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# Ion Exchange Resins Drug Delivery System: A Review

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**ABSTRACT**

Ion exchange resins are water-insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain. Ion exchange resins are a crosslinked water-insoluble polymer that contains ionizable acidic or basic functional groups and can exchange counter ions from surrounding within an aqueous solution. Research has shown that for the past few years, IER is equally suitable for drug delivery techniques, including controlled release, topical, transdermal, nasal, and taste masking. The efficacy ion-exchanged resins mainly depend upon their physical properties such as porosity, acid base strength, the degree of cross-linking, stability, purity and particle size. Ion exchange resonates with drugs that can help in reducing the dose, fluctuation in blood and tissue concentration. The ion exchange resins are complexed with a drug to form resonates by batch or column process. Microencapsulated resinates provide better control over the drug release because of the rate-controlling membrane. This review will cover various types of ion exchange resin, their property, chemistry; the role of ion exchange resin drug delivery system, its industrial, pharmaceutical and clinical applications, method preparation.

## INTRODUCTION

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes which can exchange mobile ions of similar charges with the surrounding medium reversibly and stoichiometrically. They are available in desired size ranges. Ion exchange resins have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery. Research over the last few years has revealed that ion exchange resins are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking Controlled drug delivery system are gaining moment in the recent two decades as these results in reduced frequency of dosing and patient compliance. Intensity and duration of action have been the subject of increasing multidisciplinary research. Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and can exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is an insoluble matrix normally in the form of small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate backbone. The material has a highly developed structure of pores on the surface from where the ions are trapped or released. The trapping of ions takes place only with the simultaneous release of other ions; thus, the process is called ion exchange. Ion-exchange systems are advantageous for drugs that are highly susceptible to degradation by an enzymatic process. A major advantage of the ion exchange system is the 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 the drug can be affected by variability in diet, water intake, and individual intestinal content.

**Classification of Ion Exchange Resin**

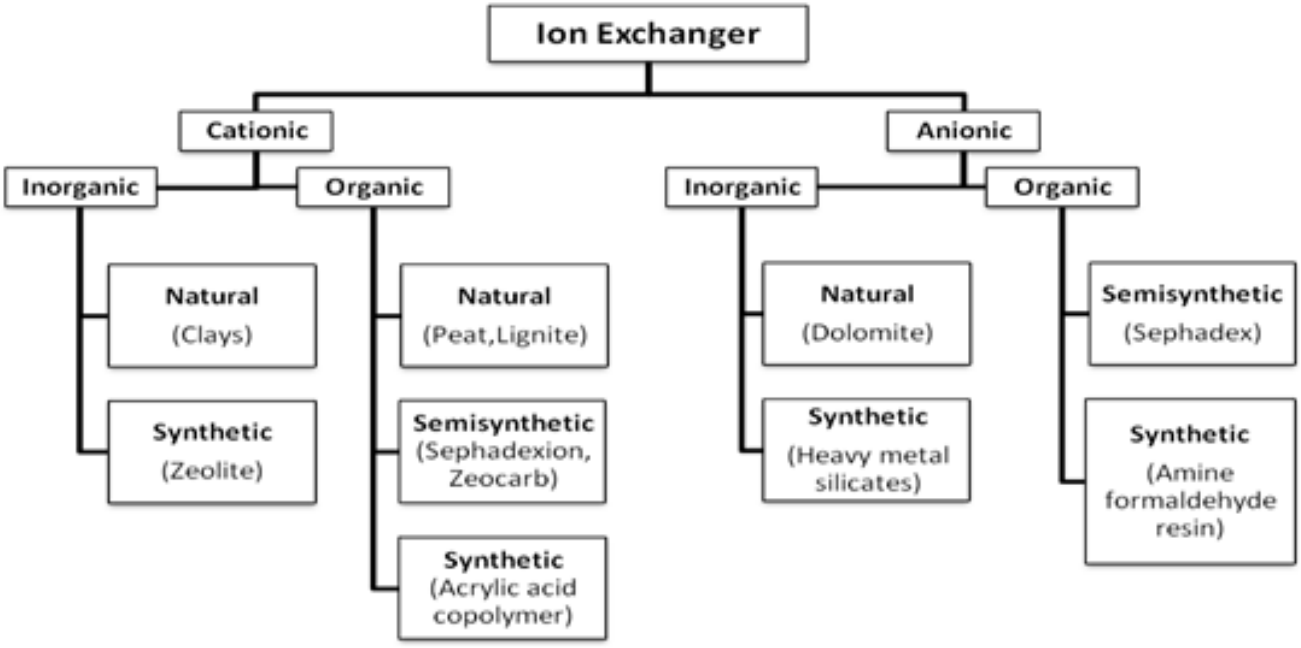


**Figure No. 1: Classification of ion exchange resin**

**Chemistry of Ion Exchange Resin**

IER are simply insoluble polyelectrolytes that are insoluble polymers which contain ionizable groups distributed regularly along the polymer backbone. The most common resins used in formulations are cross-linked polystyrene and polymethacrylate polymers. When IER are mixed with a fluid such as water, ions in the fluid can exchange with the polyelectrolyte's counterions and be physically removed from the fluid.

An ion exchange resin is a polymer with electrically charged sites at which one ion may replace another. Numerous functional groups have charge, only a few are commonly used for man-made IER. These are:

- COOH, which is weakly ionized to $-COO^{-}$
- SO3H, which is strongly ionized to $-SO3^{-}$
- NH2, which weakly attracts protons to form NH3+
- secondary and tertiary amines that also attract protons weakly

- NR3+, which has a strong, permanent charge.

**Selection of suitable IER:**

The selection of IER mainly based on the following factors:

1. Ion exchanging Capacity of the IER i.e. the concentration of the exchangeable group in the resin, usually expressed in meq /g of dry resin.

2. Degree of cross-linking in the resin matrix.

3. The particle size of the resin

4. Nature of drug and site of drug delivery.

5. Swelling ratio

6. Biocompatibility and biodegradability

7. The regulatory status of the IER

**Properties of ion exchange resins**

**Particle size:** The rate of ion exchange reaction depends on the size of the resin particles. Decreasing the size of the resin particle significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium. Porosity and swelling: The porosity of an ion-exchanger depends not only on the amount of cross-linking substances used in polymerization but mainly on polymerization procedures. The structural parameters considerably influence the swelling behavior of the resin and consequently have a marked effect on the release characteristics of drug-resinates. 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 cross-linking present in the resin.

**Cross-linkage**: The percentage of cross-linking affects the physical structure of the resin particles. Resins with a low degree of cross-linking can take up a considerable amount of water and swell into a structure that is soft and gelatinous. However, resins with a high vinyl benzene content swell very little, the particles take up only a small amount of water and consequently are somewhat and brittle.

**Available capacity:** The capacity of an ion exchanger is a quantitative measure of its ability to take-up exchangeable counter-ions and is therefore of major importance. However, in the preparation of drug resonates, the actual capacity obtained under specific experimental conditions depends on the accessibility of the functional group for the drug of interest.

**Acid-base strength**: The acid-base strength of exchange is dependent on various oncogenic groups, incorporated into the resin. The resin containing sulfonic, 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 apparent pKa values of greater than 13, 7-9, or 5-9, respectively. The pKa value of the resin will have a significant influence on the rate at which the drug will be released from resonates in the gastric fluid.

**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 a chemical attack, but degeneration in the presence of storage gamma-ray sources.

**Purity and Toxicity:** The drug resinates combinations contain 60% or more of the resins. Commercial products cannot be used as such because they contain impurities that cause toxicity. Therefore careful purification of the resin before treatment with the drug is required. The use of ion-exchange resins 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. Sustained or controlled release formulations use of ion exchange resins for oral sustained-release oral formulations occupies an important place. Microencapsulated of resinates provides better control over the drug release because of the presence of a rate controlling membrane. The absorption of the drug from coated resinates is a consequence of the counterions into the coated resinates, the release of drug ions from the drug-resin complex by the ion exchange process, and diffusion of drug ions through the membrane into the surrounding absorption environment. Drug release of the drug-resin complex and its microcapsules.

**It is controlled by three possible mechanisms**

**1. Mass or chemical reaction control:** The exchange reaction between the counter ion and drug.

**2. Particle diffusion control:** The release of drug through the porous within its particles.

**3. Membrane diffusion control**: The release of the drug across the thin layer around the particle. Pennkinetic systems further modification of the coating of resinates for improved monitoring of the drug release pattern. In this system, resinates are pre-treated with polyethylene glycol to maintain the geometry and improve the coating process and also helps in controlling the rate of swelling of the resinate matrix in water.

**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. Cholestyramine and cholesterol are used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults.

**Taste masking:** Bitter cationic drugs can get adsorbed onto the weak cation exchange resins of carboxylic acid functionally to form the non bitter complex. Further resinates can be formulated as dispersible tablets and mask the taste. Avari et al. reported taste masking of highly bitter antibiotic, sparfloxacin with indion 204weak cationic exchanger.

**Improvement of tablet disintegration properties**: Many tablets disintegrate owe their action to capacity to absorb water and swell up. Fine particle size ion-exchange resins have shown superiority as disintegration agents due to their considerable swelling pressures upon hydration.

**Improving the dissolution of poorly soluble drugs and eliminating polymorphism**: Drug resin complexation converts drug to amorphous form. Hence, a drug with poor solubility, during the process of desorption, immediately releases the drug leading to improved drug dissolution.

**Improving stability**: Complexing active ingredients with ion-exchange resins prevents harmful interaction with other components like vitamin B12 and carboxylic acid These complexes as effective as free drugs. Ion exchange resins can also be used as a carrier for immobilized enzymes to provide extended activity at localized sites.

**High purity of water:** There will always be a need for purified water in the production of pharmaceuticals. Water softening uses a cation exchange resin to exchange principally calcium and magnesium ions for sodium ions and so prevent the formation of calcium carbonate precipitates on reverse osmosis membranes.

**Applications of IER**

**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 the pharmaceutical industry, especially for pediatric 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, by adsorption into Carbopol and then encapsulating the resulting particles with hydroxypropyl methylcellulose phthalate.

**Eliminating polymorphism**

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 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 resinates 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 frequently requires specialized equipment and often there can be an agglomeration of the fine particles after grinding. The grinding can also result in melting and conversion to other crystal forms. These problems are eliminated by using the ion exchange resin approach.

**Improving stability**

The drug resin 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 the solid form some are liquids or difficult-to-handle solids. Because the physical properties of the resinates are similar to the resin, not the drug, the resinates 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, macro reticular morphology that provides excellent flowability to the formulation.

**Drug delivery applications**

**Oral drug delivery**

The major drawback of sustained-release or extended-release is dose dumping hence resulting in an increased risk of toxicity. The use of IER has occupied an important place in the development of controlled or sustained-release systems due to 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. The use of ion-exchange resins into 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 the 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 AmberliteIR120. 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.

**Transdermal drug delivery**

IER is 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. Also, ions could increase the rate and extent of ketoprofen delivery.

**Ophthalmic drug delivery**

IER also find application in ophthalmic 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 resin 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.

**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 therapeutically 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 an application in the control of cholesterol and potassium ion levels.

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