consisted of opaque yellowish colored spherical beads, approximately 20–50 mesh (300–850 mm) in diameter, which carry ionizable functional groups on their repeating positions. IER are water insoluble and are not absorbed by the body, thus accepted safe as they are free from local and systemic side effects [1,2]. IER-drug complexes (drug-resinates) are produced by loading ionic drugs onto IER following the purification and activation steps.

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Besides being inert, IER have the advantages of high drug loading, simple drug release mechanism and protection of unstable drugs which makes them a desired material in different areas of pharmaceutical technology such as oral sustained release, taste masking, rapid dissolution, and stability enhancement and also for their therapeutic activity [3,4].

History of IER

Ion exchange (IE) mechanism has been known since 1850, but it gained importance as a drug carrier after the first half of 20th century. It was a primary process for water purification in 1930s after the commercial availability of zeolite, a natural and synthetic siliceous material. First phenol-formaldehyde resin was synthesized by Adams and Holmes in 1934, and then in 1939, the

Resins Products and Chemical Company began to investigate the synthesis and production of IER under the original Adams and Holmes patent. Pharmaceutical and biomedical applications of IER were begun in 1950 after the research of Saunders and Srivatsava, whom studied the uptake and release of alkaloids from IER. They suggested that resins might act as a suitable chemical carrier for the development of sustained-release formulations. IER have since been extensively explored in the field of drug delivery [1,4].

IE mechanism

IER have highly developed structure of pores on their surfaces which the ions can be trapped or released. In IE mechanism, the trapping ions reversibly interchange with the ions of the same charge in medium (usually solution) which takes place through a stoichiometric reaction and no radical change involves in the structure and properties of the IER. Each counter ion released from the material replaced by equivalent amount of ion with the same charge until the equilibrium provided [2,4,5]. The IE is a competitive process and the drug-resinate composed is reported as the result of an “adsorption of drug on IER” mechanism rather than “complexation”. The ionic strength and pH at the site of delivery plays a key role in the liberation of immobilized drug from the resinate [6].

Classification and chemical properties of IER

IE materials can be classified into various categories according to their physical form, material origin, chemical function and nature of fixed group; however they are simply be divided into two general types as organic and minerallic (polymeric and mineral). According to their separation mechanism IE materials can also be classified into subcategories including IER, chelating adsorbents, hydrogels and IE membranes. IER is the major class amongst them, which are commercially available since 1930s [4].

Chemically, IER consist of a structural component which may be based on inorganic compounds, polysaccharides or organic synthetic resins, and an acidic or basic functional component to which the counter ion is bound [3,6]. According to the ionic nature of the material they are known as cation-exchange resins (CER) or anion-exchange resins (AER), which can be further classified as strong acid or base and weak acid or base with respect to the ionic strenght of functional component [4,6]. Classification of IER and various associated properties with some commercial examples are given in Table 1.

Table 1: Classification of IER according to ionic nature and various associated properties [7].

Parameter	CER		AER	
	Strong acid	Weak acid	Strong base	Weak base
Functional group	SO_3H PO_3H_2	COOH	NR_4^+ R_1 = methyl R_2 = methyl/ ethanol	Polyamine
Operating pH	0–14	7–14	10–14	1–7
Regenerant	Acid		Base	
Stoichiometric amount, %	200–300	100	200–300	100
Commercial examples [3]	Dowex 50 Amberlite IR120 Amberlite IRP69	Amberlite IRC50 Amberlite IRP64 Amberlite IRP88	Dowex 1 Amberlite IR400	Dowex 2 Amberlite IR4B

The most commonly used strong CER are cross-linked polystyrene-divinyl benzene (DVB) polymers with sulfonic acid (-SO_3H) groups, which have been prepared by the polymerization of polymer with sulfuric acid or chlorosulfonic acid. This group of CER is active over the entire pH range. Carboxylic acid (-COOH) type exchangers are prepared mostly by polymerization of organic acids, such as acrylic or methacrylic acid in the presence of a cross-linking agent such as DVB to yield cross-linked networking. Unlikely to strong CER, they are not active below pH=4-6; however have higher IE capacity than sulfonate exchangers [2,4]. This property makes weak CER a good candidate for taste masking of bitter drugs [8].

The majority of AER are made from cross-linked polystyrene polymers produced by chloromethylation of polystyrene beads with a subsequent treatment with ammonia (-N), primary (-NH_2), secondary (-NHR) or tertiary amines (-NR_2). Similar to strong CER, strong AER are also active over the entire pH, while the weak AER are not active at alkaline pH. Ion exchangers based on polysaccharides such as sephadex, sepharose, or cellulose has found only a limited use in the therapeutic applications [2,4].

Properties of IER

The parameters such as IE capacity, degree of cross linking, swelling ratio, particle size and porosity of resin, pH and ionic strength of the drug solution and the site of drug delivery are needed to be evaluated together for understanding the performance of drug-resinate. Also, parameters such as mixing speed and contact time during the preparation affects the performance of IER [3,6,9].

The capacity of an IER is a quantitative measure of its ability to take up exchangeable counter-ions. It refers to the number of ionic groups per unit weight or volume (meq/g or meq/mL) according to dry or wet weight of the material in given form (H^+ or Cl^-), respectively. The available capacity of IER are affected from the swelling and acid-base strenght (pKa value) of the exchanger (Table 2). The ionization of the attached functional group is dependent on the presence of water in the matrix and the cross-linking of the polymer. In aqueous media, strong IER are fully hydrated; and the ions associated with the functional group are always free to exchange with ions of same charge in the solution being processed. However, the ionization in weak IER is depending on their pKa values. Weak IER have higher exchange capacities than the strong types which also have higher drug loadings [2-4]. The pKa value of a resin also have a significant influence on the drug release rate from the drug–resinate in the gastric fluids [4,9].

Table 2: pKa values of functionalized groups in IER [4].

CER	pKa	AER	pKa
–SO_3H	1-2	– N^+	1-2
–PO_3H_2	2-5	≡ N	4-6
–COOH	4-6	= NH	6-8
–OH	9-10	– NH_2	8-10

Cross-linking is another important parameter which affects the mechanical strenght, swelling, capacity, equilibrium rate, drug loading efficiency and therefore drug release properties of IER. It depends on the percent DVB used in the copolymerization which is limited to a range of 2–16 w/w %. Below this range, mechanical strength of IER negatively affected and above 16 w/w %, the polymer structure resists swelling, so that production of a finished IER becomes difficult. If the resin has a less degree of cross-linking, which means more porosity, it will have higher ability for drug loading; however the drug release will be rapid instead of higher cross-linked resin which provides a sustained release. On the contrary, it will be difficult to introduce additional functional groups to a higher cross-linked resin. Strong functional groups such as sulfonic acid or quaternary ammonium are introduced both inside and surface of the resin, thus fewer additional functional groups can be introduced inside the resin when they are highly cross-linked and hence the total capacity of dry resin drops slightly [2,3,9].

Particles size and porosity of the resin also affects the IER performance as the rate of IE reaction changes. If the resin size significantly decreases, the time required for the reaching equilibrium with the surrounding ions also decreases. The rate of IE reactions and the limitation of ion sizes, which can penetrate into a resin matrix depend strongly on the porosity. The particle size and porosity also influence the swelling behavior of the resin and consequently have a marked effect on the release pattern of drug–resinates. As the particle size of the resin increases, the drug loading and release rate decreases due to the reduced effective diffusion coefficient and surface area [3,9].

Preparation of drug-resinate

Common procedure on preparation of resinate includes purification and re-activation of the resin prior to drug loading and then removing the excess drug. Purification can be done by cycling repeatedly between sodium and hydrogen forms with CER or chloride and hydroxide forms with AER. After washing with water and drying with a suitable way, resin generally sieved for obtaining appropriate particle size fraction. Drugs having ionic groups and short biological half life are suitable for loading [3,6,10]. Drugs can be loaded to IER by one of the techniques given below:

In “Batch technique”, after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution in a beaker until the equilibrium is established. In “Column technique”, resinate is formed by passing a concentrated solution of drug through the IER-packed column until the effluent concentration is the same as the eluent concentration [3,6]. Being much simpler and quicker than column technique, batch technique is mostly preferred for laboratory scale, a wide variety of IE media can be used and is suitable for very fine particles; however the separation of liquid and IE media is required, it can only be operated at atmospheric pressure and ambient temperature conditions, and most of all it is not efficient as

column technique. After sorption, resinate must be washed for removing excess (free, un-adhering) drug and dried before use [3,4]. Depending on the application, resinate can be dried in vacuum oven at 60°C or spray drying technique can be used [10].

Basicly, resinate preparation is a matter of mixing the resin with a solution and allowing sufficient time (approximately a few hours) for loading. Thus, mixing time has effect on resinate properties. With the increasing mixing time, drug loading increases together with swelling. High temperature may also cause swelling of resin; AER significantly get affected by temperature changes [9,10].

Applications of ion exchange resins

IER can be used for solving various problems in formulations such as taste masking, rapid dissolution, superdisintegrant, enhancing the stability. Also CER are being used for water softening of calcium and magnesium ions exchanging with sodium, thus prevent the formation of calcium carbonate precipitates [1,2,4].

Taste masking

Excessive bitterness of drugs is one of the major problems in formulating oral formulations, especially for fast disintegrating tablets and pediatric dosage forms. Since most bitter drugs possess ionic sites in their molecule, IER are good alternative as being an inexpensive method and providing simple and rapid solution to the taste masking problem. Their action of mechanism depends on pH dependently blocking the ionic sites of drugs, thus weak IER (generally CER) with preferably low cross-linked types are used [2,11]. In the average saliva pH of 6.7, the resin's charge protects the drug by making a complex, and also the 40meq/L saliva capacity of IER is high enough to carry the drug-resinate breaking before pH change but able to break down by hydrochloric acid present in the stomach [5,7,12]. Also, the drug-resinate is absolutely tasteless with no after taste in the tounge and at the same time, its bioavailability is not affected [1].

Another advantage of IER is preparation of semisolid or liquid formulations containing resinates which can be used as pediatric dosage forms. Children and infants are not only the most sensitive groups to bitter taste but also have problems on swallowing solid dosage forms. Suspension of tinidazole resinate with Kyron T134 weak polyacrylic resin could be given as an example for pediatric use [12]. Some other recent drug-resin complex studies for taste masking can be exemplified as diphenhydramine HCl-Indion 234/Tulsion 343, fexofenadine HCl-Indion 204/234/264, rizatriptan benzoate-Indion 204/214, ciprofloxacin-Indion 234 [2], dextromethorphan-Amberlite IRP64, ranitidine-Amberlite IRP69, paroxetine-Amberlite IRP88, cefpodoxime proxetil-Kyron T104, metronidazole-Kyron T134 [8], chloroquine phosphate-polyacrylic acid [13], etoricoxib-Indion 204 [14], donezepil HCl-Amberlite IRP64 [15] and clarithromycin-Tulsion 335 (Polacrilex) [16] resin which are mostly weak CER resinates; except Amberlite

IRP69 and Tulsion 335, an example of strong CER and AER resinate respectively.

Disintegrant/Super Disintegrant

Resins although insoluble, have great affinity for water and hence, act as disintegrant. Moreover, high rate of swelling due to smaller particle size makes them superdisintegrant. They must have poor solubility, good hydration capacity and flow properties with good mouth feel. Thus IER, especially weakly CER such as polymethacrylic carboxylic acid IER such as Amberlite IRP88, Indion 414 and different grades of Tulsion such as T-339, T-335, T-412 have found usage in pharmacy as tablet superdisintegrants due to their large swelling capacities [1,2,17].

Various formulation problems

In general, preparing drug-resin complex can improve the physical characteristics and stability of drugs which are hygroscopic, polymorphous or poorly soluble [1,10]. Easily oxidized drugs, such as levodopa, could be stabilized by preparing ion exchange fibers [2]. Also, stability of vitamin B12 during storage was improved by preparing resinate with a weak CER (Indion 264). Dissolution of poorly soluble drugs can be improved by IER by converting them into amorphous form which provides immediate release, hence lead to improved drug dissolution [9]. Nicotine, an unstable liquid drug is formulated as resinate with a weak CER to both improve its stability and solving technological problems such as taste masking in preparing as a chewing gum. Patented example Nicorette® gum is used for smoking cessation by providing gradual drug release through glycol mucosa by chewing the gum which offers fresh saliva as solvent for elution [2,9, 10].

Application of IER in drug delivery systems

Oral controlled and sustained release drug delivery systems of IER have been widely studied as the IE mechanism and characteristics of IER affect the release of drug of the ionic environment in the gastro-intestinal tract. The IE process might also be applicable to other areas such as the subcutaneous, intramuscular or ocular routes, where the pool of ions could be controlled [3]. Nowadays, in addition to oral controlled or sustained release, IER systems are being explored for several novel concepts, such as sigmoidal release, pH and ionic strength-responsive systems and in combination with ionthoporesis [6].

Oral controlled or sustained release systems

Drug resin complexes have various advantages in oral drug delivery, such as being a reservoir; designing liquids[12], beads[18], microparticles or simple matrices; modifying the release of drugs either by changing the performance parameters such as degree of cross-linking and particle size of the resins or by coating the resinates [1]. One of the major drawback of sustained release is dose dumping which is resulted with increased toxicity risk. IER usage can prevent dose dumping as providing a reservoir and controlling the release by ion exchange mechanism [10].

Resinates either can be filled directly in a capsule, suspended in liquids or matrices, can be compressed into tablets [19] or better control over the drug release can be provided by microencapsulation or coating[20] of resinates. One of the first patents in this area is Pennkinetic system (Pennwalt Corporation, USA), which the resinate is pretreated with polyethylene glycol 400 for controlling the rate of resinate swelling in water. The system is then coated with a water-insoluble polymer such as ethyl cellulose (EC), which modifies the diffusion pattern of ions in and out of the system. Delsym® and Pentuss® (Fisons) are some of the examples of marketed formulations for Pennkinetic systems. Both products are sustained release suspensions for cough; first one is formulated with dextromethorphan- sulfonic acid -CER coated with EC and the latter consists of codeine-sulfonic acid CER and chlorpheniramine-sulfonic acid CER where the codein resinates are coated with EC [3,6].

Another approach in modifying oral drug release is preparing hollow fibers, which are suitable polymeric materials filled with resinate. Despite the IER, IE fibers are non-cross-linked, thus a faster drug loading with a higher capacity are possible as porosity is lacked in fibers. Reduced dosing with improved patience compliance are some other advantages of IE fibers [21]. They also have potentially slower GIT transit time. Because of these advantages they can be used for controlling drug release in the small intestine, colon [1,6] or can be used as mucoadhesive carrier [21], also for enhancing the efficiency of transdermal iontophoresis [22].

Site-specific drug delivery systems

The advantages of being inert and selective makes IER good candidate for delivering drugs at the desired biological location or site. Gastric retentive and sigmoidal release systems are evaluated with IER for this purpose. Gastric retentive systems can be designed by bicarbonate charged resins coated with a semipermeable membrane, which improves gastric-residence time by floating in gastric medium and thus extended-release can be obtained [6].

However, 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 are also used for site specific delivery of drugs for cancer treatment such as doxorubicin which is ionic in nature and can be complexed with IER [1, 6].

Ophthalmic drug delivery

Betoptic S® is a drug-resinate suspension of 0.25 % betaxolol HCl, a beta-adrenergic receptor blocking agent used in antiglaucoma. It penetrates cornea very well and thus has irrirating effect on eye. Betoptic S® has been approved by FDA, and is marketed in U.S. since February 1990 [1, 3]. It consists of a CER (Amberlite IRP69) betaxolol complex in equimolar ratio to free drug in suspension and subsequent to application to the eye; drug is released relatively slower from

resinate than free drug. Bioavailability studies showed that a resinate suspension of 0.25 % was equivalent to 0.5 % Betoptic solution [3, 23]. Also delivery of ciprofloxacin complexed with polystyrene sulfonate for the treatment of eye infections was reported [1].

Nasal drug delivery

The prerequisite for nasal delivery by the IER approach is a high ion-exchange capacity of the resin. Generally, IE capacity should be 0.2 to 10 meq/g. Amberlite IRP69 and Amberlite IR120 resins (CER) were tried for preparing of pulsatile and sustained release nasal formulations of nicotine for smoking cessation [1, 24].

IER in conjunction with Iontophoresis

IER could also be explained as the presence of concentrated electrolytes with one immobile ionic species [6]. Iontophoresis is simply defined as the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized and/or unionized drugs transdermally. By incorporating IER into gels or other composite vehicles in transdermal delivery combined with iontophoresis, more accurate and homogeneous control of the ion exchange process could be achieved [25]. Also, constant pH during iontophoretic delivery could be maintained, thus alleviating the problem of skin irritation [6, 25]. Furthermore, preserving transdermal dosage form from instability during shelf life should be possible as ion exchange materials attached with the drug will form a drug reservoir.

For this combined technique, usually the ion exchange materials initially immersed into drug solution for approximately 3 h to overnight. Afterward, a drug-loaded device such as a disc, a bundle of ion exchange fibers or a hydrogel filled with IER was transferred to the donor part of a diffusion cell for in vitro or in vivo tests [25]. In vitro studies with drugs such as nicotine [26], tacrine [27], propranolol, nadolol, sodium salicylate, diclofenac sodium [22] and tramadol [28] revealed that IER are suitable as delivery vehicles in iontophoretic drug delivery.

Clinical applications of IER

In addition to the applications on drug delivery, IER are also being explored for their therapeutic activity. Cholestyramine CER is the first example of IER based drug in clinical use, which binds the bile acid in order to reduce serum cholesterol levels, and cholestipol AER is used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adult. Both two resins are mixed with fluids and administered as slurry [1, 2, 6].

In general, sulfonated and carboxylic resins with a polystyrene backbone are used for their pharmacological activity in cases such as cardiac failure, renal disease, pregnancy toxemia and cirrhosis of the liver. IER have been used as reinforcement of a low sodium diet or to enable high salt intake in the diet and have also been used for hemoperfusion and management of drug overdoses [2, 6].

CONCLUSION

As the number of patents shown in Table 3 and technological developments nowadays shows, the use of IER in drug delivery research are still have importance and commercial success. In addition to oral controlled or sustained release, IER systems are being explored for site-specific, transdermal, nasal and ophthalmic routes. Moreover, several novel concepts, such as sigmoidal release, pH and ionic strength-responsive systems and taste masking mechanism have shown the potential use of IER in drug delivery.

Table 3: Some patented examples for drug-resinate studies [5,6].

Patent no	Year	Title/Subject	Drug/polymer
US8414919	2013	Sustained drug release composition	Cimetidine, ciprofloxacin/Amylose starch
WO/2012/063257	2012	Sustained release compositions	Active drug/Resin
US8337890	2012	Modified release formulations containing drug-ion exchange resin complexes	Morphine, ibuprofen, codein/ HPMC
US8062667	2011	Modified release formulations containing drug-ion exchange resin complexes	Oxycodone, Albuterol Methylphenidate, Dextromethorphan/Amberlite IRP 69
US20110136921	2011	Sustained release composition	Venlafaxine HCl, Diclofenac sodium/ HPMC K100M
WO/2010/127100	2010	Compositions comprising an antihistamine, antitussive and decongestant in extended release formulations	Pseudoephedrine, Chlorpheniramine, Hydrocodone/ Amberlite IRP 69
USP20080118570	2008	Polymer coated drug-ion exchange resins and methods	Chlorpheniramine polistirex, sodium polystrene sulphonate Amberlite IRP 69
USP20070128269	2007	Sustained drug release compositions	Chloroquine and pyrimethamine/ HPMC K100M
USP20060263431	2006	Opioid sustained release formulation	Oxycodone, meperidine, methadone, nalbuphine, opium, pentazocine, propoxyphene/ Styrene-divinyl benzene
USP20050265955	2005	Sustained release preparations	Hydrocodone bitartrate/ Dowex 50WX8H
WO/2003/020242	2003	Sustained release preparations	Dihydrocodeine phosphate, codeine phosphate, noscapine HCl, phenylpropanolamine HCl /

			Amberlite IR 120
USP20020164373	2002	Opioid sustained release formulation	Butorphanol, fentanyl, codeine, dihydrocodeine, hydrocodone bitartrate/Hydroxyalkylcellulose/ Styrene-divinyl benzene
USP6258350	2001	Sustained release ophtalmic preparations	Pilocarpine, epinefrine etc./Poly (styrene)divinyl benzene
USP5186930	1993	Sustained release oral preparations	Phenylpropanolamine/Styrene-divinyl benzene
US5889051	1999	Solid dispersion	Misoprostol
US5932248	1999	Polymer matrix loaded with resinate	Doxorubicin and cisplatin
US5935604	1999	Resinates in microspheres	Nicotine
US6001392	1999	Coated and uncoated drug/resin complexes	Dextromethorphan, diphenhydramine
US5275820	1994	Microparticulate drug delivery vehicle with erodible matrix-containing resinates	Levobunolol HCl, pilocarpine HCl
EP0429732	1991	Sustained drug release compositions containing cation exchange resins and polycarboxylic polymers	Betaxolol, timolol etc. /Amberlite, Dowex
US4996047	1991	Coated resinate with chewable tablets, capsules, suspensions	Dextromethorphan, pseudoephedrine, phenylpropanolamine HCl
US4894239	1990	Microcapsulated resinate	Dihydrocodeine, phenylpropanolamine HCl, di-methylephedrine
US4911920	1990	Ophthalmic drug delivery formulation containing IER	Betaxolol HCl, timolol /Carbopol and -SO_3H CER
US4859461	1989	Coated resinate	Phenylpropanolamine HCl
US4859462	1989	Polymer-coated resinate	Phenylpropanolamine HCl
US4221778	1980	Pennkinetic system	Phenylpropanolamine HCl dextromethorphan, pseudoephedrine ephedrineethyl

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