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ION EXCHANGE RESINS AS CONTROLLED DRUG DELIVERY CARRIERS-A REVIEW

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ABSTRACT

Ion exchange resins (IER) are acidic or basic functional groups containing insoluble polymers which have the ability to exchange counter-ions within the surrounding aqueous solutions. Based on the nature of the exchangeable ion of the resin as cation or anion, they are classified as cationic or anionic exchange resins. Ion exchange resins have considerable properties as the drug delivery vehicles which gained the attention from the pharmaceutical scientists. Physical properties such as degree of exchange capacity, cross-linkage, ionization, porosity and swelling, particle size and form, purity, toxicity and equilibrium rate influences the affinity of ion exchange resin. Ion exchange resins are widely used for various drug delivery and therapeutic applications. It is proven that Ion exchange resin are well suitable for drug delivery technologies such as the controlled drug release including various systems such as transdermal, nasal, topical, oral and taste masking. The drawback of sustained release or extended release such as dose dumping, toxicity can be avoided by the use of ion exchange resins have effective drug-retaining properties and the prevention of dose dumping and thus they have an important place in the development of the controlled or sustained release systems. The rate of drug dissolution is improved by converting drug to amorphous from by drug resin complexation. Drug delivery at the desired site of action made possible by the use of IER. This review deals with various types of ion exchange resin, their properties, chemistry & role of IER in controlled drug delivery systems along with therapeutic applications.

Keywords: Anion exchange; Cation exchange; Resin; Controlled release; Resinates; Drug delivery

INTRODUCTION

Patient compliance have been improved by controlled drug delivery systems in the recent two decades because of reduced frequency of dosing. Ion exchange resins (IER) are used as carriers for modified drug delivery systems. Ion exchange resins (IER) are fabricated from the organic polymer having an ionizable functional group **[1]** which are having cross-linked, synthetic, high molecular weight, water insoluble polymers, that appears white or yellowish in color. Ion exchange resins are formed by complexation between IER and drugs which have been used in pharmaceutical formulations for several decades. IER are insoluble polymers have the ability to exchange counter-ions within surrounding aqueous solutions with acidic or basic functional groups present in it. An ion exchange resin appears white or yellowish small bead whose diameter ranges in between 1-2 mm. Ion exchange is a process of exchange of ions between liquid and solid when in contact with a highly insoluble body. The release characteristics of drug resonates are dependent on IER which possess specific properties like available capacity, acid base strength, particle size, porosity and swelling. Purified resins and appropriate drugs **[2-4]** have been employed in the preparation of drug resonates.

ADVANTAGES

- Do not cause any local and systemic toxicities.
- Various dosage forms like tablets, capsules, suspensions etc. Can be prepared by using drug-resinates.
- Improved patient compliance with less frequency of dosing **[5]**.
- Economic and readily available.
- They have wide applications such as taste masking, sustained and rapid release.
- Resins are having high drug loading capacity and they are effective even in low concentration (5-20% w/w).
- Over or under dosing can be avoided with the maintenance of desired Drug level range.

CLINICAL ADVANTAGES

- Reduced in local and systemic drug toxicity.
- Reduced drug level fluctuation in blood with the reduction in drug accumulation by chronic therapy.
- Stability of medical condition is achieved with the maintenance of uniform drug levels.

DISADVANTAGES:

- Reduced potential for dose adjustment.
- Patient education is necessary for proper medication in time.

- Decreased systemic availability and poor IVIVC conditions **[6]**.
- Costlier than conventional dosage forms.
- They have potential for first pass metabolism.

STRUCTURE AND CHEMISTRY OF ION EXCHANGE RESIN

IER are insoluble poly electrolytes that contain ionizable groups distributed regularly along the polymer backbone. Cross-linked polystyrene and polymethacrylate polymers **[7]** are widely used resins in formulations of various dosage forms. When IER are mixed with a fluids such as water, there is an exchange of ions in polyelectrolyte's counter ions and ions of fluid which are then physically removed from the fluid. An ion exchange resin is a polymer (normally styrene) containing electrically charged sites for replacing one ion with another. Following are the some of commonly used man-made IER.

- -COOH, which is weakly ionized to $-COO^{-}$,
- $-SO_3H$, which is strongly ionized to $–SO_3^{-}$,
- $-NH_2$, which weakly attracts protons to form NH^{+}_3,
- $-NR_3^{+}$, which has a strong, permanent charge (R stands for some organic group).

Types of Ion-Exchange Resin

Ion exchange are mainly classified into 2 types **(Figure 1)**. They are as follows:

a) Cation exchange resin

b) Anion exchange resins.

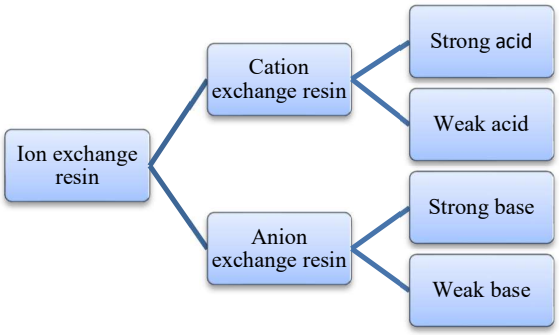

Figure 1: Classification of IER

CATION EXCHANGE RESINS

In cation exchange resins positively charged ions are exchanged by covalently attached negatively charged functional groups. Styrene and divinyl benzene undergo copolymerization that leads to the formation of cation exchange resins and the most of the benzene rings have sulfonic acid groups ($-SO_3H$) added to them. The mechanism of cation exchange process is represented by the following reaction in Eq. (1)

R- - ex+ + C+ →R- - C+ +ex+ (1)

where,

R is a resin polymer with SO^{3-} sites available for bonding with exchangeable cation (ex+)

C^+ indicates a cation in the surrounding solution getting exchanged.

Cationic exchange resin is created by co-polymerization of styrene and divinylbenze. Polystyrene was created during the polymerization process as linear chains that were then covalently joined to one another by divinylbenze cross links. This copolymer when react with sulphuric acid, most of the benzene rings in the styrene-divinylbenze polymer receive sulphonic acid groups, and results in the formation of compound is referred to as cation-exchange resin.

Cation exchange resins can be further classified into 2 types based on their affinity

- Strong acid cation exchange resins
- Weak acid cation exchange resins.

STRONG ACID CATION EXCHANGE RESINS

These are called as strong acid cation as they behave chemically in a way that is similar to a strong acid. Sulfonic acid group contains both the salt (RSO_3Na) and the acid ($R-SO_3H$) forms that are strongly ionized ($-SO_3H$). They can convert a metal salt to the corresponding acid which is represented by the reaction in Eq. (2):

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

Strong acid resins consist of highly dissociating forms hydrogen and sodium and the exchangeable Na+ and H+ are readily available for exchange over the entire pH range. The exchange capacity of strong acid resins do not depend on the solution pH.

WEAK ACID CATION EXCHANGE RESINS

These resins respond similarly to poorly dissociate organic acids. As opposed to the sulfonic acid group (SO_3H) utilized in strong acid resins, the ionizable group in a weak acid resin is a carboxylic acid (COOH). The pH of the solution has a significant impact on how well a weak acid resin dissociates. As a result, the solution pH has an impact on resin capacity. A typical weak acid resin is inadequate for de ionizing acidic metal finishing effluent because it has a restricted capacity below a pH of 6.0.

ANION EXCHANGE RESINS

Anion exchange resins include positively charged functional groups whose function is to exchange negatively charged ions **[8]**. Exchange of anions is initiated by the three-dimensional styrene-divinylbenzene copolymers to attach CH_2Cl groups to their benzene rings, and these groups are then brought into contact with a tertiary amine, such as triethylamine, to produce a conventional anion exchange resin. This

results in the strong-base exchanges chloride salt.

Anion exchange process is represented by the following mechanism in Eq. (3)

$$R+ - ex - + A- \rightarrow R+ - A- + ex- \quad (3)$$

where,

R+ is a resin polymer which indicates the number of sites available for bonding with exchangeable anion (ex-),

A- Indicates cations in the surrounding solution getting exchanged.

Anion exchange resins are mainly categorized into two types based on their affinity. They are as follows:

- Strong base anion exchange resins
- Weak base anion exchange resins

STRONG BASE ANION EXCHANGE RESINS

Strong base resins are highly ionized and can be used at a wide pH range. These resins are utilized in the hydroxide (OH) state for the deionization of water. They mainly act by reacting with anions in solution and can convert an acid solutionto pure water Eq. (4)

$$R\text{-}NH_3OH + HCl \rightarrow R\text{-}NH_3Cl + H_2O \quad (4)$$

Exhausted resin is converted into OH form by Regeneration with concentrated sodium hydroxide (NaOH)

WEAK BASE ANION EXCHANGE RESIN

Weak base resins are similar to weak acid resins which are having significant impact of pH on the level of ionization. Weak base resins are not capable for exchange above a pH range of 7.0 The weak base resin does not have an OH ion form as does the strong base resin Eq. (5)

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

As a result, regeneration just needs to neutralise the absorbed acid; OH ions are not required. It is possible to use sodium carbonate or ammonia (NH_3), two less expensive weakly basic reagents.

ROLE OF IER IN CONTROLLED DRUG DELIVERY SYSTEMS

IER have been employed for use in drug delivery systems. Because they posses unique properties such as physicochemical stability, inertness, uniform size, coating that helps them maintain their spherical shape, and equilibrium-driven repeatable drug release in an ionic environment **[9]**. IER's physical and chemical characteristics will result in a more uniform drug release than basic matrix formulations **[10]**. Following the release of drug molecules that are bound to the resins by the proper charged ions in the digestive tract, free drug molecules diffuse out of the resin as shown in the following equations (6) and (7)):

$$Resin\text{-}\ Drug+ + X+\ ´\ Resin\text{-}\ ....X^+ + Drug^+ \quad (6)$$

Resin+ Drug- + X- ´ Resin+...X^- + $Drug^-$

(7)

where, X and Y are ions in the gastrointestinal tract.

IER have been utilized as drug carriers **[11-13]** in pharmaceutical dosage forms for controlled release formulation. The delayed release of the active medication is achieved by ion exchange resin particles which consist of a semi-permeable with which the drug component has been complexed to produce an insoluble drug resin complex. The required level of medication availability delay in the gastrointestinal system over time **[14]** is controlled by semi permeable coating thickness. Moderate release of drug is possible with the formulations using strong sulphuric acid resonates as compared to the weak resinates of carboxylic acid **[15]**. These resonates of powerful cationic medicines are used in the development of sustained release solution, tablets, capsules, and other dosage forms.

MANUFACTURING OF IER AND RESONATES

Suspension polymerization is used to produce most of IER. Styrene, methyl acrylate, and acrylonitrile are some examples of neutral monomers that can be used to create polymer beads that are later chemically modified to add acid or base functionality. For instance, sodium polystyrene sulfonate is made by suspension polymerizing a mixture of styrene and divinylbenzene to create small polymeric beads. The beads are then functionalized to produce a sodium version of a strongly acidic cation exchange resin by being sulfonated with intense sulfuric acid and neutralized with sodium hydroxide **[16]**. Preparing resinates 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 is washed. Depending on the application, resinate can then be dried in a vacuum oven at 60ºC. Drying may not be necessary if the liquid solution of resinate is required. The dried resinate can be formulated into tablets, capsules, chewing gums, lozenges, suspensions because it is a free flowing powder with physical properties similar to the original resin. Fluidized bed processor is often employed for getting the best resinates by means of spray drying process. This process includes the spraying of solution on to the resin and immediate drying to get dried resinates which are having property of free flowing powders that are mostly used in the solid dosage forms. The drug release mainly depending on the efficient complex formed between the drug and the resin. Drug release can be regulated by an alternative method called as coating technique which

involves the spraying of resin solution over the drug with simultaneous drying.

PURIFICATION OF RESINS

The important step in the preparation of drug resinates is to purify the resins. Purification of resin can be achieved by washing with absolute ethanol followed by ethanol and water mixture. This mixture is finally washed with water to remove all the impurities. With a cation exchanger or an anion exchanger, purification is often accomplished by regularly cycling between the sodium and hydrogen forms or the chlorides and hydroxide forms. By soaking the resins in acidic or alkaline solutions, the conversion can be accomplished. The resin is exposed to washing with distilled water after changing its ionic form until the elute becomes neutral in reaction, and it is then dried at 50°C. By using the batch approach and the column method **[17-19]** the medicines are loaded onto the resins.

Column Method: A resin-filled column is used to filter a highly concentrated drug solution.The column approach yields the best results in terms of efficiency.

Batch Method: Using this technique, a certain amount of resin is added to the drug solution and it is stirred until equilibrium is reached. The resin must then be washed to eliminate unrelated and free drugs, and it must then air dry.

MECHANISM AND PRINCIPLE

Anion exchange resins are capable of removing anions from acidic solutions by involving basic functional groups, while cation exchange resins contain acidic functional group which helps in removing cations from basic solutions.

IER use the principle of yielding polysalt resinates by combining resins with positively or negatively charged pharmaceuticals, to prolong the effect of drug release.

$R\text{-}SO^{-}_{3}\ H+ + H_{2}N\text{-}A \rightarrow R\text{-}SO^{-}_{3}\text{–}\ H_{3}N\text{-}A$ (8)

$R\text{-}N^{+}H_{3}OH^{-} +\ HOOC\text{-}B \rightarrow R\text{-}N^{+}H_{3}\ \text{–}OOC\text{-}B+H_{2}O$ (9)

where

$H_{2}N\text{-}A$ →basic drug,

$R\text{-}SO^{-}_{3}H^{+}$→cation exchanges

HOOC-B → acidic drug

$R\text{-}NH_{3}^{+}\ OH^{-}$→ anion exchange resins.

The ion exchange resonances, when taken orally, typically spend two hours in the stomach in touch with an acidic fluid with a pH of 1.2 before moving into the intestines, where they spend several hours in contact with slightly alkaline pH.

SELECTION OF SUITABLE ION EXCHANGE RESIN

Functional group properties of the IER mainly influence the selection of IER for the drug delivery applications. Following are characteristics to be considered for selection of ion exchange resin:

- Swelling ratio & Regulatory status of the IER

- Biocompatibility and biodegradability.
- Concentration of the exchangeable group in the resin, which is usually expressed in mill equivalents per gram (meq g^{-1}) of dry resin.
- Particle size and Degree of cross linking in the resin matrix.

Exchange of large ions is influenced by a low degree of cross linking of the resin, but this process of exchange will also cause the volume changes in the resin upon conversion from one form to another form. Similarly, rapid rate of exchange which is made possible by the use of strong IER could lead to the hydrolysis of the labile drugs because of strong IER are effective acid-base catalysts. Optimal performance of drug delivery systems (DDSs) containing IER **[20-21]** possible by making a balance of all the parameters.

PROPERTIES OF ION EXCHANGE RESIN

A. Particle size and form:

The rate of ion exchange reaction is often affected by size of the resin particles. The time required for rate of reaction decreases with decrease in particle size **[22]**.

B. Porosity and swelling:

The volume of material divided by its mass is known as porosity. The porosity has a significant impact on the limiting size of ions that can enter a resin matrix. The amount of a cross-linking agent employed during the polymerization process determines the porosity **[23]**.

C. Cross-linkage

Monomers which used in the polymerization affect the cross linkage. Practical ranges of cross linkage lies in between 4 % to 16 %. The nature of resins mainly depend on the cross linking ability. For example resins with very low crosslinking tend to be watery and change dimensions markedly depending on which ions are bound.

D. Moisture Content:

Moisture content of the ion exchange resins is widely affected by that changes in cross linkage. E.g., sulfonic acid groups attract water, and this water is tenaciously held inside each resin particle.

E. Equilibration Rate

Ion exchange reactions are reversible processes with variable ion-specific equilibrium conditions. Crosslinkage definitely affects how long it takes an ion to reach equilibrium. A heavily crosslinked ion exchange resin is particularly resistive to ion diffusion through it, which lengthens the time needed to attain equilibrium. In general, the time needed to attain equilibrium conditions will increase with the size of the ion or molecule diffusing into an ion exchange particle or the degree of cross linking of the polymer.

F. Capacity:

The total number of chemical equivalents available for exchange per some unit weight or unit volume of resin is termed as the total capacity of an ion exchange resin. Capacity often expressed in terms of milli equivalents per dry gram of resin or in terms of mill equivalents per milliliter of wet resin. It becomes difficult to introduce additional functional groups if the resin is highly cross linked. Sulfonation is carried out after the cross linking has been completed and the sulfonic acid groups are introduced inside the resin particle as well as over its surface. Fewer functional groups may be inserted inside of them, which results in a modest decrease in overall capacity on a dry basis. When the capacity of a resin is measured on a wet volume basis, the situation is inverted. The amount of water is reduced by the extra crosslinking, therefore even though fewer functional groups are added to a resin that is heavily crosslinked, these groups are spaced closer together on a volume basis. When a result, as cross-linking rises, the capacity on a wet volume basis increase.

G. Particle size:

Resins are allowed to pass through screen in order to get a fairly uniform range of sizes. Mesh sizes in the following table refer to U.S. Standard screens **[24]**. Particle size decreases if we use highest mesh number as shown in **Table 1**. A higher mesh number means an arrangement of finer wires per unit area with a small opening for particles to pass through.

Table 1: Particle size of resins

MESH RANGE	DIAMETER OF PARTICLES	
	(In Inches)	(In Micrometers)
20-50	0.0331-0.0117	840-297
50-100	0.0117-0.0059	297-149
100-200	0.0059-0.0029	149-74
200-400	0.0029-0.0015	74-38
Minus 400	<0.0015	<38

H. Flow Rate:

Typically, ion exchange procedures are performed in columns with the resin atop an appropriate support. Through these columns, liquids can be handled either up-flow or down-flow. Ion exchange resins spherical particles resist having a liquid flow through or around them. The more resistance a liquid must flow against, the smaller the particle size must be. When particles with a mesh size of less than 100 are used, this resistance increases very quickly **[25]**.

APPLICATIONS OF ION EXCHANGE RESINS

Pharmaceutical applications of IER include **[26-32]**:

1. Taste masking:

Pharmaceutical industries are facing a challenge of masking of bitter taste in active

principal ingredients in oral formulations that are intended for paediatric and geriatric patients. Product value increases with masking of the unpleasant taste of a drug. Ion exchange resin is one of the inexpensive method Amongst the numerous available taste-masking methods.

E.g: carbomer used to mask the nauseating and unpleasant taste of erythromycin and clarithromycin.

2.Eliminating polymorphism:

Polymorphism is defined as 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. Pharmaceutical industries are spending huge amount of money on identify polymorphs and trying to make stable, suitably soluble forms. This problem can be reduced by ion exchange resins by using resinates.

3. Improving the dissolution of poorly soluble drugs:

Using techniques like micronization to increase the rate of dissolution can sometimes problematic because this process cause the agglomeration of fine particles after grinding which results in melting of particles. These problems are completely eliminated by using the ion exchange resin approach.

4. Improving stability:

Complexation of active ingredients with ion exchange resins prevent harmful interaction with other components. E.g. Vitamin B12 has shelf-life of only a few months and Vitamin B12 deteriorates on storage. The stability of Vitamin B12 can be prolonged to >2 years by complexing it with a weak acid cation exchange resin (Indion- 264). This complex is as effective as the free form of the Vitamins

5. Improving physical characteristics:

The majority of pharmacological compounds are solids, while some are liquids or solids that are challenging to handle. The resinates of these medications will be free-flowing solids because the physical characteristics of the resinates are comparable to those of the resin rather than the drug. The nicotine resinate found in nicotine chewing gum and lozenges is a well-known example of this. Although nicotine is a liquid, its resinate is a solid that is stable and freely flows. The resins' consistent, macroreticular shape gives the formulation outstanding flow properties.

DRUG DELIVERY APPLICATIONS: [33-39]

1. Oral drug delivery:

The major drawback of sustained release or extended release is dose dumping which can be reduced by the use of IER that are having drug retaining properties and prevention of dose dumping. The drug resinates can also be used as a drug reservoir, which affects the drug release in tablets that are made of hydrophilic polymer. Ion exchange resins

posses the properties such as physico-chemical stability, inert nature, uniform size, spherical shape assisting coating which helps in equilibrium driven reproducible drug release in ionic environment. Eg.,

1. Biphetamine used as an anti-obesity agent and for behavior control in children contains amphetamine and dextroamphetamine (1:1) sorbed to a sulphonic acid cation exchange in a capsule form, and is administered as once or twice daily.
2. The drug-resinate approach offers a unique and advantageous way to prevent the drug leakage during storage in the liquid form. In a liquid container, the ion-exchange resins can maintain the drug bound by keeping the liquid free of the resin's counter-ions. When administered orally, the ions in the gastrointestinal tract will activate drug release from the drug resinate at a gradual rate.

2. Transdermal drug delivery*:*

IER is also involved in the development of these systems. Crossing a 0.22 μm microporous membrane, the release rates of ketoprofen from carbopol-based gel vehicles containing ion exchange fibres, to which the ketoprofen had been attached, were measured. Even while the total amount of ketoprofen delivery was less, there was substantially less variation in the release rate of the medication from the vehicles than there was with basic gels. Ions may also speed up and expand the distribution of ketoprofen.

3. Ophthalmic drug delivery:

IER are also used in ophthalmic drug delivery systems. An example is Betoptic S is a sterile ophthalmic suspension which contains 0.25% betaxolol hydrochloride designed to lower elevated intraocular pressure. It is a cardioselective beta-adrenergic receptor blocking agent manufactured by Alcon Laboratories in the US. The drug resinate complex is formed by binding of positively charged drug is to a cation ion-exchange resin (Amberlite IRP 69). The bioavailability of drug in 0.25% ophthalmic suspension of the drug is improved.

4. Bioadhesive system for treatment of gastric mucosa:

Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions. 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 amoxicillin and cimetidine.

4. Diagnostic and therapeutic applications

Ion-exchange resins consists of synthetic as well as natural polysaccharides have been used with good results for diagnostic determinations. Eg. In gastric acidity. Ion-

exchange resins have wide therapeutic applications such as treatment of liver diseases, renal insufficiency, urolithic disease and occupational skin disease. Eg., sodium polystyrene sulfonate is a sulfonic cation-exchange resin used in the treatment of hyperkalemia and also used in acute renal failure.

CONCLUSION

In recent years, IER have been successfully used for masking bitter taste of drugs along with the modification of drug release by means of a complex formation with drug substances. IER have wide therapeutic and pharmaceutical applications. This article is an attempt to understand the ion exchange resins nature, their properties and their applications in various fields with the hope that researchers will utilize the resins more effectively in formulating drug delivery systems.

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