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Review Article

Applications of Ion Exchange Resin in Oral Drug Delivery Systems

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ABSTRACT

Ion Exchange Resins (IER) are insoluble polymers having styrene divinylbenzene copolymer backbone that contain acidic or basic functional groups and have the ability to exchange counter ions with the surrounding aqueous solutions. From the past many years they have been widely used for purification and softening of water and in chromatographic columns, however recently their use in pharmaceutical industry has gained considerable importance. Due to the physical stability and inert nature of the resins, they can be used as a versatile vehicle to design several modified release dosage forms The ionizable drug is complexed with the resin owing to the property of ion exchange. This resin complex dissociates*in vivo* to release the drug. Based on the dissociation strength of the drug from the drug resin complex, various release patterns can be achieved. Many formulation glitches can be circumvented using ion exchange resins such as bitter taste and deliquescence. These resins also aid in enhancing disintegrationand stability of formulation. This review focuses on different types of ion exchange resins, their preparation methods, chemistry, properties, incompatibilities and their application in various oral drug delivery systems as well as highlighting their use as therapeutic agents.

Keywords: Ion exchange resins, modified release, taste masking, polacrilin potassium, cholestyramine.

INTRODUCTION

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 classification flowchart is shown in Figure 1.

Types of ion exchange resins

Cation exchange resins

Strongly acidic cation exchange resins

They have negatively charged groups covalently bound to them and they exchange positively charged ions. The basic structure of cation exchange resin comprises of styrene and divinylbenzene. Copolymerization of styrene and divinylbenzene followed by introduction of sulfonic acid groups (-SO_3H) into most of the benzene rings yields cation exchange resins. The mechanism of exchange process can be symbolized by the following reaction:

$$(Resin^- \text{——} \ Exchange\ group^+) + A^+ \Rightarrow Resin^- \text{——} \ A^+ + Exchange\ group^+$$

Where, ($Resin^-$-Exchange $group^+$) indicates a resin polymer with cation exchange group and A^+ indicates anions in the surrounding solution.

The chemical structure of a strong cation exchange resin is shown in figure 2.

Weakly acidic cation exchange resins

These resins are similar to weak organic acids which weakly dissociate. Here the ionizable group is a carboxylic acid (COOH) as contrasting to the sulfonic acid group (SO_3H) present 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.

Anion exchange resins

Strongly basic anion exchange resin

These resins have positively charged functional groups and they exchange negatively charged ions. They are prepared by chlormethylating benzene ring of the divinylbenzene components followed by attachment of CH_2Clgroups and then these are reacted with tertiary amineswhich has a strong, permanent charge (-NR_3^+, where R stands for some organic group). The chemical structure of an anion exchange resin is shown in Figure3

The mechanism of anion exchange process can be represented by the following reaction:-

$$(Resin^+ \text{——} \ Exchange\ group^-) + A^- \Rightarrow Resin^+ \text{——} \ A^- + Exchange\ group^-$$

Where, ($Resin^+$-Exchange $group^-$) indicates a resin polymer with anionic exchange group and A^- indicates anions in the surrounding solution.

Weakly basic anion exchange resin

Weak base resins are like weak acid resins in which the degree of ionization is strongly influenced by pH due to which they exhibit minimum exchange capacity above pH of 7.0. The weak base resin does not have an OH ion form such as the strong base resin but has -NH_2, which weakly attracts protons to form NH_3^+ group[1].

Mechanism of drug release from resinates:

Anion exchange resins involve basic functional groups capable of removing anions from acidic solutions while cation exchange resins contain acidic functional group,

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capable of removing cations from basic solutions. The use of ion exchange resinto prolong the effect of drug release is based on the principle that positively or negatively charged pharmaceuticals, combined with appropriate resins yield insoluble polysaltresinates. Ion exchange resonates when administered orally, they are retained in stomach for two hours in contact with an acidic fluid of pH 1.2 and then move into the intestine at a slightly alkaline pH. Towards the large intestine, desorption from resins and absorption into the body may be slowed due to low fluid content and poor absorption in colon[2]. The formulation and *in vivo* release process is explained graphically in Figure 4.

Properties of ion exchange resins

Particle size

Fine particles render more surface area than coarse particles and less internal volume for ions to diffuse, so less time is required to establish equilibrium. Similarly, desorption of bound drug from the complex will be faster in fine particles[3]. General particle size of resin ranges from 0.25-1.25mm.

Cross linking

When an ion-exchange resin is highly cross-linked, the diffusion of various ions can be impeded. This will increase the time required to reach equilibrium and reduce the amount of loaded drug. Degree of cross linking is the divinylbenzene content which affects the degree of permeability. Resins having higher cross linking make it difficult to generate additional functional groups because sulphonation is generally accomplished after cross linking reaction. Resins with very low crosslinking tend to be watery and change dimensions markedly depending on which ions are bound. Jeong S et.al. studied the effect of crosslinking and particle size on the moisture content of resin. Dowex® 50WX2 containing 2% divinylbenzene, Dowex® 50WX4 containing 4% divinylbenzene and Dowex® 50WX8 containing 8% divinylbenzene were the resins used in the study. It was found that at 2% crosslinkage, moisture content was more and as the crosslinking was increased upto 8% the moisture content was reduced to half. The practical ranges of divinybenzene are considered to be between 2-16. It was also established that as the crosslinking was increased upto 8% the drug loading ratio also decreased significantly[3].

Total exchange capacity

The total capacity of ion-exchange resins is defined as the total number of chemical equivalents available for exchange per unit weight or unit volume of the resin. This capacity is expressed in terms of milliequivalents per dry gram (meq/g) of resin or milliequivalents per millilitre of wet resin. As stated earlier, more highly cross-linked a resin, the more difficult it becomes to introduce additional functional groups[4]. The exchange capacity governs the amount of drug that can be taken up by the resin. Comparatively, the sulfonic acid resins or amine resins have lower exchange capacity (4meq/g) than the cation exchange resins derived from acrylic acid polymers (10meq/g). This is because the amine resins have bulkier constituents which makes it difficult to introduce other functional groups[5].

Equilibration rate

Ion exchange reactions are reversible reactions with equilibrium conditions being different for different ions. Cross-linkage has a definite influence on the time required for an ion to reach equilibrium. An ion exchange resin that is highly cross-linked is quite resistant to the diffusion of various ions through it, and hence, the time required to reach equilibrium is much longer. The larger the ion or molecule diffusing into an ion exchange particle, or the more highly cross-linked the polymer, the longer the time required to reach equilibrium conditions[1].

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 to the degree of divinyl benzene cross linking present in the resin[6].

Ionogenic group on the resin

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

Resins containing sulfonic acid, phosphonic or carboxylic acid exchange group have approximate pKa values of < 1, 2-3 and 4-6 respectively. Anionic exchangers are quarternary, tertiary or secondary ammonium groups having pKa values of > 13, 7-9 or 5-9, respectively[7,1].

Stability

The resinous ion-exchangers are remarkably inert substances. At ordinary temperature and excluding the more potent oxidizing agents, divinylbenzene cross-linked resins are resistant to decomposition through chemical attack[2].

Purity and toxicity

There are purification procedures needed prior to use of resin in drug formulation to avoid possible toxicity. Commercial product cannot be used as such because they contain impurities that cause severe toxicity. Therefore, careful purification of the resin prior to treatment with the drug is required[2]. The resin can be purified by washing with absolute ethanol, ethanol-water mixtures, and eventually with water over 1 week[8].

Preparation of drug resinates

There are two methods which can be employed for preparation of drug resinates which are column process and batch process. Batch process involves simple mixing of drug with resin under continuous stirring and then the resins are washed and air dried wherein column process involves elution of concentrated drug solution through a resin column[9].The process is depicted diagrammatically in Figure 5

Drugs suitable for resinate preparation

All drugs cannot be formulated into drug resinates. There are certain criteria which the drug has to fulfill to become a candidate for drug resinate complexation which are

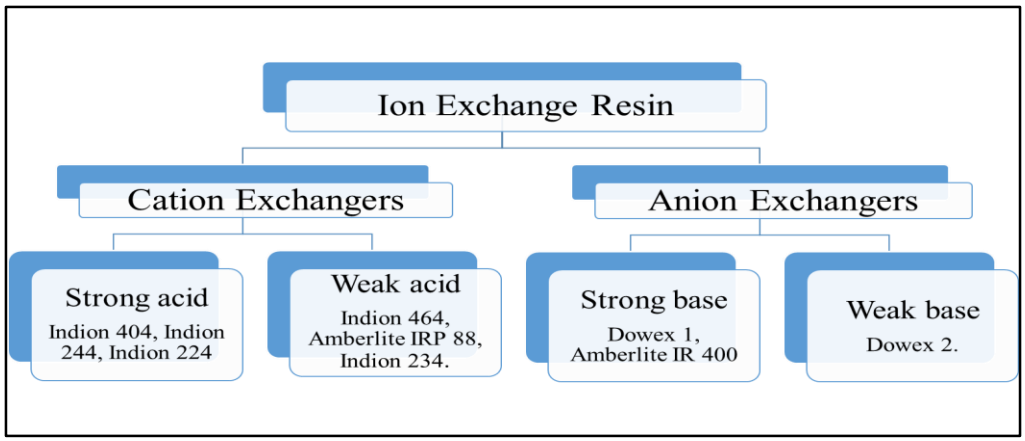

Figure 1: Classification of Ion exchange resin with examples.

The biological half-life should be within 2-6 hours.
The drug is to be absorbed from all regions of the GI tract.
The drug should be stable sufficiently in the gastric juice, otherwise it would fail in providing therapeutic efficacy.
Drug should have an acidic or basic group in the chemical structure[6].
Certain advantages of ion exchange resin formulations are elimination of over and under dosing, high drug loading capacity which prevents dose dumping and easy economic method of preparation[10].

Applications in oral drug delivery

As disintegrating agent

Polacrilin potassium is a cation exchange resin used in oral pharmaceutical formulations as a tablet disintegrant. It ionizes to give potassium cations and an anionic polymer chain[11]. The disintegration action is governed by its high swelling property. The reported concentration of polacrilin potassium as tablet disintegrant is 2-10% although 2% is considered to be sufficient[12].

Bele M .et al., hypothesized that polacrilin potassium might have a property to improve the permeability of anionicdrugs owing to the Donnan membrane phenomenon. The effect of polacrilin potassium on the permeability of diclofenac potassium, used as a model anionic drug, was tested in vitro using Franz diffusion cells. The amount of drug permeated across the dialysis membrane was significantly more in the presence of polacrilin potassium. The *in vivo* studies also showed enhanced C_{max} of 3.68 µg/ml in presence of Polacrilin potassium as compared to 2.14 µg/ml in presence of crosspovidone[11].

Kalyanka P et al. developed directly compressible orodispersible tablets of quetiapine fumarate by sublimation method. Indion 414 was used as superdisintegrant at a concentration varying from 3 to 5% and camphor was used as subliming agent. Shorter disintegration time was obtained using Indion 414 as a superdisintegrant and sublimation method proved to be useful for development of orodispersible tablet[13].

The low crosslinked anionic exchange resin Dowex1®x2 can also act as a disintegrating agent. For these resins the mechanism of disintegration appears to be governed by wicking and swelling actions[14].

For modified release

The use of resins has occupied an important place in the development of oral sustained-release systems because of their better drug retaining properties and prevention of dose dumping.

An investigation was done to develop sustained release matrix tablets of glipizide using ion exchange resin (Cholestyramine).

The release profile and retention of glipizide by matrix tablet was influenced by glipizide-ion exchange binding and sodium chloride which was added as a release modifier. Hydroxypropyl methyl cellulose was also added to modifythe drug release. The drug releases of the optimized batches were compared with the drug release of marketed formulation (GLYNASE XL-10).It was found that drug release through the formulation containing IER can be increased by incorporating a little amount of salt such as sodium chloride in it which provides the ions needed for exchange locally. Whereas, in batches without the sodium chloride, ions from the medium have to diffuse through the gel layer of HPMC and reach glipizide-IER complex to displace the drug. Also the result showed that gel layer containing ions must be present in near vicinity because the tablet which disintegrated showed less drug release than those which were intact[15].

In a study it was stated that anion exchange resins, such as cholestyramine, possess bioadhesive properties, which might be caused by their electrostatic interaction with the mucus and epithelial cell surface. The use of such bioadhesive ion exchange resin is another attractive approach in the development of targeted formulations for the GI tract. Hence diclofenac-cholestyramine yields a high peak plasma concentration, favoring drug transfer to the effect compartment leading to a rapid onset of analgesic effect. Diclofenac sodium is an anionic drug which when incorporated in an anion exchange resin, Cholestyramine leads to extended release of the drug[16].

A combination tablet of ranitidine inimmediate release form and domperidone in sustained release form was formulated using resin complexation. The weak cation exchange resin Indion 294 was selected for complexing ranitidine, as ranitidine is a basic drug which was needed in immediate release form, whereas Indion 244, a strong cation exchange resin, was chosen to produce sustained

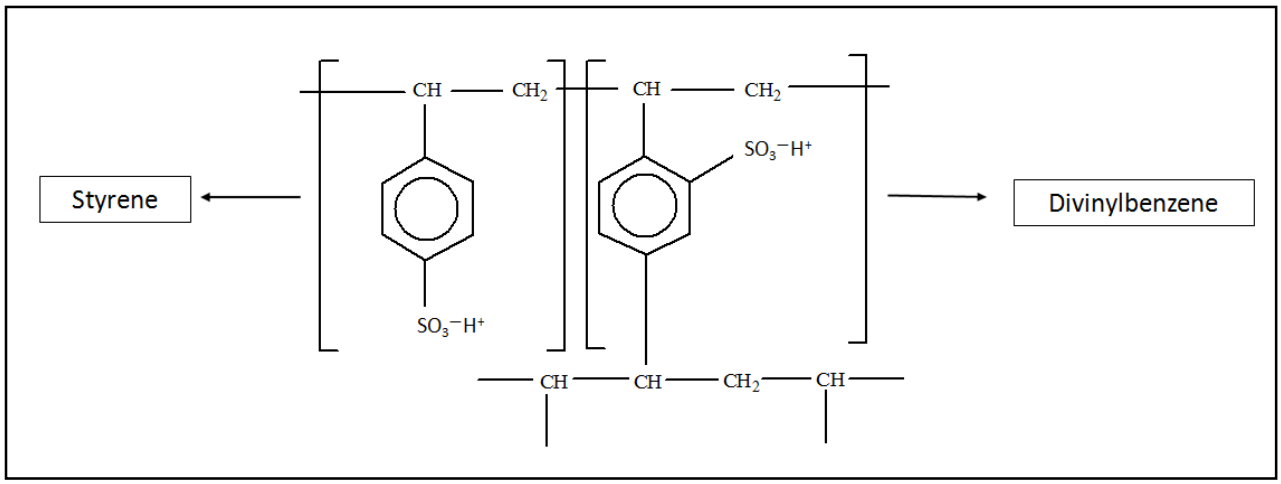

Figure 2: Structure of cation exchange resin.

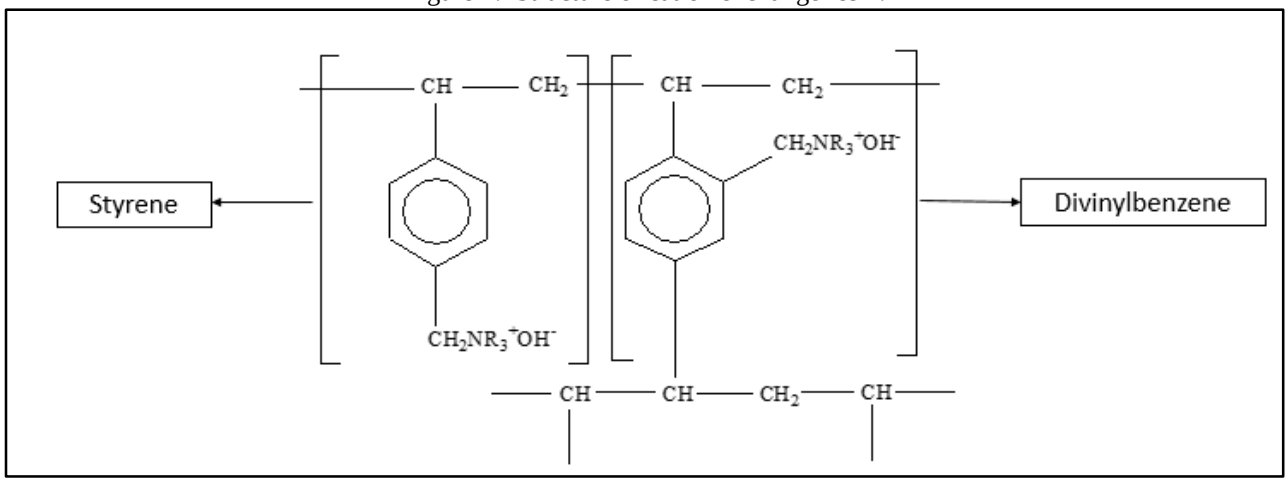

Figure 3: Structure of anion exchange resin.

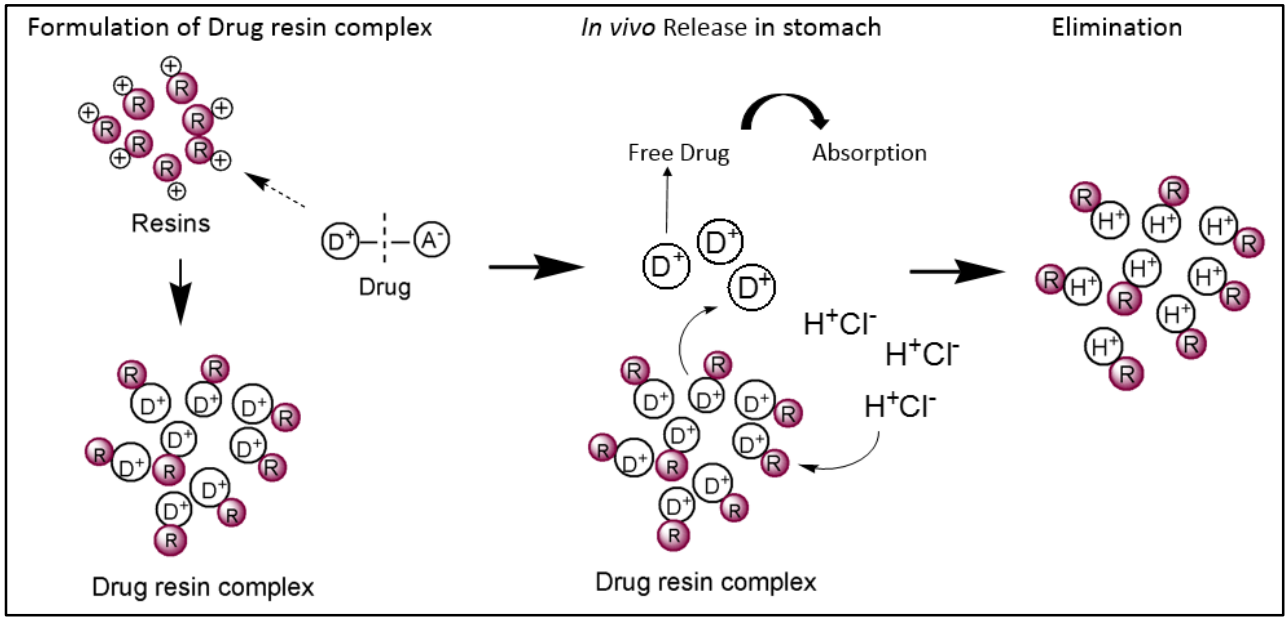

Figure 4: Formulation and In vivo release mechanism.

release resinates of domperidone, again a basic drug. Resinates were prepared using batch method and formulated into combination tablets[17].

Opioid drugs such as morphine and codeine are often associated with side effects such as stomach upset and other gastrointestinal effects. Furthermore they are often associated with addictive properties and are susceptible to

Table 1: Ion exchange resins used in modified release formulations.

Drugs	Ion exchange resin
Venlafaxine hydrochloride (Microencapsulated venlafaxine hydrochloride ion-exchange resins) [20]	Amberlite®IRP69
Ranitidine hydrochloride (Sustained release) [21]	Amberlite® IRP 69
Chlorpheniramine maleate(Oral Controlled Release) [22]	Indion® 244
Diclofenac sodium microcapsules (Prolonged drug release)[23]	Dowex®1-X2
Metformin hydrochloride microcapsules (Prolonged drug release) [24]	Amberlite® IRP69

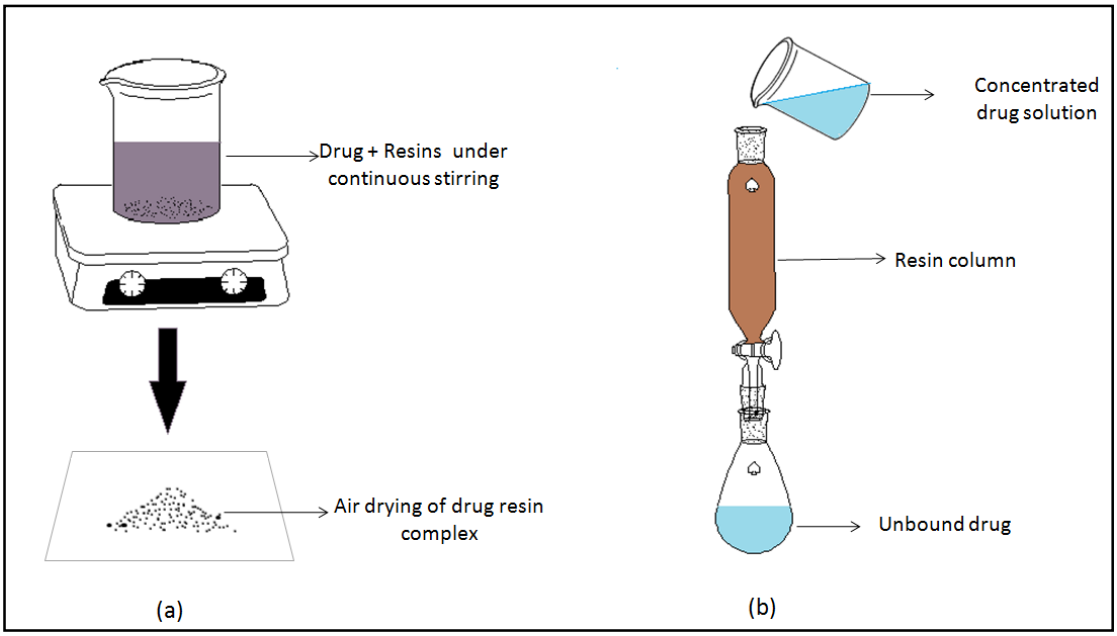

Figure 5: Methods of preparation of resinates (a) Batch process, (b) Column process.

Table 2: Ion exchange resins for taste masking.

Bitter drugs formulation	Ion exchange resin
Sumatriptan succinate (Sublingual tablets)[28]	Kyron T114®
Cefpodoxime paroxetil (Sustained release tablets)[29]	Tusion-311 ®
Etoricoxib (Drug resin complex)[30]	Indion 204®
Diphenhydramine Hydrochloride (Effervescent and Dispersible tablets)[31]	Indion 234® and Tulsion 343®
Chlorpheniramine maleate (Fast disintegrating tablet) [32]	Indion-234®
Quinine sulphate (Suspension)[33]	Indion-234®
Ketoprofen (Edible oral film strip)[34]	Cholestyramine
Donepezil Hydrochloride (Orally disintegrating tablet)[35]	Amber lite IRP-64
Clindamycin Hydrochloride (Oral suspension)[36]	Amber lite IRP-69

abuse. Mehta et al. formed resin complex with cation exchange resins which were coated with a hybrid coating comprising of a barrier coating containing a polyvinyl acetate polymer and a plasticizer and an enteric coating to avoid drug release in the stomach at acidic pH. Enteric coating is provided so that the drug gets released in the intestinal pH (i.e.at higher pH). This barrier coating and enteric coating also provides a favorable abuse resistant property to the formulation. Ion exchange resin helps in sustaining the release of drug from the resin[18].

Liquifer® is an iron controlled release suspension product, designed to provide supplemental iron as once-a-day dosage form in a pleasant tasting liquid form. The iron in the ferrous state is bound to a sulphonic acid ion-exchange resin. The rationale for developing this product is to prevent high concentrations of iron in the stomach, which may cause gastrointestinal distress. The iron-resin complex serves perfectly for this purpose because not more than 25% of the iron in the iron-resin

Table 3: Commercial formulations containing ion exchange resin

Brand name	Drug	Ion exchange resin
NovoNorm (Tablets)	Repaglinide	Polacrilin potassium
Lertus (capsules)	Diclofenac sodium	Cholestyramine
Tussionex (Extended release suspension)	Hydrocodone bitartrate and Chlorpheniramine maleate	Polistirex
Penntuss (Extended release suspension)	Codeine and Chlorpheniramine maleate	Polistirex
Delsym (Extended release liquid for cough suppression)	Dextromethorphan	Polistirex
Nicorette (Nicotine gum)	Nicotine	Polacrilex
Liquifer (Iron supplement)	Iron (Ferrous state)	Polystyrene sulfonate

Table 4: Indion resins for oral formulations[41].

Resin type	INDION desig-nation	Matrix type	Functional group	Standard ionic form	Particle size mm	Moisture content %	Total exchange capacity (meq/ml)	Applications
Weakly acidic cation exchange	204	Crosslinked Polyacrylic	—COO^-	H^+	<0.15	≤5	10.0*	Taste masking of bitter drugs such as Norfloxacin, Ofloxacin, Roxithromycin, Dicyclomin Hydrochloride, Famotidine etc.
Weakly acidic cation exchange	214	Crosslinked Polyacrylic	—COO^-	H^+	<0.15	≤5	10.0*	Taste masking of bitter drugs such as Azithromycin
Strongly acidic cation exchange	224	Styrene Divinylbenzene	—SO_3^-	H^+	0.2-1.2	≤3	4.8*	Sustained release agent in drug formulation
Weakly acidic cation exchange	234	Crosslinked Polyacrylic	—COO^-	K^+	<0.15	≤10	-	Taste masking of bitter drugs such as Ciprofloxacin, Chloroquine Phosphate etc. as well as tablet disintegration.
Weakly acidic cation exchange	234 S	Crosslinked Polyacrylic	—COO^-	K^+	<0.075	≤10	-	Taste masking of bitter drugs as well as tablet disintegration.
Strongly acidic cation exchange	244	Styrene divinylbenzene	—SO_3^-	H^+	<0.15	≤10	4.5*	Sustained release agent in drug formulation
Strongly acidic cation exchange	254	Styrene Divinylbenzene	—SO_3^-	Na^+	<0.15	≤10	-	Sustained release agent in drug formulation
Weakly acidic	264	Crosslinked	—COO^-	H^+	<0.15	≤5	10.0*	Stabilisation of Vitamin B_{12}

cation exchange		Polyacrylic						
Strongly acidic cation exchange	284	Styrene divinylbenzene	—SO_3^-	Na^+	0.3-1.2	≤70	1.0	Sustained release agent in drug formulation
Weakly acidic cation exchange	294	Crosslinked Polymethacrylic	—COO^-	K^+	<0.15	≤10	-	Tablet disintegrant/ taste masking. Product meets specifications of Polacrilin Potassium, USP.
Strongly acidic cation exchange	404	Styrene divinylbenzene	—SO_3^-	Ca^{++}	<0.15	≤8	-	Treatment of hyperkalaemia.
Weakly acidic cation exchange	414	Crosslinked Polyacrylic	—COO^-	K^+	<0.15	≤10	-	As super- disintegrant in mouth disperse tablets, iron & calcium pellets.
Strongly basic anion exchange	454	Styrene divinylbenzene	—N^+R_3	Cl^-	>0.075-45% <0.15-1%	≤12	1.8-2.2**	Cholestyramine resin-used for lowering serum cholesterol levels. Taste masking, drug stabilization, controlled release & active ingredient.
Weakly acidic cation exchange	464	Crosslinked Polymethacrylic	—COO^-	H^+	<0.15	≤5	9.5*	Nicotine taste masking.

**meq/dry gm*

*** sodium glycocholate exchange capacity*

complex would be solubilized in the stomach with normal gastric fluid levels, thus allows reduced gastrointestinal irritation. In addition, iron in resinate form improves taste, reduces tooth staining, and minimizes possible overdoses as compared to conventional products[19].

Fluidized bed Wurster process has been recently used for coating of drug loaded ion exchange resin to form microcapsules that helps in achieving prolonged release of the drug. Ion exchange resin, together with a versatile coating material would be a possible method to prepare a variety of prolonged release microcapsules[23,24]. Table 1 enlists a few examples of ion exchange resins used for modified release formulation.

Another approach of controlled drug delivery is to formulate ion exchange resin into a multiparticulate system such as microspheres. Sriwongjanya.*et.al.,* bound some water soluble cationic drug namely chlorpheniramine maleate, propranolol hydrochloride, pseudoephedrine hydrochloride with Amberlite ® IRP 69 and then microencapsulated with an aqueous solvent evaporation method. The resins were then dispersed in an organic polymer solution comprising of ethylcellulose, poly (methyl methacrylate), Eudragit RS 100 followed by emulsification in aqueous phase. The drug release was found to be dependent on the binding affinities of the drug and the resin. It was repored that there was no drug release from the Eudragit ® RS 100 polymer which would possibly be an effect of interaction between the quaternary ammonium groups of polymer and the sulfonic groups of Amberlite®IRP 69. Pseudoephedrine Hydrochloride was reported to be released faster as compared to chlorpheniramine and propranolol[25].

Sulfopropyl dextran ion-exchange microspheres was formulated for the drug Doxorubicin as an effective delivery system for tumor treatment. Various drug release rates were achieved by varying the drug loading. Doxorubicin microspheres of sulfopropyl dextran showed significant effect on cancer cells *in vitro*[26].

For taste masking

The fact that drug release from ion-exchange materials is highly dependent on the physiological pH and electrolyte concentration within the GI tract can be applied for taste masking of drugs. Typically, the ionized drug and the ion-exchanger form a stable complex under buccal conditions (pH 6.7, low ion concentration) for the relatively short period of exposure, making the drug unavailable for taste sensation. When drug comes across low pH the drug is effectively released.

A study was conducted at Ranbaxy Laboratory for taste masking of Clarithromycin, an antibacterial agent, which is extremely bitter in taste. The research dealt with

development of taste masked resinate of clarithromycin using Tulsion-335, an acidic cation exchange resin.

Evaluation of taste masking and dissolution rate of the drug from resin using various ratios of drug resin complex was carried out (i.e. 1:1, 1:2, 1:3, and 1:4)

The dissolution rate studies in phosphate buffer pH 6.8 showed that approximately 75 % of drug was dissolved in 5 minutes, while in the same period the dissolution of clarithromycin from drug resin complex in 1:3 ratio was below 50%. The dissolution of clarithromycin is thus reduced at salivary pH from the complex[27].

Orodispersible tablet of Doxylamine succinate was formulated and evaluated by Puttewar T et. al. It is an extremely bitter drug which prevents morning sickness in pregnant women therefore it is very essential to mask the bitter taste. Taste masking by ion exchange resin, Indion 234 was employed because of its better drug loading and taste masking.

From the *in vivo* evaluation it was concluded that initially the drug resin complex shows some degree of bitterness but after two minute the bitter taste sensation was totally masked indicating a score 0 in degree of bitterness[37].(Puttewar T. *et al.*,2010). Table 2 enlists some resins used for taste masking of bitter drug formulations

Other applications

Ion exchange resin have the ability to enhance the rate of dissolution of poorly soluble drugs having ionizable properties. Complexation of Atorvastatin calcium with anion exchange resin, Duolite®AP143/1093 enhanced the dissolution rate as well as solubility as compared with the untreated form[38].

Resins also help in stabilization of formulations. The oldest example is of resinate stabilized Vitamin B12. Alone Vitamin B12 has a stability of less than few months but resinate stabilizes the formulation for more than 2 years. Problems of handling deliquescence material while formulation can also be solved by resinate complex formation. Sodium valproate which is known to be highly deliquescent, when complexedwith various ion exchange resins, remains free flowing while the pure drug liquefies under the same conditions[39].

Certain resins also have therapeutic applications such ascholestyramine, acts as a bile acid sequestrant. It acts by removing bile acids from the body and hence lowering cholesterol levels. Some examples of marketed cholestyramine formulations are Questran, Prevalite, Cholestyramine Light, Questran Light[40]. Another example of a therapeutic resin is sodium polystyrene sulfonate which is a cation exchange resin used to treat hyperkalemia. It affects the exchange of sodium and potassium in the body. Kayexalate is a marketed formulation of sodium polystyrene sulfonate.

Some examples of commercialized formulations containing ion exchange resins are listed in table 3. Table 4 enlists pharmaceutical grade Indion resins for oral formulations along with their properties and various applications.

Challenges in formulation

One of the major drawbacks of ion exchange resin formulation is that they are not sufficiently dispersible in water. The lack of dispersibility in water affects the pharmacokinetic profile of the drug. Malkowska S. et al. developed a pharmaceutical ion exchange resin with a high degree of dispersibility in water. The problem of poor dispersibility was overcomed by granulating ion exchange resin using a sugar or sugar alcohol and sufficient amount of water, alcohol or aqueous alcohol to facilitate granulation due to which the water dispersibility was found to be increased to a greater extent[42].

Another problem associated with ion exchange resin, especially cation exchangers gives a sandy feel in mouth that remains in the mouth after oral administration. The cation exchange resin therapy is most popular for daily potassium control in hyperkalemia resulting from chronic and acute renal failure and daily dose of 5 to 30g is required which is quite a large dose. Due to this large dose sandy feel remains in the mouth and throat, and the unpleasant feel may lead to poor compliance. To combat this problem a gelling agent i.e. carboxymethyl cellulose sodium was incorporated in the formulation which causes swelling without disintegration therefore, the sandy feel in the mouth and throat, is reduced and the taste and easiness in oral administration are both improved. The dosage form is granules,powders, or dry syrups, and more preferably in the form of dry syrups[43].

Incompatibilities

Ion-exchange resins are incompatible with strong oxidizing agents, amines, and particularly tertiary amines. There is a history of major incompatibility of ion exchange resins with parabens like methyl and propylparaben.

To investigate this further Elder D et al., manufactured ion-exchange resin development batches, Drug + Resin and only Resin as placebo containing different levels of propylparaben. The percentage of free propylparaben in placebo formulations is much greater than in formulations containing drug substance. This study proved that the drug resin complex binds to the parabens and there is a decreased concentration of propylparaben in drug resin formulation as compared to the placebo. Hence preservative to be used in the resin formulation must be chosen carefully to avoid incompatibilities[44].

Characterization and evaluation of resinates

By monitoring the DSC curves of the drug resin complex, characterization of the resinate complex can be done. FTIR spectrum of the complex can be analyzed. Micromeritic properties of the resins like shape, bulk density, flow properties, tap density, packing ability can be studied to enhance easy formulation[17].

In vitro testing of the drug resin complexes can be done on column and batch exposure of the resinates to the simulated gastric fluid and simulated intestinal fluid[6].

In vivo testing of the drug includes serum concentration level determination, urinary excretion, and toxicity. The complex will release the active content only when it is replaced by the ion which has the same charge. In addition, release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. After the counter ion exchange process is complete, the resin will simply be eliminated from the body with whatever

counter-ions have replaced the drug. The highly insoluble resin never dissolves, and is not absorbed[2].

CONCLUSION

The various uses of ion exchange resins and a summary of basic principles involved in ion exchange process have been discussed. Since resins are inert and non-toxic, they are not absorbed by the body and can be widely used in the pharmaceutical industry.Currently the approach of taste masking with the help of ion exchange resin is widely accepted in the industry due to its economic and simple method of preparation. Few of the regulatory approved resins include polacrilex resin, polacrilin potassium, sodium polystyrene sulfonate and cholestyramine. Various site specific drug delivery systems can be achieved with the use of appropriate resin complex for tumor targeting. Moreover, many novel ideas, such as, bioadhesive, floating, sigmoidal release, pH, ionic strength-responsive formulations and modulated osmotic systems have shown the potential use of ion exchange resins in drug delivery.

REFERENCE

1. Enein A, Singh I, Rehni A, Kalra R, Joshi G , Kumar M, Hassan Y. Ion Exchange Resins: Drug Delivery and Therapeutic Applications, Fabad J. Pharm. Sci 2007; 32: 91-100.
2. Srikanth M, Sunil S, Rao N, Uhumwangho M, Murthy K. Ion-Exchange Resins as Controlled Drug Delivery Carriers, J. Sci. Res 2010; 2 (3): 597-611.
3. Jeong S, Park K. Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix. International Journal of Pharmaceutics 2008; 361: 26–32.
4. Anand V, Kandarapu R, Garg S. Ion-exchange resins: carrying drug delivery forward, Drug Discovery Today2001; 6(17): 905-914.
5. Guo X, Chang R, Hussain M. Ion-Exchange Resins as Drug Delivery Carriers. Journal of pharmaceutical sciences 2009; 98 (11): 3886-3902.
6. Devi M, Krishna P. Advances In Controlled And Novel Drug Delivery (edited by Jain N), Edn 1,CBS & Distributors, New Delhi, 2001, 290-302.
7. Deshmukh H, Dubal A, Desai O, More N, Sha J, Chavan N. Ion Exchange Resins: Pharmaceutical Importance and Recent Advancements, Universal Journal of Pharmacy 2012; 01 (01): 12-18.
8. Motycka S, Nairn J. Influence of Wax Coatings on Release Rate of Anions from Ion-Exchange Resin Beads. Journal of Pharmaceutical Sciences 1978; 67(4): 500-503.
9. Venkatesh DP, Karki R, Goli D, Jha S. Over View- Ion Exchange Resins In Controlled Drug Delivery System, World Journal Of Pharmacy And Pharmaceutical Sciences 2013; 2(6): 4764-4777.
10. Sivaneswari S, Veena D, Sai Sumana P, Subhashree P, Ramya L, Rajalakshmi R, Chandana P, Karthikeyan E. Ion exchange resins as drug delivery carriers, Journal of Chemical and Pharmaceutical Research 2015; 7(4):1436-1445.
11. Bele M, Derle D. Effect of Polacrilin Potassium as Disintegrant on Bioavailability of Diclofenac Potassium in Tablets: a Technical Note, AAPS PharmSciTech 2012; 13(3): 756-759.
12. Heng P, Desai P, Liew C. Review of Disintegrants and the Disintegration Phenomena. Journal of Pharmaceutical Sciences 2016; 105: 2545-2555.
13. Panzade P, Kalyankar P, Lahoti S. Formulation Design and Optimization of Orodispersible Tablets of Quetiapine Fumarate by Sublimation Method. Indian Journal of Pharmaceutical Sciences 2015; 77(3): 267-273.
14. Akkaramongkolporn P, Pattarakan N, Opanasopit P, NgawhirunpatT, RojanarataT. Evaluation of Some Anionic Exchange Resins as Potential Tablet Disintegrants. Tropical Journal of Pharmaceutical Research 2014; 13(10): 1585-1592.
15. P Prashant, J Saurabh, J Pooja. Formulation And Evaluation Of Sr Matrix Tablets Of Glipizide Using Ion Exchange Resin, International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(2): 119-125.
16. Jhunjhunwala H, Naik A. New Dimension in Pain Management: Diclofenac-Colestyramine. Indian Journal of Clinical Practice 2012; 22 (12): 23-27.
17. Bhalekar M, Kadam N, Patil N, Gawale N, MadgulkarA. Novel ion exchange resin-based combination drug-delivery system for treatment of gastro esophageal reflux diseases, Brazilian Journal of Pharmaceutical Sciences 2010;46(2): 335-342.
18. Mehta K, Tu Y, Chaudhuri A, Perumal A. 2012. Abuse Resistant Opioid Drug-Ion Exchange Resin Complexes Having Hybrid Coatings. Patent US 8,202,542 B1.
19. Suhagiya V, GoyaniA, Gupta R. Taste Masking By Ion Exchange Resin And Its New Applications: A Review,IJPSR 2010; 1(4): 22-37.
20. Liu. H, Zhang C, Li X, Zhao X, Sun T, Ju Y, Li N and Pan W,Study of the Formulation Parameters Affecting the Preparation of Microencapsulated Ion-Exchange Resins Containing Venlafaxine Hydrochloride, Indian Journal of Pharmaceutical Sciences2007;69 (4): 550-555.
21. Khan S, Guha A, Yeole P and Katariya P. Strong Cation. Exchange Resin for Improving Physicochemical Properties and Sustaining Release of Ranitidine Hydrochloride, Indian Journal of Pharmaceutical Sciences2007; 69 (5): 626-632.
22. Kadam A, Sakarkar D, Kawtikwar P. Development and Evaluation of Oral Controlled Release Chlorpheniramine-Ion Exchange Resinate Suspension, Indian Journal of Pharmaceutical Sciences 2008;70 (4):531-534.
23. Ichikawa H, Fujioka K, Adeyeye M, Fukumori Y. Use of ion-exchange resins to prepare 100 mm-sized microcapsules with prolonged drug-release by the Wurster process. International Journal of Pharmaceutics 2001; 216: 67–76.
24. Cao J, Liu H, Pan W, Sun C, Feng Y, Zhong H, Shi S, He Y. The preparation of the sustained release metformin hydrochloride microcapsules by the Wurster fluidized bed. Pak. J. Pharm. Sci. 2014; 27(4):779-784.

25. Sriwongjanya M, Bodmeier R. Entrapment of drug-loaded ion-exchange particles within polymeric microparticles, International Journal of Pharmaceutics 1997; 158 :29-38.
26. Liu Z, Cheunga R, Wu X , Ballingera J, Bendayan R, Rauth A. A study of doxorubicin loading onto and release from sulfopropyl dextran ion-exchange microspheres. Journal of Controlled Release 2001; 77: 213–224.
27. Kaushik D, Kumar A, Singh N. Taste Masking of Clarithromycin using Complexation with Ion exchange resin, Int.J.PharmTech Res 2014; 6(1): 203-211.
28. Prajapati S, Patel P, Patel C. Formulation and evaluation of sublingual tablets containing Sumatriptan succinate, Int J Pharm Investig2012; 2(3): 162–168.
29. Bhoyar P, Bhanarkar A, Nagulwar D, Amgaonkar Y, Tripathi A, Bhandarkar S, Muraleedharan R, Mahore J. Taste masked sustained release tablets of Cepodoxime paroxetil, International Journal of Research in Pharmaceutical Sciences 2011; 2(2): 104-109.
30. Patra S, Samantaray R, Pattnaik S , Barik B. Taste masking of Etoricoxib by using ion-exchange resin, Pharmaceutical Development and Technology2010; 15(5): 511-517.
31. Bhise K, Shaikh S, Bora D. Taste Mask Design and Evaluation of an Oral Formulation Using Ion Exchange Resin as Drug Carrier, AAPS PharmSciTech 2008;9(2): 557-562.
32. Yewale CP, RathiMN, Kore GG , Jadhav GV, Wagh MP. Formulation and development of taste masked fast-disintegrating tablets (FDTs) of Chlorpheniramine maleate using ion-exchange resins, Pharm DevTechnol 2013; 18(2):367-76.
33. Patravale V, Prabhu N. Taste masking of QuinineSulphate, Indian Journal of Pharmacaceutical Science 2005; 233-235.
34. Chwen M, Krumme M. 2012, Edible oral strip or wafer dosage form containing ion exchange resin for taste. Patent WO2012167878 A1.
35. Kim J, Cho S, Cui J , Cao Q, Oh E, Lee B. In vitro and in vivo correlation of disintegration and bitter taste masking using orally disintegrating tablet containing ion exchange resin-drug complex, International Journal of Pharmaceutics2013;455: 31–39.
36. Alayoubi A, Daihom B, Adhikari H, Mishra S, Helms R and Hassan A. Development of a taste-masked oral suspension of clindamycin HCl using ion exchange resin Amberlite IRP 69 for use in paediatrics. Drug Development and Industrial Pharmacy 2016; 42(10): 1-11.
37. Puttewar T, Kshirsagar M, Chandewar A, Chikhale R. Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin, Journal of King Saud University (Science) 2010; 22: 229–240.
38. Kulthe V, Chaudhari P. Drug Resinates an Attractive Approach of Solubility Enhancement of Atorvastatin Calcium. Indian J Pharm Sci 2013; 75(5): 523–532.
39. New uses of ion exchange resins in pharmaceutical formulations. (2016). Retrieved 16 December 2016, from http://www.theartofformulation.com/Formulations_doc/unique_solutions.pdf.
40. Drugs. (2000). Cholestyramine - brand name list from drugs.Com. Retrieved December 10, 2016, from https://www.drugs.com/ingredient/cholestyramine.html.
41. Indion ion exchange resins. Properties and applications-summarized data. (2016). Indion Resins. Retrieved 31 December 2016, from http://www.ionindia.com/pdf/Resin%20Summary%20Data%20Sheet.pdf.
42. Malkowska S, Buxton I, Prater D, Norman A. 1991. Pharmaceutical Ion Exchange Resin Composition. Patent 5,071,646.
43. Kamakura M, Imai H. 2000. Cation exchange resin preparation. Patent US 6,280,717 B1.
44. Elder D.Pharmaceutical Applications of Ion-Exchange Resins, Journal of Chemical Education 2005; 82(4): 575-587.