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REVIEW ARTICLE

ION EXCHANGE RESINS AND THEIR APPLICATIONS

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ABSTRACT:

Ion exchange resins are cross-linked water insoluble polymer-carrying, ionisable 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.

Keywords: Ion exchange resins, taste masking, resin drug complex, controlled release

INTRODUCTION

Ion exchange resins are cross-linked, water insoluble, polymer-carrying, ionisable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and hence, a drug-resin complex (drug resinate) is formed[1]. The drug is released from resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion. 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. 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. 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[2]. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950[3,4,5] .

Structure and Chemistry of Ion Exchange Resin

IER are simply insoluble polyelectrolyte's that are insoluble polymers which contain ionizable groups distributed regularly along the polymer backbone. The most common resins used in formulations are cross-linked polystyrene and polymethacrylate polymers. When IER are mixed with a fluid such as water, ions in the fluid can exchange with the polyelectrolyte's counter ions and be physically removed from the fluid. An ion exchange resin is a polymer (normally styrene) with electrically charged sites at which one ion may replace another. Natural soils contain solids with charged sites that exchange ions, and certain minerals called zeolites are quite good exchangers. Ion exchange also takes place in living materials because cell walls, cell membranes and other structures have charges. In natural waters and in wastewaters, there are often undesirable ions and some of them may be worth recovering. For example, cadmium ion is dangerous to health but is usually not present at concentrations that would justify recovery. On the other hand, silver ion in photographic wastes is not a serious hazard, but its value is quite high. In either case, it makes sense to substitute a suitable ion such as sodium for the ion in the wastewater. Synthetic ion exchange resins are usually cast as porous beads with considerable external and pore surface where ions can attach. The resins are prepared as spherical beads 0.5 to 1.0 mm in diameter. These appear solid even under the microscope, but on a molecular scale the structure is quite open (Fig. 1). Whenever there is a great surface area, adsorption plays a role. If a substance is adsorbed to an ion exchange resin, no ion is liberated. Testing for ions in the effluent will distinguish between removal by adsorption and removal by ion exchange. Of course, both mechanisms may be significant in certain cases, and mass balances comparing moles removed with moles of ions liberated will quantify the amounts of adsorption and ion exchange [6].

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Commonly used for man-made ion exchange resins. These are:

• -COOH, which is weakly ionized to $-COO^-$

• $-SO_3H$, which is strongly ionized to $-SO_3^-$

• $-NH_2$, which weakly attracts protons to form NH_3+

• -secondary and tertiary amines that also attract protons weakly

• $-NR3^+$, which has a strong, permanent charge (R stands for some organic group)

These groups are sufficient to allow selection of a resin with either weak or strong positive or negative charge.

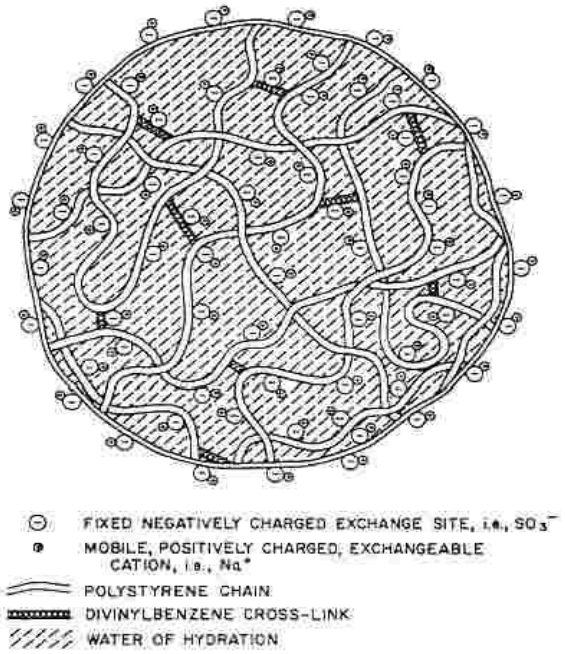

Figure 1: Expanded view of polystyrene bead

Classification of IER (Ion Exchange Resins)

Ion exchange resins are broadly classified into two main categories, as cation exchange resins and anion exchange resins.

1. Cation Exchange Resins:- whose exchangeable ions are positively charged: Cation exchange resins are prepared by the copolymerization of styrene and divinyl benzene and have sulfonic acid groups ($-SO_3H$) introduced into most of the benzene rings. The mechanism of cation exchange process can be represented by the following reaction:

$$Resin^- - ex^+ + C^+ \text{ ------} \rightarrow Resin- - C^+ + ex^+$$

Where, $Resin^-$ indicates a polymer with SO_3-sites available for bonding with exchangeable cation (ex^+), and C^+ indicates a cation in the surrounding solution getting exchanged.

Cation exchange resins can be further classified into:

A) Strong Acid Cation Exchange Resins

Strong acid resins are so named because their chemical behaviour is similar to that of a strong acid. These resins are highly ionized in both the acid ($R-SO_3H$) and salt (RSO_3Na) form of the sulfonic acid group ($-SO_3H$). They can convert a metal salt to the corresponding acid by the reaction:

$$2(R-SO_3H) + NiCl_2 \text{-----} \rightarrow (R-SO_4)\ Ni + 2HCl$$

The hydrogen and sodium forms of strong acid resins are highly dissociated, and the exchangeable Na^+ and H^+ are readily available for exchange over the entire pH range. Consequently, the exchange capacity of strong acid resins is independent of the solution pH.

These resins would be used in the hydrogen form for complete deionization; they are used in the sodium form for water softening (calcium and magnesium removal). After exhaustion, the resin is converted back to the hydrogen form (regenerated) by contact with a strong acid solution, or the resin can be convened to the sodium form with a sodium chloride solution. For the above reaction, hydrochloric acid (HCl) regeneration would result in a concentrated nickel chloride ($NiCl_2$) solution.

B) Weak Acid Cation Exchange Resins

These resins behave similarly to weak organic acids that are weakly dissociated. In a weak acid resin the ionizable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO_3H) used in strong acid resins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, resin capacity depends in part on the solution pH. A typical weak acid resin has limited capacity below a pH of 6.0, making it unsuitable for deionizing acidic metal finishing waste water.

2. Anion Exchange Resins:-

Whose exchangeable ions are negatively charged: These are prepared by first chlormethylating the benzene rings of styrene-divinyl benzene copolymer to attach CH2Cl groups and then causing these to react with tertiary amines such as triethylamine. The mechanism of anion exchange process can be represented by the following reaction:

$$Resin^+ - ex^- + A^- \text{ ----} \rightarrow Resin^+ - A^- + ex^-$$

Where, $Resin^+$ indicates a polymer with N^+ sites available for bonding with exchangeable anion (ex^-), and A^- indicates cations in the surrounding solution getting exchanged.

Anion exchange resins can be further classified into:

A) Strong Base Anion Exchange Resins

Like strong acid resins, strong base resins are highly ionized and can be used over the entire pH range. These resins are used in the hydroxide (OH) form for water deionization. They will react with anions in solution and can convert an acid solution to pure water:

$$R-NH_3OH + HCl \text{ ------} \rightarrow R-NH_3Cl + HOH$$

Regeneration with concentrated sodium hydroxide (NaOH) converts the exhausted resin to the OH form (Jain, N.K, 2001)

B) Weak Base Anion Exchange Resins

Weak base resins are like weak acid resins in that the degree of ionization is strongly influenced by pH.

Consequently, weak base resins exhibit minimum exchange capacity above a pH of 7.0. The weak base resin does not have an OH ion form as does the strong base resin.

$$R\text{-}NH_2 + HCl \text{ --------} \rightarrow R\text{-}NH_3Cl$$

Consequently, regeneration needs only to neutralize the absorbed acid; it need not provide OH ions. Less expensive weakly basic reagents such as ammonia (NH_3) or sodium carbonate can be employed.

Table of Types of Ion Exchange Resins:-

Type	Exchange species	Polymer backbone	Commercial Resins
Strong cation	$-SO_3H$ $-SO_3Na$	Polystyrene DVB Sodium Polystyrene	Amberlite IR 120, Dowex 50, Indion 244, Purolite C100HMR, Kyron-T-154 Tulsion T-344, Amberlite IRP 69, Indion 254
Weak cation	-COOH $-COO^-K^+$	Methacrylic acid DVB	Amberlite IRC 50, Indion 204, Purolite C102DR, Kyron-T-104, Kyron-T-114, Doshion P544(R), Tulsion T-335 Tulsion T-339, Amberlite IRP88, Indion 234, Kyron-T-134
Strong anion	N+R3	Polystyrene DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	N+R2	Polystyrene DVB	Amberlite IR 4B, Dowex 2

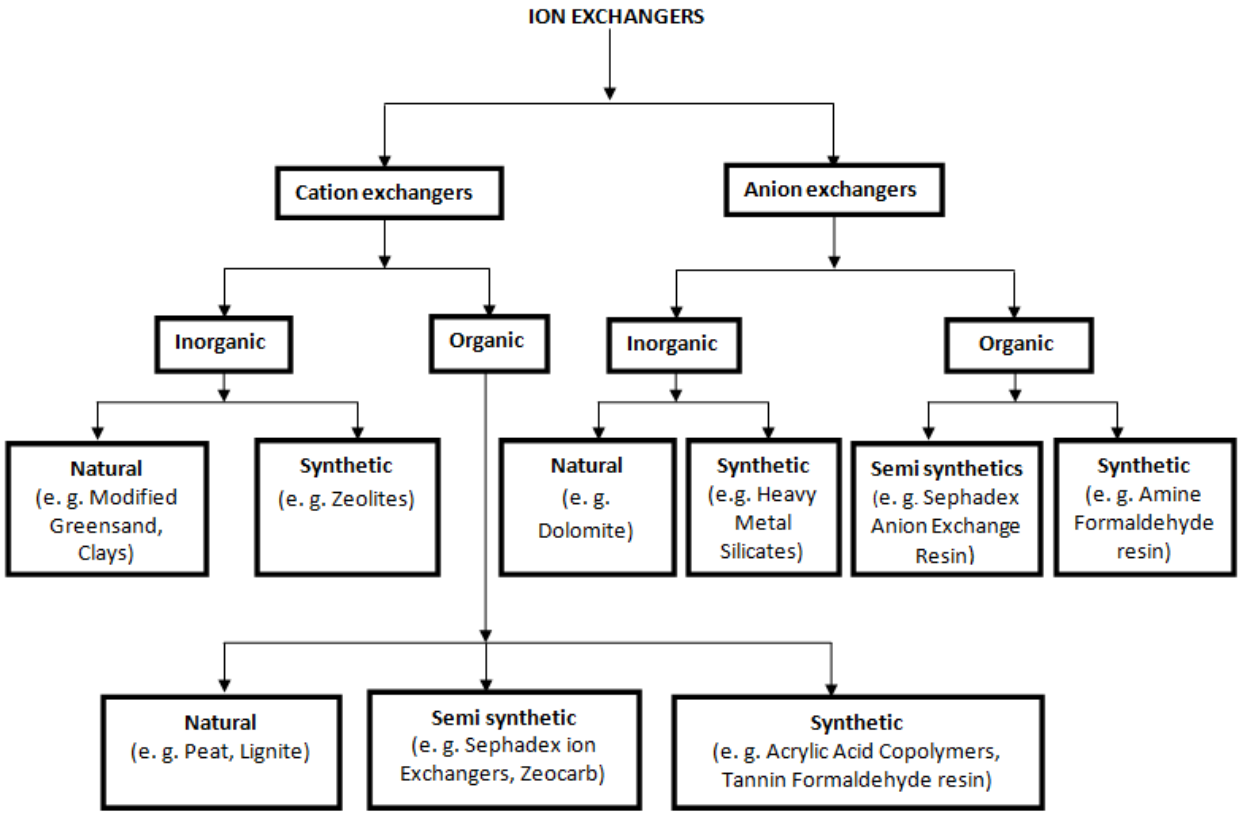

Figure 2: Classification of ion exchangers

Selection of Suitable Ion Exchange Resin:

The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER[7]. 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 mill equivalents 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;

• 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.

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 micro sieves by screening. The particle size of IER can also be determined by microscopy, Coulter counter[9] 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)[10]. 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[11].

• Moisture content – determined by Karl Fischer titrimetry. Excess water can be removed by drying in vacuum desiccators[12].

• IE capacity – the IE capacity of strong CER is determined as meq g–1 by evaluating the number of moles of Na^+, which are absorbed by 1 g of the dry resin in the hydrogen form[13,14]. 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.

Mechanism of binding of ion exchange resin with drugs:

The principle property of resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions adsorbed on the resin as illustrated in equation 1 and 2.

$$Re\text{-}So_3 - Na^+ + Drug^+ \rightarrow Re\text{-}SO_3 - Drug^+ + Na^+ \quad \text{——————1}$$

$$Re\text{-}N(CH_3)\text{-}Cl^- + Drug^- \rightarrow Re\text{-}N(CH_3)\text{-}Drug^- + Cl^- \quad \text{——————2}$$

These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resins for particular ions. Relative affinity between ions may be expressed as a selectivity co-efficient derived from mass action expression13 given in equation no. 3.

$$KDM = \frac{[D]\,R\ [M]S}{[D]S\ [M]R}$$

Where, $[D]_R$ = Drug concentration in resin

$[D]_S$ = Drug concentration in the solution

$[M]_S$ = Counter ion concentration in the solution

$[M]_R$ = Counter ion concentration in the resin

Factors that influence selectivity include valency, hydrated size, pKa and the pH of the solutions.

Borodkin *et al*. used selectivity coefficient to express the interaction of eleven amino drugs with potassium salt of polacrin, a polycarboxylic acid resin. When loading of resin with an ion of less affinity, the exchange may be driven towards the direction of unfavourable equilibrium by flooding the influence with high concentration or by using chromatographic column procedures.

Resinate preparation:

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[16]. 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[17]. 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.

1. Batch technique – after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution until the equilibrium is established[18] and;

2. 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.

Drug release from IER:

The rate and completeness of drug desorption in-vivo will be controlled by the diffusion rate of the drug through the polymer phase of the resin,(usually a function of molecular weight),the selectivity of the drug for the resin ,and the concentration of the electrolytes particularly in the hydrogen ion, in the desorption environment[19].

More hydrophobic drugs will usually elute from the resin at a lower rate, as will drugs with a relatively high selectivity for the carboxylic acid functional structure

In the resin other resin-sorbate interactions are possible, and these can have a pronounced effect upon loading capacities and rates.

An example of this might be the presence of the transition metal in the structure of the sorbate molecule which can result in considerable selectivity through the formation of a coordination compound with the resin.

Properties of IER:

1. Exchange capacity: The capacity of an ion exchanger is a quantitative measure of its ability to take up exchangeable Counter-ions and refers to the number of ionic groups per unit weight or volume (meq per g or meq per mL). The weight-based value is generally much greater than the volume-based value since the resin is highly hydrated. However, in preparing drug– resinates, the actual capacity obtainable under specific experimental conditions would depend upon the accessibility of the functional groups for the drug of interest. The so-called ''available capacity'' will be related to the drug physicochemical properties and will be inferior to the total capacity. The exchange capacity may limit the amount of drug that may be sorbed onto a resin and the potency of a drug–resin complex. Weak cation exchangers derived from acrylic acid polymers have higher exchange capacity (~10 meq/g) than the sulfonic acid (~4 meq/g) or amine resins because of bulkier ionic substituent's and the polystyrene matrix. Therefore, higher drug loads may often be achieved with the carboxylic acid resins[20].

2. Cross-linkage: The degree of cross-linking depends on the percent DVB used in the copolymerization. The Ion-exchange products available today are limited to a range of 2–16 wt% DVB. Below 2 wt%, the finished ion-exchange materials lack the mechanical strength to resist the volume changes, which occur under normal operation. Above 16 wt%, the polymer structure resists swelling, so that production of a finished ion exchanger becomes difficult and costly. The amount of DVB determines the extent of swelling and shrinking of ion-exchange resins. The swelling would affect the rate of hydration, the volume expansion of the resin in a column, the rate of exchange of ions, and the capacity of the resin to sorb large molecules. Even after sorption, some large molecules may be difficult to elute unless the DVB fraction is quite low. The excellent swelling properties of the ion-exchange resins, such as potassium salt of polymethacrylic acid resin (Amberlite IRP-88), has been practically used as a tablet disintegrating agent[21,22].

3. Ionization: In all ion exchangers, the ionization of the attached functional group is dependent on the Presence of water in the matrix. The amount of water that an ion-exchange resin will imbibe, in turn, is dependent on the cross-linking of the polymer. The ionization of the functional group determines the type and the strength of an ion exchanger. In aqueous media, strong acid cation and strong base anion-exchange resins are fully hydrated; and the ions associated with the functional group are always free to exchange with ions of like charge in the solution being processed. However, the ionization in weak acid cation and weak base anion exchangers is different. The value at which ionization becomes effective (pKa value) in resins containing sulfonic, phosphoric or carboxylic acid exchange groups is <1, 2–3, and 4–6, respectively. Anion exchangers with quaternary, tertiary, or secondary ammonium groups have apparent pKa values of >13, 7– 9, and 5– 9, respectively. The pKa value of a resin will have a significant influence on the drug release rate from the drug–resinate in the gastric fluids.

4. Particle size and form: The rate of ion exchange reaction depends on the size of the resin particles. Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern[20].

5. Porosity and swelling: Porosity is defined as the ratio of volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity depends upon the amount of cross-linking substance used in polymerization method. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional to the degree of DVB cross linking present in the resin[23].

6. Stability: The ion exchange resins are inert substances at ordinary temperature and excluding the more potent oxidizing agents are resistant to decomposition through chemical attack. These materials are indestructible. They get degraded and degenerated in presence of gamma rays[23].

7. Purity and toxicity: It is necessary to establish the safety/toxicity of the ion-exchange resins because of very high fraction of the resin in drug–resin complex (>60%). Most commercial products cannot be used as such because they contain impurities that cause severe toxicity besides some pharmaceutical grade resins (Amberlite IRP series from Rohm&Haas).Therefore, a thorough purification of the resin is required to eliminate the impurities for the pharmaceutical application. Purified ion exchange resins are insoluble and nontoxic. However, administration of large enough quantities of ion-exchange resin may disturb the ion strength in the gastrointestinal fluids and cause harmful side effects[24,25].

8. Selectivity of resin for counter ion: Since ion exchange resin involves electrostatic forces, selectivity mainly depends on relative charge and ionic radius of hydrated ions competing for an exchange site and to some extent on hydrophobicity of competitor ion[23].

APPLICATION OF ION EXCHANGE RESINS

(A) Pharmaceutical Application

1) Sustained release formulations such as capsules, liquids, oral tablet, etc. Gastrointestinal sustained release mechanism:-Bioavailability of drug absorbed on ion exchange resins depends on both transits of the particles through the G.I. tract and drug release kinetic. Drug release or dissolution from the resin can in turn occurs only by replacement of the drug by another ion with the same charge. Since, the exchange is an equilibrium process, it depends on the body fluids, ionic constitution and fluid volume. Additionally release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. The net result of all the phenomena is a sustained release system[5,6,32].

If the drug resin complex is administered orally a small amount of drug may be released. This would be followed

by significant and continuous release in the stomach where drug is exposed to high acid and chloride concentrations. Anionic exchange resins and strong cation exchangers release a limited amount of drug in the stomach as shown in Eq. 1& 2.

$$Re\text{-}SO_3 - Drug^+ + H^+ \; Re\text{-}SO_3 - H + + Drug^+ \quad \text{----- 1}$$

$$Re\text{-}N(CH_3)^+ \; Drug^- + Cl^- \; Re\text{-}N(CH_3) + Cl^- + Drug^- \text{----- 2}$$

In contrast drug bound to weakly acidic carboxylic acids released much more readily in the stomach as illustrated in Eq.3

$$Re\text{-}COO - Drug^+ + H + Re\text{-}COOH + Drug^+ \text{------3}$$

The high effective pKa of the resin drives the equilibrium towards the formation of undissosiated acid in a low pH environment. This may promote rapid drug release. In the intestine the neutral pH should keep all ionic sites on the resins ionized and the exchange process should occur continuously.

2) Taste masking (Chewable or Dispersible tablet of bitter drugs):-Certain drugs that have very bitter taste can be made relatively tasteless by adsorbing the drug on ion exchange resin although all the ion exchange resins can be useful for this purpose, the proper selection on ionic character of drug and release characteristics. Weak cation exchange resins can be used to formulate chewable or dispersible tablet of bitter drugs, for example Rodec decongestant tablet containing pseudoephedrin. Weak cation exchangers are most preferable for their ability to remain undissociated at alkaline pH of mouth, and thus masking the taste of bound drug and further releasing it rapidly at acidic pH of stomach. Avari and Bhalekar reported taste masking of highly bitter antibiotic, sparfloxacin with Indion 204 weak cation exchanger. Resins have been used with success to prepare stable and tasteless dosage forms. Taste masking in chewable tablets having amino containing drugs like dextromethorphon, ephedrine, pseudoephedrine, etc. have been successfully carried out by using weak cation exchange resin[33].

3) Chewing gum for buccal absorption:-Nicotine 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 flavored chewing gum base provides gradual drug release through buccal mucosa as the gum is chewed offering fresh saliva as solvent for elution

4) Bioadhesive system for treatment of gastric mucosa:-. Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions.94 Hence ion exchange resins may be useful in mucoadhesive systems for topical treatment of stomach such as H. pylori infection for prolonging the gastric residence of amoxycillin and cimetidine.

5) Tablet Disintegration [Improved tablet Disintegration properties]:- Many tablets disintegrant owe their action to capacity to absorb water and swell up. Fine particle size ion exchange resins have shown superiority as disintegrating agent due to their considerable swelling pressure upon hydration. Advantages of ion exchange resins over conventional disintegrating agents are

1. Rate of permeation of water and subsequent swelling is very fast and cut down the disintegration time.

2. Ion exchange resins do not have adhesive tendency on hydration; hence tablet disintegrates evenly without formation of lumps.

3. Ion exchange resin is effective in low concentration as disintegrants.

4. Ion exchange resin incorporation confirms greater hardness to tablet.

5. Ion exchange resin work equally efficiently with hydrophilic as well as hydrophobic formulations, especially with the later where the conventional disintegrant are ineffective.

Because of their unusually large swelling capacities polymethacrylic carboxylic acid ion exchange resins have found usage in pharmacy as tablet disintegrants; for example pollacrilline a potassium salt of weakly acidic cation exchange resin with methacrylic acid divinyl benzene matrix[35,36].

Borodkin and Yunker investigated chances of interference of cation exchanger disintegrants with drug availability and assay. They concluded that such agents should not affect total in vivo availability. It was questionable, however, if any significant delay in absorption would occur. While assaying amine drugs buffers above 7 or below 3 or solutions with high cation concentration may be used to effect complete drug elution.

6) Targeted drug delivery system [Anticancer drug]:- This concept is based on the chemoembolished of drug-loaded microspheres via the tumour arterial supply. Because of their physical size microspheres can be entrapped in the capillary beds along with their load of cytotoxic drugs can be delivered to well vascularised tumour tissues. B.N.gray has studied the in vitro release of cytotoxic agents from cytotoxic agents from ion exchange resins.

7) 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.

8) Improved dissolution of poorly soluble drugs:-The slow dissolution of poorly soluble drugs is well known problem responsible for poor bioavailability. The release rate of such drugs from resonates can be much quicker than the dissolution rate of the pure drug. Eg. Indomethacins which are soluble up to ca 6ppm in simulated gastric fluid, but are release very quickly from resinate. the commercially available product Indomethacin uses micronization of the drug powder to achieve rapid dissolution[34]. Not all poorly soluble drugs are amenable to micronization because of the problems including low melting point, dust formation and agglomeration.ion exchange resins are convenient

alternative. The rapid dissolution occurs due to two factors:

1. Each individual molecule is bound to a functional site- there is no crystal lattice energy to overcome.

2. The ion exchange materials are relatively hydrophilic and so allow water and aqueous solutions easy access in to the 3-dimensional structure- eliminating problems with 'wetting-out' the drug. However this technique like micronization increases the rate of dissolution. It does not increase the solubility of the drug.

9) Anti-deliquescence: Deliquescence is the property of a solid whereby it absorbs so much water that it dissolves in the water it absorbs. This problem is very difficult to solve, and requires the use of specialized equipments or careful scheduling of a production in dry seasons[6]. A very recent discovery by Rohm and Hass research laboratories show that using resinates can eliminate deliquescence during manufacturing and storage. Rohm and Hass have filed the patent application for it. They have found that resonates of deliquescent and highly hygroscopic drug retain the properties of the resin and are not deliquescent and remain free flowing powders. Their water absorption characteristics are similar to those of unloaded resin. so, that any formulation equipment that can handle the resin can handle the resinate of the deliquescent drug without need for special manufacturing conditions. For example sodium valproate is a drug which is well known to be highly deliquescent. However they have found that valproate resinates remain free-flowing even after exposure to ambient air.

10) Polymorphism: Unlike deliquescence, polymorphism is a very common problem in pharmaceutical industry and huge sums of money are spent trying to identify polymorphs and trying to make stable, suitably soluble forms[6]. Failure to resolve such problems can result in significant stability problems for the final dosage form. Ion exchange resin presents a unique way to deal with the problem. a drug resinate is an amorphous solid that cannot crystallize or even form hydrates. In addition the release of the drug from the resinate is independent of the crystal form that was used to make it. Consequently using resinates completely eliminate any problem with polymorphism.

(B) Drug Delivery Applications

1. Oral drug delivery

The major drawback of sustained release or extended release is dose dumping hence resulting in increased risk of toxicity. The use of IER has occupied an important place in the development of controlled or sustained-release systems due of their better drug retaining properties and prevention of dose dumping. The drug resinates can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablet[2]. The use of ion exchange resins into drug delivery systems have been encouraged because of their physicochemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment[2].

2. Nasal drug delivery

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[31].

3. Transdermal drug delivery

IER are also involved in the formulation of transdermal drug delivery systems. The release rates of ketoprofen from the carbopol-based gel vehicles containing ion exchange fibers to which the ketoprofen had been bound were determined across 0.22 μm microporous membrane. The fluctuation of the release rate of ketoprofen from the vehicles was much lower compared with that of simple gels, though the cumulative amount of ketoprofen delivery was less. In addition ions could increase the rate and extent of ketoprofen delivery[31].

4. Ophthalmic drug delivery

IER also find application in ophthalamic drug delivery systems. An example is Betoptic S which is a sterile ophthalmic suspension and it contains 0.25% betaxolol hydrochloride. It is a cardio selective beta-adrenergic receptor blocking agent manufactured by Alcon Laboratories in the US. It is an ocular resinate ophthalmic product designed to lower elevated intraocular pressure. The drug resinate complex is formed when the positively charged drug is bound to a cation ion-exchange resin (Amberlite1 IRP 69). The 0.25% ophthalmic suspension of the drug showed an increased bioavailability[31-33] .

(C) Diagnostic and therapeutic applications

Synthetic as well as natural polysaccharides based on ion-exchange resins have been used with good results for diagnostic determinations. eg. In gastric acidity. They have also found applications as adsorbents of toxins, as antacids, and as bile acid binding agents. Ion-exchange resins have been successfully used therapeutic in the treatment of liver diseases, renal insufficiency, urolithic disease and occupational skin disease. For instance, sodium polystyrene sulfonate is a sulfonic cation-exchange resin used in the treatment of hyperkalemia and also used in acute renal failure. Phenteramine, a sympathomimetic amine is indicated for short term use in the management of exogeneous obesity in a regimen of weight reduction utilizing caloric restriction. It also has application in the control of cholesterol and potassium ion levels[5, 20].

Marketed Ion Exchange Resin as Taste Masking Agent[26-30]

Weak Cation Exchangers

Product name (Resin)	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Amberlite IRP64	Methacrylic	-coo-	H+	10meq/kg	Spiramycin, ranitidine, dextromethorphan, Dimenhydrinate.
Amberlite IRP88	Methacrylic	-coo-	K+	-	Talampicillin HCl, paroxetine, beta-lactum antibiotics
Tulsion 335	Methacrylic	-coo-	H+	10meq/g	Norfloxacin, ofloxacin, roxithromycin
Tulsion 339	Methacrylic	-coo-	K+	-	Chloroquine phosphate, quinine sulphate, ciprofloxacin, paracetamol
Kyron-T-104	Methacrylic	-coo-	H+	-	Cefuroxime Axetil, Cefpodoxime Proxetil, Norfloxacin
Kyron-T-114	Methacrylic	-coo-	H+	-	ItoprideHCl, Ofloxacin, Tramadol HCl
Indion 204	Crosslinked polyacrylic	-coo-	H+	10meq/g	Norfloxacin, ofloxacin, Famotidine, roxithromycin, dicyclomine HCl,
Indion 214	Crosslinked polyacrylic	-coo-	H+	10meq/g	Azithromycin
Indion 234	Crosslinked polyacrylic	-coo-	K+	-	Ciprofloxacin, chloroquine phosphate
Indion 464	Crosslinked polymethacrylic	-coo-	H+	9.5meq/g	Nicotine taste masking
Kyron-T-134	Crosslinked polyacrylic	-coo-	K+	-	Amodiaquine HCl,Cetirizine Di HCl, ChloroquinePhosphate Cefaclor Metronidazol
Purolite C102DR	Methacrylic	-coo-	H+	-	cardio-tonics and anti- depressants
Doshion P544	Methacrylic	-coo-	H+	-	Roxithromycin

Strong Cation Exchangers

Product name	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Amberlite IRP69	Styrene DVB	$-SO_3H$	Na+	4.3 eq/kg	ranitidine
Tulsion 344	Styrene DVB	$-SO_3H$	Na+	-	Dextromethorphan, dicyclomine HCl
Kyron-T-154	Styrene DVB	$-SO_3H$	Na+	-	Erythromycin Stearate

Strong Anion Exchanger

Product name	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Indion 454	Crosslinked polystyrene	$N+R_3$	Cl		

CONCLUSION

IERs have been used in pharmacy and medicine for various functions, which include tablet disintegration, bioadhesive systems, sustained release systems. In recent years IER have been successfully utilized for masking of taste of bitter drugs.IER play a major role in the modification of drug release by forming a complex with drug substances. This article has attempted to review the literature bring to light the chemistry, properties, method of preparation as well as its different applications.

REFERENCES

1. Sharma BK , Instrumental methods of chemical analysis (Analytical chemistry), 23rd ed., Goel Publishing House, Delhi, 2004, 123.
2. Anand V, Kandarapu R and Garg, S, Ion-exchange resins: carrying drug delivery forward. Drug Discov. Today 2001; 6, 905–914.
3. Jain, N.K.; "Advances in controlled and Novel drug Delivery", First Edition, 2001, 290-306.
4. Borodkin S and Sundberg DP, Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. J. Pharm. Sci. 1971: 60, 1523–1527.
5. Singh, I., Rehni, A.K., Kalra,R., Joshi,G., Kumar,M., Aboul-Enein,H.Y., Ion Exchange Resins: Drug Delivery and Therapeutic Applications, J. Pharm. Sci., 32(2007), 91-100.
6. Hughes,L., New uses of ion exchange resins in pharmaceutical formulation, Pharm. Tech. 2005;17, 38
7. Saunders L: Ion-exchange resins in organic analysis. J. Pharm. Pharmacol 1953; 5:569–578.
8. Raghunathan Y: Sustained release drug delivery system I: coated ion-exchange resin system for Phenylpropanolamine and other drugs. J. Pharm. Sci 1981; 70:379– 384.
9. Torres D: Comparison between aqueous and non-aqueous solvent evaporation methods for microencapsulation of drug-resin complexes. Int. J. Pharm 1998; 173:171–182.
10. Kunn R: Macroreticular ion-exchange resins. J. Am. Chem. Soc 1982; 84: 305–306.
11. Hongpaibal Y: Preparation and evaluation of controlled release Indomethacin microspheres. Drug Dev. Ind. Pharm 1984; 10:1597–1616.
12. Parag Y and Nairn JG: Rate of release of organic carboxylic acids from ion- exchange resins. J. Pharm. Sci 1988; 77: 872–875.
13. Sawaya A: Binding mechanism of Doxorubicin in ion exchange albumin microcapsules. J. Pharm. Sci 1987; 76:475–480.
14. Liu Z: Synthesis and characterization of surface-hydrophobic ion-exchange microspheres and the effect of coating on drug release rate. J. Pharm. Sci 2000; 89:807–817.
15. Kalmen C and Kressman TR: Ion exchange in organic and biochemistry. Wiley interscience, New York 1957, 502.
16. Kotycka S and Nairn JG: Influence of wax coatings on release rate of anions from ion-exchange resin beads. J.pharm.sci 1978; 67:500-503.
17. Jeffery GH: Ion exchange. Vogel's Text Book of Quantitative Chemical Analysis, ELBS&Longman, 1989, 186-214.
18. Sanghavi NM: Ion-exchange resins as matrices for controlled drug release. Indian Drugs 1988; 26:27–32.
19. Amberlite IRPTM 64 product datasheet, http:// www.rohmhass.com /ionexchange/ pharmaceuticals Accessed 15 July 2008.
20. Irwin WJ, Belaid KA, and Alpar HO: Drug. Dev. Ind.Pharm 1987; 13:2047-2066.
21. Chang RK, Shinwari M, Leonzio M, Wu LS, Pang J and Hussain MA: Evaluation of the disintegrant properties for an experimental cross-linked poly alkylammonium polymer. Int J Pharm 1998; 173:87–92.
22. Van Abbe NJ and Ress JT: Amberlite resin XE-88 as a tablet disintegrant. J Amer Pharm Ass Sci 1958; 47:487–489.
23. Swarbik J: Ion exchange resins and sustained release. Encyclopedia of Pharmaceutical Technology 2003; 8:203-217.
24. Becker BA and Swift JG: Effective reduction of the active toxicity of certain pharmacologic agents by use of synthetic ion-exchange resins. Toxicol Appl Pharmacol 1959; 1:42–54.
25. Freed SC, Keating JW and Hays EE: Amphetamine-resin complex for prolonged appetite suppression. Ann Int Med 1956; 44:1136–1141.
26. Husada PT: Tulsion-ion exchange resin for pharmaceutical formulation. http://www.signahusada.com Accessed 15 Dec 2009.
27. http://www.rohmhaas.com/ionexchange/pharmaceuticals/...doc/.../Irp88.PDF Accessed 15 Dec 2009
28. http://www.corelpharmachem.com/products.html Accessed 15 Dec 2009
29. http://www.ionresins.com/pds/234%20PDS.pdf Accessed 15 Dec 2009
30. http://www.purolite.com/.../pdfs/AppGuide_ExcipientsPH_10_15_08.pdf Accessed 15 Dec 2009
31. Martin, G. J., Ion Exchange and Adsorption Agents in Medicine (Little Brown & Co., Boston, MA, 1955).
32. Sengupta, A. R., Ion exchange and solvent extraction – a series of advances, volume 18, CRC press Newyork 103-150.
33. Avari J.G., Bhalekar M., " Cation Exchange Resins for Taste Masking and rapid dissolution of Sparfloxacine" Indian Drugs, (41), (2004) 19-23.
34. N Abbe NJ and Rees JT: J. Amer. Pharm.Asso.Sci 1998; 47:487.
35. Oletta V and Werfield RB. US Patent 1963; 3091574.

