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Review

Ion-Exchange Resins as Controlled Drug Delivery Carriers

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Abstract

Ion exchange resins (IER) are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. Based on the nature of the exchangeable ion of the resin as a cation or anion, it is classified as cationic or anionic exchange resins, respectively. 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. Modified release of drugs from resinate (drug-resin complexes) is another potential application of ion exchange resins. Due to the versatile utility of ion exchange resins, they are being used for various drug delivery and therapeutic applications. Resins used are polymers that contain appropriately substituted acidic groups, such as carboxylic and sulfonic for cation exchangers; or basic groups, such as quaternary ammonium group for anion exchangers. This review addresses different types of ion exchange resin, their properties, the chemistry; role of IER in controlled drug delivery systems, its therapeutic applications, methods of preparation of IER along with their resonates.

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

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1. Introduction

Controlled drug delivery systems are gaining momentum in the recent two decades as these results in reduced frequency of dosing and patient compliance. Intensity and duration of action has been the subject of increasing multidisciplinary research. One of the attractive methods for modified drug delivery systems is the use of ion exchange resins (IER) as carriers for such systems [1]. Complexes between IER and drugs are known as

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ion exchange resonates, which have been used in pharmaceutical formulations for several decades.

IER are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is exhibited like small bead with a diameter between 1-2 mm. It is usually white or yellowish and it is fabricated from an organic polymer substrate backbone [2]. 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 [3]. The drug is released from the resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion [4]. Due to the presence of high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. IER have specific properties like available capacity, acid base strength, particle size, porosity and swelling, on which the release characteristics of drug resinates are dependent [5]. Drug resinates are generally prepared with purified resins and appropriate drugs.

Ion-exchange systems are advantageous for drugs that are highly susceptible to degradation by enzymatic process. A major advantage of ion exchange system is 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 drug can be affected by variability in diet, water intake and individual intestinal content.

2. Structure and 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 [6]. 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 (normally styrene) with electrically charged sites at which one ion may replace another. There are numerous functional groups that have charge, only a few are commonly used for man-made IER. These are:

- -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^{+},
- -secondary and tertiary amines that also attract protons weakly,
- $-NR_3^{+}$, which has a strong, permanent charge (R stands for some organic group).

These groups are sufficient to allow selection of a resin with either weak or strong positive or negative charge.

3. Types of Ion-exchange Resins

There are two major classes of ion-exchange polymers [7] (See Fig. 1): (a) Cation and (b) anion exchange resins. These are discussed in the following two sub-sections.

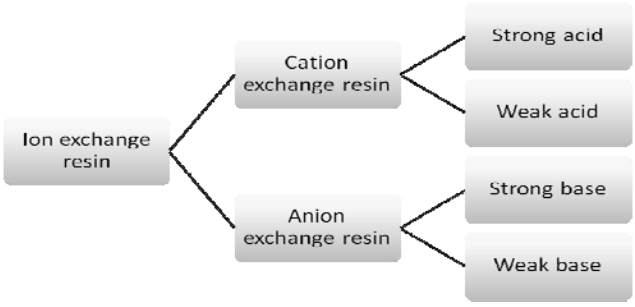

Fig. 1. Classification of IER.

3.1. *Cation exchange resins*

Cation exchange resins contain covalently bound negatively charged functional groups and exchanges positively charged ions. There are prepared by the copolymerization of styrene and divinyl benzene and have sulfonic acid groups (-SO_3H) introduced into most of the benzene rings (Fig. 2). The mechanism of cation exchange process can be represented by the following reaction in Eq. (1):

$$R\text{- - ex+} + C+ \rightarrow R\text{- - C+} + ex+ \quad (1)$$

where, R is a resin polymer with SO_3-sites available for bonding with exchangeable cation (ex+), and C+ indicates a cation in the surrounding solution getting exchanged (Fig. 3).

Fig. 2. Chemical structure of (I) styrene (II) divinyl benzene.

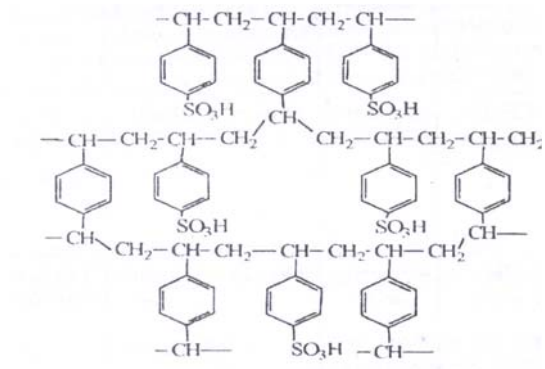

Fig. 3. Chemical structure of a cation exchange resin

Cation exchange resins can be further classified into (a) strong acid cation exchange resins and (b) weak acid cation exchange resins.

3.1.1. 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 ($R\text{-}SO_3H$) and salt (RSO_3Na) form of the sulfonic acid group ($-SO_3H$). They can convert a metal salt to the corresponding acid by the reaction in Eq. (2):

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

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 [8].

3.1.2. Weak acid cation exchange resins

These resins behave similarly to weak organic acids that are weakly dissociated. In a weak acid resin the ionisable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO_3H) used in strong acid resins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. 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.

3.2. *Anion exchange resins*

Anion exchange resins have positively charged functional groups and there exchanges negatively charged ions. These are prepared by first chlormethylating the benzene rings of 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 4 while the mechanism of anion exchange process can be represented by the following reaction in Eq. (3):

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

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

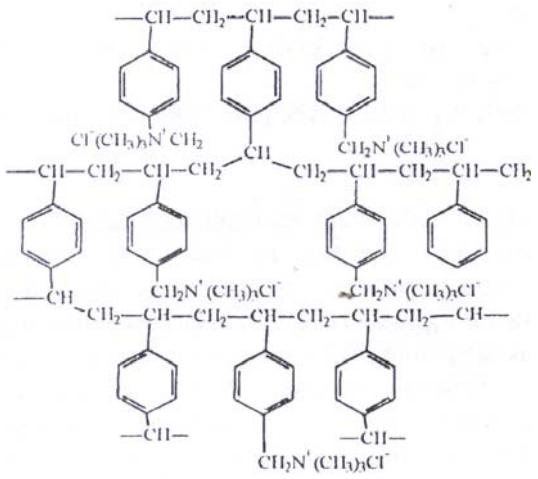

Fig 4. Chemical structure of an Anion exchange resin

Anion exchange resins can be further classified into [9] two which are as follows:

3.2.1. *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 Eq. (4):

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

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

3.2.2. 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 Eq. (5):

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

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.

A typical cation-exchange resin is prepared by the copolymerization of styrene and divinylbenze. During the polymerization, polystyrene formed as a linear chains and these become covalently bonded to each other by divinylbenze 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-divinylbenze polymer, and the final substance formed is known as cation-exchange resin.

A typical anion exchange resin is prepared by first chloromethylating 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 (Table 1).

Table. 1. Chemical constituents for IER.

Sl.	Resin type	Chemical constitution	Usual form
1.	Strongly acidic cation exchanger	Sulfonic acid groups attached to a system and divinyl benzene copolymer	$R\text{-}SO_3^-H^+$
2.	Weakly acidic cation exchanger	Carboxylic acid groups attached to an acrylic and divinyl benzene copolymers	$R\text{-}COO^-Na^+$
3.	Strongly basic anion exchanger	Quaternary ammonium groups attached to a styrene and divinylbenzene copolymer	$[\phi\text{-}CH_2N\text{-}(CH_3)_3^+]Cl^-$
4.	Weakly basic anion exchanger	Polyalkylamine groups attached to a styrene and divinyl benzene copolymer	$[\phi\text{-}NH\text{-}(R)]Cl^-$

4. Role of IER in Controlled Drug Delivery Systems

The major drawback of controlled release is dose dumping, resulting in increased risk of toxicity. The usage of IER during the development of controlled release formulations plays a significant role because of their drug retarding 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 [10, 11].

The use of IER into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment [12]. The physical and chemical properties of the IER will release the drug more uniformly than that of

simple matrix formulations [13]. Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins as shown below in Eqs. (6) and (7):

$$Resin^{-}\,Drug^{+} + X^{+} \rightarrow Resin^{-}....X^{+} + Drug^{+} \quad (6)$$

$$Resin^{+}\,Drug^{-} + X^{-} \rightarrow Resin+...X^{-} + Drug^{-} \quad (7)$$

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

IER have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation [14-16]. The prolonged release of the active drug is accomplished by providing a semi-permeable coating around discrete, minute, ion exchange resin particles with which 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 which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time [17]. Several preparations involving strong resonates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resinates of carboxylic acid [18]. Hence, resinates of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.

5. Manufacture of IER and Resonates

Most 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; 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 [19].

A few resins are made directly from acidic monomers; for example, polacrilex 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 usually dried and then ground to a fine powder, typically in the range of 40–150 μm in size [20].

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 washed. Depending on the application, resinate can then be dried in a vacuum oven at 60ºC. In cases where resinate is to be used in a liquid suspension drying may not be necessary, and in some cases the loading suspension can be used directly without filtration. The dried resinate will be a free flowing powder with physical properties similar to the original resin, which can be formulated into tablets, capsules, chewing gums, lozenges, suspensions and troches. It can also be coated in typical coating equipment such as fluid bed coaters.

The best approach for getting resinates is spray drying process in which fluidized bed processor can be used. In this process, the solution can be sprayed on the resin and

simultaneous drying takes place to get dried resinates which is free flowing powder mostly used in the solid dosage forms. The drug release mainly depending on the efficient complex formed between the drug and the resin. For further regulating drug release an alternative method is coating. In this technique the resin solution can be sprayed over the drug along with simultaneous drying. The advantage of this process is that it allows uniform distribution of the drug resinate mixture.

6. Mechanism and Principle

Anion exchange resins 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 based on the principle that positively or negatively charged pharmaceuticals, combined with appropriate resins to yield insoluble polysalt resinates.

$$R\text{-}SO^-_3\ H^+ + H_2N\text{-}A \leftrightarrow R\text{-}SO^-_3 - H_3N\text{-}A \quad (8)$$

$$R\text{-}N^+H_3OH^- + HOOC\text{-}B \leftrightarrow R\text{-}N^+H_3 - OOC\text{-}B + H_2O \quad (9)$$

H_2N-A $\rightarrow$ basic drug, R-$SO^-_3H^+ \rightarrow$ cation exchanges, HOOC-B $\rightarrow$ acidic drug

R-$NH_3^+OH^-$ $\rightarrow$ anion exchange resins.

Ion exchange resinates administered orally are likely to spend about two hours in the stomach in contact with an acidic fluid of pH 1.2, and then move into the intestine where they will be in contact for several hours with a fluid of slightly alkaline pH [21].

7. Important Properties of IER

During the process of developing formulations with IER, some of the important properties normally considered by researchers include the following:

Particle size and form: The rate of ion-exchange reactions depends on the size of the resin particles. Decreasing the size of resin particle significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium [22].

Porosity and swelling: 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. Porosity of the ion-exchangers depends upon polymerization procedures. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional so the degree of divinyl benzene cross linking present in the resin [23].

Cross linkage: 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. The fraction of DVB determines to what extent the ion exchange resin is free to swell and shrink. The swelling in turn affects the rate of

hydration, the volume expansion of resin to absorb large molecules. Even after absorption, some large molecules may be difficult to evaluate absorption, some large molecules may be difficult to elute unless the DVB percentage is low. The swelling capacity of the ion exchange resin when wetted has been put to practical use with the potassium form of the polymethacrylic acid resin, Amberlite IRP-88, as a tablet disintegrating agent [24]. Resins with low cross linking can take considerable amount of water and swell into a structure that is soft and gelatinous.

Available capacity: The capacity of an ion-exchanger is a quantitative measure of its ability to take up exchangeable counter-ions and is therefore a major importance. The exchange capacity refers to the number of ionic sites per unit weight or volume. The weight basis value is highly hydrated. The exchange capacity may limit the amount of drug that may be absorbed on a resin and hence the potency of a complex. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities than sulphonic acid or amine resins because of bulkier ionic substituent's and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins.

Acid base strength: The acid or base strength of an exchanger is dependent on the various ionogenic groups, incorporated into the resin. The P_{ka} 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, vinylbenzene cross-linked oesins are resistant to decomposition through chemical attack.

Purity and toxicity: Since drug resin combinations contain 60% or more of the resin, it is necessary to establish toxicity of the ion-exchange resins. Commercial product cannot be used as such because they contain impurities that cause severe toxicity [25]. Therefore, careful purification of the resin prior to treatment with the drug is required.

8. General Preparation of Drug Resonates and Drug Loading

The foremost step in the preparation of drug resinates is to purify the resins carefully. Purification is generally done by cycling repeatedly between the sodium and hydrogen forms with a cation exchanger (or) between the chloride and hydroxide forms with anion exchanges [5]. After thoroughly washing with water and subsequent air drying, the resin is sieved to get a series of fractions. Drugs to be formulated into resinates should have in their chemical structure acidic or basic groups with its biological half life ($t_{1/2}$) between the range of 2 to 6 hrs. It should be well absorbed from all the areas of the gastrointestinal tract and also it should be stable in the gastric juice [5].

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

(a) Column process – A highly concentrated drugs solution is eluted through a bed or column of the resin, until equilibrium is established.

(b) Batch process – The resin particles are stirred with a large volume of concentrated drug solution. Subsequently the resin is to be washed to remove adhering free and un-associated drug and thereafter it is air dried.

9. Evaluation of Drug Resonates

The *invitro* test demonstrates the release pattern of a drug from resinate preparation dosage form. It depends on size of resinate, degree of cross linkage of resin with drug, nature of the resins, nature of the drug and test conditions that is ionic strength of the dissolution medium [26].

In vivo procedures used for estimating drug activity of resinates include serum concentration level determination, urinary excretion, and toxicity studies. Bioavailability of drug from drug–resinate complexes depends on both transit of the particles through the gastrointestinal tract and drug release kinetics. The complex will release the active content only when it replaced by the ion which has the same charge. Since the exchange is an equilibrium process, it will depend on the ionic constitution and the fluid volume of the body fluid. In additional, release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. Thus, agitation and time of exposure play a key role in drug release.

Stomach emptying with fine particles will likely follows a first order or distributional process. In the intestine, the neutral pH should keep all ionic sites ionized, and the exchange process should occur continuously. The absorption into the body of solubilised drug should drive the equilibrium further toward drug release. In the large intestine, desorption from resins and absorption into the body may be slowed considerably due to low fluid content, entrapment in faecal matter, and poor absorption in colon. The highly insoluble resin never dissolves, and should not be absorbed. It will simply be eliminated from the body with whatever counter-ions have replaced the drug.

10. Applications of IER

10.1. *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 pharmaceutical industry especially for paediatric 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 hydroxylpropyl methylcellulose phthalate [27-30]

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/or conformations of the molecules in the crystal lattice [31, 32]. 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 completely 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 frequent requires specialized equipment and often there can be agglomeration of the fine particles after grinding [33]. The grinding can also result in melting and conversion to other crystal forms. These problems are completely eliminated by using the ion exchange resin approach.

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 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 solid form there are some that 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 [34]. 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, macroreticular morphology, that provides excellent flowability to the formulation.

10.2. *Drug delivery applications*

Oral drug delivery
The major drawback of sustained release or extended release is dose dumping hence resulting in increased risk of toxicity. The use of IER has occupied an important place in the development of controlled or sustained-release systems due of their better drug retaining properties and prevention of dose dumping. The drug resinates can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets [35-37]. The use of ion exchange resins into drug delivery systems have been

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, has been developed that provided an optimal combined pulsatile and sustained plasma nicotine profile for smoking cessation. Amberlite IRP69 and Amberlite IR120 are similar cationic exchange materials with the same ion exchange capacity but due to a smaller particle size range (10-150 μm). Amberlite IRP69 had a better flow property and a better adsorptive capacity than Amberlite IR120 [38]. 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 [39, 40].

Transdermal drug delivery
IER are also involved in the formulation of transdermal drug delivery systems. The release rates of ketoprofen from the carbopol-based gel vehicles containing ion exchange fibers to which the ketoprofen had been bound were determined across 0.22 μm microporous membrane [40, 41]. The fluctuation of the release rate of ketoprofen from the vehicles was much lower compared with that of simple gels, though the cumulative amount of ketoprofen delivery was less. In addition ions could increase the rate and extent of ketoprofen delivery.

Ophthalmic drug delivery
IER also find application in opthalamic drug delivery systems. An example is Betoptic S which is a sterile ophthalmic suspension and it contains 0.25% betaxolol hydrochloride. It is a cardioselective beta-adrenergic receptor blocking agent manufactured by Alcon Laboratories in the US. It is an ocular resinate ophthalmic product designed to lower elevated intraocular pressure. The drug resinate complex is formed when the positively charged drug is bound to a cation ion-exchange resin (Amberlite® IRP 69). The 0.25% ophthalmic suspension of the drug showed an increased bioavailability [42].

10.3. *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 therapeutic 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 exogeneous obesity in a regimen of weight reduction utilizing caloric restriction. It also has application in the control of cholesterol and potassium ion levels.

11. Some IER Available in the Market

The use of IER to form drug adsorbates for sustained release [43, 44] was closely associated with Strasenburgh Laboratories, an affiliate of Pennwalt Corporation, which was granted several patents in this area [45, 46]. Their first significant application involved amphetamine adsorbed onto a sulfonic acid cation exchange resin (Biphetamine) which is use in appetite suppression and for also for behavior control in children [47].The drug is administrated once or twice daily. Other products that have been introduced commercially since the initial work with amphetamine include Penntuss which is a combination of Codeine and Chlorpheniramine. This is a liquid suspension used as a cough suppressant and relief of cold. It is taken twice daily. Both drugs are bound to a sulfonic acid cation-exchange resin. The chlorpheniramine-resinates are uncoated due to much high affinity for the resin while the codeine-resinates are coated with ethylcellulose [48]. Other products used for cough and cold include phenylpropanolamine, chlorpheniramine, and dextromethorphan. Some other examples include Ionamin (phentermine) and Tussionex (hydrocodone polistirex and chlorpheniramine polistirex) both are marketed by Medeva Pharmaceuticals, Inc.) [49-54]. However, Table 2 gives a summary of some IER with their doses and suppliers.

Table 2. Some IER used in pharmaceutical formulations.

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

12. Conclusion

IER play a major role in the modification of drug release by forming a complex with drug substances. This article has attempted to review the literature bring to light the chemistry, properties, method of preparation as well as its different applications with the hope that researchers will utilise the resins more effectively in formulating controlled drug delivery systems.

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