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A REVIEW ON ION EXCHANGE RESINS AS DRUG DELIVERY SYSTEM

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Abstract

Ion exchange resins (IER) are cross-linked water insoluble polymer carrying ionizable functional groups. Insoluble functional groups that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. Ion exchange resins are categorized as either cationic or anionic exchange resins based on the type of exchangeable ions they contain. These resins are composed of polymers with specific acidic groups like carboxylic or sulfonic for cation exchangers, and basic groups like quaternary ammonium for anion exchangers.The efficacy of ion exchange resins mainly depends upon their physical properties such as degree of exchange capacity, cross-linkage, ionization, porosity and swelling, particle size and form, purity, toxicity and equilibrium rate. Ion exchange resins (IER) have garnered significant interest among pharmaceutical scientists due to their versatile properties as carriers for drug delivery. Scientist over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking. The drawback of sustained release or extended release is dose dumping, resulting in increased risk of toxicity. Ion exchange resins play a crucial role in the advancement of controlled or sustained release systems due to their effective drug retention properties and the prevention of dose dumping. Synthetic ion exchange resins have found applications in pharmacy and medicine, serving purposes such as taste masking and sustained or controlled drug release. This review addresses different types of ion exchange resin, their applications, role of IER in controlled drug delivery systems.

Keywords: Ion exchange resins, Drug release, Taste masking, Drug delivery

INTRODUCTION

Ion exchange resins (IER) are cross-linked, synthetic, high molecular weight, water insoluble polymers, usually white or yellowish, fabricated from the organic polymer having an ionizable functional group. Control drug delivery systems (Novel Drug) are gaining momentum in the last two decades as they offer decrease frequency of dosing and patient compliance. One of the best techniques for modified drug delivery systems is the use of ion exchange resins (IER) as carriers for such systems [2]. Complexes between IER and drugs are known as ion exchange resonates, which have been used in pharmaceutical formulations for several decades [2,3]

The drug is released from resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion [3]. Resins, characterized by their high molecular weight and water-insolubility, exhibit non-absorbent properties within the body, making them inert. Ion exchange resins (IER) have gained significant recognition among pharmaceutical researchers due to their versatile qualities as carriers for drug delivery. In recent years, there has been substantial research dedicated to exploring the potential of IER in the development of innovative drug delivery systems and various other biomedical applications. The use of IER has occupied an important place in the development of controlled- or sustained-release systems because of their better drug-retaining properties and prevention of dose dumping [1]. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking [3]. IER are insoluble polymers which carry acidic or basic functional groups and that have the capability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is like a small bead with a diameter in between 1-2 mm. These are generally white or yellowish and it is fabricated from an organic polymer substrate backbone [4]. Ion exchange is a reversible process in which ions of like sign are exchanged in between liquid and solid when in contact with the highly insoluble body [5]. Ion-exchange systems are beneficial for drugs that are highly susceptible to degradation by enzymatic process. An important advantage of this ion exchange system is the low cost.

Advantages of IER

1. Reduction in frequency of drug administration.
2. Can be used for several purposes such as taste masking, sustained and rapid release.
3. Reduction in drug level fluctuation in blood.
4. Reduction in drug toxicity (local/systemic).
5. Improvement in the bioavailability of some drugs.
6. Enhanced patient compliance.
7. Economic and readily available.

Disadvantages of IER

1. Decreased systemic availability in comparison to immediate release conventional dosage forms and poor in vitro and in vivo correlations [1].
2. Dose dumping is serious problem.
3. Requirement for additional patient education for proper medication in proper time.

Structure and Chemistry of Ion Exchange Resin

IER are simply insoluble polyelectrolyte 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 [7]. When IER are mixed with a fluid such as water, ions in the fluid can exchange with the polyelectrolyte counter Ions 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.

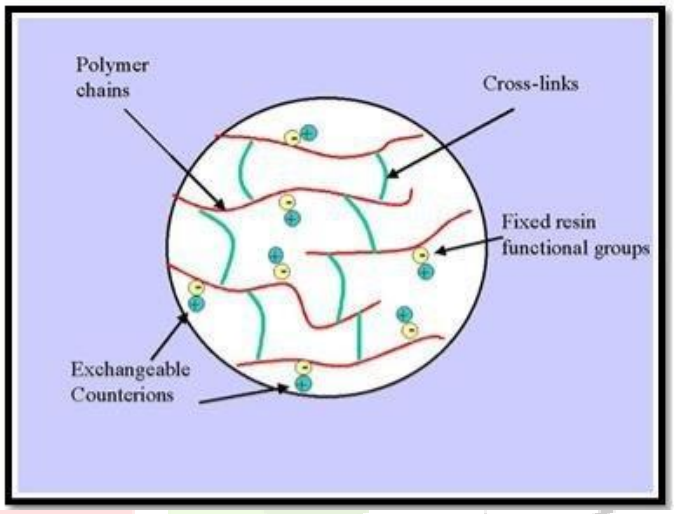

Fig.1: Expanded view of resin bead

Commonly used for man-made ion exchange resins. These are:

• -COOH, which is weakly ionized to $-COO^{-}$

• -SO3H, which is strongly ionized to $-SO3^{-}$

• -NH2, which weakly attracts protons to form NH3+

• -secondary and tertiary amines that also attract protons weakly

• -NR3+ , which has a strong, permanent charge (R stands for some organic group)

Classification of ion exchange resins

There are two classes of ion-exchange polymers 12 (Fig. 1)

A. Cation exchange resin

B. Anion exchange resins.

These are discussed in the following two sub-sections:

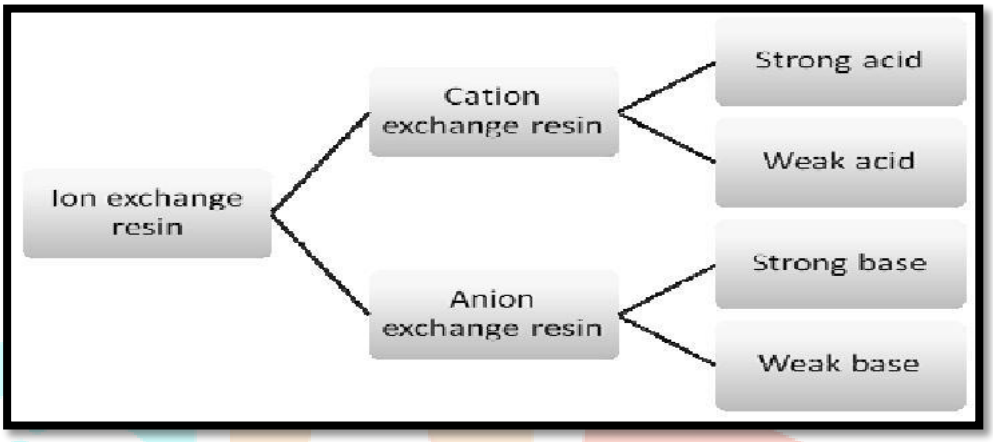

Fig.2: Classification of IER

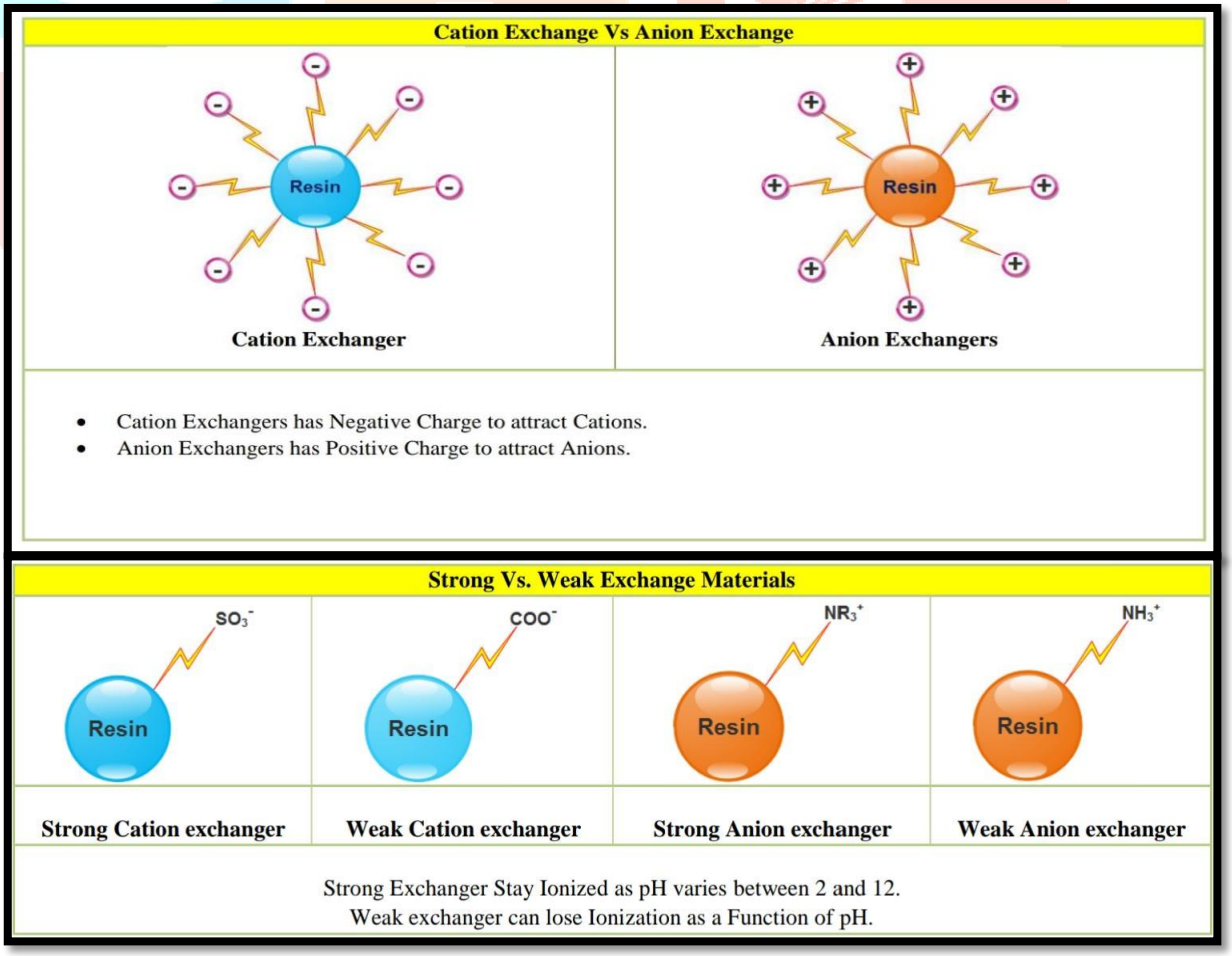

fig.3: Schematics of Cation & Anion Exchange Resin

A. Cation Exchange Resins

Whose exchangeable ions are positively charged: Cation exchange resins are prepared by the copolymerization of styrene and divinyl benzene and have sulfonic acid groups (-SO3H) introduced into most of the benzene rings. The mechanism of cation exchange process can be represented by the following reaction:

$$\mathbf{Resin^{-} - ex+ + C+ \rightarrow Resin^{-} - C+ + ex+}$$

Where, Resin-indicates a polymer with SO3-sites available for bonding with exchangeable cation (-ex+), and C+ indicates a cation in the surrounding solution getting exchanged.

1) Strong Acid Cation Exchange Resins

Strong acid resins are so named because their chemical behavior of the resin is usually similar to that of a strong acid. These resins are highly ionized in both of the acid (R-SO3H) and salt (RSO3Na) form of the sulfonic acid group (-SO3H). They can convert a metal salt to the corresponding acid by the help of reaction :

$$\mathbf{2(Resin\text{-}SO3H) + NiCl2 \rightarrow (Resin\text{-}SO4)\ Ni + 2HCl\ (2)}$$

The hydrogen (H+) and sodium (Na+) forms of that strong acid resins are generally highly dissociated, and where the exchangeable Na+ and H+ are available for exchange over the entire pH range. Consequently, the exchange capacity or the ability of strong acid resins is independent of the solution pH [12].

2) Weak acid cation exchange resins

These resins behave similarly to weak organic acids that are weakly dissociated. In weak acid resins, the ionizable group is carboxylic acid (-COOH), whereas strong acid resins use sulfonic acid (-SO3H) groups. The extent to which a weak acid resin undergoes dissociation is greatly affected by the pH of the solution it's in. As a result, the resin's capacity is partially determined by the pH of the solution. Typically, a weak acid resin has a restricted capacity when the solution's pH is below 6.0, making it unsuitable for deionizing acidic metal finishing waste water.

B. Anion exchange resins

The anion exchange resins having positively charged functional groups and generally exchanges negatively charged ions. These are prepared by first chlormethylating the benzene rings of styrene-divinyl benzene copolymer to attach CH2Cl groups and then causing these to react with tertiary amines such as triethylamine. The mechanism of anion exchange process can be represented by the following reaction:

$$\mathbf{Resin+ - ex^{-} + A^{-} \rightarrow Resin+ - A^{-} + ex^{-}}$$

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

1) Strong base anion exchange resin

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

Resin-NH3OH + HCl → Resin-NH3Cl + H2O

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

2) Weak base anion exchange resin

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

Resin-NH2 + HCl → Resin-NH3Cl

Accordingly, regeneration needs only to neutralize the absorbed acid; it does not need provide OH ions. Inexpensive weakly basic reagents such as ammonia (NH3) or sodium carbonate can be generally employed.

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 [13, 15].

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 [16]. The physical and chemical properties of the IER will release the drug more uniformly than that of simple matrix formulations [11]. 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 resin.

Resin- Drug+ + X+ → Resin-….X+ + Drug+

Resin+ Drug- + X- → Resin+…X- + Drug-

IER have been used as a drug carrier in pharmaceutical dosage forms for the controlled release formulations[17-19]. The prolonged release of an active drug is accomplished by providing a semi-permeable coating. On the Ion exchange resin particles, the drug component has been complexed to form an insoluble drug resin complex. The semi-permeable coating creates a diffusion barrier and the thickness of that diffusion barrier which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time. Many of the preparations which generally involving strong resinates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resinates of carboxylic acid. Hence, resinates of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles[21-22].

MECHANISM OF IER

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.

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[19].

Factors Affecting Loading Of Drug Into & Release From The Ion-exchange Material

Ion exchange process depends upon various factors like relative affinity, Cross linkage of eesin, particle size, pH, form of resin, Size of exchanging ions, selectivity of counter ions, mixing times etc.

Factor	Mechanism of Effect
1. Ion-exchanger Dependent	
Ion-exchange capacity	Donnan potential, number of ionic binding sites.
Nature of fixed ionic groups	Ionisation, selectivity
Preloaded counter-ion	pH, selectivity
Particle size	Surface area, particle diffusion
Degree of cross linking	Pore size of ion exchanger, particle diffusion
2. Drug Dependent	
Lipophilicity	Binding affinity
pka	Ionisation
Stearical properties	Binding accessibility
Molecular size	Diffusion coefficient, binding affinity, binding accessibility
3. External Conditions	
Concentration of solution	Donnan potential
pH	Ionisation of drug and ion-exchanger
Temperature	Porosity of ion-exchanger, diffusion
Agitation	Film diffusion

Table 1: Factors Affecting Loading of Drug into & Release from the Ion-Exchange Material

APPLICATIONS OF IER

- ✓ Water Production
- ✓ Wastewater Treatment
- ✓ Radioactive Waste Treatment
- ✓ Recovery of metals
- ✓ Chemical analysis
- ✓ Enzyme immobilization
- ✓ Separation and Purification in Food Industry

Pharmaceutical Applications

I. Taste Masking

The excessive bitterness of the active principal ingredients (APIs) in oral formulations is the major taste problem faced by the pharmaceutical industry. The bitterness of formulations can influence selection by physicians and markedly affect patient compliance [10]. 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 a simple, rapid and cost-effective method of taste masking.

II. Rapid Dissolution

Ion exchange drug resonate complexes have a faster rate of dissolution. Ion exchange resin matrices are hydrophilic and hence allow Water/aqueous solutions to enter the dimensional resin structure, thereby enhancing the dissolution rate.

III. Chewing gum for buccal absorption

Nicotine is a widely used patented product for smoking cessation program. It contains nicotine adsorbed on an ion exchange resin with carboxylic acid functionality and formulated in a flavored chewing gum base provides gradual drug release through buccal mucosa as the gum is chewed offering fresh saliva as solvent for elution.

IV. Cholesterol reducer

Cholestyramine resin USP, When used as an active ingredient binds bile acids, this Leads to replenishment of bile acids; through increased metabolism of serum cholesterol resulting in lowered serum cholesterol levels.

V. Targeted drug delivery system [Anticancer drug]

This concept is based on the chemoembolished of drug-loaded microspheres via the tumour arterial supply. Because of their physical size microspheres can be entrapped in the capillary beds along with their load of cytotoxic drugs can be delivered to well vascularised tumour tissues. B.N.gray has studied the in vitro release of cytotoxic agents from cytotoxic agents from ion exchange resins.

Drug Delivery Applications of IER

- ✓ Oral drug delivery
- ✓ Ophthalmic drug delivery
- ✓ Nasal drug delivery
- ✓ Targeted drug delivery system
- ✓ Transdermal drug delivery
- ✓ Bioadhesive System

CONCLUSION

In recent years, Ion Exchange Resins (IER) have demonstrated their effectiveness in masking the bitter taste of pharmaceutical drugs. These resins play a crucial role in altering drug release patterns by forming complexes with the active drug compounds. In the fields of pharmacy and medicine, IERs have found diverse applications, including tablet disintegration. This article aims to provide a comprehensive review of the literature, covering topics such as resin manufacturing, properties, preparation methods, and various applications. The objective is to encourage researchers to harness these resins more efficiently in the formulation of advanced drug delivery systems.

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