



## A Review on Ion Exchange Resins as Drug Delivery System

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### ABSTRACT

Ion exchange resins (IER) are cross-linked water insoluble polymer carrying ionizable functional groups. Ion exchange resin have received attention from the pharmaceutical scientists because of their considerable properties as the drug delivery vehicles. The efficacy of ion exchange resins mainly depends upon their physical properties such as degree of exchange capacity, cross-linkage, ionization, porosity and swelling, particle size and form, purity, toxicity and equilibrium rate. Research over the last several years has revealed that ion exchange resin are equivalently suitable for drug delivery technologies, including the controlled release, usually in transdermal, nasal, topical, oral and taste masking. The drawback of sustained release or extended release is dose dumping, resulting in increased risk of toxicity. The use of ion exchange resin has an important place in the development of the controlled or sustained release systems because they have effective drug-retaining properties and the prevention of dose dumping. Synthetic ion exchange resins have been used in the pharmacy and medicine for taste masking or controlled release of drug. Drug resin complexation generally converts drug to amorphous form leading to improve the drug dissolution. Some of the system studies have reported the use of IER for drug delivery at the desired site of action. Sulfonated and carboxylic resins with a polystyrene backbone are generally used in clinical medicine. This review addresses various types of ion exchange resin, its properties as well as its applications.

**Keywords:** Ion exchange resin, taste masking, resin drug complex.

### INTRODUCTION

Ion exchange resins (IER) are cross-linked, synthetic, high molecular weight, water insoluble polymers, usually white or yellowish, fabricated from the organic polymer having an ionizable functional group. Novel drug delivery systems are gaining momentum in the last two decades as they offer decrease frequency of dosing and patient compliance. One of the best techniques for modified drug delivery systems is the use of ion exchange resins (IER) as carriers for such systems<sup>1</sup>.

IER are insoluble polymers which carry acidic or basic functional groups and that have the capability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is like a small bead with a diameter in between 1-2 mm. These are generally white or yellowish and it is fabricated from an organic polymer substrate backbone<sup>2</sup>. Ion exchange is a reversible process in which ions of like sign are exchanged in between liquid and solid when in contact with the highly insoluble body<sup>3</sup>. The drug is released from the resinate by exchanging with ions in the gastrointestinal fluid followed by drug diffusion<sup>4</sup>. Due to the appearance of high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The effectiveness of ion exchange resins mainly depends upon their physical properties such as degree of exchange capacity, cross-linkage, ionization, porosity and swelling, particle size and form, purity and toxicity, equilibrium rate. Drug resinates are usually formulated with purified resins and drugs<sup>5,6</sup>.

Research over the past some years has revealed that the IER are equivalently suitable for delivery technologies, together with controlled release, transdermal, nasal, topical, oral and taste masking. Synthetic ion exchange resins have been used in pharmacy and medicine for masking the taste of the drug or controlled release of drug as early as 1950. Ion-exchange systems are beneficial for drugs that are highly susceptible to degradation by enzymatic process. An important advantage of this ion exchange system is the low running cost<sup>7,8</sup>.

### Advantages

- Economic and readily available.
- 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).
- Need for less dosing
- Resins have high drug loading<sup>9</sup>.

### Clinical Advantages

- Reduction in frequency of drug administration
- Improved patient compliance



- Reduction in drug level fluctuation in blood
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of the medical condition (because of more uniform drug levels)
- Improvement in the bioavailability of some drugs because of spatial control.
- Economical to the health care providers and the patient <sup>10</sup>.

#### Disadvantages

- Reduced potential for dose adjustment.
- Cost of the single unit dosage form is higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication in proper time.
- Decreased systemic availability in comparison to immediate release conventional dosage forms and poor in vitro and in vivo correlations <sup>11</sup>.

#### Types of Ion-Exchange Resin

There are two classes of ion-exchange polymers <sup>12</sup> (Fig. 1)

- Cation exchange resin
- Anion exchange resins. These are discussed in the following two sub-sections.

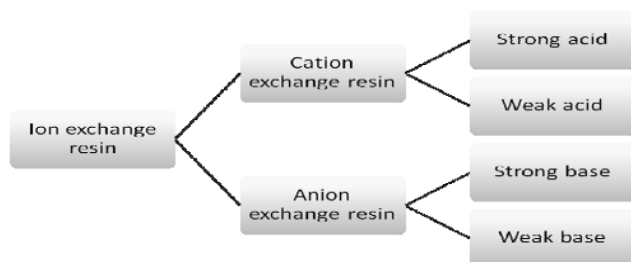
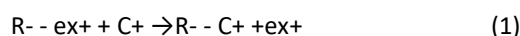


Figure 1: Classification of IER.

#### 1. Cation exchange resins

The Cation exchange resins generally contain covalently bound negatively charged functional groups and exchanges positively charged ions. These are usually prepared by the process co-polymerization of styrene and divinyl benzene and this have sulfonic acid groups (-SO<sub>3</sub>H) introduced into the most of the benzene rings (Fig. 2). The mechanism of cation exchange process can be generally represented by these following reactions in the Eq. (1):



Where, R is the resin polymer with the SO<sub>3</sub>-sites available for bonding with that exchangeable cation (ex+), and C+ indicates that a cation in the surrounding solution gets exchanged (Fig. 3).



Figure 2: Chemical structure of (I) styrene (II) divinyl benzene

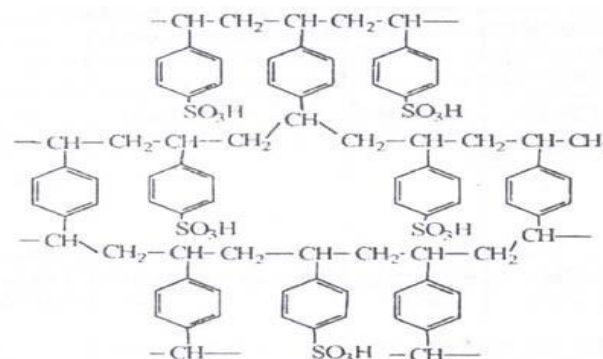


Figure 3: Chemical structure of a cation exchange resin

The 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 behavior of the resin is usually similar to that of a strong acid. These resins are highly ionized in both of the acid (R-SO<sub>3</sub>H) and salt (RSO<sub>3</sub>Na) form of the sulfonic acid group (-SO<sub>3</sub>H). They can convert a metal salt to the corresponding acid by the help of reaction in Eq. (2):



The hydrogen (H<sup>+</sup>) and sodium (Na<sup>+</sup>) forms of that strong acid resins are generally highly dissociated, and where the exchangeable Na<sup>+</sup> and H<sup>+</sup> are available for exchange over the entire pH range. Consequently, the exchange capacity or the ability of strong acid resins is independent of the solution pH <sup>13</sup>.

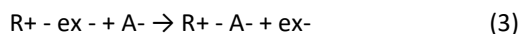
#### Weak acid cation exchange resins

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 that the sulfonic acid group (SO<sub>3</sub>H) used in strong acid resins. The dissociation degree of the weak acid resin is generally strong influenced by the solution pH. Accordingly, capacity of the resin depends in part on the solution pH. A weak acid resin has the limited capacity below a pH of 6.0, making it inappropriate for deionizing acidic metal finishing wastewater.

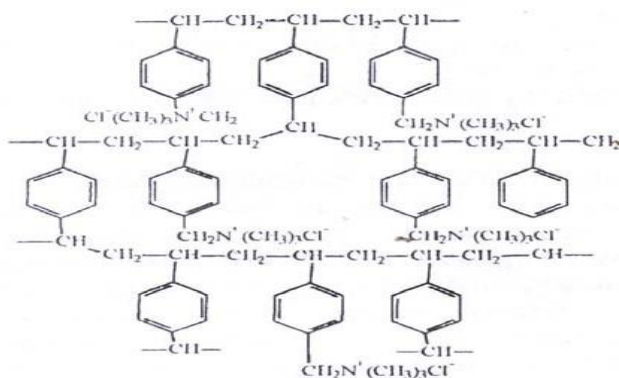
#### 2. Anion exchange resins

The anion exchange resins having positively charged functional groups and generally exchanges negatively charged ions. These are prepared by first

chloromethylation the benzene rings of styrene-divinylbenzene copolymer is to attach CH<sub>2</sub>Cl groups and then causing these to react with tertiary amines such as the triethylamine. The chemical structure of an anion exchange resin is shown in the Fig 4 where the mechanism of an anion exchange process can be generally represented by the following reaction in Eq. (3):



Where, the R<sup>+</sup> indicates that a resin polymer with the number of the sites available for bonding with exchangeable anion (ex<sup>-</sup>), and the A<sup>-</sup> indicates cations in the surrounding solution gets exchanged.



**Figure 4:** Chemical structure of an Anion exchange resin

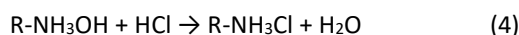
The Anion exchange resins can be further classified into

(a) strong acid anion exchange resins and

(b) weak acid anion exchange resins.

#### **Strong base anion exchange resin**

The strong base resins are highly ionized and this can be used over the entire pH range. These resins are being used in the hydroxide (OH) form for the water deionization. They are reacting with anions in solution and they can convert an acid solution to pure water in Eq. (4):



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

#### **Weak base anion exchange resin**

The weak base resins are like as the weak acid resins in which the degree of ionization is strongly influenced by pH. Therefore, the weak base resins exhibit minimum exchange capacity above the pH of 7.0. The weak base resin does not have the OH ion form as does the strong base resin Eq. (5):



Accordingly, regeneration needs only to neutralize the absorbed acid; it does not need provide OH ions. Inexpensive weakly basic reagents such as ammonia (NH<sub>3</sub>) or sodium carbonate can be generally employed. A cation-exchange resin is prepared by the process of copolymerization of the styrene and divinylbenzene while

during the polymerization, polystyrene formed a linear chain and these become covalently bonded to each other by the cross links of divinylbenzene. If the sulphuric acid is then allowed to react with this copolymer, the sulphonic acid groups are then introduced into the most of the benzene rings of styrene-divinylbenzene polymer, and the final substance formed is generally called as cation-exchange resin. An anion exchange resin is generally prepared by chloromethylation and the benzene rings of that three-dimensional styrene-divinylbenzene copolymers which is attach to -CH<sub>2</sub>Cl groups and then causing to react with the tertiary amine, such as the trimethylamine. This will give the chloride salt of the strong-base exchanges (Table 1)<sup>14</sup>

**Table 1:** Chemical constituents for IER.

Sr no.	Resin type	Chemical constitution	Usual form
1	Strongly acidic cation exchanger	Sulfonic acid groups attached to a system and divinyl benzene copolymer	R-SO <sub>3</sub> -H <sup>+</sup>
2	Weakly acidic cation exchanger	Carboxylic acid groups attached to an acrylic and divinyl benzene copolymers	R-COO-Na <sup>+</sup>
3	Strongly basic anion exchanger	Quaternary ammonium groups attached to a styrene and divinylbenzene copolymer	[φ-CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup> Cl <sup>-</sup> ]
4	Weakly basic anion exchanger	Polyallylamine groups attached to a styrene and divinyl benzene copolymer	[φ-NH(R)] Cl

#### **ROLE OF IER IN CONTROLLED DRUG DELIVERY SYSTEMS**

The main disadvantage of controlled release is dose dumping, resulting in increased/enhance risk of safety/toxicity. The use of IER at the time of the development of controlled release formulations plays an important role because of their drug retarding properties and prevention of dose dumping. The drug resins can also be used as the drug reservoir, which has caused the change of the drug release in hydrophilic polymer tablets<sup>15</sup>.

The uses of Ion exchange resin into the drug delivery system have been encouraged because of their physico-chemical stability, uniform size, inert nature, spherical shape assisting coating and the 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<sup>16</sup>. Drug molecules are attached to the resins that are released by the charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins as shown below in Eq. (6) and (7):





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

IER have been used as a drug carrier in pharmaceutical dosage forms for the controlled release formulations<sup>17-18</sup>. The prolonged release of an active drug is accomplished by providing a semi-permeable coating. On the Ion exchange resin particles, the drug component has been complexed to form an insoluble drug resin complex. The semi-permeable coating creates a diffusion barrier and the thickness of that diffusion barrier which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time. Many of the preparations which generally involving strong resins of sulphuric acid (cation exchange resins) provided more moderate release than the weak resins of carboxylic acid. Hence, resins of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles<sup>19,20</sup>.

### Manufacture of IER and Resonates

Most of the IER are made by the process of suspension polymerization. In some cases, the monomers are neutral (e.g. styrene, methyl acrylate and acrylonitrile) and the resulting polymer beads are then chemically modified to introduce the acid or base functionality<sup>21</sup>.

Some resins are made directly from acidic monomers; for example, polacrilix resin is made by suspension polymerization of a mixture of methacrylic acid and divinylbenzene with no further functionalization. For use in pharmaceutical formulations, the resins are generally dried and then ground to a fine powder, typically in the range of 40–150 µm in size<sup>22</sup>.

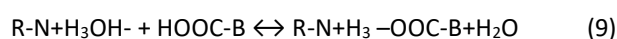
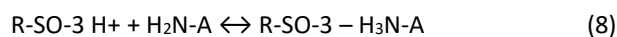
Preparing resins from resins is matter of mixing the resin with a solution and allowing sufficient time (typically a few hours) for loading. The resin/fluid slurry is then filtered and washed the filtrate. Depends on the application, in a vacuum oven at 60°C the resin can be dried where resin is to be used in a liquid suspension drying may not be necessary, and in some cases without filtration directly loading suspension can be used. As similar to the original resin, the dried resin will be the free-flowing powder with their physical properties, and that can be formulated into tablets, capsules, chewing gums, lozenges, suspensions and troches. This can also be coated in the typical coating equipment such as fluid bed coaters.

The best and main approach for getting resins is spray drying process in which fluidized bed processor can be used. In this process, the solution can be sprayed on the resin and simultaneous drying takes place to get dried resins which is free flowing powder mostly used in the solid dosage forms. The drug release mainly depends on the systematic complex formed between the drug and the resin. For further regulating drug release an alternative/another method is the coating. In the coating technique, over the drug the resin solution can be sprayed

along with simultaneous drying. The main advantage of this process is that it allows uniform distribution of the drug resin mixture.

### MECHANISM AND PRINCIPLE

Anion exchange resins which are generally involve basic functional groups capable of removing anions from acidic solutions while Cation exchange resins contain acidic functional group, capable of removing cations from basic solutions. The use of IER to prolong the effect of drug release is generally based on the principle that positively or the negatively charged pharmaceuticals, combined with appropriate resins to get insoluble poly-salt resins.



$\text{H}_2\text{N-A} \rightarrow$  basic drug,  $\text{R-SO}_3\text{H} \rightarrow$  cation exchanges, and

$\text{HOOC-B} \rightarrow$  acidic drug  $\text{R-NH}_3\text{OH} \rightarrow$  anion exchange resins.

The Ion exchange resins, administered orally are generally spend about two hours in the stomach in contact with an acidic fluid of pH 1.2, and then reach into the intestine where it will be in contact for several hours with a fluid of slightly alkaline pH.<sup>23</sup>

### Selection of Suitable Ion Exchange Resin:

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

- Capacity of the IER [i.e. the concentration of the exchangeable group in the resin, usually expressed in mill equivalents per gram (meq g<sup>-1</sup>) of dry resin];
- Degree of cross linking in the resin matrix;
- Particle size of the resin;
- Drug nature and site of drug delivery. The main important to evaluate the resin in the pH- and ionic-strength environment, simulating the in vivo situation;
- Swelling ratio;
- Biocompatibility and biodegradability;
- Regulatory status of the IER

For example, a low degree of cross linking of the resin will facilitate the exchange of large ions, but it will also cause the volume changes in the resin upon conversion from one form to another form. Similarly, the use of a strong IER will give a rapid rate of exchange, but it could also cause hydrolysis of the labile drugs because of strong IER are effective acid-base catalysts. Therefore, a fine balance of all the parameters needs to be made to achieve optimal performance of drug delivery systems (DDSs) containing IER.<sup>24,25</sup>



## PROPERTIES OF ION EXCHANGE RESIN

### Particle size and form:

The rate of ion exchange reaction usually depends upon the size of the resin particles. As the size of the resin particles decrease significantly time required for the reaction also decreases to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern and smaller the particle size affords a faster release pattern<sup>26</sup>

### Porosity and swelling:

Porosity is defined as the ratio of volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, and depends strongly on the porosity. The porosity depends on the amount of cross-linking substance used in polymerization method. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is generally inversely proportional to the degree of DVB cross linking present in the resin.<sup>27</sup>

### Cross-linkage

The amount of crosslinking generally depends on the proportions of different monomers which used in the polymerization step. Practical ranges are 4 % to 16 %. Resins with very low crosslinking tend to be watery and change dimensions markedly depending on which ions are bound.

### Exchange capacity

The capacity of an ion exchanger is a quantitative measure of its capability to take up exchangeable counter-ions and refers to the number of ionic groups per unit weight or volume (meq per g or meq per mL). The weight-based value is generally much greater than the volume-based value since the resins are highly hydrated. However, in preparing drug-resinates, the actual capacity obtainable under specific experimental conditions would depend upon the accessibility of the functional groups for the drug of interest. So "available capacity" will be generally related to the drug physicochemical properties and will be inferior to the total capacity. The exchange capacity may limit the amount of drug that may be sorbed on to a resin and the potency of a drug-resin complex. Weak cation exchangers derived from acrylic acid polymers that have higher exchange capacity (10 meq/g) than the sulfonic acid (4 meq/g) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore, higher drug loads may often be usually achieved with the carboxylic acid resins.

### Moisture content

A physical property of the ion exchange resins that generally changes with changes in cross linkage is the moisture content of the resin. For an example sulfonic acid groups attract water, and this water is tenaciously held inside each resin particle. The quaternary

ammonium groups of the anion resins behave in a similar manner.

### Purity and toxicity

It is necessary to establish the safety/toxicity of the ion-exchange resins because of very high fraction of the resin in drug-resin complex (>60%). Most of the commercial products can't be used such as because they generally contain impurities that causes severe toxicity besides some pharmaceutical grade resins (Amberlite IRP series from Rohm & Haas). Therefore, a thorough purification of the resin is required to eliminate the impurities for the pharmaceutical application. Purified ion exchange resins are generally non-toxic and insoluble. However, administration of large enough quantities of ion-exchange resin should disturb the ion strength in the gastrointestinal fluids and causes harmful side effects<sup>28,31</sup>.

## APPLICATIONS OF IER

### Pharmaceutical applications

Some pharmaceutical applications of IER include:

#### Taste masking

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

#### Eliminating polymorphism

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

#### Improving the dissolution of poorly soluble drugs

Ion exchange drug resin complex can be used to increase the dissolution rate of the poorly soluble drug. This can be problematic when using micronization to increase the rate of dissolution, because it generally requires several specialized equipment and often there



can be agglomeration of the fine particles after grinding. The grinding can also be result in melting and conversion to other crystal forms. These problems are entirely eliminated by use of ion exchange resin approach.

### Improving stability

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

### Improving physical characteristics

Most of the drug substances are in solid form, some are in liquids or difficult-to handle solids. Since the physical properties of the resins are similar or same as compared to the resin and not to the drug, the resins of these drugs will be free-flowing solids. A very well accepted example of this is the nicotine resinate generally used in nicotine chewing gums and lozenges. Nicotine is in liquid form while its resinate is stable, free-flowing solid. The resins have a uniform, macroreticular morphology, which provides very good flowability to the formulation.<sup>32-34</sup>

### Drug delivery applications

#### Oral drug delivery

The major disadvantage of sustained release or extended release is dose dumping hence results in increased risk of toxicity. The use of IER plays a very important place in the development of the controlled or sustained-release systems because of their better drug retaining properties and prevention of dose dumping. The drug resins can be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets. Using ion exchange resins into drug delivery systems have been normally encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment.

#### Nasal drug delivery

A novel nasal formulation, in the form of a nicotine-Amberlite resin complex powder, have been generally developed that provided that the optimal combined pulsatile and the sustained plasma nicotine profile for the smoking cessation. Amberlite IRP69 and the Amberlite IR120 are the same cationic exchange materials with the same ion exchange capacity, but due to the small particle size which ranges (10-150  $\mu\text{m}$ ). Amberlite IRP69 have better flow property and a better adsorptive capacity than the Amberlite IR120.

#### Transdermal drug delivery

Ion exchange resin are also involved in the formulation of transdermal drug delivery systems. The release rates of

the ketoprofen from that Carbopol-based gel vehicle which contain the ion exchange fibers to which the ketoprofen had been bound were the determined across 0.22  $\mu\text{m}$  microporous membrane [40, 41]. The fluctuation of the release rate of the ketoprofen from the vehicles was lower compared with that of the simple gels, though out the cumulative amount of ketoprofen delivery was less

#### Ophthalmic drug delivery

IER find application in ophthalmic drug delivery systems. An example is Betoptic S which is the sterile ophthalmic suspension and it generally contains 0.25% betaxolol hydrochloride. It is a cardio selective beta-adrenergic receptor blocking agent manufactured by the Alcon Laboratories in the US. This is the ocular resinate ophthalmic product designed to lower elevated the intraocular pressure. The drug resinate complex is generally 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 the bioavailability.

#### Diagnostic and therapeutic applications

Synthetic as well as natural polysaccharides based on ion-exchange resins have been generally used with results for diagnostic determinations. eg. In gastric acidity. They also found applications as adsorbents of toxins, as antacids, and as bile acid binding agents, etc. Ion-exchange resins are successfully used therapeutic in the treatment of liver diseases, renal insufficiency, and occupational skin disease<sup>35</sup>.

### CONCLUSION

In recent years, IER have been successfully used for masking of taste of bitter drugs. IER play a 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 function which include tablet disintegration. This article has attempted to review the literature bring its manufacturing, properties, method of preparation as well as its different applications with the hope that researchers will utilise the resins more effectively in formulating drug delivery systems.

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