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ION EXCHANGE RESINS AS DRUG DELIVERY CARRIERS

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ION EXCHANGE RESINS AS DRUG DELIVERY CARRIERS

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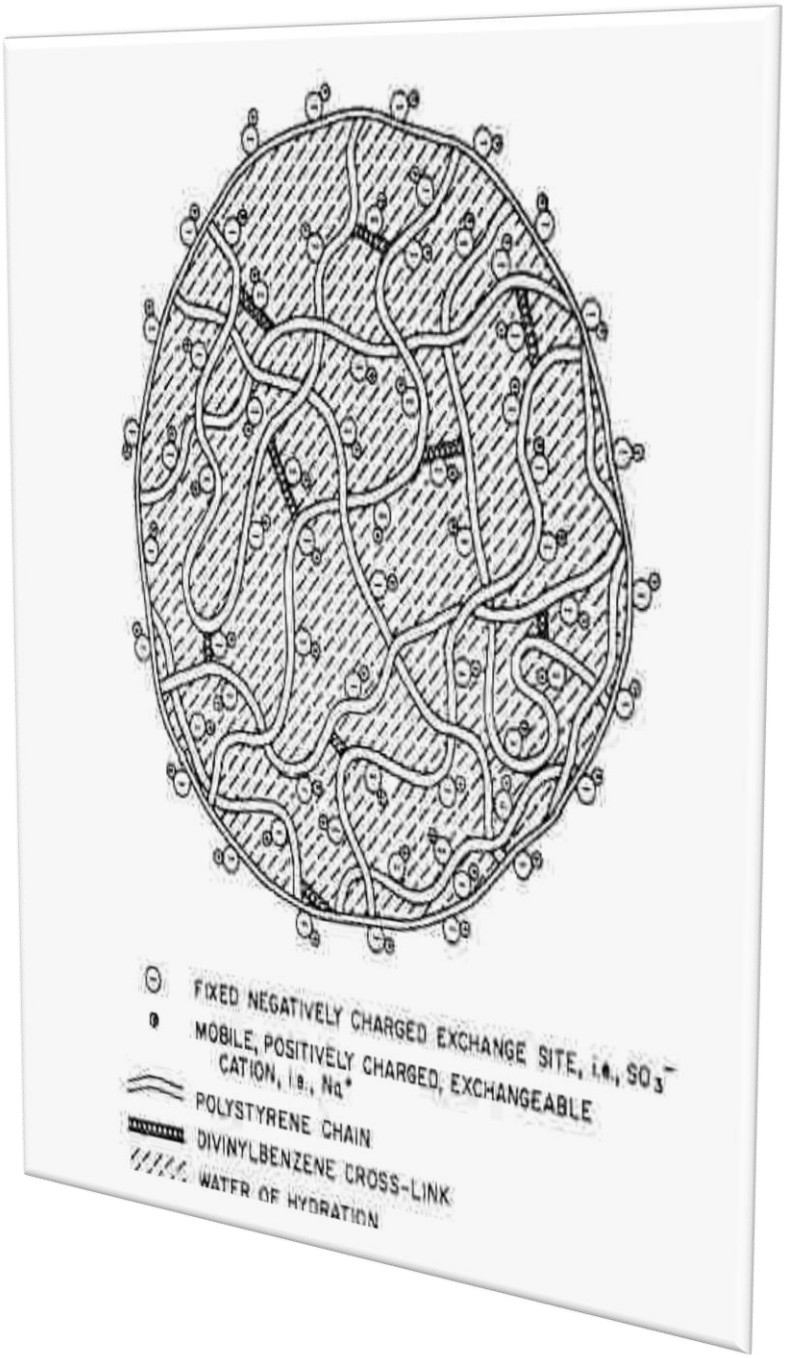
1. Introduction

- Ion exchange resins (IERS) are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them.
- An ion exchange resin is an insoluble matrix (or support structure) normally in the form of small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate backbone.
- The material has a highly developed structure of pores on the surfaces from where the ions are trapped or released. The trapping of ions takes place only with simultaneous release of other ions; thus, the process is called ion exchange.

2. Chemistry

- An ion exchange resin is a polymer (normally styrene) with electrically charged sites at which one ion may replace another.
- Natural soils contain solids with charged sites that exchange ions, and certain minerals called zeolites are quite good exchangers.
- Ion exchange also takes place in living materials because cell walls, cell membranes and other structures have charges.
- Synthetic ion exchange resins are usually cast as porous beads with pore surface where ions can attach.
- Spherical beads 0.5 to 1.0 mm in diameter.



3. **Advantages**

- Maintain drug levels in desired range
- Increased patient compliance
- Need for less dosing
- Economic and readily available.
- Free from local and systemic toxicities.

- Drug-resinates can be formulated into various dosage forms like tablets, capsules, suspensions etc.
- Can be used for several purposes such as taste masking, sustained and rapid release.
- Effectively useful in low concentration (5-20%w/w).
- Resins have high drug loading property.

<u>Clinical Advantages</u>

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

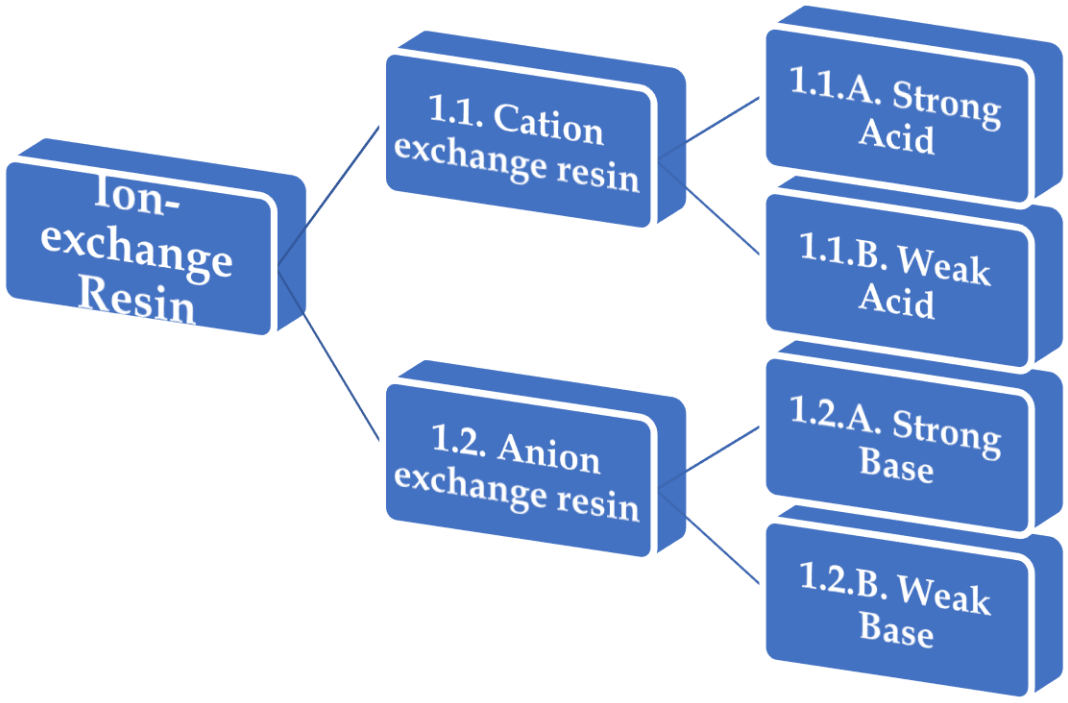
Disadvantages

- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms and poor *in vitro* and *in vivo* correlations

COMMON ION EXCHANGE RESIN:

Name of the Drug	Ion Exchange Resin
Ciprofloxacin	Indion-234
Azithromycin	Indion-214
Chloroquine phosphate	Indion-234
Chloprquine sulphate	Indion-234
Dextromethorphan hydrobromide	Indion-234
Norfloxacin	Indion-204

4. **Types of Ion-exchange Resins**



1.1. Cation exchange resin

- 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:

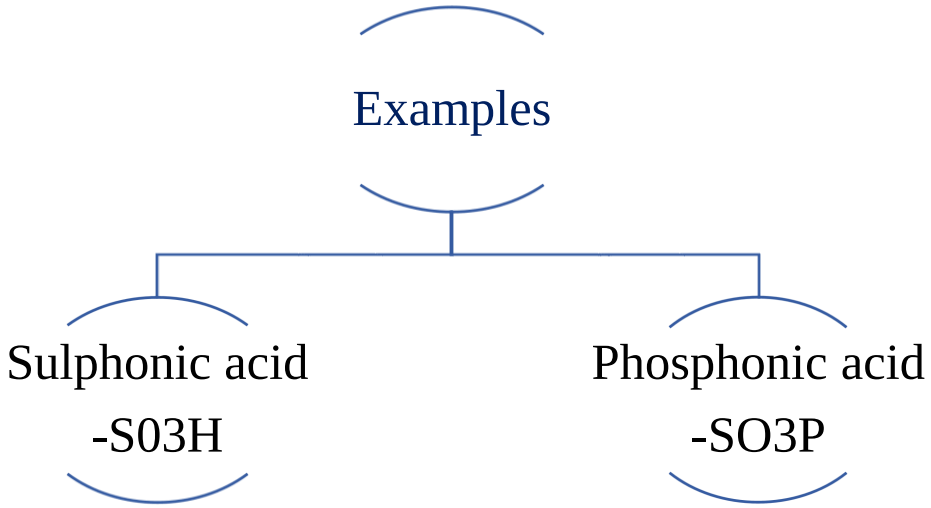
Resin- - ex+ + C+ → Resin- - C+ +ex+

- 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 (6).

1.1.A. Strong Acid Cation Exchange Resins

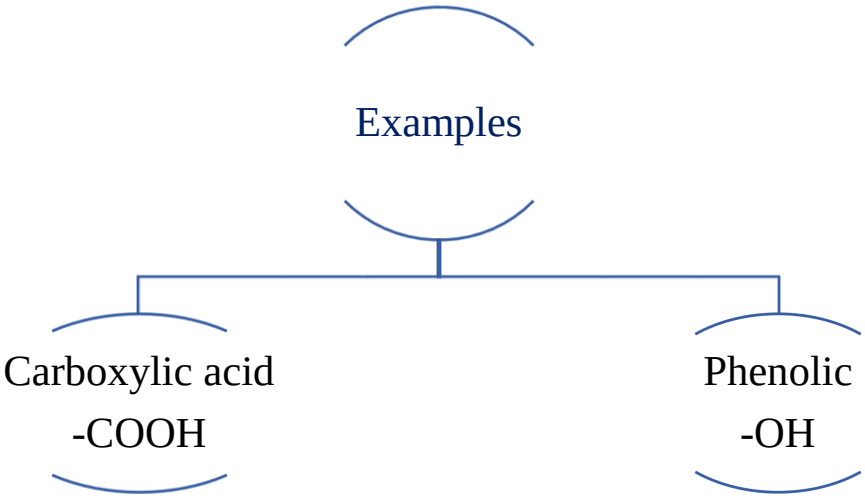
- Strong acid resins are so named because their chemical behavior is similar to that of a strong acid.
- These resins are highly ionized in both the acid (R-SO3H) and salt (RSO3Na) form of the sulfonic acid group (-SO3H). They can convert a metal salt to the corresponding acid by the reaction:

2(R-SO3H) + NiCl2 → (R-SO4)Ni + 2HCl



1.1.B. Weak Acid Cation Exchange Resins

- These resins behave similarly to weak organic acids that are weakly dissociated.



1.2.Anion exchange resin

- Whose exchangeable ions are negatively charged.
- 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:

Resin+ - ex - + A- → Resin+ - A- + ex-

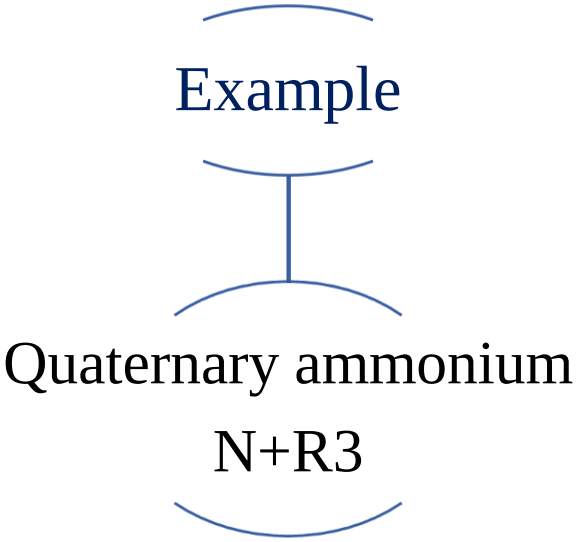
- Where, Resin+ indicates a polymer with N+ sites available for bonding with exchangeable anion (ex-), and A- indicates cations in the surrounding solution getting exchanged (8).

1.2. Anion exchange resin

1.2.A. Strong Base Anion Exchange Resins

- Like strong acid resins, strong base resins are highly ionized and can be used over the entire pH range. These resins are used in the hydroxide (OH) form for water deionization. They will react with anions in solution and can convert an acid solution to pure water:

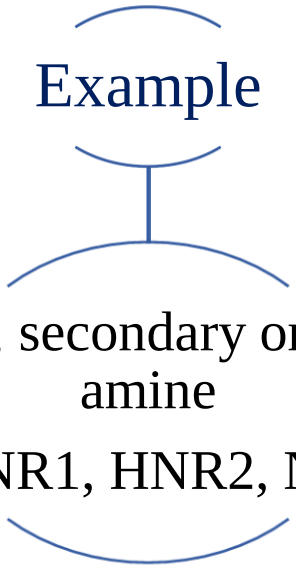
  R-NH3OH + HCl → R-NH3Cl + HOH



1.2.B. Weak Base Anion Exchange Resins

- Weak base resins are like weak acid resins in that the degree of ionization is strongly influenced by pH. Consequently, weak base resins exhibit minimum exchange capacity above a pH of 7.0. The weak base resin does not have a OH ion form as does the strong base resin (9).

  R-NH2 + HCl → R-NH3Cl



5. **Properties of Ion Exchange Resins**

Cross linkage

- The amount of crosslinking depends on the proportions of different monomers used in the polymerization step. Practical ranges are 4 %

to 16 %. Resins with very low crosslinking tend to be watery and change dimensions markedly depending on which ions are bound.

Moisture Content

- A physical property of the ion exchange resins that changes with changes in cross linkage is the moisture content of the resin. For example sulfonic acid groups attract water, and this water is tenaciously held inside each resin particle. The quaternary ammonium groups of the anion resins behave in a similar manner (10).

Capacity

- The total capacity of an ion exchange resin is defined as the total number of chemical equivalents available for exchange per some unit weight or unit volume of resin.
- The capacity may be expressed in terms of mill equivalents per dry gram of resin or in terms of mill equivalents per milliliter of wet resin.
- The more highly cross-linked a resin, the more difficult it becomes to introduce additional functional groups (11).

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 (12).

Flow Rate

- Ion exchange processes are usually carried out in columns with the resin resting on a suitable support. Liquids may be processed either up-flow or down-flow through such columns.
- The smaller the particle size, the greater will be this resistance against which a liquid must flow.

- This resistance goes up very rapidly when particles smaller than 100 mesh are employed (14).

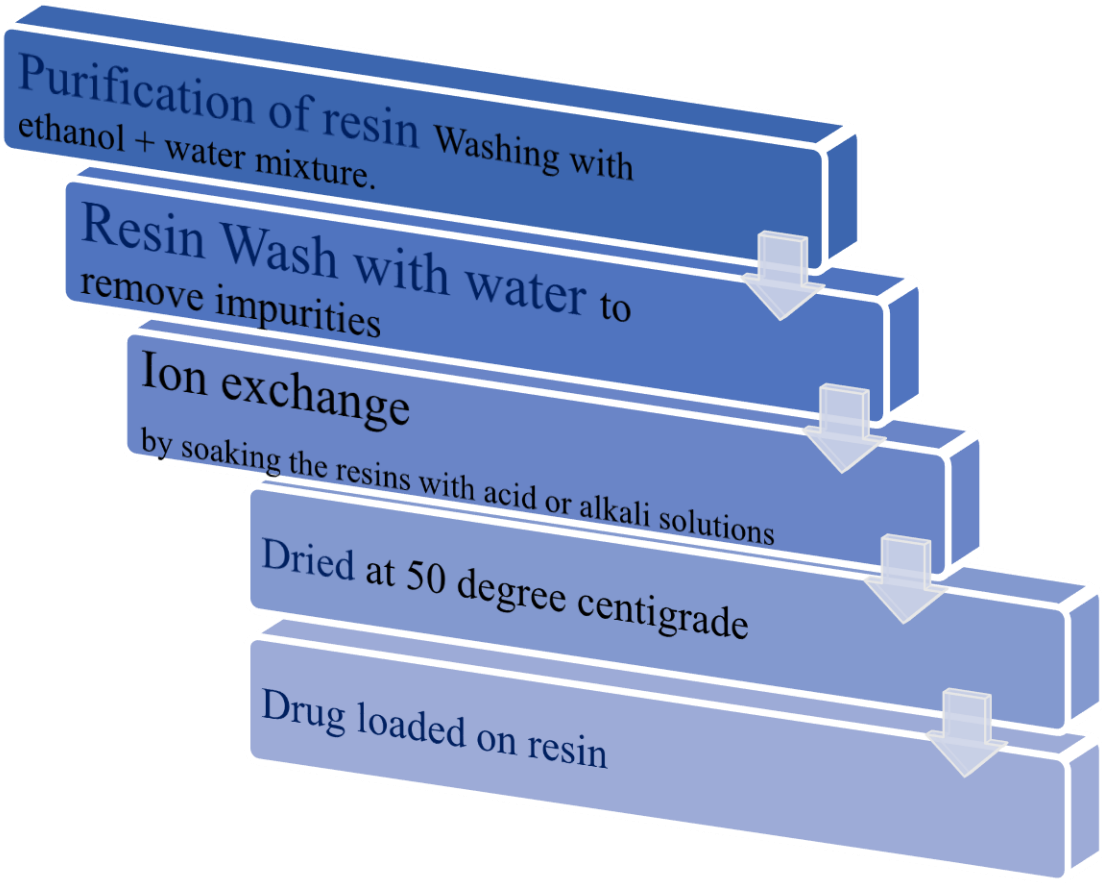
Particle size

- The physical size of the resin particles is controlled during the polymerization step. Screens are used to sieve resins to get a fairly uniform range of sizes. Mesh sizes in the following table refer to U.S. Standard screens. A higher mesh number means more and finer wires per unit area and thus a smaller opening (13).

Mash ranges	**Diameter of particles**	
	Inches	Micrometers
20 – 50	0.0331-0.0117	840-297
50 – 100	0.0117-0.0059	297-149
100 – 200	0.0059-0.0029	149-74
200 – 400	0.0029-0.0015	74-38
minus 400	< 0.0015	< 38

6. **Method of Preparation (Resinates)**

Preparation of drug resinate: is done by



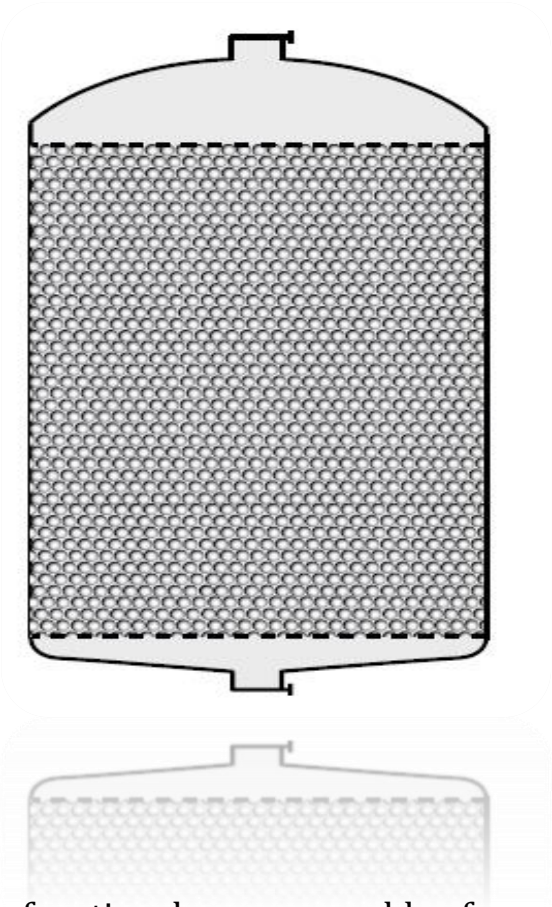
The drugs are loaded on to the resins by column method and batch method .

Column Method

- Highly concentrated drug soln passed
- By column contains resins
- Max. efficiency is obtained

Batch Method

- Drug soln. agitated with resin
- Until equilibrium is attained
- Resin is washed to remove free and un associated drug
- Air dried



7. **Mechanism and Principle**

Anion exchange resins involve basic functional groups capable of removing anions from acidic solutions.

Cation exchange resins contain acidic functional group, capable of removing cations from basic solutions (15).

<u>In The Stomach:</u>

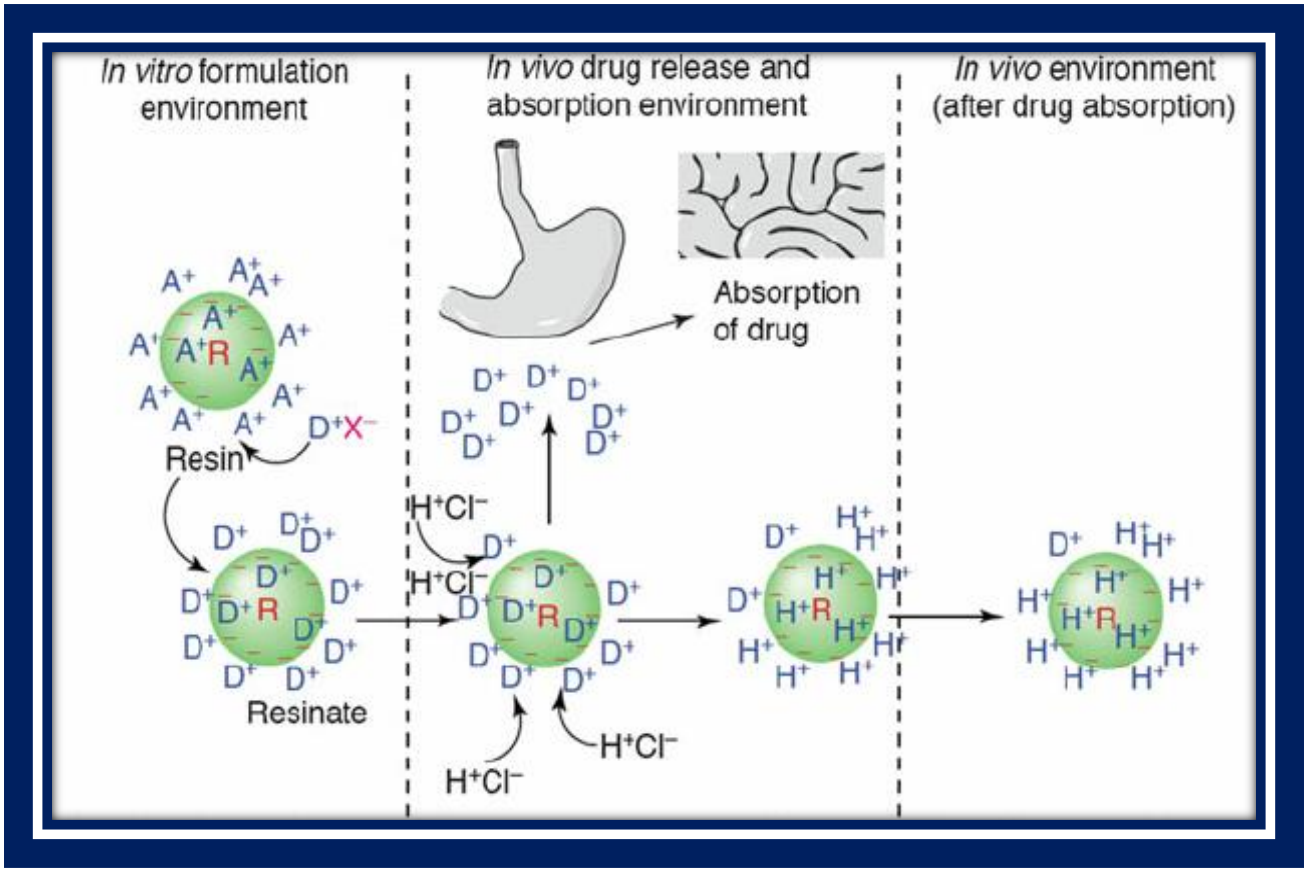
1) Drug resinate + HCl ↔ acidic resin + drug hydrochloride

2) Resin salt + HCl ↔ resin chloride + acidic drug

<u>In The Intestine:</u>

1) Drug resinate + NaCl ↔ sodium resinate + drug hydrochloride

2) Resin salt + NaCl ↔ resin chloride + sodium salt of drug



Role of IER in Controlled Drug Delivery Systems

- ❑ Drawback of controlled release is dose dumping, resulting in increased risk of toxicity.
- ❑ IER have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation. The prolonged release of the active drug by providing a semi-permeable coating around discrete, minute, ion exchange resin particles with which the drug component has been complexed to form an insoluble drug resin complex.
- ❑ The semi-permeable coating creates a diffusion barrier and the thickness of which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time.

8. **Applications in Various Formulation-Related Problems**

Taste Masking

- Excessive bitterness of the active principal ingredients (APIs) and oral formulations is the major taste problem faced by the pharmaceutical industry.

- Bitterness of formulations can influence selection by physicians and markedly affect patient compliance (16).
- 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.

Drugs Taste Masked By Various Grades Of Indion Ion Exchange Resin

Product Name	Applications	Matrix Type	Functional Group	Standard Ionic From	Particle Size Range, mm	% Moisture	Total ion exchange capacity
INDION 204	Taste masking of bitter drugs such as Norfloxacin, ofloxacin	Crosslinked poly-acrylic	$-COO^-$	H+	≤0.15	≤5	10.0
INDION 224	Sustained release agent in drug formu-lations	Styrene/DVB	$-SO_3^-$	H+	0.2-1.2	≤3	4.8
INDION 264	Stabilisation of Vitamin B_{12}	Crosslinked poly-acrylic	$-COO^-$	H+	≤0.15	≤5	10.0
INDION 294	Tablet disintegrant/ Taste masking.	Crosslinked poly-acrylic	$-COO^-$	K+	≤0.15	≤10	NA
INDION 404	Treatment of hypercalemia. Product meets specs of Calcium polystyrene sulfonated, BP	Styrene/DVB	$-SO_3^-$	Ca++	≤0.15	≤8	NA
INDION 414	As superdisintegrant in mouth disperse tablets	Crosslinked poly-acrylic	$-COO^-$	K+	≤0.15	≤10	NA

Rapid Dissolution

- Ion exchange drug resinate 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.
- Moreover, each individual drug molecule is bound to a functional site of the resin molecule resulting in reduction of crystal lattice energy, which may be responsible for enhancing the rate of drug dissolution bound to resin (17).

Powder Processing Aid

- Hygroscopic drugs are susceptible to agglomeration due to the presence of moisture. Adsorption of such drugs onto ion exchange resins may lead to a decrease in their hygroscopicity.
- Furthermore, because the resins have a uniform, macro reticular morphology, they provide excellent flow ability to the formulation (18).

Stability

- The drug resinate is frequently more stable than the original drug. Vitamin B12 has a shelf-life of only a few months, but the resinate is stable for more than two years.
- Another example is nicotine; it discolors quickly on exposure to air and light, but the resinate, used in nicotine chewing gums and lozenges, is much more stable (19).
- Ion exchange fibers provide a promising alternative to control drug delivery and to store drugs that are degraded easily.

Deliquescence

- Deliquescence can be defined as the conversion of a solid substance into a liquid as a result of absorption of water vapor from the air. Although this is not a common problem, it has been very difficult to solve and requires the use of specialized equipment or careful scheduling of production during dry seasons.
- Sodium valproate, a highly deliquescent drug, has been found to show free flowing properties after complexation with ion exchange resins.
- The amount of water absorbed decreased with increasing amount of valproate in the resinate. Similar results have been obtained with resinates of rivastigmine bitartrate (20).

Disintegration

- Ion exchange resins, because of their excellent swelling property when immersed in water, can be used as a tablet disintegrating agent.
- Mouth dissolving tablets of roxithromycin, dicyclomine and montelukast sodium were prepared with different disintegrating agents and compared for their disintegrating properties (21).

Oral drug delivery

- The major drawback of sustained release or extended release is dose dumping hence resulting in increased risk of toxicity.
- The use of IER has occupied an important place in the development of controlled or sustained-release systems due of their better drug retaining properties and prevention of dose dumping.
- The use of ion exchange resins into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment (22).

9. **Drug Delivery Applications**

Nasal drug delivery

- A novel nasal formulation, in the form of a nicotine-Amberlite resin complex powder, has been developed that provided an optimal combined pulsatile and sustained plasma nicotine profile for smoking cessation (23).

Transdermal drug delivery

- IER are also involved in the formulation of transdermal drug delivery systems. The release rates of ketoprofen from the carbopol-based gel vehicles containing ion exchange fibers to which the ketoprofen had been bound were determined across 0.22 μm microporous membrane (24).