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TASTE MASKING BY ION EXCHANGE RESIN AND ITS NEW APPLICATIONS: A REVIEW

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ABSTRACT

More than 50% of pharmaceutical products are orally administered for several Reasons and undesirable taste is one of the important formulation problems that is Encountered with such oral products. Taste of a pharmaceutical product is an important parameter governing compliance. Hence taste masking of oral Pharmaceuticals has become important tool to improve patient compliance and the Quality of treatment especially in paediatrics. Different methods have been suggested for Masking of taste of bitter drugs, which includes, coating of drug particles with inert agents, taste masking by formation of inclusion complexes, molecular complexes of drug with other chemicals, solid dispersion system, microencapsulation, multiple emulsions, using liposome's, Prodrugs and mass extrusion method but ion exchange resin is one of most extensively Used method to overcome this problem. Ion-exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug-delivery vehicles. In the past few years, IER have been extensively studied in the development of novel drug-delivery systems (DDSs) and other biomedical applications. Also Recently the New Applications of Ion Exchange Resin like Opthalmic Drug Delivery, Anti-Deliquescence, Improve Solubility, and Polymorphism has confirmed. This review highlights complete account of ion exchange resin and its application in drug delivery research are-discussed.

INTRODUCTION: One of the popular approaches in the taste masking of bitter drugs is based on Ion Exchange resin (IER). IER are solid and suitably insoluble high molecular weight poly- electrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 19501. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert[2]. The long-term safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix.

Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected[3]. IER have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Several IER products for oral and peroral administration have been developed for immediate release and sustained release purposes. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, site-specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical and taste masking systems.

POLYMER MATRIX: The most commonly used polymer backbone for anion exchange and strong cation exchange resin is based on polystyrene. Divinylbenzene (DVB) is included in the copolymerization for cross linking the polymer chains. The amount of DVB, usually expressed as percentage by weight has a strong effect on the physical properties. The weak cation exchange resins are generally polyacrylic or polymethacrylic acids with DVB as cross linking agents depending on the presence of ions4. Four major types of ion exchange resins are available which are summarized in Table 1.

CLASSIFICATION OF ION EXCHANGE RESINS (IER): The various ion exchange materials available can be classified as shown in Fig. 1 on the basis of nature of structural and functional components and ion exchange Process. Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger.

Table 1: Common ion exchange resin

Type	Exchange species	Polymer backbone	Commercial Resins
Strong cation	$-SO_3H$	Polystyrene DVB	Amberlite IR 120, Dowex 50, Indion 244, Purolite C100HMR, Kyron-T-154
	$-SO_3Na$	Sodium Polystyrene	Tulsion T-344, Amberlite IRP 69, Indion 254
Weak cation	-COOH		Amberlite IRC 50, Indion 204, Purolite C102DR, Kyron-T-104, Kyron-T-114, Doshion P544(R), Tulsion T-335
	$-COO-K^+$	Methacrylic acid DVB	Tulsion T-339, Amberlite IRP88, Indion 234, Kyron-T-134
Strong anion	N^+R_3	Polystyrene DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	N^+R_2	Polystyrene DVB	Amberlite IR 4B, Dowex 2

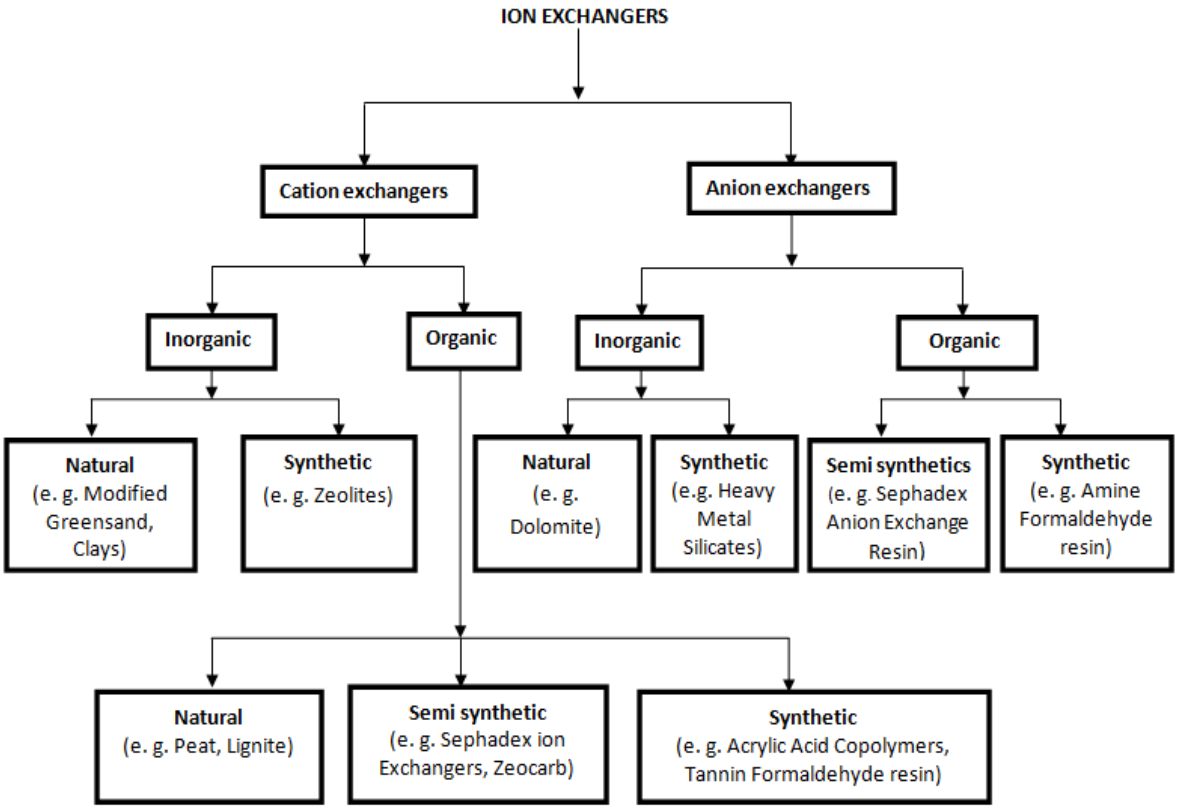

Figure 1: Classification of ion exchange resins

Within each category, they are further classified as inorganic and organic resins. The functional group in cation exchanger and anion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively. The strong cation exchanger contains sulphuric acid sites [Dowex-50] whereas weak cation exchangers [Amberlite IRC-50, Indion 204] are based on carboxylic acid moieties. The strong anion exchange resins [Dowex-1] have quaternary amine ionic sites attached to the matrix, whereas weak anion exchanger [Amberlite IR 4B] has predominantly tertiary amine substituents. Inorganic and organic exchange resin is further categorized into synthetic, semi-synthetic and natural depending on their source[4].

SELECTION OF SUITABLE ION EXCHANGE RESIN: The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER[5]. However, the following points 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–1) of dry resin];
- Degree of cross linking in the resin matrix;
- Particle size of resin;
- Nature of drug and site of drug delivery. It is also 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 volume changes in the resin upon conversion from one form to another. 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 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.

CHARACTERIZATION OF IER: As the performance of DDSs depends on the quality of IER, it is important to evaluate IER at each stage of the preparation of resinates. The following parameters are generally evaluated:

- Particle size – measured directly with a set of micro sieves by screening[6]. The particle size of IER can also be determined by microscopy, Coulter counter [7] and other available techniques.
- Porosity – the porosity of dry IER can be determined through nitrogen adsorption at − 195°C, and by measuring the true density (mercury displacement)[8]. Scanning electron Microscopy reveals the internal pore structure. The use of an air-compression pycnometer for the determination of porosity has also been reported in the literature[9].
- Moisture content – determined by Karl Fischer titrimetry. Excess water can be removed by drying in vacuum desiccators[10].
- IE capacity – the IE capacity of strong CER is determined as meq g–1 by evaluating the number of moles of Na^+, which are absorbed by 1 g of the dry

resin in the hydrogen form[11, 12] Similarly, the IE capacity of a strong basic AER is evaluated by measuring the amount of Cl^- taken up by 1 g of the dry resin in the hydroxide form.

MECHANISM OF BINDING OF ION EXCHANGE RESIN WITH DRUGS: The principle property of resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions adsorbed on the resin as illustrated in equation 1 and 2.

$$Re\text{-}So_3^- Na^+ + Drug^+ \Longleftrightarrow Re\text{-}SO_3^- Drug^+ + Na^+ \quad \text{.....1}$$

$$Re\text{-}N(CH_3)^+ Cl^- + Drug^- \Longleftrightarrow Re\text{-}N(CH_3)^+ Drug^- + Cl^- \quad \text{.....2}$$

These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resins for particular ions. Relative affinity between ions may be expressed as a selectivity co-efficient derived from mass action expression[13] given in equation no. 3.

$$KDM = \frac{[D]_R\,[M]_S}{[D]_S\,[M]_R}$$

Where,

$[D]_R$ = Drug concentration in resin

$[D]_S$ = Drug concentration in the solution

$[M]_S$ = Counter ion concentration in the solution

$[M]_R$ = Counter ion concentration in the resin

Factors that influence selectivity include valency, hydrated size, p^{Ka} and the pH of the solutions.

Borodkin *et al*. used selectivity coefficient to express the interaction of eleven amino drugs with potassium salt of polacrin, a polycarboxylic acid resin. When loading of resin with an ion of less affinity, the exchange may be driven towards the direction of unfavorable equilibrium by flooding the influence with high concentration or by using chromatographic column procedures[3].

RESINATE PREPARATION: Once the selection of a resin is made, the next step involves preparing its complex with drug, before designing a suitable delivery system. The main hurdle is to optimize the conditions of preparation, in order to obtain the desired drug loading in the resinates. Generally, the following steps are involved in the preparation of resinates:

- Purification of resin by washing with absolute ethanol, ethanol and water mixture[14]. Final washing with water removes all the impurities.
- Changing the ionic form of IER might occasionally be required to convert a resin from one form to another, if it does not have the desired counter ions[15]. Strongly acidic CER are usually marketed in Na^+ form and strongly basic AER in Cl^- form. They are generally converted into hydrogen and hydroxide forms, respectively. The conversion can be achieved by soaking the resins with acid or alkali solutions, respectively. After changing the ionic form, the resin is subjected to washing with distilled water

until elute becomes neutral in reaction, and finally is dried at 50°C.

Preparation of resinate is normally done by two techniques:

- Batch technique – after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution until the equilibrium is established[16] and;
- Column technique – resinate is formed by passing a concentrated solution of drug through the IER-packed column until the effluent concentration is the same as the eluent concentration.

DRUG RELEASE FROM IER:

- The rate and completeness of drug desorption in-vivo will be controlled by the diffusion rate of the drug through the polymer phase of the resin,(usually a function of molecular weight),the selectivity of the drug for the resin ,and the concentration of the electrolytes particularly in the hydrogen ion, in the desorption environment[17].
- More hydrophobic drugs will usually elute from the resin at a lower rate, as will drugs with a relatively high selectivity for the carboxylic acid functional structure
- In the resin other resin-sorbate interactions are possible, and these can have a pronounced effect upon loading capacities and rates.
- An example of this might be the presence of the transition metal in the structure of the sorbate molecule which can result in considerable selectivity through the formation of a coordination compound with the resin.

PROPERTIES OF IER:

1. EXCHANGE CAPACITY: The capacity of an ion exchanger is a quantitative measure of its ability 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 resin is 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. The so-called ‘‘available capacity’’ will be 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 onto a resin and the potency of a drug–resin complex. Weak cation exchangers derived from acrylic acid polymers 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 achieved with the carboxylic acid resins[18].

2. CROSS-LINKAGE: The degree of cross-linking depends on the percent DVB used in the copolymerization. The Ion-exchange products available today are limited to a range of 2–16 wt% DVB. Below 2 wt%, the finished ion-exchange materials lack the mechanical strength to resist the volume changes, which occur under normal operation. Above 16 wt%, the polymer structure resists swelling, so that

production of a finished ion exchanger becomes difficult and costly. The amount of DVB determines the extent of swelling and shrinking of ion-exchange resins. The swelling would affect the rate of hydration, the volume expansion of the resin in a column, the rate of exchange of ions, and the capacity of the resin to sorb large molecules. Even after sorption, some large molecules may be difficult to elute unless the DVB fraction is quite low. The excellent swelling properties of the ion-exchange resins, such as potassium salt of polymethacrylic acid resin (Amberlite IRP-88), has been practically used as a tablet disintegrating agent[19, 20].

3. IONIZATION: In all ion exchangers, the ionization of the attached functional group is dependent on the Presence of water in the matrix. The amount of water that an ion-exchange resin will imbibe, in turn, is dependent on the cross-linking of the polymer. The ionization of the functional group determines the type and the strength of an ion exchanger. In aqueous media, strong acid cation and strong base anion-exchange resins are fully hydrated; and the ions associated with the functional group are always free to exchange with ions of like charge in the solution being processed. However, the ionization in weak acid cation and weak base anion exchangers is different. The value at which ionization becomes effective (pKa value) in resins containing sulfonic, phosphoric or carboxylic acid exchange groups is <1, 2–3, and 4–6, respectively. Anion exchangers with quaternary, tertiary, or secondary ammonium groups have apparent pKa values of >13, 7– 9, and 5– 9, respectively. The pKa value of a resin will have a significant influence on the drug release rate from the drug–resinate in the gastric fluids[18].

4. PARTICLE SIZE AND FORM: The rate of ion exchange reaction depends on the size of the resin particles. Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern[18].

5. 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, depends strongly on the porosity. The porosity depends upon 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 inversely proportional to the degree of DVB cross linking present in the resin[2].

6. STABILITY: The ion exchange resins are inert substances at ordinary temperature and excluding the more potent oxidizing agents are resistant to decomposition through chemical attack. These materials are indestructible. They get degraded and degenerated in presence of gamma rays[2].

7. 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 commercial products cannot be used as such because they contain impurities that cause 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 ionexchange resins are insoluble and nontoxic. However, administration of large enough quantities of ion-exchange resin may disturb the ion strength in the gastrointestinal fluids and cause harmful side effects[21, 22].

8. SELECTIVITY OF RESIN FOR COUNTER ION: Since ion exchange resin involves electrostatic forces, selectivity mainly depends on relative charge and ionic radius of hydrated ions competing for an exchange site and to some extent on hydrophobicity of competitor ion[2].

MARKETED RESINS USED AS TASTE MASKING AGENT[23, 24, 25, 26, 27]: There are various marketed resin used for taste masking which are summarized with the examples of bitter drugs in the table 2.

APPLICATIONS OF ION EXCHANGE RESIN (IER) IN PHARMACEUTICAL FORMULATIONS:

1. TASTE MASKING IN CHEWABLE TABLETS AND CHEWING GUMS: Many drugs taste very bitter, thus limiting their use in chewable tablets. The ion-exchange resin complex or drug-resinates offers a method to eliminate the bitter taste and not delay the onset of action. For example, pseudoephedrine is taste-masked by sorbing it into a polymethacrylic acid ion-exchange resin (Amberlite® CG-50) in the chewable Rondec® decongestant tablet. Additional taste masking was achieved by coating the drug-resinate with a polymer mixture of 4:1 ethyl cellulose and hydroxypropyl methylcellulose[28].

Nicorette® is a widely used patented product for smoking cessation. It contains nicotine sorbed to a carboxylic acid ion-exchange resin in a flavoured chewing gum base. The drug-resinate offers a slower drug release for absorption through the buccal mucosa as the gum is chewed. Nicotine is gradually available over a 30- min period by the mechanical chewing activity and the slow elution from the resin particles. It was demonstrated that the ion-exchange equilibrium was rapid and incomplete due to the fixed fluid volume surrounding the chewing gum, but continuous chewing made fresh solvent (saliva) available for the complete release of the drug. A very fine particle size was used in the chewing gum to avoid grittiness of the ion-exchange resin[29]. Other resins used for this purpose are Indion-464, Tulsion-335, Amberlite IRP64, Purolite C115HMR, Kyron-T-104 and Kyron-T-114.

2. DRUG STABILIZATION: Complexing active ingredients with ion exchange resins prevent harmful interaction with other components e.g. Vitamin B_{12} has shelf-life of only a few months and Vitamin B_{12} deteriorates on storage. This necessitates addition of overages, leading to significant increase in the cost of the formulations. The stability of Vitamin B_{12} can be prolonged to >2 years by complexing it with a weak acid cation exchange resin (Indion- 264). This complex is as effective as the free form of the Vitamins[23]. Example of resins used for this purpose are Indion-464, Tulsion-335, amberlite IRP64, Purolite C100HMR.

Table 2: Marketed Ion Exchange Resin as Taste Masking Agent; WEAK CATION EXCHANGERS

Product name (Resin)	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Amberlite IRP64	Methacrylic	-coo$^-$	H^+	10meq/kg	Spiramycin, ranitidine, dextromethorphan, Dimenhydrinate.
Amberlite IRP88	Methacrylic	-coo$^-$	K^+	-	Talampicillin HCl, paroxetine, beta-lactum antibiotics
Tulsion 335	Methacrylic	-coo$^-$	H^+	10meq/g	Norfloxacin, ofloxacin, roxithromycin
Tulsion 339	Methacrylic	-coo$^-$	K^+	-	Chloroquine phosphate, quinine sulphate, ciprofloxacin, paracetamol
Kyron-T-104	Methacrylic	-coo$^-$	H^+	-	Cefuroxime Axetil, Cefpodoxime Proxetil, Norfloxacin
Kyron-T-114	Methacrylic	-coo$^-$	H^+	-	ItoprideHCl, Ofloxacin, Tramadol HCl
Indion 204	Crosslinked polyacrylic	-coo$^-$	H^+	10meq/g	Norfloxacin, ofloxacin, Famotidine, roxithromycin, dicyclomine HCl, Azithromycin
Indion 214	Crosslinked polyacrylic	-coo$^-$	H^+	10meq/g	
Indion 234	Crosslinked polyacrylic	-coo$^-$	K^+	-	Ciprofloxacin, chloroquine phosphate
Indion 294	Crosslinked polymethacrylic	-coo$^-$	K^+	-	
Indion 464	Crosslinked polymethacrylic	-coo$^-$	H^+	9.5meq/g	Nicotine taste masking
Kyron-T-134	Crosslinked polyacrylic	-coo$^-$	K^+	-	Amodiaquine HCl,Cetirizine Di HCl, ChloroquinePhosphate Dicyclomine HCl QuinineSulphate,Ibuprofen Roxithromycin, Cefaclor Metronidazol Benzoate, Dextrometharphan, Cloxacillin Sodium, Erythromycin Estolate, Ciprofloxacin HCl , Erdosteine , Azithromycin
Purolite C102DR	Methacrylic	-coo$^-$	H^+	-	cardio-tonics and anti- depressants
Doshion P544	Methacrylic	-coo$^-$	H^+	-	Roxithromycin

STRONG CATION EXCHANGERS

Product name	Matrix	Functional group	Standard ionicform	Exchange capacity	Examples of Drugs
Amberlite IRP69	Styrene DVB	-SO_3H	Na^+	4.3 eq/kg	ranitidine
Tulsion 344	Styrene DVB	-SO_3H	Na^+	-	Dextromethorphan, dicyclomine HCl
Kyron-T-154	Styrene DVB	-SO_3H	Na^+	-	Erythromycin Stearate

STRONG ANION EXCHANGERS

Product name	Matrix	Functional group	Standard ionic form	Exchange capacity	Examples of Drugs
Indion 454	Crosslinked polystyrine	-N^+R_3	Cl^-	-	

3. CONTROLLED RELEASE DOSAGE FORMS: A drug- resinate incorporated in a tablet or capsule form has long been considered as one of the methods for controlled release applications. For example, Biphetamine® has been used for several decades as an anti-obesity agent and for behavior control in children. The product contains amphetamine and dextroamphetamine (1:1) sorbed to a sulphonic acid cation exchange in a capsule form, and is administered as once or twice daily[30]. Adderal® also contains the same active drug.

4. CONTROLLED RELEASE ORAL LIQUID SUSPENSIONS: Ion-exchange resin as drug delivery carrier used mostly in controlled release liquid preparations. Liquid suspensions containing microparticles or pellets offer many advantages for pediatric and geriatric patients. However, liquid dispersion systems often have physical and chemical stability problems, such as the leaching of the drug from the microparticles into the suspending vehicle and potential interactions of the carrier or coating material with the vehicle during storage[31]. The drug-resinate approach offers a unique and advantageous way to prevent the drug leakage during storage in the liquid form[32]. In a liquid container, the ion-exchange resins can maintain the drug bound by keeping the liquid free of the resin's counter-ions. When administered orally, the ions in the gastrointestinal tract will activate drug release from the drug-resinate at a gradual rate. A rate-controlling coating can often be applied onto the drug-resinates to achieve the desired release profile if the drug-resinates does not achieve the desired controlled release profile.

The Pennkinetic system developed by the Pennwalt Corporation is the most notable application of the ion-exchange resins for the preparation of controlled release liquid suspensions[33]. In this system, the drug-resinates are further treated with an impregnating agent, for example, PEG 4000, to retard the rate of swelling in the water and subsequently are coated with ethylcellulose film, to act as a rate-controlling barrier to regulate the release of the drug from the system. The advantages of this type of gastrointestinal drug delivery systems are as follows;

1. The rate of the drug release is relatively constant and is not dependant on pH condition, enzyme activities, and temperature of the GI tract.

2. The system is administered in the form of large number of particles, which helps to eliminate the release differences due to changes in gastrointestinal motility and gastric emptying, because the dose will be more evenly distributed in the GI tract.

3. It can be prepared in liquid suspension form and can eliminate the bitter taste of the drug.

Several commercially available controlled release liquid suspensions using ion-exchange resins are discussed below;

Delsym® (Dextromethorphan): Delsym® is a liquid suspension product, designed to provide relief of coughs as twice-a-day dosage form in a flavored liquid form. The active drug is bound to a sulphonic acid ion-exchange resin and then the drug-resinates are coated with ethylcellulose. The bioavailability of the product is

equivalent to the dextromethorphan HBr solution[34].

Liquifer® (Iron): Liquifer® is an iron controlled release suspension product, designed to provide supplemental iron as a once-a-day dosage form in a pleasant-tasting liquid form[35].The iron in the ferrous state was 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 no more than 25% of the iron in the iron-resin 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.

Penntuss® (Codeine and Chlorpheniramine): Penntuss® is a liquid suspension product designed for 12h cough/cold relief. Two drugs are bound to a sulphonic acid cation-exchange resin, and the codeine resinates are coated with ethylcellulose while the Chlorpheniramine-resinates are uncoated due to much high affinity for the resin[36].

5. OPTHALMIC SUSPENSION: Betoptic S® is the sterile ophthalmic suspension containing 0.25% betaxolol HCL, a cardioselective beta-adrenergic receptor blocking agent, in a resin suspension formulation. This is the first drug-resinate ocular product approved by the FDA and is marketed in U.S. since February 1990[37]. It was designed to lower elevated intraocular pressure. Alcon Laboratories main purpose of developing this product is to improve the ocular comfort of betaxolol solution upon instillation without compromising the efficacy. The enhanced comfort of Betoptic S® is based on drug-resin complex in which the positively charged drug is bound to a cation exchange resin (Amberlite® IRP 69). Since Betaxolol HCL and the resin are present in Betoptic S® in approximately equimolar ratio, conditions in the suspension allow about 85% of the drug to be bound to the cation-exchange resin beads. In order to obtain ultra fine ophthalmic quality suspension, the ion-exchange resin beads are milled to a mean diameter of 5µm, which is smaller in size to steroid particles found in opthalamic formulations.

In the eye, the drug is released from the drug-resinate by exchanging with sodium ions in tears. Thus the drug is released relatively slow in the tear. Since betaxolol is released into the tear more slowly from Betoptic S® than from Betoptic solution, ocular comfort is enhanced. In addition, carbomer 934P, a water soluble polyacrylic acid polymer is added to stabilize the suspension and increase the ocular residence time. Bioavailability studies showed that 0.25% resinate suspension was equivalent to 0.5% Betoptic solution.

Also in two U.S. patents, Chang teaches the use of pH sensitive and thermo-sensitive gelling agents to slow down the drug release and to stabilize the suspension. The preparations are particularly suitable for ocular delivering of drugs (e.g., epinephrine, levobunolol) [38, 39].

6. TABLET DISINTEGRATION [IMPROVED TABLET DISINTEGRATION PROPERTIES]: Many tablets disintegrant owe their action to capacity to absorb water and swell up. Fine particle size ion exchange resins have shown superiority as disintegrating agent due to their considerable swelling pressure upon hydration. Advantages of ion exchange resins over conventional disintegrating agents are;

1. Rate of permeation of water and subsequent swelling is very fast and cut down the disintegration time.
2. Ion exchange resins do not have adhesive tendency on hydration; hence tablet disintegrates evenly without formation of lumps.
3. Ion exchange resin is effective in low concentration as disintegrants.
4. Ion exchange resin incorporation confirms greater hardness to tablet.
5. Ion exchange resin work equally efficiently with hydrophilic as well as hydrophobic formulations, especially with the later where the conventional disintegrants are ineffective.

Because of their unusually large swelling capacities polymethacryllic carboxylic Acid ion exchange resins have found usage in pharmacy as tablet disintegrants; for example pollacrilline a potassium salt of weakly acidic cation exchange resin with methacrylic acid divinyl benzene matrix[40, 41].

Borodkin and Yunker investigated chances of interference of cation exchanger disintegrants with drug availability and assay. They concluded that such agents should not affect total in vivo availability. It was questionable, however, if any significant delay in Absorption would occur. While assaying amine drugs buffers above 7 or below 3 or Solutions with high cation concentration may be used to affect complete drug elution[42].

Examples of resins used for this purpose are Indion-234S, Tulsion-339, Amberlite IRP88, Kyron-T-314, and Purolite C115KMR

7. BIOADHESIVE SYSTEM FOR TREATMENT OF GASTRIC MUCOSA: Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions[43]. Hence ion exchange resins may be useful in mucoadhesive systems for topical treatment of stomach such as *H. pylori* infection for prolonging the gastric residence of amoxicillin and cimetidine[44].

8. CHOLESTEROL REDUCER: Cholesterol is essential for human and animal life, but an excess of cholesterol in the blood is one of the most important and recognized risk factors in cardio-vascular disease. Cholesterol is converted by the liver into bile acids, which, when discharged into the Duodenum, emulsify ingested fats, thereby assisting digestion. The bile acids are absorbed through the intestine and are returned to the liver, where they are converted, through a chain of reactions, to low density lipoprotein (LDL) cholesterol.

The metabolism of cholesterol is subject to a delicate balance. This balance can be disrupted to the point where there is such a high accumulation of LDL cholesterol in the blood that it precipitates as cholesteryl esters on the walls of blood vessels, restricting flow and

leading to potential heart attacks. It can, therefore, be advantageous, in such cases, to reduce cholesterol levels. Cholestyramine is a non-absorbable, non-metabolisable anion exchange resin which, by complexing the bile acids, prevents their re-absorption and allows them to pass through the body. The reduction of bile acids causes a depletion of hepatic cholesterol, which, in turn, stimulates the transformation of LDL cholesterol into hepatic cholesterol, thereby reducing LDL cholesterol levels and lowering the total cholesterol level in the blood[27].

The advantage of Cholestyramine over other drugs is that there are little side effects. Besides the treatment of hypercholesterolemia, Cholestyramine has other medical Applications, such as: improving diarrhoeal states by significantly reducing the activity of endotoxins; treating vitamin D_3 overdose; and as recent studies indicate, regression in arteriosclerosis. Listed in pharmacopoeia as “Cholestyramine”, Purolite A430MR is a powdered Anion exchange resin in the chloride form. The powder resin is flavored by the Pharmaceutical Company, and prepared in doses to be dispersed in water or fruit juice for oral consumption. Examples of resins used for this purpose are Indion-454, Tulsion-412(CHL), Duolite AP143/1093, and Purolite A430MR.

9. IMPROVED DISSOLUTION OF POORLY SOLUBLE DRUGS: The slow dissolution of poorly soluble drugs is well known problem responsible for poor bioavailability. The release rate of such drugs from resinates can be much quicker than the dissolution rate of the pure drug[44].

Eg. Indomethacin which is soluble up to ca 6ppm in simulated gastric fluid, but is release very quickly from resinate. the commercially available product indomethacin uses micronization of the drug powder to achieve rapid dissolution[44].Not all poorly soluble drugs are amenable to micronization because of the problems including low melting point, dust formation and agglomeration.ion exchange resins are convenient alternative. The rapid dissolution occurs due to two factors,

1. Each individual molecule is bound to a functional site-there is no crystal lattice energy to overcome.

2. The ion exchange materials are relatively hydrophilic and so allow water and aqueous solutions easy access in to the 3-dimensional structure- eliminating problems with ‘wetting-out' the drug.

However this technique like micronization increases the rate of dissolution. It does not increase the solubility of the drug.

10. ANTI-DELIQUESCENCE: Deliquescence is the property of a solid whereby it absorbs so much water that it dissolves in the water it absorbs. This problem is very difficult to solve, and requires the use of specialized equipments or careful scheduling of a production in dry seasons[44]. A very recent discovery by Rohm and Hass research laboratories show that using resinates can eliminate deliquescence during manufacturing and storage. Rohm and Hass have filed the

patent application for it. They have found that resonates of deliquescent and highly hygroscopic drug retain the properties of the resin and are not deliquescent and remain free flowing powders. Their water absorption characteristics are similar to those of unloaded resin.so, that any formulation equipment that can handle the resin can handle the resinate of the deliquescent drug without need for special manufacturing conditions.

For example sodium valproate is a drug which is well known to be highly deliquescent. However they have found that valproate resinates remain free-flowing even after exposure to ambient air.

11. POLYMORPHISM: Unlike deliquescence, polymorphism is a very common problem in 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 problems can result in significant stability problems for the final dosage form[44]. Ion exchange resin presents a unique way to deal with the problem. a drug resinate is an amorphous solid that cannot crystallize or even form hydrates. In addition the release of the drug from the resinate is independent of the crystal form that was used to make it. Consequently using resinates completely eliminate any problem with polymorphism.

12. TREATMENT OF HYPERKALEMIA: Excess potassium in the blood is a common condition in chronic renal failure and is potentially life threatening. The action of the resin is simple ion exchange .the resin is in sodium or calcium form and this ions are exchanged with the excess potassium in the blood stream as the resin pass through the GI tract. Typical dosage amounts are 15-60 g per day for extended period of time. Formulations are either powder sachet or aqueous suspensions[23]. Various resin used for this purpose are Indion-404, Tulsion-344, Tulsion-345, Purolite C100NaMR, Purolite C100CaMR.

13. SITE-SPECIFIC DELIVERY OF DRUGS FOR CANCER TREATMENT: Entrapment of anticancer drugs within the particulate carriers (microspheres, microcapsules) is a popular approach for the development of delivery systems for cancer treatment. Several anticancer drugs (e.g. doxorubicin) are ionic in nature and can be complexed with IER. Attempts have been made to deliver some of these drugs in a controlled-release fashion to the anticancer cells with the help of IER[45, 46]. These studies revealed that the drug loading is at its maximum level with the IER complex approach. The mechanism of complexation of doxorubicin with ion-exchange albumin microcapsules was studied[11]. These studies proved the chemical Stability of anticancer drugs in IER microcapsules.

CONCLUSION: Taste masking of drug by ion exchange resin is economical, simple and convenient method. Various techniques are used to mask the bitter taste of drug. But one of the most Economical method for taste masking is the use of ion exchange resin. Ion exchange resins have been used in pharmacy and medicine for various functions, which include tablet disintegration, bioadhesive systems, sustained release systems. The use of IER in drug delivery research is gaining

importance and commercial success. In addition to oral drug delivery, IER systems are being explored for site-specific, transdermal, nasal and ophthalmic Routes. Moreover, several novel concepts, such as sigmoidal Release, floating, pH and ionic strength-responsive systems, have shown the potential use of IER in drug delivery.

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