



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Ion Exchange Resin: A Novel Drug Delivery System An overview

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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.

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

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Received 04 April 2019, Accepted 16 April 2019

Please cite this article as: Mhetre RM *et al.*, Ion Exchange Resin: A Novel Drug Delivery System An overview . American Journal of PharmTech Research 2019.

INTRODUCTION

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.^{1,2}

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. 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.³

Ion-exchange systems are advantageous for drugs that are highly susceptible to degradation by enzymatic process. A major advantage of ion exchange system is low running cost. It requires little energy and the regenerated chemicals are cheap. Furthermore, if well maintained, resin beds can last for many years before replacement. However, the limitation is that the release rate is proportional to the concentration of the ions present in the area of administration. More so, the release rate of drug can be affected by variability in diet, water intake and individual intestinal content^{4,5}

Physical properties, chemistry and classification of IER¹⁹

In general, IER consist of spherical beads of approximately 0.5–1.2 mm in diameter. The most common type is an opaque yellow in colour, although other colours are also reported. The constitution of each spherical particle of IER is similar to that of 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. 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.⁵ 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 while there are numerous functional groups that have charge; only a few are commonly used for man-made ion exchange resins.^{6, 8, 19}

These are:

- -COOH, which is weakly ionized to -COO^-
- -SO₃H, which is strongly ionized to -SO_3^-
- -NH₂, which weakly attracts protons to form NH_3^+
- -secondary and tertiary amines that also attract protons weakly
- -NR₃⁺, which has a strong, permanent charge

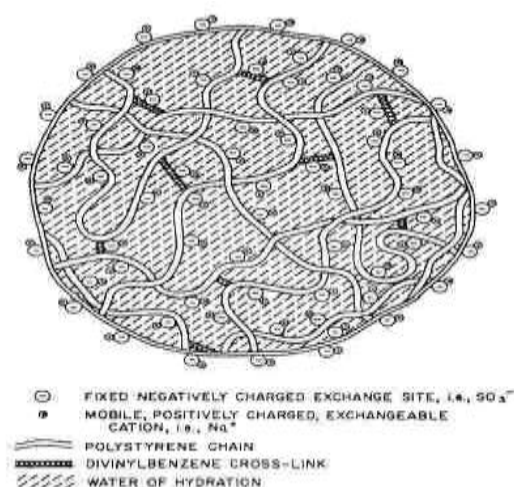
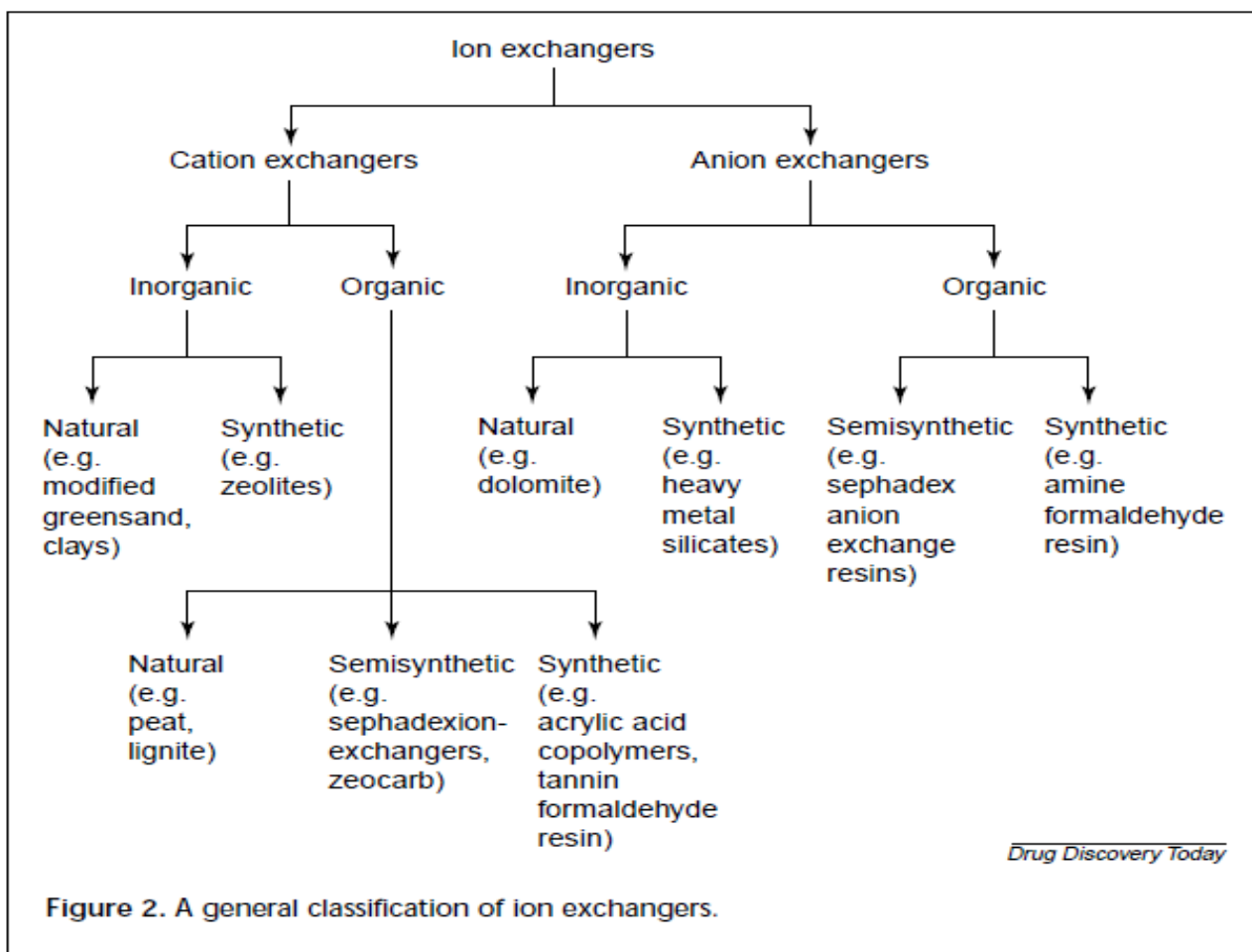


Figure 1: Expanded view of a polystyrene bead.

Classification:¹⁹

A general classification of ion exchangers is given in Fig. 2.



Ion exchange resins are broadly classified into two main categories, as cationic exchange resins and anion exchange resins.^{7,8,9,19}

Cation exchange resin

Its exchangeable ions are positively charged. Cation exchange resin binds with drug having anionic functionality (NH₂ group or HCl salts) which are given in table 2.^{7,8,9,19}

Type of resin	Drug characteristics req. for formation of IER drug complex	Drug that binds
Cation exchange resins	Drugs having anionic functionality (NH ₂ gr., HCL salt etc)	Dextromethrphin, Nicotin,, Amoxicillin, verapamil, metformin , ciprofloxacin , procainamide , diphenhydramine, propranolol
Anion exchange resins	Drugs having cationic functionality(COOH gr. Na salt etc)	Diclofenac sodium, sodium valproate.

Cation exchange resin can be further classified into:

Strong cation exchange resin

These are formed by the copolymerization of styrene and DVB and have sulphonic acid group (SO_3^-H) introduced into most of the benzene ring

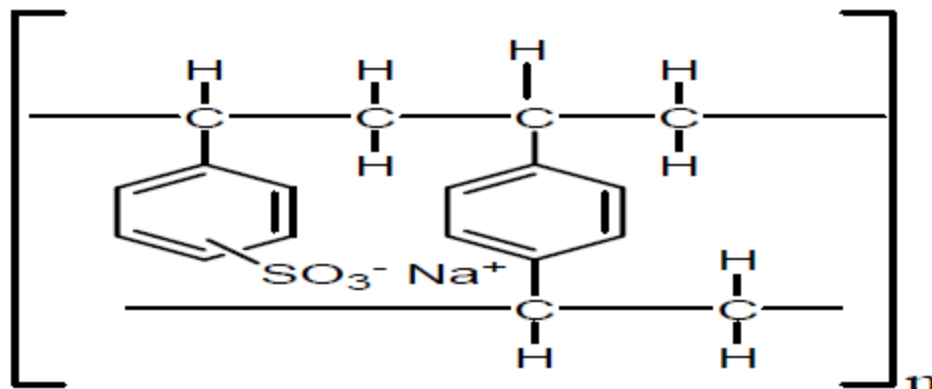
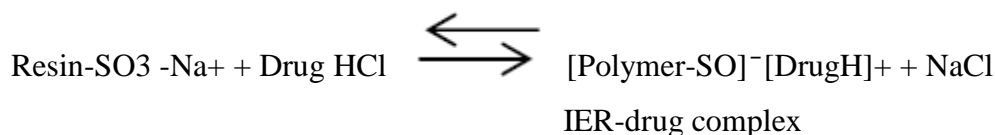


Figure 1: Chemical structure of a resin (sodium polystyrene sulphonate)

It has two highly ionized forms - acid (RSO_3H) and salt (RSO_3Na). They behave similar to strong acids. Both forms of resin are highly dissociated and the exchangeable sodium and hydrogen ion are readily available for exchange over entire pH range. Consequently, the exchange capacity of strong cation exchange resins is independent of solution pH. It mainly binds with drug existing as HCl salt form such as Metformin HCl, Ciprofloxacin HCl and Procainamide HCl in the following way:^{7,8,9,19}



Weak cation exchange resin

These are generally polyacrylic or poly methacrylic acid with di vinyl benzene as cross linking agent. They behave similar to week acid. The resin structure is shown below.

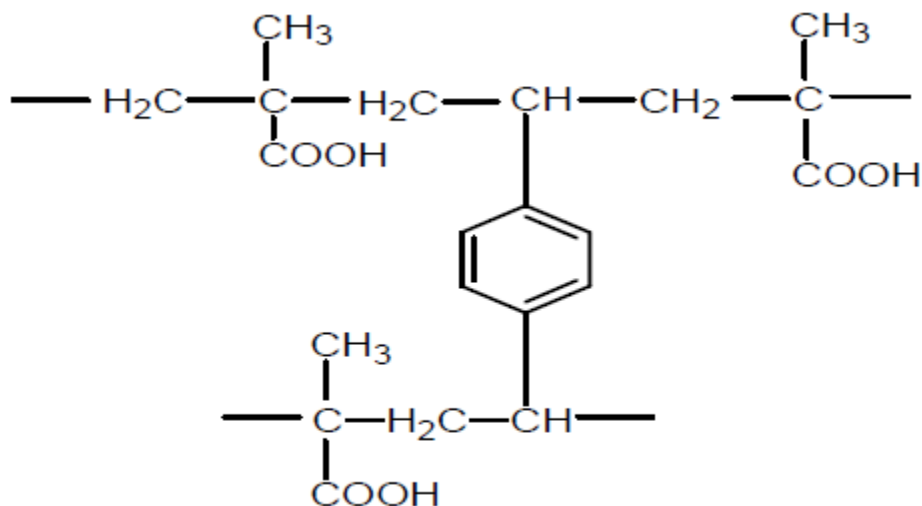
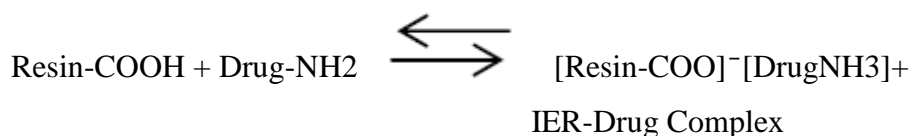


Figure 2: Structure of polyacrylic acid resin

Here the ionisable group is a carboxylic acid (COOH). The degree of dissociation and hence the resin capacity of weak cation exchange resin is strongly influenced by solution pH. It binds with drug having NH₂ group such as Amoxicillin in the following way.



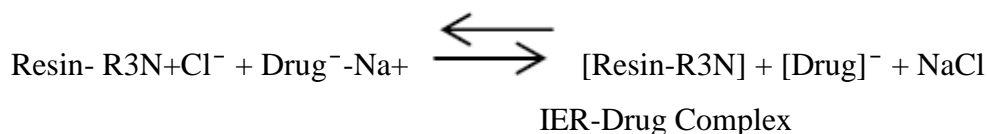
Anion exchange resin

Its exchangeable ions are negatively charged. Drugs with cationic functionality (e.g. COOH group or NaCl salt etc.) bind with this type of resin which is given in table 2.

Anion exchange resins can be further classified into:

Strong anion resin

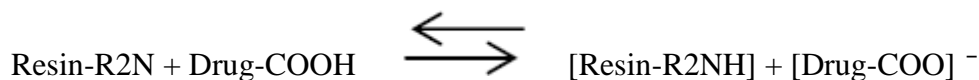
They are prepared by first chlor-methylating the benzene rings of styrene-divinylbenzene copolymer to attach CH₂Cl groups and then causing these to react with tertiary amine such as triethylamine. They behave similar to strong base and available in hydroxyl form (R-NH₃OH). It has R₃N⁺ group which binds with drugs existing as sodium salt in the following way:



Like strong cation resin, these resins are highly ionized and can be used over entire pH range.

Weak anion exchange resin

It has R₂N group which binds with drug having COOH group in the following manner.



How to select a suitable IER?

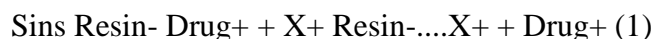
The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER. However, the following points need to be considered during selection:

- Capacity of the IER [i.e. the concentration of the exchangeable group in the resin, usually expressed in milli 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 resin in the pH- and ionic-strength environment, simulating the *in vivo* situation;
- Swelling ratio;
- Biocompatibility and biodegradability; and
- Regulatory status of the IER.^{7,8,9}

Role of IER in Controlled Drug Delivery Systems

The major drawback of controlled release is dose dumping, resulting in increased risk of toxicity. The usage of IER during the development of controlled release formulations plays a significant role because of their drug retarding properties and prevention of dose dumping. The drug resins can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets.^{1,2}

The use of IER 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. The physical and chemical properties of the IER will release the drug more uniformly than that of simple matrix formulations. Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the re as shown below in Eqs. (1) And:



Where,

X and Y are ions in the gastrointestinal tract.

IER have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation. 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. Several preparations involving strong resonates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resonates of carboxylic acid. Hence, resonates of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.^{10,11}

Manufacture of IER and Resonates

Most IER are made by the process of suspension polymerization. In some cases the monomers are neutral (e.g. styrene, methyl acrylate and acrylonitrile) and the resulting polymer beads are then chemically modified to introduce the acid or base functionality; for example, sodium polystyrene sulfonate is prepared by suspension polymerization of a mixture of styrene and divinylbenzene to make small polymeric beads. The beads are then sulfonated using concentrated sulphuric acid and neutralized with sodium hydroxide to give the functionalized product - a sodium form of a strongly acidic cation exchange resin. A few resins are made directly from acidic monomers; for example, polacrilex resin is made by suspension polymerization of a mixture of methacrylic acid and divinylbenzene with no further functionalization. For use in pharmaceutical formulations, the resins are usually dried and then ground to a fine powder, typically in the range of 40–150 μm in size.^{10,11} Preparing resins from the resins is a matter of mixing the resin with a solution and allowing sufficient time (typically a few hours) for loading. The resin/fluid slurry is then filtered and the filtrate washed. Depending on the application, resinate can then be dried in a vacuum oven at 60°C. In cases where resinate is to be used in a liquid suspension drying may not be necessary, and in some cases the loading suspension can be used directly without filtration. The dried resinate will be a free flowing powder with physical properties similar to the original resin, which can be formulated into tablets, capsules, chewing gums, lozenges, suspensions and troches. It can also be coated in typical coating equipment such as fluid bed coaters.

The best approach for getting resins is spray drying process in which fluidized bed processor can be used. In this process, the solution can be sprayed on the resin and simultaneous drying takes place to get dried resins which is free flowing powder mostly used in the solid dosage forms. The drug release mainly depending on the efficient complex formed between the drug and the resin. For further regulating drug release an alternative method is coating. In this technique the resin solution can be sprayed over the drug along with simultaneous drying. The advantage of this process is that it allows uniform distribution of the drug resinate mixture.^{1,2,10,11}

Mechanism Of Binding Of IER With Drugs

The mechanism of binding of drug to IER involves the electrostatic interactions between the resins and oppositely charged drugs and also the hydrophobic interaction as shown in the fig.1. The driving force behind this exchange is due to the electronic differences between the ions. The reversibility of this interaction is exploited in oral drug delivery in which the resins may carry the drug and release the payload in a certain region of the GIT due to a pH change or presence of competing ion.

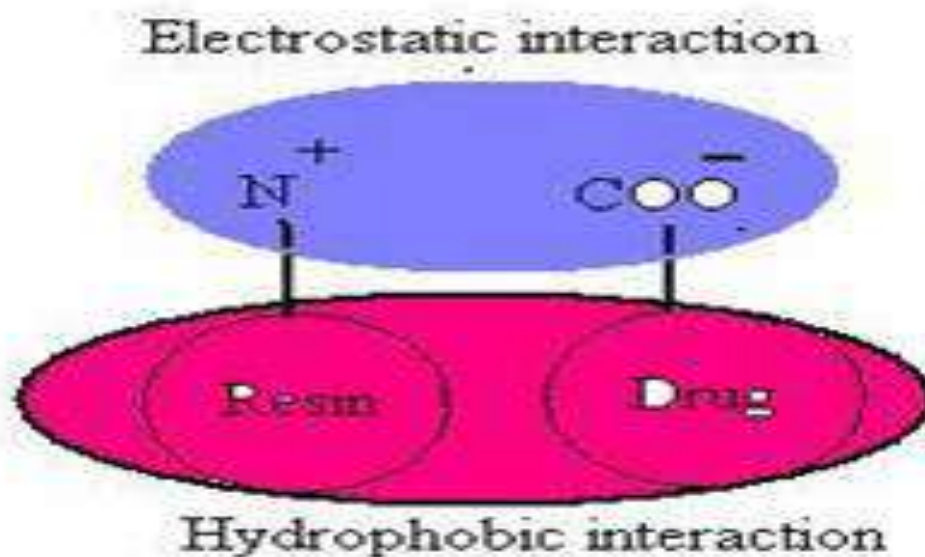
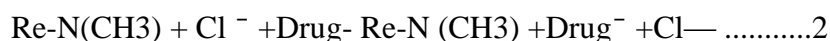


Figure 1: Electrostatic and hydrophobic interaction seen in drug resin complex

Drugs can be loaded onto the resins by an exchanging reaction, which is a reversible process illustrated in equation 1 and 2. A drug-resin complex (drug resinates) is formed. The drug is released from resins by exchanging with ions in the GI fluid, followed by drug diffusion.



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 expression given in equation 3.

$$K = \frac{[\text{D}]\text{R} [\text{M}]\text{S}}{[\text{D}]\text{S} [\text{M}]\text{R}}$$

Where

K = Selectivity co-efficient

$[\text{D}]\text{R}$ = Drug concentration in resin

$[\text{D}]\text{S}$ = Drug concentration in the solution

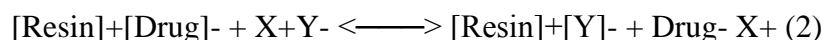
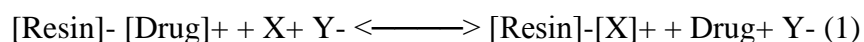
$[\text{M}]\text{S}$ = Counter ion concentration in the solution

[M]R = Counter ion concentration in the resin

Factors that influence selectivity coefficient include valency, hydrated size, pKa and the pH of the solutions. Higher the K values, greater the degree of ion exchange. The ions with higher selectivity co-efficient will replace the ions with lower selectivity co-efficient in the resin molecule^{12,13}

Mechanism of Release Of Drug From Resinate

Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract shown below,



Where, X and Y are ions in the gastrointestinal tract (either gastric HCl or intestinal NaCl). 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. The sustained-release profiles of drug can be obtained by using a mix of uncoated and semi permeable coated resins and by selecting a degree of cross-linking and particle size of the resins without a coating process.^{12,13}

Factors Affecting Loading of Drug onto Resins

1. Cross linkage of Resin

Higher grades have finer pore structure thus reducing loading efficiency with increase in cross linking. Low cross linkage increases the loading efficiency but also increases release rates.

2. Particle Size

Particle size does not have effect on drug loading. It affects only rate of exchange of ions species. The rate of exchange decreases with bead diameter due to reduction in diffusive path lengths hence larger particle size affords a slow release pattern.

3. pH

Protonated fractions of moderately weak acid or basic drug and weak functionality resin undergoes change with pH changes thereby increasing/decreasing drug resin interaction and hence loading.

4. Form of Resin

It was found that resins of H⁺ form have high loading capacity, as it possesses lower pH value than Na⁺. It has been found that drugs loaded onto H⁺ form of resin degrades while that a Na⁺ form does not degrade.

5. Size of exchanging ions or drug-

larger the size of exchanging ions, slower will be the diffusion rates and release.

6. Selectivity of Counter ions

The ions with low selectivity for resins such as H^+ gets replaced easily resulting in higher drug loading.

7. Mixing Time

Drug loading increases rapidly in the initial 9 h and further increases between 20-30 h. probably because of surface absorptive phenomenon.¹⁵

Properties of Ion Exchange Resin¹⁹

a. Cross-linking

The amount of cross linking depends on the percentage of different monomers used in polymerization process. The percentage of cross-linking affects the physical structure, moisture content, loading capacity, swelling and porosity of the resin particles. Extent of cross linkage has tremendous effect on drug loading efficiency. If resin is having less degree of cross linking, then it is more porous and the extent of swelling due to hydration is more. Whereas, if it is less cross linked, then it has less swelling. Because of this, the drug loading ability of less cross linked resin is high than more cross linked. But, the drug release from former is rapid and sustained from latter ones.¹⁹

b. Particle size

The usual range particle size range of commercial resin is within 0.25-1.25 mm. Particle size does not have effect on drug loading. It affects only rate of exchange of ions species. The rate of exchange decreases with bead diameter due to reduction in diffusive path lengths hence larger particle size affords a slow release pattern. Decreasing the size of the resin particles significantly improve the kinetic of ion exchange reaction i.e. decreases the time required for the reaction to reach equilibrium with the surrounding medium. Preferably the particle size is within the range of about 40 microns to about 250 microns for liquid dosage forms although particles up to about 1,000 micron can be used for solid dosage forms, e.g., tablets and capsules.¹⁹

c. Swelling

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. Low cross linking resins with functional group of sulphonic acid or quaternary ammonium contain large amount of water resulting in swelling.¹⁹

d. Porosity

The porosity depends upon the amount of crosslinking substance used during polymerization method. The limiting size of the ions or drugs, which can penetrate into a resin matrix, depends strongly on the porosity.¹⁹

e. Exchange capacity

It is the number of chemical equivalents of ions or drugs, that can be taken up by a unit amount of resin (dry weight/wet weight/ wet volume). It is expressed in term of meq per gram or meq per ml. The weight basis values (meq per gm) are much higher than the volume based exchange capacity since the wet resin is highly hydrated. Carboxylic acid resins derived from acrylic acid polymers (e.g. Indion® 204) have higher exchange capacities (10meq/gm) than sulfonic acid (about 4meq/gm) or amine resins because of bulkier ionic substituents and the polystyrene matrix.¹⁹

f. Acid base strength

The acid or base strength of IER depends on various ionogenic groups incorporated into resins. Resins containing sulphonic, phosphonic or carboxylic acid exchange groups have approximate pKa values of <1, 2, 3 and 4-6, respectively. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having pKa values of >13, 7- 9 or 5-9, respectively. The pKa values of resin will have significant influence on the rate at which the drug will be released from the resinate in the gastric fluid.¹⁹

g. Stability

At ordinary conditions of temperature, oxygen, light and humidity resins are found stable and inert in nature. These materials are indestructible. They get degraded and degenerated in presence of gamma rays.¹⁹

h. Purity and toxicity

Since drug resin combination contains 60% or more of the resin, it is necessary to establish its toxicity. Commercial product cannot be used as such. Careful purification of resins is required. Resins are not absorbed by body tissue and are safe for human consumption. Test for toxicological tolerance showed that it does not have any pronounced physiological action at recommended dosage and is definitely non-toxic.¹⁹

i. 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.¹⁵

Some IER Available in the Market

The use of IER to form drug adsorbates for sustained release was closely associated with Strassenburgh Laboratories, an affiliate of Pennwalt Corporation, which was granted several patents in this area. Their first significant application involved amphetamine adsorbed onto a sulfonic acid cation exchange resin (Biphphetamine) which is used in appetite suppression and for also for behaviour

control in children. The drug is administrated once or twice daily. Other products that have been introduced commercially since the initial work with amphetamine include Penntuss which is a combination of Codeine and Chlorpheniramine. This is a liquid suspension used as a cough suppressant and relief of cold. It is taken twice daily. Both drugs are bound to a sulfonic acid cation-exchange resin. The chlorpheniramine-resinates are uncoated due to much high affinity for the resin while the codeine-resinates are coated with ethyl cellulose. Other products used for cough and cold include phenylpropanolamine, chlorpheniramine, and dextromethorphan. Some other examples include Ionamin (phentermine) and Tussionex (hydrocodone polistirex and chlorpheniramine polistirex) both are marketed by Medeva Pharmaceuticals, Inc.) .However, Table 3 gives a summary of some IER with their doses and suppliers. ^{16,17,19}

Table 3: Some IER used in pharmaceutical formulations.

Component Name	Commercial Name	Supplier	Daily Intake
Prolacrillex Resin	Amberliteirp 64	Roham And Hass., Philadelphia	270mg
Polacridine Potassium	Amberliteirp 88	Roham And Hass. , Philadelphia	270mg
Sodiumpolystyrene Sulfonate	Amberliteirp 88	Roham And Hass. , Philadelphia	60gm
Cholesteramine Resin	Dauolite API 43	Roham And Hass. , Philadelphia	24 gm in divided doses

Evaluation of Drug Resonates ^{14,20}

The *in-vitro* test demonstrates the release pattern of a drug from resinate preparation dosage form. It depends on size of resinate, degree of cross linkage of resin with drug, nature of the resins, nature of the drug and test conditions that is ionic strength of the dissolution medium.

In vivo procedures used for estimating drug activity of resinates include serum concentration level determination, urinary excretion, and toxicity studies. Bioavailability of drug from drug–resinate complexes depends on both transit of the particles through the gastrointestinal tract and drug release kinetics. The complex will release the active content only when it replaced by the ion which has the same charge. Since the exchange is an equilibrium process, it will depend on the ionic constitution and the fluid volume of the body fluid. In additional, release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. Thus, agitation and time of exposure play a key role in drug release.

Stomach emptying with fine particles will likely follows a first order or distributional process. In the intestine, the neutral pH should keep all ionic sites ionized, and the exchange process should occur continuously. The absorption into the body of solubilized drug should drive the equilibrium further

toward drug release. In the large intestine, desorption from resins and absorption into the body may be slowed considerably due to low fluid content, entrapment in faecal matter, and poor absorption in colon. The highly insoluble resin never dissolves, and should not be absorbed. It will simply be eliminated from the body with whatever counter-ions have replaced the drug.^{14,20}

Applications of IER¹⁰

Pharmaceutical applications

Some pharmaceutical applications of IER include:

Taste masking

Masking of bitter taste in active principal ingredients in oral formulations poses a major challenge to pharmaceutical industry especially for paediatric and geriatric patients. Masking of the unpleasant taste of a drug improves compliance and product value. Amongst the numerous available taste-masking methods, ion exchange resins are inexpensive and can be used to develop. Previously some workers used carbomer to mask the nauseating and unpleasant taste of erythromycin and clarithromycin, into Carbopol and then encapsulating the resulting particles with hydroxylpropyl methylcellulose phthalate

Marked ion exchange resins

Weak Cation Exchangers^{10,12,16,17,18, 19,20}

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
Kyron-T-114	Methacrylic	-coo-	H+	-	Proxetil, Norfloxacin
Indion 204	Crosslinked polyacrylic	-coo-	H+	10meq/g	ItoprideHCl, Ofloxacin, Tramadol HCl
					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, Chloroquine Phosphate
Purolite C102DR	Methacrylic	-coo-	H+	-	Cefaclor Metronidazol
Doshion P544	Methacrylic	-coo-	H+	-	cardio-tonics and anti-depressants
					Roxithromycin

Strong Cation Exchangers ^{17,18}

Product name	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Amberlite IRP69	Styrene DVB	-SO ₃ H	Na+	4.3 eq/kg	ranitidine
Tulsion 344	Styrene DVB	-SO ₃ H	Na+	-	Dextromethorphan, dicyclomine HCl
Kyron-T-154	Styrene DVB	-SO ₃ H	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		

Eliminating polymorphism ^{10,16}

Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. This is a common problem in the pharmaceutical industry and huge sums of money are spent trying to identify polymorphs. and trying to make stable, suitably soluble forms. Failure to resolve such a problem can result in significant stability and stability problems for the final dosage form. Ion exchange resins present a unique way to deal with the problem because using resins completely eliminates any problem with polymorphism.

Improving the dissolution of poorly soluble drugs

Ion exchange drug resinate complexes can be used to enhance the dissolution rate of a poorly soluble drug. Using micronization to increase the rate of dissolution can be problematic, because it frequent requires specialized equipment and often there can be agglomeration of the fine particles after grinding. The grinding can also result in melting and conversion to other crystal forms. These problems are completely eliminated by using the ion exchange resin approach.

Improving stability

The drug resinate is frequently more stable than the original drug. For instance, vitamin B12 has a shelf-life of only a few months while its resinate has more than two years. Another example is nicotine which discolors on exposure to air and light, but the resinate used in manufacturing nicotine chewing gums and lozenges is much more stable.

Improving physical characteristics

Most drug substances are in solid form there are some that are liquids or difficult-to-handle solids. Because the physical properties of the resins are similar to the resin not the drug, the resins of these drugs will be free-flowing solids. A very well established example of this is the nicotine resinate used in nicotine chewing gums and lozenges. Nicotine is in liquid form but its resinate is a stable, free-flowing solid. The resins have a uniform, macroreticular morphology, that provides excellent flowability to the formulation.

Drug delivery applications ^{10,16,19,20}**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 resins can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets. The use of ion exchange resins into drug delivery systems have been 608 *Ion-* encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment.

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. ^{10,16,19,20}

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. ^{10,16,19,20}

Ophthalmic drug delivery

IER also find application in ophthalmic drug delivery systems. An example is Bet optic 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. ^{10,16,19,20}

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 exogenous obesity in a regimen of weight reduction utilizing caloric restriction. It also has application in the control of cholesterol and potassium ion levels. ^{10,16,19,20}

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. At present, cholestyramine and cholestipol (Anion Exchange Resin) are

used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults. Colestimide, a 2-methylimidazoleepichlorohydrin polymer, is a new bile-acid-sequestering resin that is four-fold as powerful at lowering low-density lipoprotein cholesterol (LDL-C) as the conventional resin (cholestyramine). Colestimide has been reported to lower blood glucose levels in patients with type 2 diabetes complicated by hypercholesterolemia .^{10,16,19,20}

Chewing gum for glycol absorption

Nicorette gum is a widely used patented product for smoking cessation program. It contains nicotine adsorbed on an ion exchange resin with carboxylic acids 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^{10,16,19,20}.

Hyperkalaemia treatment

Sodium polystyrene sulphonate and calcium polystyrene sulphonate are given orally or by retention enema for treatment of hyperkalaemia associated with anuric and severe oliguric renal insufficiency. They may also be used to treat hyperkalaemia in patients requiring dialysis .^{10,16,19,20}

Others

Strongly or weakly basic anion exchange resins are reported for recovery of antibiotic rifamycin S from rifamycin B, by curtailing complex, multi-step processes involved in separation. The suffocated cross linked styrene-divinylbenzene resins have been patented to adsorb mannose from a mixture of glucose and mannose.^{10,16,19,20}

CONCLUSION:

As evidenced by the number of patents and technological developments 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.

REFERENCES

1. Jain, N.K.; “Advances in controlled and Novel drug Delivery”, First Edition, 2001, 290-306.
2. Borodkin S and Sundberg DP, Polycarboxylic acid ion- exchange resin adsorbates for taste

- coverage in chewable tablets. *J. Pharm. Sci.* 1971; 60, 1523–1527.
3. 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.
 4. Singh I., Rehni A.K., Kalra R., Joshi G., Kumar M., Ion exchange resins: drug delivery and therapeutic application, *J. Pharm. Sc.* 2007;32: 91-100.
 5. Mahore J.G, Wadher K.J, Umekar M.J, Bhoyar P.K, Ion Exchange Resin: Pharmaceutical applicatoion and recent advancement, *Int. J. Pharm. Sci. Rev. Res.* 2010; 1 (2): 8-13.
 6. Liovich D.K., Ion exchange resins, [www.google/ionexchange resin \[SubsTech\]](http://www.google/ionexchange%20resin%20%5BSubsTech%5D).
 7. Chatap V.K., Sharma D.K., Desh P.T., Deshmukh, Taste masking Property of ion exchange resin: A Review, *Pharma Times.* 2008; 40(6): 22-26.
 8. Mahesh V, Chaubal, Synthetic- Polymer Based Ion Exchange Resins : Excipients & Actives, Drug delivery tech. com, (2001- 2006); article 149,
 9. Irwin W.J., Belaid K.A., Alpar H.O., Drug-delivery by ion-exchange. Part III. Interaction of ester pro-drugs of propranolol with cationic exchange resins, *Drug Dev. Ind. Pharm.* 1987;13: 2047-2066.
 10. Namdeo J., Drug delivery and therapeutic application of ion-exchange resins: An update, *J. Pharm. Sci.* 2007;5 (4):148-156.
 11. Kasture AV Wadodkar SG, Mahadik KK, More HN. A Textbook of Pharmaceutical Analysis and Instrumental Methods. 8th ed., Pierce Scientific, Rockford ,IL,USA 2002. p. 39-47.
 12. Bhalekar M, Avari JG, Jaiswal SB. Cation-exchanger in pharmaceutical formulation. *Ind J Pharm Sci* 38(4): 184-187, 2004.
 13. Chen L, Yang G, Zhang J. A study of the exchange kinetics of ion exchange fiber. *React Funct Polym* 29: 139-144, 1996.
 14. Cheng YH, Watts P, Hinchcliffe M, Hotchkiss R, Nankervis R, Faraj NF, Smith A, Davis SS, Illum L. Development of a novel nasal nicotine formulation comprising an optimal pulsatile and sustained plasma nicotine profile for smoking cessation. *J Control Release* 79(1-3): 243-254, 2002.
 15. Jeong SH, Park K. Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. *Int J Pharm* 353(1 2): 195-204, 2008.
 16. Husada PT: Tulsion-ion exchange resin for pharmaceutical formulation. <http://www.signahusada.com> Accessed 15 Dec 2009.
 17. http://www.purolite.com/.../pdfs/AppGuide_ExcipientsPH_10_15_08.pdf Accessed 15 Dec 2009

18. Irwin WJ, Belaid KA, and Alpar HO: Drug. Dev. Ind.Pharm 1987; 13:2047-2066.
19. Sharma Vijay, Chauhan Dr. C. S.¹ Ion Exchange Resins And Their Applications Journal of Drug Delivery & Therapeutics; 2014, 4(4), 115-123.
20. S. Sivanewari, D. Veena, P. Sai Sumana, P. Subhashree, L. Ramya, R. Rajalakshmi, P. J. Chandana and E. Karthikeyan , Ion exchange resins as drug delivery carriers Journal of Chemical and Pharmaceutical Research, 2015, 7(4):1436-1445.

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