ION EXCHANGE RESINS:
PHARMACEUTICAL APPLICATIONS AND RECENT ADVANCEMENT

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ABSTRACT:
Ion exchange resins are cross-linked water insoluble polymer-carrying, ionizable functional groups. IER have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking. The major drawback of sustained release of extended release or extended release 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. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug. Drug resin complexation converts drug to amorphous form leading to improved drug dissolution. Several studies have reported the use of IER for drug delivery at the desired site of action. Sulfonated and carboxylic resins with a polystyrene backbone are most widely used in clinical medicine. Chemical deterioration of the resins is the result of several different processes. The FDA has the responsibility to define conditions under which safe food additives may be used in the production and preparation of foods and beverages.

Key words – Ion exchange resins, taste masking, resin drug complex, controlled release

HISTORY
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]

INTRODUCTION
Ion exchange resins are cross-linked, water insoluble, polymer-carrying, ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and hence, a drug-resin complex (drug resinate) is formed.[7] Ion exchange can be define as a reversible process in which ions of like sign are exchanged between liquid and solid, a highly insoluble body in contact with it.[8] The drug is released from the resinates by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion.[9] Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert.

IER have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Several IER products for oral and peroral administration have been developed for immediate release and sustained release purposes. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking.[10] Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.[11,12]

APPLICATIONS OF ION EXCHANGE RESINS

Taste Masking
The taste perception of bitter drugs is experienced in the mouth at taste buds. Taste masking has therefore become a potential tool to improve patient compliance. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. Generally, less cross-linked IER are helpful in taste masking [13]. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7[14] and cation concentration of about 40meq/L [15,16] in the saliva are not able to break the drug resin complex but it is weak enough to break down
by hydrochloric acid present in the stomach.[17] Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.[18] Examples of drugs in which this technique has been successfully demonstrated include ranitidine[19], paroxetine [20] and dextromethorphan.[21] Same principle of taste masking has been implemented in the rapidly disintegrating dosage form prepared using Zydus technology. [22] Studies have also showed the taste masking in case of quinolone category antibacterial ciprofloxacin hydrochloride using Indion 234. [23, 24]

Disintegrant/Superdisintegrant

Majority of tablet disintegrants have rapid water uptake capacity due to swelling. Because of their unusually large swelling capacities polymethacrylic carboxylic acid ion exchange resins have found usage in pharmacy as tablet disintegrants; for example polacrilline a potassium salt of weakly acidic cation exchange resin with methacrylic acid divinyl benzene matrix. [25, 26] Resins although insoluble, have great affinity for water and hence, act as disintegrant. [27] Moreover, because of their smaller particle size the rate of swelling is high making them superdisintegrant. Like conventional disintegrant, they don’t lump but additionally impart strength to the tablets. Potential superdisintegrant ability of Indion 414 has been reported by Purnima et al for mouth dissolve tablets of roxithromycin, montelukast sodium and dicyclomine hydrochloride. [27]

Improved Dissolution [20]

Drug resin complexation converts drug to amorphous form. Hence, drugs with poor solubility, during the process of desorption, immediately releases the drug leading to improved drug dissolution.

Drug stabilization

Vitamin B12 deteriorates on storage. This necessitates addition of overages, leading to significant increase in the cost of the formulations. The stability of Vitamin B12 can be prolonged by complexing it with a weak acid cation exchange resin (Indion- 264). This complex is as effective as the free form of the Vitamins. [28] Thus the introduction of Indion-264 in the formulation significantly reduces the overages.

Powder Processing Aid [25]

Handling qualities of hygroscopic drugs and drugs having caking tendency have been improved due to complexation with the resin. The fixed rigid structure of resins was seen to be responsible for that.

High purity water [29]

There will always be a need for purified water in the production of pharmaceuticals. Water softening uses a cation exchange resin to exchange principally calcium and magnesium ions for sodium ions and so prevent the formation of calcium carbonate precipitates on Reverse Osmosis membranes. Feed water is passed down through the resin bed which is in the sodium form. The polyvalent cations are absorbed onto the resin and the sodium ions are released. After a preset volume, or time, the system is taken off line and automatically regenerated with a brine solution.

IER: APPLICATIONS IN DRUG DELIVERY SYSTEMS

ORAL MODIFIED RELEASE FORMULATIONS

The major drawback of sustained release of extended release or extended release 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 drug resinate can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets. [30,31] Recently, multiple-unit sustained-release dextromethorphan (dmp) resinate tablets consisting of dmp resinate and direct compression fillers were prepared by using direct compression method. The release of dmp was mainly controlled by resinate.

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. [22] 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) [32] Moreover, IER impart flexibility in designing a variety of delivery systems, such as liquids[33–35], beads [36,37], microparticles[38–40] and simple matrices[41].

Drug, molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion diffusion of free drug molecules out of the resins as shown below.

Resin’Drug+ +X+…………………..> Resin’…X’++Drug’ (1)

Resin’Drug+ +X+…………………..>Resin’…X’++Drug (2)

Where, X and Y are ions in the gastrointestinal tract.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resinate and by selecting a degree of cross-linking and particle size of the resins without a coating process. [42] Ion exchange resins have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation. [43-45]

The prolonged release of the active drug is accomplished by providing a semi-permeable coating around discrete, minute, ion exchange resin particles with which the drug component has been complexed to form an insoluble drug-resin complex. The semi-permeable coating creates a diffusion barrier and the thickness of which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time.[46] Several preparations involving strong resinate of sulfuric acid (cation exchange resins) provided more moderate release than the weak resinate of carboxylic acid.[47] Hence, resinate of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and microparticles.[48] Mainly, Amphetamine, [49], Propranolol HCl[50], Dextroamphetamine[50],...
codeine[50] and Chlorpheniramine (Penn kinetic system by Pennwalt Corporation USA) [50] are Complexed with strong cation exchanger for slow release.

Simple resenates

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. [51]

Microencapsulated or coated resenates [52, 53]

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. Microencapsulation of resinates can be achieved by airsuspension coating (Wurster process), interfacial polymerization, solvent evaporation or pan coating.

Hollow fiber system

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. [54]

SITE-SPECIFIC DRUG DELIVERY SYSTEMS

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;

• 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. [55-65]

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. [55] Some IER, especially AER, such as cholesteryamine, 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. Similar types of applications were found with bioadhesive IER [59-60] These systems are also useful in the delivery of diagnostics.

Sigmoidal-release systems

The drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of the active substance. [66] 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 responsible for pulsatile release. [64, 65]

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. Recently various attempts have been made to deliver some of these drugs in a controlled-release fashion to the cancer cells with the help of IER. [62,63] 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. [67]

Ophthalmic drug delivery

Ophthalmic drug delivery of Betaxolol from resin involves release of drug from drug resin complex. BETOPTICS, flocculated suspension has been approved by FDA, and is marketed in U.S. since February 1990. Microparticulates of ion exchange resin have been reported for betaxolol (antiglaucoma drug) as a sustained ophthalmic drug delivery. [68] Moreau et. al reported a delivery of ciprofloxacin complexed with polystyrene sulfonate for the treatment of eye infections. [69]

Nasal drug delivery [70]

A composition was developed to deliver nicotine in a pulsatile fashion to the systemic circulation via the nasal route. 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.

**Iontophoretically assisted transdermal DDSs**

In vitro studies with nicotine, tacrine, propranolol, nadolol and sodium salicylate revealed that IER are more suitable as delivery vehicles in iontophoretic drug delivery. [71]

**THERAPEUTIC APPLICATIONS**

**Cholesterol reducer**

Cholestyramine resin USP, when used as an active ingredient, binds bile acids; this leads to replenishment of bile acids; through increased metabolism of serum cholesterol resulting in lowered serum cholesterol levels. [72]

**Chewing gum for glycol absorption [73, 74]**

Nicorette gum is a widely used patented product for smoking cessation program. It contains nicotine adsorbed on an ion exchange resin with carboxylic acid functionality and formulated in a flavoured chewing gum base, which provides gradual drug release through glycol mucosa as the gum is chewed offering fresh saliva as solvent for elution.

**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. [75] In hypertension and edema, dietary restriction of sodium to less than 0.5 g per day is difficult. IER have been used as reinforcement to a low sodium diet or to enable high salt intake in the diet. IER also have been used for hemoperfusion and management of drug overdoses (poisoning). Present, cholestyramine and cholestipol (AER) are used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults. [76]

**CHEMICAL DETERIORATION OF THE RESINS**

Chemical deterioration of the resins is the result of several different processes. [77] Breaking of covalent bonds between the resin matrix and functional groups results in losses of the groups and reduction (or even total loss) of the ion exchange capacity.

Exposing of strong anion exchange resins to the combined influence of a strong alkali and elevated temperature results in chemical altering and/or loss of the functional groups. Organic substances sorbed can cycle, i.e. regenerated and washed. Physically block the functional groups and/or alter the resin non-exchange sorption capacity. [78]

**REGULATION OF ION EXCHANGE RESINS FOR THE FOOD, WATER AND BEVERAGE INDUSTRIES**

The FDA has the responsibility to define conditions under which safe food additives may be used in the production and preparation of foods and beverages. These conditions are written in the Code of Federal Regulation (CFR), title 21, part 173 (secondary direct food additives permitted in food for human consumption). Section 25 of this part deals specifically with the use of ion exchange resins. The three major conditions spelled out by this law are:

1. The resin must be one of a preapproved generic list of resin compositions (listed in 21 CFR 173.25), of which the ingredients used to produce the resins comply with FDA food additive regulations;
2. The resin must be ‘subjected to preuse treatment by the manufacturer and/or user in accordance with the manufacturer’s directions’;
3. The resin must be ‘found to result in no more than 1 part per million of organic extractives.’ [79]

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