Ion-exchange resins: carrying drug delivery forward

Vikas Anand, Raghupathi Kandarapu and Sanjay Garg

Ion-exchange resins (IER), or ionic polymer networks, have received considerable attention from pharmaceutical scientists because of their versatile properties as drug-delivery vehicles. In the past few years, IER have been extensively studied in the development of novel drug-delivery systems (DDSs) and other biomedical applications. Some of the DDSs containing IER have been introduced into the market. In this review, the applications of IER in drug delivery research are discussed.

Vikas Anand
Raghupathi Kandarapu
and *Sanjay Garg
Department of Pharmaceutics
National Institute of
Pharmaceutical
Education and Research
(NIPER)
Sector 67, S.A.S. Nagar
Punjab 160 062
India
*tel: +91 172 214 682
fax: +91 172 214 692
e-mail:
gargsanjay@yahoo.com
web: www.niper.nic.in

▼ Ion exchange (IE), particularly base exchange, has been the subject of several scientific investigations since the middle of the 20th century. In the beginning, it was primarily a significant process in the field of agricultural and organic analytical chemistry, which later attracted research by healthcare professionals into this subject. Until 1934, natural and synthetic siliceous materials, known as zeolites, were available for use as IE adsorbents for the purification of water[1]. In 1934, Adams and Holmes synthesized phenol-formaldehyde resin and showed that this resin can be used as a substitute for zeolites. In 1939, the Resins Products and Chemical Company began investigations into the synthesis and production of ion-exchange resins (IER) under the original Adams and Holmes patent. In fact, it paved the way for the application of IER to several industrial processes and biomedical applications[2].

It was not until 1950 however, that IER were studied for pharmaceutical and biomedical applications. At this time, Saunders and Srivatsava studied the uptake and release of alkaloids from IER and suggested that these resins might act as a suitable chemical carrier for the development of sustained-release formulations[3]. IER have since been extensively explored in the field of drug delivery, leading to some important patents[4–6]. Research over the past few years has revealed that IER are equally suitable for drug-delivery technologies, including controlled release, transdermal, site-specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical, and taste-masked systems.

IE: the process in drug delivery

IE is the reversible interchange of ions (of like charge) between a liquid and a solid phase, involving no radical change in the structure and properties of the solid[1]. The solid phases in the IE process are referred to as IER, and are usually the polymers with integrated ionic moieties. Based on the nature of the ionic species being interchanged, the IE process is known as either cation exchange (CE) or anion exchange (AE). The IER used in these processes are referred to as cation-exchange resin (CER) or anion-exchange resin (AER), respectively. The IE process is competitive in nature.

In practice, drug in an ionic form (usually in solution) is mixed with the appropriate IER to form a complex, known as 'resinate'. The performance of resinate is governed by several factors, such as:

- the pH and temperature of the drug solution;
- the molecular weight and charge intensity of the drug and IER;
- geometry;
- mixing speed;
- ionic strength of the drug solution;
- degree of cross linking and particle size of the IER;
- the nature of solvent; and
- contact time between the drug species and the IER[7–10].

The chemistry of the resinate is such that the drug retains its characteristics, but is immobilized on a solid support[8–10]. The interactions between the IER and drug, although primarily chemical in nature, are also partially

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a result of physical adsorption[11]. These interactions are commonly referred to as 'adsorption on IER', rather than complexation on most occasions. The IE process, therefore, is generally regarded as a double-decomposition process, in which the IER used are able to provide the type of ion required to replace the one that is adsorbed from the solution. The ion of the IER, which can be exchanged for a drug counterpart, is called a 'counter ion'. The affinity of counter and drug ions towards the IER is competitive. When resinate from the delivery system reaches the site of delivery, the exchange process is reverted, resulting in the liberation of free-drug ions. Therefore the ionic strength and pH at the site of delivery plays a key role in the liberation of immobilized drug from the resinate. Drug delivery at the desired target via the IE process occurs because of the presence of highly activated counter ions at the site, resulting in the exchange of ions and drug release. The IER devoid of drug is eliminated or biodegraded from or at the site of delivery[12]. Figure 1 depicts the factors that affect the IE process involved in the delivery of a cationic drug.

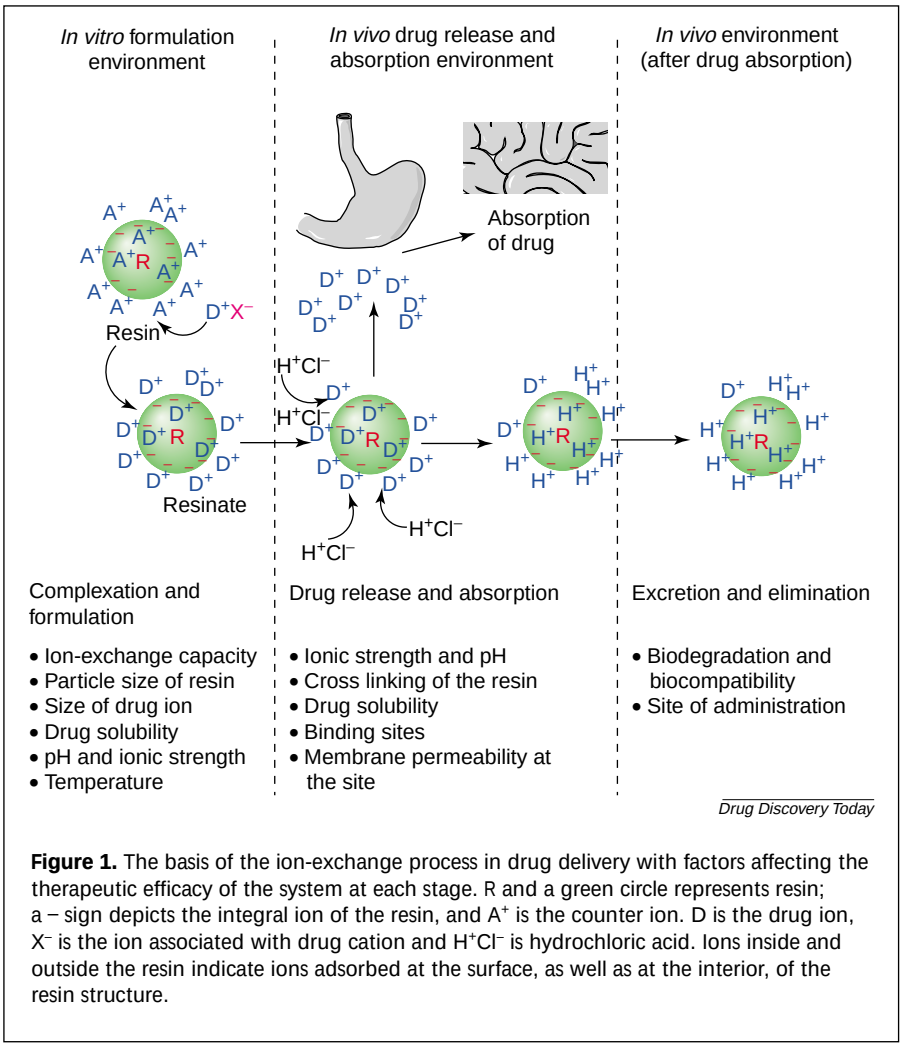

Figure 1. The basis of the ion-exchange process in drug delivery with factors affecting the therapeutic efficacy of the system at each stage. R and a green circle represents resin; a – sign depicts the integral ion of the resin, and A^+ is the counter ion. D is the drug ion, X^- is the ion associated with drug cation and H^+Cl^- is hydrochloric acid. Ions inside and outside the resin indicate ions adsorbed at the surface, as well as at the interior, of the resin structure.

Physical properties, chemistry and classification of IER

In general, IER consist of spherical beads of approximately 0.5–1.2 mm in diameter. The most common type are an opaque yellow in colour[13], although other colours are also reported. The constitution of each spherical particle of IER is similar to that of an homogeneous gel. The shrinkage or expansion of the spherical volume that takes place is based on the ionic environment in which the IER is present[14]. The insolubility of IER depends on the nature of the counter ion and the extent of cross-linking of the basic skeleton, and hence careful consideration should be given to the selection of IER in drug delivery. Commercially available IER, with many cross linkages, swell in water to 2–3 times their original weight. Despite strong swelling, the chemical stability remains satisfactory[15].

Chemically, IER are made up of two components: a structural component consisting of the polymer matrix, and a functional component to which the counter ion is bound. The structural component of IER consists of a stable acrylic polymer of styrene-divinylbenzene copolymer, whereas the functional component can be acidic (commonly sulfonic or carboxylic) or basic (amine). IER can be classified based on the nature of the structural and functional components and IE process. A general classification of ion exchangers is given in Fig. 2.

How to select a suitable IER

The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER[16]. However, the following points need to be considered during selection:

- capacity of the IER [i.e. the concentration of the exchangeable group in the resin, usually expressed in milliequivalents per gram (meq g^{-1}) of dry resin];
- degree of cross linking in the resin matrix;
- particle size of resin;
- nature of drug and site of drug delivery. It is also important

to evaluate the resin in the pH- and ionic-strength environment, simulating the *in vivo* situation;
- swelling ratio;
- biocompatibility and biodegradability; and
- regulatory status of the IER.

For example, a low degree of cross linking of the resin will facilitate the exchange of large ions, but it will also cause volume changes in the resin upon conversion from one form to another. Similarly, the use of a strong IER will give a rapid rate of exchange, but it could also cause hydrolysis of the labile drugs because strong IER are effective acid-base catalysts. Therefore, a fine balance of all the parameters needs to be made to achieve optimal performance of drug-delivery systems (DDSs) containing IER.

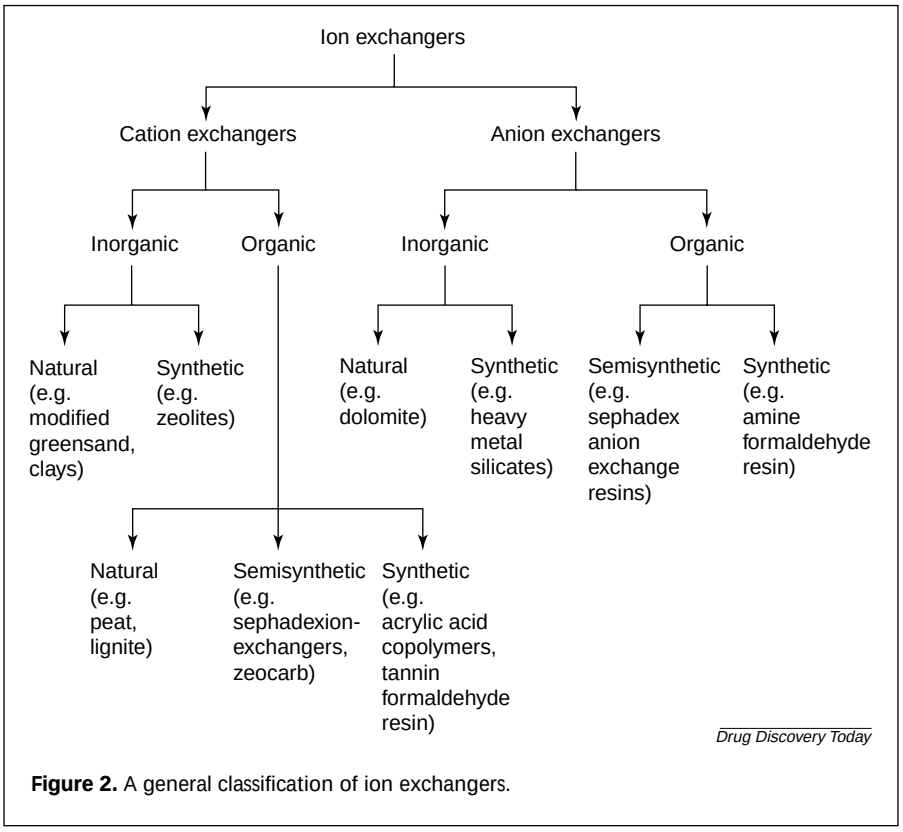

Figure 2. A general classification of ion exchangers.

Characterization of IER

As the performance of DDSs depends on the quality of IER, it is important to evaluate IER at each stage of the preparation of resinates. The following parameters are generally evaluated:
- Particle size – measured directly with a set of microsieves by screening[17]. The particle size of IER can also be determined by microscopy[9], Coulter counter[18] and other available techniques.
- Porosity – the porosity of dry IER can be determined through nitrogen adsorption at –195°C, and by measuring the true density (mercury displacement)[19]. Scanning electron microscopy reveals the internal pore structure. The use of an air-compression pycnometer for the determination of porosity has also been reported in the literature[20].
- Moisture content – determined by Karl Fischer titrimetry. Excess water can be removed by drying in a vacuum desiccator[21].
- IE capacity – the IE capacity of strong CER is determined as meq g^{-1} by evaluating the number of moles of Na^+, which are adsorbed by 1 g of the dry resin in the hydrogen form[22,23]. Similarly, the IE capacity of a strong basic AER is evaluated by measuring the amount of Cl^- taken up by 1 g of the dry resin in the hydroxide form.

Resinate preparation and evaluation

Once the selection of a resin is made, the next step involves preparing its complex with drug, before designing a suitable delivery system. The main hurdle is to optimize the conditions of preparation, in order to obtain the desired drug loading in the resinates. Generally, the following steps are involved in the preparation of resinates:
- Purification of resin by washing with absolute ethanol, ethanol and water mixture[24]. Final washing with water removes all the impurities.
- Changing the ionic form of IER might occasionally be required to convert a resin from one form to another, if it does not have the desired counter ions[25]. Strongly acidic CER are usually marketed in Na^+ form and strongly basic AER in Cl^- form. They are generally converted into hydrogen and hydroxide forms, respectively. 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.
- Preparation of resinate is normally done by two techniques:
  (a) Batch technique – after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution until the equilibrium is established[26]; and
  (b) 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.

IER: applications in drug delivery research

Although the principle of IE has been used for a long time in agricultural and organic analytical chemistry, its application in drug delivery research only came to prominence in the 1950s. In theory, drug release from resinate relies on the ionic environment and should therefore be less susceptible to other conditions, such as enzyme content, at the site of absorption[12]. Therefore the suitability of the IER approach to drug delivery depends on the route and target of the delivery. Peroral controlled- and sustained-release DDSs have been widely studied with this approach, because of the ionic environment in the gastro-intestinal tract (GIT), for the exchange process. The IE process might not be optimally applicable to the skin, external canals (e.g. nasal and ear), or other areas with limited quantities of eluting ions. By contrast, the subcutaneous and intramuscular routes, where the pool of ions is more controlled, would appear better suited for this approach.

Controlled- or sustained-release systems

A major drawback of controlled- or sustained-release systems is dose dumping, resulting in increased risk of toxicity. The use of IER has occupied an important place in the development of controlled- or sustained-release systems because of their better drug-retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (chemical) properties of IER will release the drug more uniformly than that of simple matrices (because of physical properties only)[3]. Moreover, IER impart flexibility in designing a variety of delivery systems, such as liquids[27–30], beads[24,31,32], microparticles[33–35] and simple matrices[26].

Simple resinates Resinates alone are the simplest forms of controlled- or sustained-release delivery systems. Resinates can be filled directly in a capsule, suspended in liquids, suspended in matrices or compressed into tablets. Drug from the resinate will be slowly released and absorbed as compared to the drug particles, but will also be significantly faster than the modified resinates (coated or microencapsulated). The release of diclofenac at the desired rate to avoid gastric irritation was achieved for arthritic patients[36].

Microencapsulated or coated resinates Several scientists have succeeded in using microencapsulated or coated resinates[8,27,28,31], and most of the patented and marketed formulations belong to this category. Microencapsulation of resinates provides better control over the drug release because of the presence of a rate-controlling membrane. The absorption of the drug from coated resinates is a consequence of the entry of the counter ions into the coated resinate, release of drug ions from the drug–resin complex by the IE process, and diffusion of drug ions through the membrane into the surrounding absorption environment. Often, water-insoluble coating materials are used, such as ethyl cellulose or waxes. The release rate at the desired level can be tuned by optimization of coating thickness[37]. Microencapsulation of resinates can be achieved by air-suspension coating (Wurster process), interfacial polymerization, solvent evaporation or pan coating.

Pennkinetic systems Further modification of the coating of resinates for improved monitoring of the drug-release pattern has been the concept of Pennkinetic systems (Fisons BV, Rochester, NY, USA, originally patented by Pennwalt Corporation)[38]. In this system, resinate is pretreated with polyethylene glycol 400 to maintain the geometry and improve the coating process. The pretreated resinates are then coated with ethyl cellulose or any other water-insoluble polymer. Polyethylene glycol helps in controlling the rate of swelling of the resinate matrix in water, while an outer-ethyl cellulose coating modifies the diffusion pattern of ions in and out of the system. Two over-the-counter (OTC) products, dextromethorphan cough syrup (Delsym, Fisons) and codeine and chlorpheniramine syrup (Phentuss, Fisons), are examples of marketed formulations of Pennkinetic systems. Table 1 gives a comprehensive account of literature reports of various DDSs using IER.

Hollow fiber systems Hollow fiber systems have advantages of high surface area to volume ratio, loading flexibility, membrane permeability, and potentially slower GIT transit time. These characteristics could provide a method to obtain controlled release for drugs in the small intestine and/or in the colon. Hollow fibers made from suitable polymeric materials are filled with resinate to obtain a controlled- or sustained-release profile.

In vitro and *in vivo* release of phenylpropanolamine (PPA) from polyurethane fibers filled with PPA-Dowex 50 W complex (resinate) have shown sustained effect[39]. However, the miniaturization of the system and the optimization of the release was necessary for the delivery of drugs. Such systems can be used for oral drug delivery. Biodegradable hollow fibers can be used for drug delivery in the form of implants[40].

Site-specific DDSs

Delivering drugs at the desired biological location or site could have several advantages in therapeutics, such as:

- localizing the required drug concentration to maintain a minimum effective concentration throughout the treatment;

Table 1. Drug delivery systems using ion-exchange resin (IER)

Ion-exchange resin	Drug	Type of system	Remarks	Refs
Dowex 1-X2, 1-X4, 1-X8	Theophylline	Microencapsulated resinate	The pattern of release of the drug was dictated by the cross linking of the resin and the coating process used	32
Amberlite IR-120 and Amberlite XE-69	PPA	Pennkinetic	Polyethylene glycol pretreatment of resinates to prevent resin hydration and swelling	17
Eudragit RS and Eudragit L	Indomethacin	Microspheres	80% of the drug was released by zero-order kinetics	20
Eudragit RS 100 and Eudragit RL 100	Theophylline	Eudragit retard microcapsules	Microcapsules gave apparent first-order release profile and batch reproducibility	71
Amberlite IL-120	Metoclopramide	Resinate	Method for determining diffusion-controlled release drug from resinate was presented	72
Amberlite and Dowex IER	Propranolol	Resinate	Various factors affecting loading and release studied	8,9
Indion CRP 244, Amberlite IR-120, Duolite C 20 and Duolite CB2210	Propranolol HCl, CPM maleate, Ephedrine HCl, Verapamil HCl, PPA HCl	Resinate and microencapsulated resinate	Drug release was influenced by acid–base strength and molecular weight of the drug	26
Dowex 50 W	PPA	Fibers filled with resinate	Polyurethane fibers encapsulated resinate were prepared and evaluated for *in vitro* and *in vivo* release	39
Amberlite CG 50 R, Amberlite CG 120 R	Diphenhydramine HCl, CPM HCl, PE HCl	CAB coated resinates	Drug release varies from drug to drug and also from resin to resin and was not greatly affected by temperature and ageing	29
Amberlite CG-50 W	CPM maleate	Microencapsulated resinate	Polymethylmethacrylate-coated resinates of higher diameter were prepared and finely divided solids added to reduce the microcapsule size and to control drug release	73
Dowex 1-X2, 1-X4, 1-X8	Theophylline	Microencapsulated resinate	Membrane-controlled release was observed in coated resinates with low cross-linking and particle-diffusion control in resins with high cross-linking	74
Resicat ABM Na-042	Codeine	Resinate	Two binding sites for Na^+ and, hence, two release rate processes were discovered and confirmed	10, 75
Dowex 50 W-X4	Terbutaline	Microencapsulated resinate	Polymer solvent affects the release of drug from the microcapsules prepared by oil/oil or oil/water solvent evaporation method	18, 76
Indion 244	Bromhexine	Microencapsulated resinate	Controlled release oral liquid suspension was formulated	28
Dowex 1-X2	Diclofenac sodium	Microencapsulated resinate	Flexible coating of Eudragit RS 30 D having thickness of few micrometers on resinate by wurster process can give a good control over drug release	39

Abbreviations: CAB, cellulose acetate butyrate; CPM, chlorpheniramine; PE, pseudoephedrine; PPA, phenylpropanolamine.

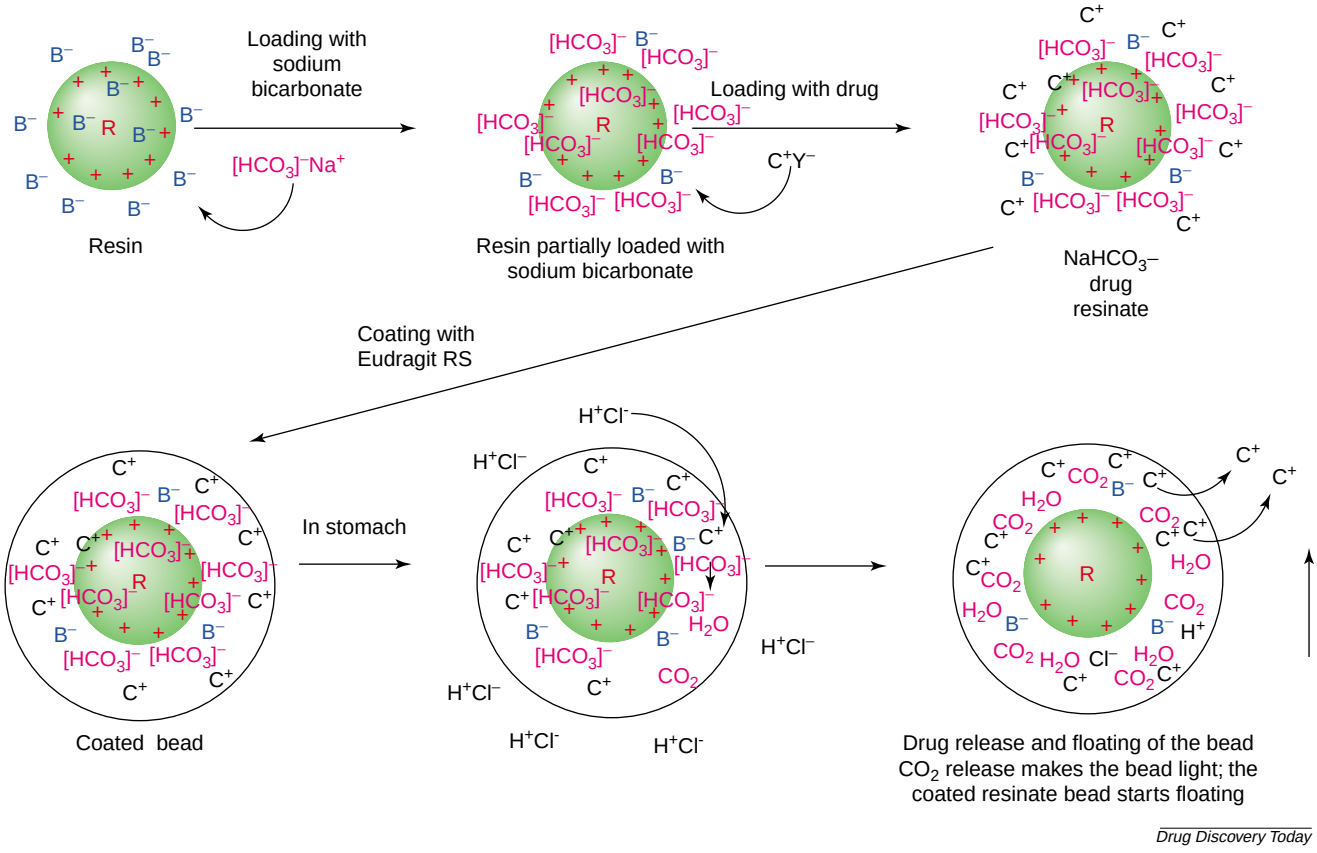

Figure 3. A schematic representation for the preparation of floating beads and the mechanism of floating. R and the green circle represents the resin; a + sign inside the resin depicts the integral ion of the resin, and B^- is the counter ion. C^+ is the drug ion, Na^+ is sodium ion, Y^- is ion associated with the drug ion and H^+Cl^- is hydrochloric acid. Ions inside and outside the resin indicate adsorption at the surface, as well as at the interior, of the resin structure.

- reducing the systemic toxicity, especially with cytotoxic anticancer drugs; and
- bifurcating the hostile environment of the drugs to prevent the drug degradation.

Several studies have reported the use of IER for drug delivery at the desired site of action[41–51].

Gastric retentive systems

Prolonged gastric retention of the drug formulations could improve the bioavailability and reduce drug wastage, especially for those predominantly absorbed from the stomach. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. Floating dosage forms are one of the alternatives designed to prolong gastric residence of drugs. A novel floating extended-release system consisting of a bicarbonate-charged resin coated with a semipermeable membrane was studied for improving gastric-residence time[41]. Drugs can simultaneously be complexed with the resin. The system floats in the stomach because of the exchange of chloride ions for bicarbonate counterparts, releasing the carbon dioxide. The released gas is trapped inside the membrane, causing the system to float. The preparation and mechanism of floating beads with a core of IER is illustrated in Fig. 3. Similar observation of floating controlled release was made with theophylline as a model drug[42]. Gamma scintigraphy studies revealed that such dosage forms can be retained in the stomach for 24 h in human volunteers[43].

Some IER, especially AER, such as cholestyramine, possess bio/mucoadhesive properties, which might be caused by their electrostatic interaction with the mucin and epithelial cell surface. The use of such bioadhesive IER is another attractive approach in the development of targeted formulations for the GIT. This approach would enhance the localized delivery of antibiotics, such as tetracycline, to the sites of *Helicobacter pylori* colonization (fundus), which conventional dosage forms fail to reach[44]. Similar types of applications were found with bioadhesive IER[45–47]. These systems are also useful in the delivery of diagnostics.

Site-specific delivery of drugs for cancer treatment

Entrapment of anticancer drugs within the particulate carriers (microspheres, microcapsules) is a popular approach for the development of delivery systems for cancer treatment. Several anticancer drugs (e.g. doxorubicin) are ionic in nature and can be complexed with IER. Attempts have been made to deliver some of these drugs in a controlled-release fashion to the anticancer cells with the help of IER[48,49]. These studies revealed that the drug loading is at its maximum level with the IER complex approach. Sawaya *et al.* studied the mechanism of complexation of doxorubicin with ion-exchange albumin microcapsules[22]. These studies proved the chemical stability of anticancer drugs in IER microcapsules.

Sigmoidal-release systems

The drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of the active substance[52]. Accordingly, the maintenance of a constant drug-blood level is not always required, as in the case of nitrates, antibiotics and contraceptive steroids. To avoid the development of tolerance, the rhythmic variations of blood concentration must be maintained for such medicaments. 'Time controlled', instead of 'rate controlled', dosage forms have been designed to meet the requirement of pulsatile release.

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 be responsible for pulsatile release[50,51].

Taste-masked oral DDSs

The taste of pharmaceutical preparations is an important parameter governing patient compliance and commercial success in the market. The scope of IER for masking the undesirable taste of pharmaceuticals is unlimited. At salivary pH (6.8), resinate remains in intact form, making the drug unavailable for the taste sensation. As the formulation enters the upper segment of the GIT the environment changes to acidic and drug release takes place[53]. Polystyrene matrix CER have been used to mask the bitter taste of chlorpheniramine maleate, ephedrine hydrochloride and diphenhydramine hydrochloride[54]. The ionic binding of the drugs to polymeric materials such as Carbopol is emerging as an important mechanism of taste masking. Erythromycin and clarithromycin have been taste masked by binding to carbopol[53]. Chloroquine phosphate[55] and dicyclomine hydrochloride have been successfully taste masked with IER recently [Nanda, A. (2000) Thesis: Development and evaluation of novel taste masked suspension and mouth dissolving dosage forms of dicyclomine hydrochloride. National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India]. However, as IER could also retard the release of drugs, a proper and careful selection of IER is essential to yield optimal taste masking without affecting the bioavailability. Generally, less cross-linked IER are helpful in taste masking[56].

Nasal or ophthalmic DDSs

Attempts have been made to deliver therapeutic peptides or synthetic drugs via nasal mucosa with the IER-complexation approach. A composition was developed to deliver nicotine in a pulsatile fashion to the systemic circulation via the nasal route[57]. An excess amount of nicotine, as an immediate dose, was either dispersed in a non-IE material or overloaded in IER. The excess uncomplexed nicotine was thus available for immediate absorption, while the complexed portion served as the depot for prolonging the absorption. 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^{-1} (Ref. 58).

A sustained drug delivery composition, comprising an aqueous carrier and microspheres containing a pharmaceutically active material complexed with IER was developed for the treatment of glaucoma[59,60]. These ophthalmic systems contained carbopol, which provided appropriate bioadhesion to the formulation. Betaxolol hydrochloride was delivered in a controlled manner by this approach.

Ionic strength and pH-responsive membrane bags

IE membranes are ion filters of selective permeability[61]. The permeability of ions *in vivo* is controlled by pH at the respective site, ionic strength, and drug properties. Polyacrylic acid-grafted porous polyvinylidene membrane (PAA–PVDF membrane) facilitates the transport of cationic drugs and repels anionic ones because of partial ionization of the carboxylic groups in the grafted chain. At low pH, the membrane pores are open and the drugs can diffuse through the membrane easily. However, at pH 7.0, the grafted chains partially block the pores and thus decrease the diffusion flux of the bigger drug molecules (molecular weight >9400) fivefold[62,63]. Ionic strength also affects the release of drugs from such membranes as a result of interaction between the ions held by the membranes and the free ions present in the environment. Salicylic acid-release from acrylic resin films increased in direct proportion to the ionic strength of the dissolution medium[63]. Polyacrylic

Table 2. Some of recent patents for the use of ion-exchange resin (IER) in drug delivery

US patent number	Issue date	Type of system	Model drug(s)	Remarks
4,221,778	September 9 1980	Pennkinetic system	PPA HCl, Dextromethorphan, Pseudoephedrine, Ephedrineethyl	Swelling of resinate is retarded by polyethylene glycol and coating of cellulose controls release of drug
4,859,461	August 22 1989	Coated resinate	PPA hydrochloride	HPMC, HPC, Sorbitol, HPS and PVP used as impregnating agents to improve coating
4,859,462	August 22 1989	Polymer-coated resinate	PPA hydrochloride	HPMC, HPC, Sorbitol, HPS and PVP used as impregnating agents to improve coating
4,894,239	January 16 1990	Microcapsulated resinate	Dihydrocodeine, PPA and di-methylephedrine	Polyacrylate, polymethacrylate, polyamide, and acrylate-methacrylate coatings for controlling drug release
4,911,920	March 27 1990	Ophthalmic drug delivery formulation containing IER	Betaxolol hydrochloride, Timolol	Carbopol and sulfonic acid CER controls drug delivery
4,996,047	February 26 1991	Coated resinate	Dextromethorphan, Pseudoephedrine, PPA	Different oral pharmaceutical formulations, chewable tablets, capsules, suspensions
5,275,820	January 4 1994	Microparticulate drug delivery vehicle with erodible matrix-containing resinates	Levobunolol hydro-chloride, Pilocarpine hydrochloride	Bioadhesive property, sustained release and improved stability of formulation
5,837,226	November 17 1998	Ocular microsphere delivery system	–	Microspheres comprising a core of ion-exchange resin; non-erodible coating controls the release rate
5,889,051	March 30 1999	Solid dispersion	Misoprostol	Stabilization of prostaglandin drug
5,932,248	August 3 1999	Polymer matrix loaded with resinate	Doxorubicin and cisplatin	Targeting of the pharmaceutically-active compound to the desired site
5,935,604	August 10 1999	Resinates in microspheres	Niocotine	Nicotine replacement formulation gives initial rapid release and absorption of nicotine, a pulse effect, followed by controlled release
6,001,392	December 14 1999	Coated and uncoated drug/resin complexes	Dextromethorphan, Diphenhydramine	Sustained release antitussive formulation

Abbreviations: CER, cation-exchange resin; HPC, hydroxypropylcellulose; HPMC, hydroxypropylomethylcellulose; HPS, hydroxypropylsorbitol; PPA, phenylpropanolamine; PVP, polyvinylpyrrolidine.

membrane bags of similar behaviour can be prepared by grafting of the appropriate functional moiety.

Pulsatile and site-specific delivery of drugs such as insulin, gastric acid inhibitors, nitrates, general hormone replacement and immunization has been reported, using the modified IE membranes. A glucose-responsive system capable of adjusting drug-release rates based on external and internal physiological factors was reported[64,65].

Implantation devices for water-soluble and charged drugs

Polydimethylsilicone is widely used in several implantation devices because of its minimal body tissue response and relatively high tissue diffusivities of hydrophobic solutes. Limited permeability of charged or water-soluble drugs has restricted the use of silicones in drug delivery. Electrostatic repulsion between the resin and the cations can increase their diffusion rate through polydimethylsilicone membranes. Trimethylbenzyl ammonium chloride polymer, an AER, along with cations in the silicone tubes was studied, and an increase in the diffusion of cations was observed in the following order: iron > calcium > sodium > potassium[66]. Resin introduces an additional force, which reduces the activation energy required for each ion to permeate the membrane. This approach could be employed in the delivery of cationic drugs from silicone implantation devices.

Iontophoretically assisted transdermal DDSs

IER could be considered as concentrated electrolytes with one immobile ionic species (the fixed ionic group). The addition of IER to gels or other composite vehicles complicates the process of passive drug release[67]. However, transdermal systems can be developed, in which the drug release can be controlled by electric current. Another advantage of such a system is exposure to a relatively constant pH during iontophoretic delivery, thus alleviating the problem of skin irritation. *In vitro* studies with nicotine, tacrine, propranolol, nadolol and sodium salicylate revealed that IER are more suitable as delivery vehicles in iontophoretic drug delivery[67,68]. However, the *in vivo* suitability of these systems needs to be established.

Clinical applications of IER

Sulfonated and carboxylic resins with a polystyrene backbone are most widely used in clinical medicine. The pharmacological activity of these resins is attributed to their ability to adsorb ions, which are more selective to the resin than the counter ion of the resin. Resins are mostly used in conditions of sodium- and water-retention, such as cardiac failure, renal disease (nephrotic syndrome), toxemia of pregnancy and cirrhosis of the liver[69]. In hypertension and edema, dietary restriction of sodium to less than 0.5 g per day is difficult. IER have been used as reinforcement of a low sodium diet or to enable high salt intake in the diet.

IER have also been used for hemoperfusion and management of drug overdoses (poisoning). At present, cholestyramine and cholestipol (AER) are used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults[70]. Both resins are mixed with fluids and administered as a slurry.

Concluding remarks

As evidenced by the number of patents and technological developments (Table 2), the use of IER in drug delivery research is gaining importance and commercial success. In addition to oral drug delivery, IER systems are being explored for site-specific, transdermal, nasal and ophthalmic routes. Moreover, several novel concepts, such as sigmoidal release, floating, pH and ionic strength-responsive systems, have shown the potential use of IER in drug delivery. However, these novel concepts of drug delivery with IER need further studies on *in vitro* and *in vivo* evaluation and establishment of correlation. Also, there is a need to miniaturize the delivery devices or systems with desired performance.

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