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Role of ion exchange resins in Pharmaceuticals

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ABSTRACT:

Ion exchange consists of the interchange of ions between two phases. The ion exchange resins (IER), a cross-linked polymer network, is the insoluble phase to which an ion is electrostatically bound. The efficacy of ion exchange resins mainly depends upon their physical properties such as degree of cross-linking, porosity, acid-base strength; stability, purity, and particle size. IER is equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking. The use of IER is 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 also been used in pharmacy and medicine for taste masking or controlled release of drugs. Drug resin complexation converts the drug to an amorphous form leading to an improved drug dissolution process.

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INTRODUCTION:

An ion-exchange resin comprises one of the most important scientific developments of the 20th century. An ion exchange resin is a resin or polymer that acts as a medium for ion exchange [1]. It is an insoluble matrix normally in the form of small microbeads, usually white or yellowish, fabricated from an organic polymer substrate. The ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. Ion exchange resins are simply insoluble polyelectrolytes that are insoluble polymers that contain ionizable groups distributed regularly along the polymer backbone [2].

The most common resins used in formulations are cross-linked polystyrene and polymethacrylate polymers. The main objective of this study is to water softening, environmental remediation, wastewater treatment,

hydrometallurgy, Chromatography, biomolecular separations, and catalysis are very essential [3]. Ion-exchange resins are useful because of the insolubility of the resin phase. After contact with the ion-containing solution, the resin can be separated by the filtration method. They have also been used as catalysts, both in place of homogeneous catalysts such as sulfuric acid and to immobilize metallic catalysts [4-5].

The objective of this review is to summarize the various pharmaceutical roles of ion exchange resin.

Table 1. Examples of ion exchange resin.

Component Name	Commercial Name	Daily Intake
Polacrilex resin	Amberlite IRP64	Estimated daily intake: 270 mg
Polacrilin potassium	Amberlite IRP88	Estimated daily intake: 270 mg
Sodium polystyrene Sulfonate	Amberlite IRP69	Maximum daily intake: 60 g
Cholestyramine resin	Duolite AP143	Maximum recommended dose for cholesterol reduction: 24 g in divided doses

PREPARATION OF ION EXCHANGE RESINS:

Most the IERs are made by the process of suspension polymerization. In some cases, the monomers are neutral (e.g., styrene, methyl acrylate, and acrylonitrile, as given in Table 1) 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 take and individual intestinal content [6]. A typical cation-exchange resin is prepared by the copolymerization of styrene and Divinylbenzene. During the polymerization, polystyrene formed as a linear chain, and these become covalently bonded to each other by Divinylbenzene cross-links. If sulphuric acid is then allowed to react with this copolymer, sulphonic acid groups are introduced into most of the benzene rings of the styrene-divinylbenzene polymer, and the final substance formed is known as cation-exchange resin. A typical anion exchange resin is prepared by the first chloromethylation of the benzene rings of the three-dimensional styrene-divinylbenzene copolymers to attach $–CH_2Cl$ groups and then causing these to react with a tertiary amine, such as trimethylamine. This gives the chloride salt of strong-base exchanges [7-8].

PROCESSING OF ION EXCHANGE RESINS:

Ion exchange is a reversible process in which ions of like sign are exchanged between liquid and solid when in contact with a highly insoluble body. The drug is released from resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion. Due to the presence of high molecular weight water-insoluble polymers, the resins are not absorbed by the body and are therefore inert. IER has specific properties like available capacity, acid-base strength, particle size, porosity, and swelling, on which the release characteristics of drug resonates are dependent. Examples of IER were given in table1. Drug resinates are generally prepared with purified resins and appropriate drugs [9-10].

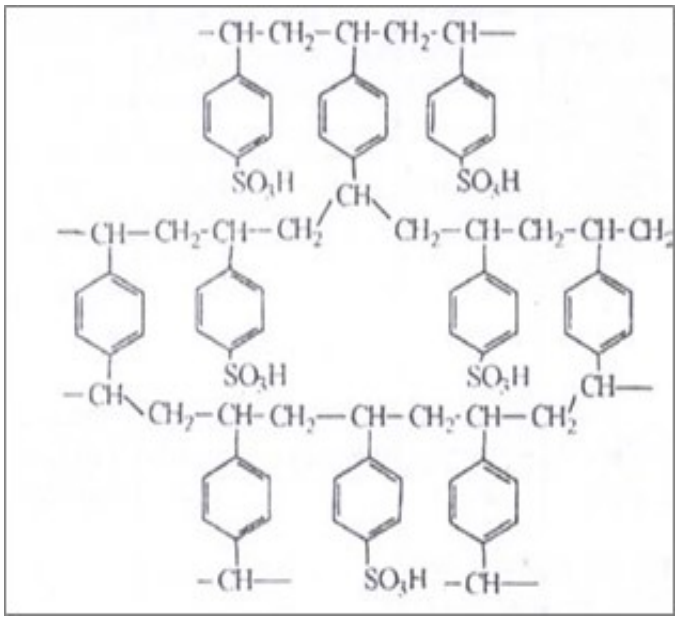

Fig 1. Chemical structure of a Cation exchange resin.

IMPORTANT PROPERTIES OF ION EXCHANGE RESINS [11-13]:

Particle size:

Decreasing the size of resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium. The rate of ion-exchange reactions depends on the size of the resin particles.

Porosity:
Porosity is defined as the ratio of the volume of the material to its mass. The size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity of the ion-exchangers depends upon polymerization procedures.

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 divinylbenzene crosslinking present in the resin.

Cross linkage:
Resins with low cross-linking can take a considerable amount of water and swell into a structure that is soft and gelatinous. The percentage of cross-linking affects the purely physical structure of the resin particles. The degree of cross-linkage is controlled by the percent of Divinylbenzene (DVB) used in the copolymerization.

Table 2. Chemical constituents for IER.

Sl. No.	Resin type	Chemical constitution	Usual form
1	Strongly acidic cation exchanger	Sulfonic acid groups attached to a system and divinylbenzene copolymer	R-SO3-H+
2	Strongly acidic cation exchanger	Carboxylic acid groups attached to an acrylic and divinylbenzene copolymers	R-COO-Na+
3	Strongly acidic cation exchanger	Quaternary ammonium groups attached to a styrene and divinylbenzene copolymer	[φ-CH2N-(CH3)3+]Cl-
4	Strongly acidic cation exchanger	Polyalkylamine groups attached to a styrene and divinyl benzene copolymer	[φ-NH-(R)]Cl-

Acid-base strength:
The acid or base strength of exchange is dependent on the various ionogenic groups, incorporated into the resin. The PKa value of the resin will have a significant influence on the rate at which the drug will be released from resinate in the gastric fluids.

Stability:
The resinous ion exchangers are remarkably inert substances. At ordinary temperature and excluding the more potent oxidizing agents, vinyl benzene cross-linked resins are resistant to decomposition through the chemical attack.

Purity and toxicity:
Since drug resin combinations contain 60 % or more of the resin, it is necessary to establish the toxicity of the ion-exchange resins. Commercial products cannot be used as such because they contain impurities that cause severe toxicity. Therefore, careful purification of the resin prior to treatment with the drug is required.

ADVANTAGES OF ION EXCHANGE RESIN [14]:
- IERs have temporary or permanent applications.
- Immediate results
- Standard tank sizes are available for small to intermediate flows, which allows for quick installation
- Minimal maintenance with standard tank size systems
- Waste disposal able be handled by the supplier
- Capable of meeting low-level discharge permit requirements
- Eliminate over or under dosing
- Maintain drug levels in the desired range
- Increased patient compliance
- Need for less dosing
- Free from local and systemic toxicities.
- Drug resinates can be formulated into various dosage forms like tablets, capsules, suspensions, etc.
- Can be used for several purposes such as taste masking, sustained and rapid release
- Effectively useful in low concentration (5-20%w/w).
- Resins have high drug loading and probability of dose dumping.

DISADVANTAGES [15]:
- Generally, not effective for low pH.
- Suspended solids need to be removed prior to treatment.
- Ongoing operational cost.
- Resin fouling.
- Resin regeneration.

- Generally, not effective for complex mixtures of metals.
- Generally, not effective for high concentrations of Fe, Mn, Al.
- Increase potential for first-pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability.

CLASSIFICATION OF ION-EXCHANGE RESINS:

Ion exchange resins are classified as cation exchangers, which have positively charged mobile ions available for exchange, and anion exchangers, whose exchangeable ions are negatively charged. Both anion and cation resins are produced from the same basic organic polymers. They differ in the ionizable group attached to the hydrocarbon network.

It is the functional group that determines the chemical behaviour of the resin. Resins can be broadly classified as strong or weak acid cation exchangers or strong or weak base anion exchangers. In an ion-exchange process, cation or anions in a liquid solution replace dissimilar and displaceable ions of the same charge contained in the ion exchange resin [16-19].

Cation exchange resins:

Cation exchange resins contain covalently bound negatively charged functional groups and exchange positively charged ions. They are prepared by the copolymerization of styrene and divinylbenzene and have Sulfonic acid groups (-SO_3H) introduced into most of the benzene rings as shown in fog.1. The mechanism of the cation exchange process can be represented by the following reaction.

$R^-ex^+ + C^+ \rightarrow R^{--}C^+ + ex^+$ ……(1)

Where, R is a resin polymer with SO3-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 strong acid cation exchange resins and weak acid cation exchange resins.

Strong acid cation exchange resins:

The chemical behaviour of these resins 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.

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

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.

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 wastewater.

Anion exchange resins:

Anion exchange resins have positively charged functional groups and their exchange negatively charged ions. These are prepared by first chloromethylating the benzene rings of the styrene-Divinylbenzene copolymer to attach CH_2Cl groups and then causing these to react with tertiary amines such as triethylamine. The chemical structure of an anion exchange resin is shown in Fig 2. While the mechanism of the anion exchange process can be represented by the following reaction.

$R^+\text{-}ex^- + A^- \rightarrow R^+\text{-}A^- + ex^-$ ….(3)

Where, R^+ indicates a resin polymer with a number of sites available for bonding with exchangeable anion (ex), and A^-indicates cation in the surrounding solution getting exchanged.

Strong base anion exchange 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.

$R\text{-}NH_3oh + HCl \rightarrow R\text{-}NH_3Cl + H_2O$ ….(4)

Regeneration with concentrated sodium hydroxide (NaOH) converts the exhausted resin to the OH form.

Weak base anion exchange resin:

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

$R\text{-}NH_2 + HCl \rightarrow R\text{-}NH_3Cl$ ….(5)

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.

Applications of Ion exchange resin [19-21]:

Laboratory and field tests have proved the practicability of the use of resinous exchangers in the softening of water, the partial or complete removal of salts from water, sugar solutions, and protein solutions, in the recovery of traces of copper and other valuable metals, in the removal of iron and acids from industrial effluents and commercial products.

Water softening:

Ion exchange resins are used to replace the magnesium and calcium ions found in hard water with sodium ions. When the resin is fresh, it contains sodium ions at its active site. When in contact with a solution containing calcium and magnesium ions, the magnesium and calcium ions preferentially migrate out of the solution to the active sites on the resin, being replaced in solution by sodium ions. The resin can be recharged by washing it with a solution of high concentration of Na ions.

Water purification:

Ion exchange resins are used to remove poisons and heavy metal ions from the solution, replacing them with more innocuous ions, such as sodium and potassium. Few ion exchange resins remove chlorine or organic contaminants from water. This is usually done by using an activated charcoal filter mixed with the resin. Magnetic ion exchange resins can remove organic ions. Domestic water purification resin is not usually recharged.

Production of high purity water:

The water of high purity is required for many pharmaceutical purposes. Such water is produced by using ion-exchange processes or a combination of membrane and ion exchange methods. Cations are replaced with hydrogen ions using cation exchange resins and anions are replaced with hydroxyl ions using anion exchange resins. Then the hydrogen and hydroxyl ions are combined to produce water molecules. The purification process is then performed in several steps with mixed bed ion exchange columns.

Metal separation process:

Ion exchange processes are used to separate and purify metals including, separating uranium from plutonium and other actinides by the PUREX process (plutonium-uranium extraction process).

Taste masking:

Ion exchange resins are used in the manufacturing of pharmaceutical formulations as well as fruit juice such as orange juice, where they are used to remove bitter-tasting components and so improve the flavour.

Recovery of natural products:

The potential of ion-exchange resins for the recovery of natural products was illustrated by the separation of thiamine from riboflavin. The application of this method may proceed in two directions - as an analytical tool or in the recovery of thiamine from waste solutions.

Catalysis by Anion-Exchange Resins:

Appropriate anions ionically bound to strong base anion-exchange resins were applied as catalysts in organic reactions under conditions where exchange could not occur. The resin in the hydroxide form was thus able to catalyze the formation of nitro alcohols from aldehydes and nitromethane.

Improving stability:

The drug resinate is frequently more stable than the original drug. For instance, vitamin B_{12} has a shelf-life of only a few months while its resin has more than two years.

Role of IER in Controlled Drug Delivery Systems:

The use of IER in drug delivery systems has been encouraged because of their physicochemical stability, inert nature, uniform size, spherical shape assisting coating, and equilibrium-driven reproducible drug release in an ionic environment. The physical and chemical properties of the IER will release the drug more uniformly than that simple matrix formulation. Drug molecules attached to the resins are released by appropriately charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins. IER has been used as drug carriers in pharmaceutical dosage forms for controlled release formulation.

CONCLUSION:

In recent years, IER has been successfully used for masking the taste of bitter drugs. IER plays an important role in the modification of drug release by forming a complex with the drug substances. IERs have been used in pharmacy and medicine for various functions which include tablet disintegration. This article has attempted

to review the literature and its manufacturing, properties, method of preparation as well as its different applications with the hope that researchers will utilize the resins more effectively in formulating drug delivery systems. Ion exchange resins find a variety of applications in the pharmaceutical field including purity testing, stability testing, taste-masking application, recovery of naturally occurring materials, separation methods like chromatography, and various drug delivery systems such as nasal, ophthalmic; controlled release, and sustained release dosage forms.

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