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PHARMACEUTICAL ION EXCHANGE RESINS – A REVIEW

Ajay Bilandi[1]* and Amiya Kanta Mishra[2]

[1*]Research Scholar at Bhagwant University, Ajmer, Rajasthan, India.
[2] Principal, College of Pharmaceutical Sciences, Puri, Orissa, India.

ABSTRACT

Ion exchange resins are water insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain and have the ability to exchange counter-ions within aqueous solutions surrounding them. About 90 % of all ion exchange resins are based on a polystyrenic matrix. Synthetic ion exchange resins are usually cast as porous beads with considerable external and pore surface where ions can attach. 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 ($R\text{-}SO_3H$) and salt (RSO_3Na) form of the sulfonic acid group ($\text{-}SO_3H$). Ion exchange is a process in which mobile ions from an external solution are exchanged for ions that are electrostatically bound to the functional groups contained within a solid matrix. There are various pharmaceutical grade resins like AMBERLITE® IRP88 , DUOLITE™ AP143/1083, INDION 204 , INDION 264 , TULSION® 335 TULSION® 345 , Kyron T etc. used as tablet disintegrant, active ingredients, as carrier for basic (cationic) drugs, application with compatible coating technique, mask objectionable taste associated with certain basic drugs, potassium reduction in blood, cholesterol reduction in blood, reduction of bile acid, treatment of hyperkalaemia and Stabilization of vitamin B12. This review covers the IER structure, chemistry, kinetics, ion exchange process, , loading of drug on resin, pharmaceutical grade resins ,drug delivery applications etc.

Keywords: Ion Exchange Resins, Cross-Linked Polymers, Pharmaceutical Grade Resins, Sustained Release, Taste Masking.

INTRODUCTION

An ion-exchange resin or ion-exchange polymer is an insoluble matrix (or support structure) normally in the form of small (0.5-1 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate. The beads are typically porous, providing a high surface area. The trapping of ions occurs with concomitant releasing of other ions; thus the process is called ion-exchange. There are multiple types of ion-exchange resin. The most commercial resins are made of polystyrene sulfonate [1].

An organic ion exchange resin is composed of high-molecular weight polyelctrolytes that can exchange their ions for ions of similar charge from the surrounding medium. Each resin has a distinct number of mobile ion sites that set the maximum quantity of exchanges per unit of resin [2].

A cation exchange resin with a negatively charged matrix and exchangeable positive ions (cations). Ion exchange materials are sold as spheres or sometimes granules with a specific size and uniformity to meet the needs of a particular application [3].

For pharmaceutical applications an ion Exchange Resins must be fine, free flowing powders, capable of exchanging ions and/or ionic groups, insoluble in all solvents at all pH, not be absorbed by the body and particle size in ranges between 25-150 microns [4].

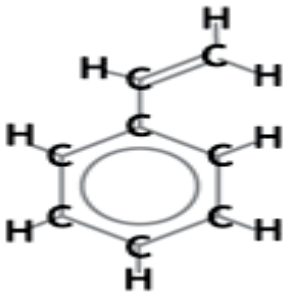
IER STRUCTURE

About 90 % of all ion exchange resins are based on a polystyrenic matrix. The "building block" used to make this plastic skeleton is styrene monomer, an aromatic compound also called vinyl benzene. Below are the chemical formulas:

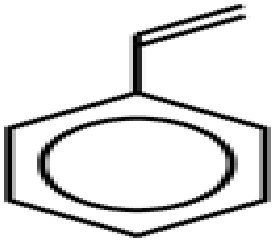
The vinyl double bond of this molecule enables polymerisation. The next picture shows the polymerised styrene, albeit only with four visible styrene groups. In reality, millions of groups are attached together in very long chains.

Corresponding Author:- **Ajay Bilandi** Email:- ajay_bilandi2001@yahoo.com

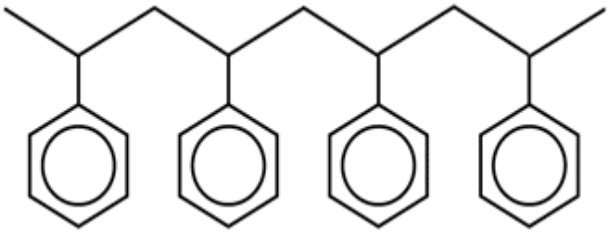
Chemical formula of styrene



Simplified representation of styrene



A small fraction of a polystyrene chain



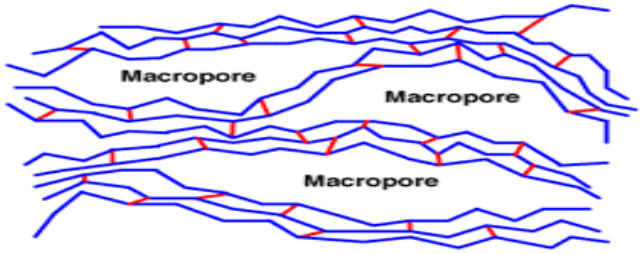
The resulting linear polymer chains are entangled together, but have little physical strength: they are relatively soft, and after activation they would probably dissolve in water. To give the polymer a more stable tri-dimentional structure, the polystyrene chains are cross-linked with another molecule at the time of polymerisation. The cross-linking molecule must be able to polymerise at two or three ends. The most common cross-linker is divinylbenzene (abbreviated as DVB).

The polymerisation process is usually done in a suspension medium, either in stirred reactors (batch polymerisation) or in special "jetting" equipment. The polymers formed are very small spherical beads (200 to 500 µm in diameter). The jetting process produces very uniform bead sizes, whilst batch polymerisation results in various bead sizes with a near-Gaussian particle size distribution. These beads will swell to a size of 300 to 1200 µm in the subsequent functionalisation and hydration steps.

Gel and Macroporous resin structure

In the polymerisation process described above, the cross-linker is more or less evenly distributed throughout the matrix. The voids between the chains of polystyrene are called pores. They are very small and their size is only a few Å, but the size is relatively constant: the matrix has a pseudo-crystalline structure, similar to glass, and as a result the finished ion exchange resiin beads are **transparent**. In the picture below, the polystyrene chains are shown in blue without the aromatic chemical details, and the "bridges" formed by DVB are shown in red.

Gel structure



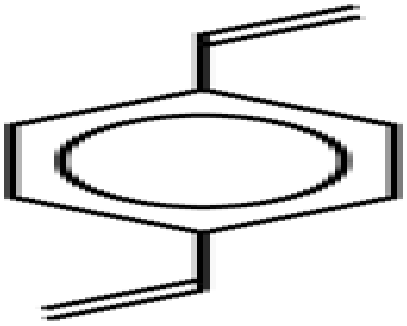
There is a limit to the quantity of DVB that can be used in gel type resins: too much DVB creates a stucture with very small pores, which in the final product may be a disadvantage, as larger ions cannot enter the resin beads. Additionally, highly cross-linked polymers are more difficult to activate.

To overcome this problem, create artifical porosity in the tri-dimensional matrix. To this effect, a third component — called porogen or phase extender — is incorporated in the reaction mixture, which does not react with the monomers, but only takes room in the system. Once the polymerisation reaction is finished, the porogen is washed out and leaves voids in the polymer structure. These are the macropores.

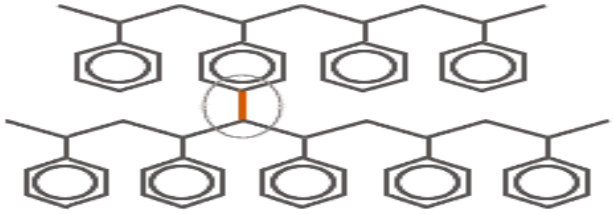
Macroporous structure

Macroporous resins have a double porosity: the small pores of the matrix itself and the large macropores created by the phase extender. The final resins are opaque. They are very stable, as the matrix is usually highly cross-linked. They also very porous, thus can exchange large ions.

Divinylbenzene (DVB)



Cross-linked polystyrene.



The second bond of the DVB molecule is shown in red and attaches to the next chain of linear polystyrene. The more DVB is added to the initial reaction mixture, the more rigid is the polymer.

Most ion exchange resins are polymerised in such a way that spherical beads are obtained. This can occur either in a stirred reactor or with a jetting process. In the latter case, the bead size is very uniform [5].

CLASSIFICATION OF IER

Classification based on functional groups

There are four main types differing in their functional groups:

i) Strongly acidic - typically consist of sulfonic acid groups.
ii) Strongly basic - consist of quaternary amino groups.
iii) Weakly acidic - mostly, carboxylic acid groups
iv) Weakly basic -primary, secondary, and/or ternary amino groups.

Classification based on interactive ion- Ion exchange resins are broadly classified into two main categories:

i) Cation Exchange Resins – whose exchangeable ions are positively charged.

Preparation-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.

Mechanism-The mechanism of cation exchange process can be represented by the following reaction: $Resin^- - ex^+ + C^+ \rightarrow Resin^- - C^+ + ex^+$

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

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 ($R\text{-}SO_3H$) 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:

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

Weak Acid Cation Exchange Resins

These resins behave similarly to weak organic acids that are weakly dissociated. In a weak acid resin the ionisable 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.

ii) *Anion Exchange Resins* whose exchangeable ions are negatively charged.

Preparation-These are prepared by first chloromethylating the benzene rings of styrene-divinyl benzene copolymer to attach CH_2Cl groups and then causing these to react with tertiary amines such as triethylamine.

Mechanism-The mechanism of anion exchange process can be represented by the following reaction:

- $Resin^+ - ex^- + A^- \rightarrow Resin^+ - A^- + ex^-$

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

Anion exchange resins can be further classified into:

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:

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

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 [10].

IER CHEMISTRY

An ion exchange resin is a polymer (normally styrene) with electrically charged sites at which one ion may replace another.

Synthetic ion exchange resins are usually cast as porous beads with considerable external and pore surface where ions can attach. 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.

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.

While there are numerous functional groups that have charge, only a few are commonly used for man-made ion exchange resins. These are:

- $-COOH$ which is weakly ionized to $-COO^-$
- $-SO_3H$ which is strongly ionized to $-SO_3^-$
- $-NH_2$ that weakly attracts protons to form NH_3^+
- -secondary and tertiary amines that also attract protons weakly
- $-NR_3^+$ that 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[12].

ION EXCHANGE PROCESS

Ion exchange is a process in which mobile ions from an external solution are exchanged for ions that are

electrostatically bound to the functional groups contained within a solid matrix. When the functional groups are negatively charged the exchange will involve cations and when they are positively charged they involve anions [14].

Ion-exchange reaction**,** any of a class of chemical reactions between two substances (each consisting of positively and negatively charged species called ions) that involves an exchange of one or more ionic components. Ions are atoms, or groups of atoms, that bear a positive or negative electric charge. In pairs or other multiples they make up the substance of many crystalline materials, including table salt. When such an ionic substance is dissolved in water, the ions are freed—to a considerable extent—from the restraints that hold them within the rigid array of the crystal, and they move about in the solution with relative freedom. Certain insoluble materials bearing positive or negative charges on their surfaces react with ionic solutions to remove various ions selectively, replacing them with ions of other kinds. Such processes are called ion-exchange reactions [15].

Ion exchange is an adsorption phenomenon where the mechanism of adsorption is electrostatic. Electrostatic forces hold ions to charged functional groups on the surface of the ion exchange resin. The adsorbed ions replace ions that are on the resin surface on a 1:1 charge basis.

The ion-exchange reaction is a reversible, selective and stoichiometric interchange of mobile ions of like charges between the ion-exchanger and the external liquid phases. Each counter-ion that is released from the ion-exchanger is replaced by an equivalent amount of another ionic species of same sign and valence due to the electro neutrality requirement. Based on the nature of the ionic species being exchanged, the ion-exchange process is either anionic or cationic.

Ion-exchanger A^- + B^- ←→ Ion-exchanger$^+$ B^- + A^-

When the ion-exchanger is placed in an electrolyte solution containing counter-ions which are different from those bound to the ion-exchanger, the migration of the first few external ions into the ion-exchanger and bound ions into the surrounding external solution creates an electrical potential difference (Donnan potential) between the ion exchanger and the external solution phases. The created Donnan potential accomplishes the interchange of counter-ions between the two phases until an equilibrium stage (Donnan equilibrium) is reached, that is, the equality of electrochemical potentials for each mobile ion between the phases. The higher the Donnan potential, the stronger is the co-ion exclusion from the ion-exchanger and, on the other hand, the stronger is the attraction of counter-ions towards the ion-exchanger. In a concentrated external solution the Donnan potential is low and, thus, the interaction between the mobile counter-ion and the ion exchanger is weak, achieving high rates of ion-exchange.

When an ion exchanger particle is brought in contact with a solution there is a static liquid film formed around it, the thickness of which may vary between 810 and 100 mm, depending on the rate of flow of liquid past the particle. The ion exchange reaction occurring between the resin particle and the solution will involve five distinct steps:

(a) Diffusion of the ions through the bulk solution in order to reach the ion exchanger particle,

(b) Diffusion of the ion through the hydrated film surrounding the particle,

(c) Diffusion of the ion across the film–particle interface,

(d) Diffusion of the ion through the particle,

(e) The actual chemical reaction involving the exchange of ions.

Providing that the concentration of ions in the solution is not extremely low steps (a), (c) and (e) are generally fast and do not determine the rate of the reaction. It is only step (b) (diffusion through the hydration film) or step (d) (diffusion through the particle) that controls the kinetics of the overall process, although sometimes both may determine the rate simultaneously. This is a simplified picture of the mechanism of an ion exchange process and its kinetics. The kinetics may be affected by a number of parameters, such as the nature of the exchanger, the nature of the counter ions, the extent of agitation, the concentration of the counter ions, etc [17].

In short, there are two types of diffusion that must be considered in ion exchange equilibrium. The first is called film diffusion or the movement of ions from a surrounding solution to the surface of an ion exchange particle. The second is called internal diffusion and is the movement of ions from the surface to the interior of an ion exchange particle. Film diffusion is usually the controlling reaction in dilute solutions whereas internal diffusion is controlling in more concentrated solutions [18].

7. PHARMACEUTICAL GRADE RESINS

Amberlite® IRP88 (Polacrilin Potassium Nf)

AMBERLITE IRP88[1] resin is a weakly acidic potassium form cation exchange resin supplied as a dry powder. It is widely used as a tablet disintegrant in oral dosage formulations of drug products. AMBERLITE IRP88 resin is the potassium salt of a crosslinked polymer derived from methacrylic acid. Its swelling properties upon hydration provide its utility as a tablet disintegrant. AMBERLITE IRP88 resin has been proposed for use in taste masking applications, specifically for B-lactam antibiotics.

Amberlite™ IRP69 (Sodium Polystyrene Sulfonate USP):

AMBERLITETM IRP69 is a insoluble, strongly acidic , sodium form cation exchange resin supplied as dry powder. Amberlite IRP69 is suitable for use for pharmaceutical; applications both as an active ingredients and as carrier for basic (cationic) drugs. It can be used for

sustained release application with compatible coating technique.

Amberlite[tm] IRP64 (Polacilex Resin)

AMBERLITE[TM] IRP64 is weakly acidic, insoluble , hydrogen form cation exchange resin supplied as fine dry powder. It is suitable to use in pharmaceutical applications,primarily as carrier for certain basic (cationic) drugs and related substances.It is also used to mask objectionable taste associated with certain basic drugs.

Duolite[tm] AP 143/1093

DUOLITETM AP 143/1093 is in soluble strongly basic, anionic exchange resin available in chloride form supplied as dry fine powder. It is use in pharmaceutical applications either as active ingredients or as carrier for acidic (anionic) drug substance.

Indion 414

INDION 414 is a high purity pharmaceutical grade weak acid cation exchange resin, supplied as a dry powder in potassium form. It is suitable for use in pharmaceutical applications such as tablet disintegration and taste masking of bitter drugs.

Indion 404 (Calcium Polystyrene Sulfonate)

INDION 404 (Calcium Polystyrene Sulfonate) is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in calcium form as a free flowing powder. Formulations containing INDION 404 are recommended for treatment of hyperkalamia associated with anuria and severe aliduria.It is also used to treat hyperkalamia in patients requiring dialysis on regular hoemodialysis or on prolonged peritoneal dialysis.

Indion 294 (Polacrilin Potassium)

INDION 294 is a high purity pharmaceutical grade strong acid cation exchange resin, supplied in potassium form as a free flowing powder. It is use in pharmaceutical applications such as taste masking and tablet disintegration.

Indion 284

INDION 284 is a high purity pharmaceutical grade strongly acidic cation exchange resin, supplied as moist beads. It is suitable for use in pharmaceutical applications for sustained release of drugs.

Indion 264

INDION 264 is a high purity pharmaceutical grade weak acid cation exchange resin, supplied in the hydrogen form as free flowing powder.It is suitable for pharmaceutical application for stabilization of drugs like vitamin B12.

Indion 214

INDION 214 is a high purity pharmaceutical grade weak acid cation exchange resin, supplied as a dry powder on Hydrogen form as a free flowing powder. It is specially designed for taste masking of bitter bulky drugs such as Azithromycin.It is suitable for use in pharmaceutical applications for sustained release of drugs.

Indion 204

INDION 204 is a high purity pharmaceutical grade weak acid cation exchange resin, supplied in hydrogen form as a free flowing powder. It is suitable for pharmaceutical applications such as taste masking of bitter drugs.

Indion 224

INDION 224 is a high purity pharmaceutical grade weak acid cation exchange resin, supplied as dry beads. It is suitable for pharmaceutical applications such as sustained release of drugs.

Indion 244

INDION 244 is a high purity pharmaceutical grade strongly acidic cation exchange resin, supplied as dry free flowing powder. It is suitable for pharmaceutical applications such as sustained release of drugs and taste masking.

Indion 254

INDION 254 is a high purity pharmaceutical grade strongly acidic cation exchange resin, supplied as dry free flowing powder. It is suitable for pharmaceutical applications such as sustained release of drugs and taste masking.

Indion 264

INDION 264 is a high purity pharmaceutical grade weak acidic cation exchange resin, supplied in hydrogen form as dry free flowing powder. It is suitable for pharmaceutical applications such as stabilization of vitamin B12.

Tulsion® 335 – (Polacrilex / Polacrilex S) :

Tulsion® 335 is a weally acidic Nicotine Polacrilex preparation. It is suitable for pharmaceutical applications such as cynocobalamin loading / stabilization of vitamin B12 and taste msking of Norfloxacin, Roxithromycin, and Ofloxacin Etc.

Tulsion® 339 – (Polacrilin Potassium USP)

Tulsion® 339 is a weally acidic Polacrilin Potassium USP preparation. It is a good Tablet Disintegrant & Taste masking agent for various drugs like Chloroquine phosphate, Quinine sulphate, Ciprofloxacin, Paracetamol and added to tablets in a 0.5 to 4% of total tablet weight. it shows faster rate of swelling & offers fast tablet disintegration and no lump formation after disintegration. High compatibility with excipients and common therapeutic agents make it more useful. It is insoluble in gums and does not have adhesive tendency.

Tulsion 339 does not stick to punches and dyes. It is non drug specific.

Tulsion® 344 – (Sodium Polystyrene Sulphonate USP)

Tulsion® 344 is a Strong Acid Sodium Polystyrene Sulphonate USP preparation. It is suitable for pharmaceutical applications such as Sustained release - E.g. – Dextromethorphan, Potassium reduction in blood and Taste masking e.g. - Dextromethorphan, Dicyclomine HCl

Tulsion® 345 – (Calcium Polystyrene Sulphonate BP)

It is suitable for pharmaceutical applications such as Potassium reduction in blood.

Tulsion® 412 (CHL) – (Cholestyramine resin USP)

It is suitable for pharmaceutical applications such as Cholesterol reduction in blood, Reduction of bile acid etc [19].

Kyron T

Kyron range is derived from cross linked polyacrylic polymer used in pharmaceutical industry for taste masking of bitter drugs and for drug stabilization. It is white to off white fine powder, swellable in water. Drugs like vitamin B12 degrade during storage, stabilization of such drugs can be done by Kyron polymers. Kyron T resins are available in traditional grades and ready to use grades**.**

✓ The foremost step in the preparation of drug resinates is to purify the resins carefully.

Purification is generally done by cycling repeatedly between the cations present in the ion exchange resins in case of a cation exchanger (or) between the anions present in the ion exchange resins in case of an anion.

After thoroughly washing with water and subsequent air drying, the resin is sieved to get a series of fractions. Drugs to be formulated into resinates should have in their chemical structure acidic or basic groups with its biological half life (t1/2) between the range of 2 to 6 hrs. It should be well absorbed from all the areas of the gastrointestinal tract and also it should be stable in the gastric juice.

Loading of drugs is done by two ways: (a) column process, and (b) batch process:

Batch process

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. Preparing resonates from the resins by batch process 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 60ºC. 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 resinates is spray drying process in which fluidized bed processor can be used. Simultaneous drying takes place to get dried resinates 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.

Column method

In a typical column procedure for preparing complex of an amine drug on a strong cation exchange resin, the resin is slurred in water. The slurry is added to the column and backwashed with water to eliminate air pocket and distribute the beads. Acid, typically 0.1N HCl is added to convert the acid form (H+ ion) followed by washing with water. Then a salt solution of drug is added, followed by rewashing with water. The cake is removed from column, filtered and oven dried [25].

FACTORS AFFECTING LOADING OF DRUG ONTO RESINS

Cross linkage of Resin - Cross linkage of Resins affects porosity and swelling properties of resins. Low cross linkage agents swell remarkably upon hydration. 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.

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.

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

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.

Size of exchanging ions- larger the size of exchanging ions, slower will be the diffusion rates and release [26].

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

Mixing Time – Drug loading increases rapidly in the initial 9 h and further increases between 20-30 h. probably because of surface absorptive phenomenon [26].

Drug delivery applications of IER

A) Oral drug delivery

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.65 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, psedoephedrin, etc.have been successfully carried out by using weak cation exchange resin.

Chewing gum for buccal absorption

Nicorette 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.

Sustained release formulations such as capsules, liquids, oral tablet, etc.

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 tablets.

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. BiphetamineR a capsule containing an equal quantity of amphetamine & dextroamphetamine complexed to a sulphonic acid cation exchange resin has been used for antiobesity agent and for behavioral control of children.

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.

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.

B) 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.

C) 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.

D) Ophthalmic drug delivery

IER also find application in opthalamic drug delivery systems. An example is Betoptic S which is a

sterile ophthalmic suspension and it contains 0.25% betaxolol hydrochloride. It is a cardioselective 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 [28]. Microparticulates of ion exchange resin drug complex have been used for ophthalmic drug delivery of Betaxolol, an antiglaucoma agent.

E) Drug stabilization

Complexing active ingredients with ion exchange resins prevents harmful interaction with other components e.g. Vitamin B12. 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 Vitamin. Thus the introduction of INDION 264 in the formulation significantly reduces the overages. Ion exchange resin can also be used as carrier for immobilized enzymes to provide extended activity at localized sites.

F) 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.

G) 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 [29].

Table 1. Examples of ion exchange resins as per classification [6]

Type	Exchange species	Polymer backbone	Commercial resins
Strongly acidic	$-SO_3H$	Polystyrene DVB	Amberlite IR 120, Dowex 50
Weakly acidic	-COOH	Methacrylic acid DVB	Amberlite IRC 50, Indion 234
Strongly basic	N^+R_3	Polystyrene DVB	Amberlite 400,Dowex 1
Weakly basic	N^+R_2	Polystyrene DVB	Amberlite 4B, Dowex 2

Table 2. Traditional Grades Kyron T [20]

Kyron	T-104	T-114	T-134	T-154	T-159	T-123
Pharmacopoeia	In house	In house	Polacrilin potassium USP	Sodium polystyrene Sulphonate USP	In house	In house
Type	Weak acid	Weak acid	Weak acid	Strong acid	Strong acid	Weak base
Functionality	$-COO^-$	$-COO^-$	$-COO^-$	$-SO^-_3$	$-SO^-_3$	Secondary amine
Ionic form	Hydrogen	Hydrogen	Potassium	Sodium	Hydrogen	Free base
Matrix	Polyacrylic copolymer	Polyacrylic copolymer	Polyacrylic copolymer	Polystyrene copolymer	Polystyrene copolymer	Polystyrene copolymer
Moisture content (%)	<10	<5	<10	<10	<10	<10
Appearance	White to off white free flowing powder	White to off white free flowing powder	White to off white free flowing powder	off White to golden yellow free flowing powder	off White to golden yellow free flowing powder	White to off white free flowing powder

Table 3. Ready to use Grades [20]

Kyron	T-111	T-112	T-112B	T-113
Pharmacopoeia	In house	In house	In House	In house
Drug to be masked	Ciprofloxacin	Azithromycin	Azithromycin	Ibuprofen
Dose	250mg / 5ml	100mg / 5ml	200mg / 5ml	100mg / 5ml

Table 4. Pharmaceutical Grade Resins

Pharmaceutical Grade Resins	Polymer backbone / Matrix Type	Pharmaceutical Applications
AMBERLITE® IRP88	Polacrilin Potassium Nf	Tablet disintegrant. , Taste masking of B-lactam antibiotics
AMBERLITE™ IRP69	Sodium Polystyrene Sulfonate USP	Active ingredients and as carrier for basic (cationic) drugs, sustained release application with compatible coating technique.
AMBERLITE™ IRP64	Polacilex Resin	Mask objectionable taste associated with certain basic drugs [21].
DUOLITE™ AP143/1083	Cholestyramine Resin USP	Active ingredients or as carrier for acidic (anionic) drug substance, Taste masking & Drug stabilization Controlled/sustained release formulations
DUOLITE™ AP 143/1093	Cholestyramine Resin USP & EP, Sodium Polystyrene Sulfonate USP, Polacrilin Potassium NF	Active ingredients or as carrier for acidic (anionic) drug substance, Taste masking & Drug stabilization Controlled/sustained release formulations [22].
INDION 204	Cross linked Polyacrylic	Taste masking of bitter drugs
INDION 214	Cross linked Polyacrylic	Sustained release of drugs
INDION 414	Cross linked Polyacrylic	Tablet disintegration and taste masking of bitter drugs
INDION 224	Styrene DVB	Sustained release of drugs
INDION 234	Cross linked Polyacrylic	Taste masking of bitter drugs such as ciprofloxacin, chloroquin phosphate etc. as well as tablet disintegration.
INDION 234 S	Cross linked Polyacrylic	Taste masking of bitter drugs and tablet disintegration.
INDION 244	Styrene DVB	Sustained release of drugs and taste masking
INDION 254	Styrene DVB	Sustained release of drugs and taste masking
INDION 264	Cross linked Polyacrylic	Stabilization of vitamin B12
INDION 284	Styrene DVB	Sustained release of drugs.
INDION 294	Polacrilin Potassium / Cross linked Polymethacrylic	Taste masking and tablet disintegration.
INDION 404	Styrene DVB	Treatment of hyperkalaemia.
INDION 454	Styrene DVB	Lowering serum cholesterol levels, Taste masking & Drug stabilization Controlled/sustained release formulations
INDION 464	Cross linked Polymethacrylic	Nicotine taste masking [23].
TULSION® 335	Polacrilex / Polacrilex S	Cynocobalamin loading / stabilization of vitamin B12 and taste masking of Norfloxacin, Roxithromycin, and Ofloxacin Etc [24]
TULSION® 339	Polacrilin Potassium USP	Tablet Disintegrant & Taste masking agent for Chloroquine phosphate, Quinine sulphate, Ciprofloxacin, Paracetamol and added to tablets in a 0.5 to 4% of total tablet weight
TULSION® 344	Sodium Polystyrene Sulphonate USP	Sustained release , Potassium reduction in blood and Taste masking of Dextromethorphan, Dicyclomine HCl ,Dextromethorphan
TULSION® 345	Calcium Polystyrene Sulphonate BP	Potassium reduction in blood
TULSION® 412 (CHL)	Cholestyramine resin USP	Cholesterol reduction in blood, Reduction of bile acid etc.

Table 5. Factors affecting loading of drug into and release from the ion-exchange material [21]

Factor	Mechanism of Effect
1. Ion-exchanger dependent	
Ion-exchange capacity	Donnan potential, number of ionic binding sites.
Nature of fixed ionic groups	Ionisation, selectivity
Preloaded counter-ion	pH, selectivity
Particle size	Surface area, particle diffusion
Degree of cross linking	Pore size of ion exchanger, particle diffusion
2. Drug dependent	
Lipophilicity	Binding affinity
pka	Ionisation
Stearical properties	Binding accessibility
Molecular size	Diffusion coefficient, binding affinity, binding accessibility
3. External conditions	
Concentration of solution	Donnan potential
pH	Ionisation of drug and ion-exchanger
Temperature	Porosity of ion-exchanger, diffusion
Agitation	Film diffusion

Figure1. Ion Exchange Resins

Figure 2. Chemical Structure Of Cation Exchange Resin[7].

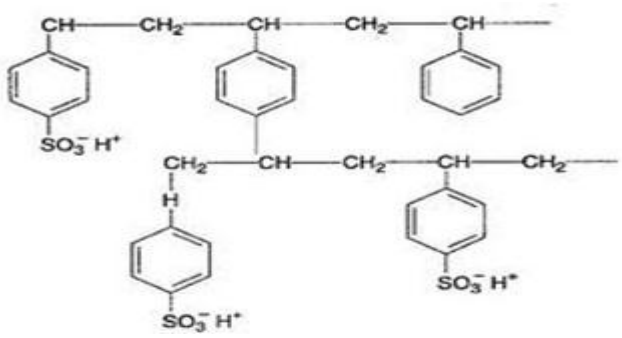


Figure 3. Chemical structure of cation exchanger. The exchangeable ions are marked $^{+}$. The whole structure is permeated by solvent molecules, usually water[8] (not shown).Cation exchange resins can be further classified into:

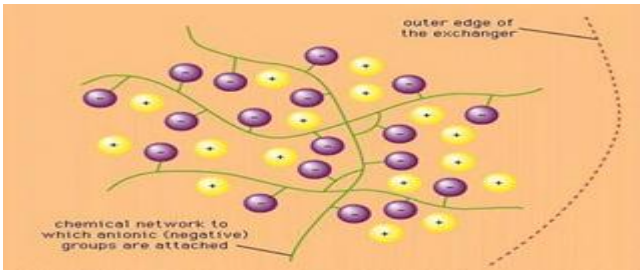


Figure 4. Chemical Structure Of Anion Exchange Resin [9]Anion exchange resins can be further classified into:

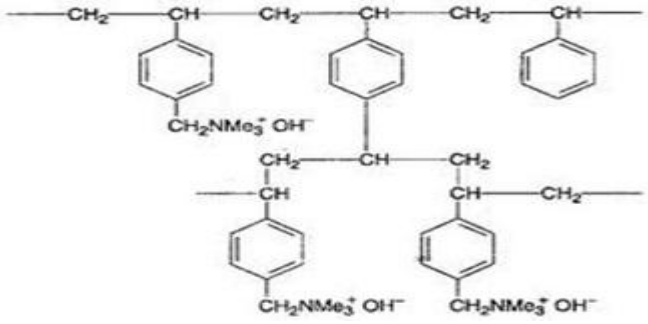


Figure 5. Ion Exchange Chemistry
$R\text{-}NH_2 + HCl \rightarrow R\text{-}NH_3Cl$

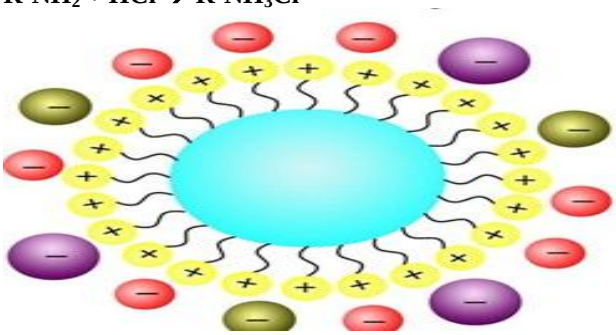


Figure 6. Ion Exchange Process [13]

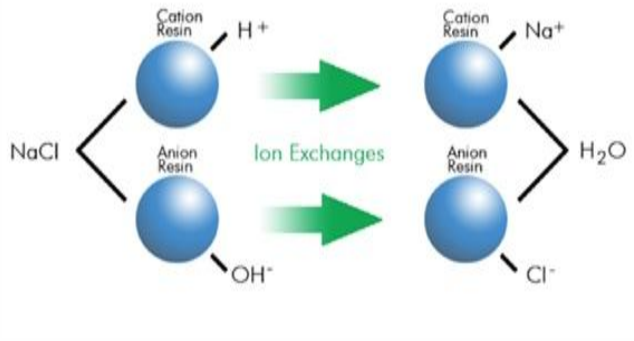


Figure 7. Ion Exchange process

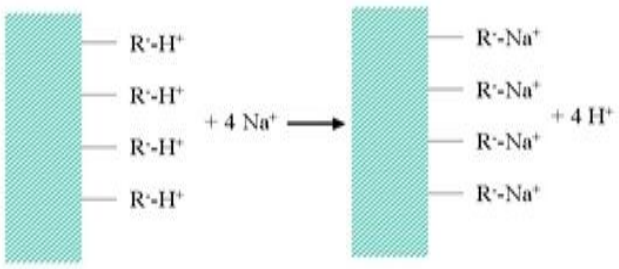
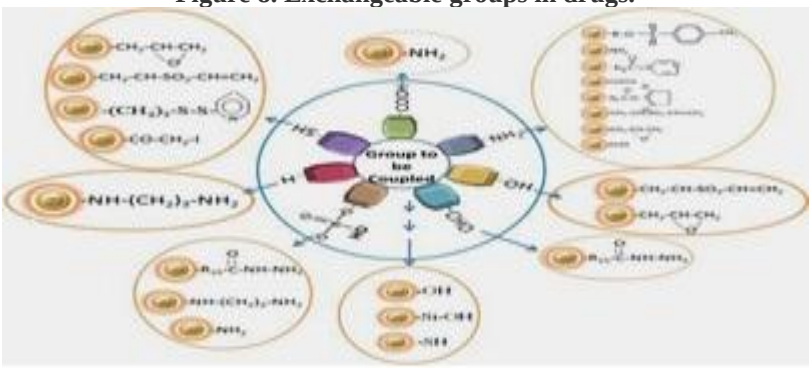
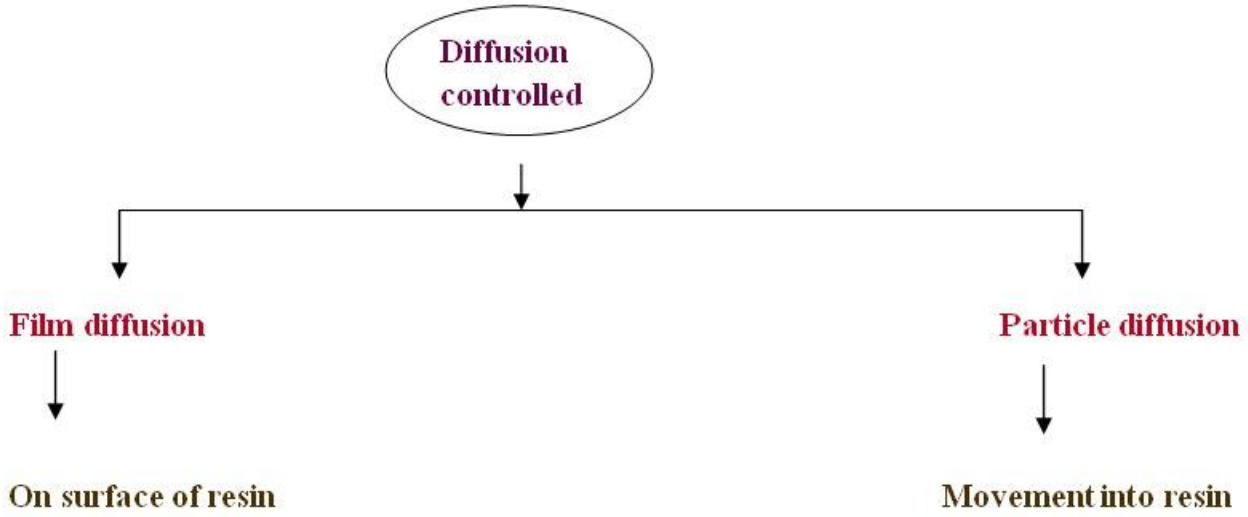


Figure 8. Exchangeable groups in drugs.



KINETICS OF ION EXCHANGE PROCESS[16]



CONCLUSION

Ion exchange resins having its own importance in novel drug delivery system due to its complexation property with drugs without any interaction with drug and drug can be release at desired site of action. Because of its complexation property it used as disintegrator, dissolution enhancer, taste masking agent, in novel drug delivery system, to improve stability, and for handling of deliquescent and hygroscopic substances.

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