ION EXCHANGERS USED IN CONTROLLED DRUG DELIVERY

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INTRODUCTION

- Ion-exchange resins have been studied in pharmaceutical applications since the early 1950s, leading to patenting and commercialisation of some resin based formulations.
- Resins have found use as pharmacologically-active ingredients and as pharmaceutical excipients that improve drug stability, mask the taste of a drug, enhance the dissolution of poorly soluble drugs, or achieve sustained or controlled drug delivery.
- Advantageous properties, such as a high capacity for drug loading, an easily executed loading procedure, good drug-retaining properties, and more uniform drug release makes the ion exchange resins, as such, attractive for drug delivery systems.
DEFINITION

• Ion-exchange materials, such as macroreticular resins, gels, membranes and fibers, contain two components: a water insoluble structural component consisting of a polymer framework, and a functional component consisting of fixed acidic or basic ion-exchange groups.

• ADVANTAGE:
  • Ion exchange systems are advantageous for drugs that are highly susceptible to degradation by enzymatic processes, since they offer a protective mechanism by temporarily altering the substrate.
ION EXCHANGE RESINS

• Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium.
• Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert.
• Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger. 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 exchanger [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 resins are further categorised into synthetic, semi-synthetic and natural depending on their source.
Ion exchangers

Cation exchangers

Inorganic
  - Natural (modified greenstand clay)
  - Synthetic (Zeolite)

Organic
  - Natural (Ignite, Copolymers Tannin formaldehyde resin)
  - Synthetic (acrylic acid)
  - Semisynthetic (Sephadex IER Zeoczrch)

Anion exchangers

Inorganic
  - Natural (Dolomite)
  - Synthetic (Heavy metal silicates)

Organic
  - Synthetic (Amine formaldehyde resin)
  - Semisynthetic (Sephadex IER)
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 crosslinking the polymer chains.
• The weak cation exchange resins are generally polyacrylic or polymethacrylic acids with DVB as crosslinking agents depending on the presence of ions.
# Common Ion Exchange Resins

<table>
<thead>
<tr>
<th>Type</th>
<th>Exchange species</th>
<th>Polymer backbone</th>
<th>Commercial Resins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong cation</td>
<td>-SO$_3$H</td>
<td>Polystyrene DVB</td>
<td>Amberlite IR 120, Dowex 50, Indion 244</td>
</tr>
<tr>
<td></td>
<td>-SO$_4$Na</td>
<td>Sodium Polystyrene</td>
<td>Tulsion T-344, Amberlite IRP 69, Indion 254</td>
</tr>
<tr>
<td>Weak cation</td>
<td>-COOH</td>
<td>Methacrylicacid DVB</td>
<td>Amberlite IRC 50, Indion 204, Tulsion T-335</td>
</tr>
<tr>
<td></td>
<td>-COO-K$^+$</td>
<td></td>
<td>Tulsion T-339, Amberlite IRP88, Indion 234</td>
</tr>
<tr>
<td>Strong anion</td>
<td>N$^+$R$_3$</td>
<td>Polystyrene DVB</td>
<td>Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143</td>
</tr>
<tr>
<td>Weak anion</td>
<td>N$^+$R$_2$</td>
<td>Polystyrene DVB</td>
<td>Amberlite IR 4B, Dowex 2</td>
</tr>
</tbody>
</table>
MECHANISM OF ION-EXCHANGE

- The ion-exchange reaction is a reversible, selective and stoichiometric interchange of mobile ions of like charges between the ion exchanger and the external liquid phases.
- Each counter-ion that is released from the ion-exchanger is replaced by an equivalent amount of another ionic species of same sign and valence due to the electroneutrality requirement.
- Based on the nature of the ionic species being exchanged, the ion-exchange process is either anionic or cationic.
FACTORS AFFECTING ION-EXCHANGE

• The ion-exchange process is affected by

  ➢ Ion-exchanger dependent factors
  ➢ Drug dependent factors
  ➢ External conditions
Ion-exchanger dependent factors

- **Ion-exchange capacity**

  - Theoretically, the fixed ionic groups largely determine the ion-exchange behaviour of the ion-exchange materials.
  
  - The number of the groups determines the ion-exchange capacity, while the chemical nature of the groups greatly affects the equilibrium of ion-exchange.

  - The number of the ionisable groups per specified amount of ion-exchanger expresses the theoretical ion-exchange capacity of the material and, it can be used to characterize the ion-exchangers.
• **Nature of fixed ion-exchange groups**

• The strength of interactions formed between the mobile counter-ions and the fixed ion-exchange groups may also depend on the chemical nature of the functional groups (*e.g.*–SO$_3$H vs. -COOH).

• Lipophilic drugs were bound stronger into the strong sulfonic acid groups compared to the weak carboxylic acid groups, while the opposite was true with a hydrophilic drug.
• **Preloaded counter-ion**

• The nature of the preloaded counter-ions may affect the binding of drugs and other compounds into the ion-exchanger.

• This may be attributed primarily to two factors. Firstly, ion-exchangers in the base/acid form may change the solubility of the drug in the solution phase and simultaneously the dissociation degree of the ion-exchanger, as the pH of the surrounding solution changes by the release of OH⁻/H⁺-ions from the ion-exchange material during the drug loading process.

• Secondly, dissimilar selectivity of the ion-exchangers (i.e. the selection by the ion-exchanger of one counter-ion in preference to the other) towards the different counter-ions may induce differences in the drug loading/release behaviour, although the binding selectivity of the organic drug-ions is normally higher than that of smaller inorganic ions.
• **Particle size and degree of cross-linking**

• While the ion-exchange equilibrium is primarily dependent on the chemical structure of the ion-exchanger, the kinetics of the exchange reaction depends strongly on the physical structure of the ionic polymer.

• As the degree of cross-linking is increased, the rate of drug/compound release from the resin is generally slower due to the decreased moisture content of the resin framework.

• Reduction of the pore diameter by increased cross-linking may ‘block out’ ions having an effective diameter larger than the diameter of the pore and, therefore, hinder their uptake and release.
Drug dependent factors

- **Lipophilicity**

  - Physicochemical characteristics of drugs have often an influence on the selectivity of ion-exchange.
  - Drugs possessing higher lipophilicity have higher affinity towards the ion-exchangers.
  - Their loading into the ion-exchangers is more effective and the release is reduced compared to the more hydrophilic drugs.
  - This is due to the contribution of the chemical partition coefficient to the equilibrium distribution of the drugs between the ion-exchanger and external solution phases.
• **pKa and sterical properties**

• Drug pKa is essential for the ion-exchange process, as only ionised drugs can be bound into the ion-exchange groups via ionic bonding.

• The relative affinity (i.e. selectivity) of ion-exchangers for different drugs may depend on the structure of the charged functional groups of the drugs.
• **Molecular size**

• Analogously to the increase of the cross-linking in the ion-exchangers, the increase of molecular size may achieve lower drug loading into the ion-exchangers, especially in the case of highly cross-linked resins, as the larger drugs are unable to diffuse into the inner part of the ion-exchanger.
External conditions

- Concentration and valence of external ions
  - The Donnan potential between the ion-exchanger and external solution phases depends strongly on the concentration of the surrounding ions, which then affects the rate and extent of ion-exchange.
  - At higher valence, the extracting counter-ions are more strongly attracted to the ion-exchanger (electroselectivity), enabling more efficient drug release.
• **pH of surrounding solution**

  The pH of the external solution may have a strong effect on the ionisation of both the drug and the ion-exchanger, which in turn affects the ion-exchange.

• **Temperature and agitation**

  Higher rates of drug incorporation into and release from the ion-exchangers have been observed with increasing temperature and/or agitation.

  The diffusion rate of ions into the ionic binding sites of the ion-exchanger gets higher as the temperature is increased.
DRUGS SUITABLE FOR RESINATE PREPARATIONS

Drugs that are to be formulated into resinates should satisfy the following conditions.

- Drugs should have acidic or basic groups in their chemical structure.
- The biological half-life should be between 2-6 hrs.
- The drug is to be absorbed from all regions of the GI track.
- Drugs should be stable sufficiently in the gastric juice, otherwise, their therapeutic effectiveness will drop drastically.
RATIONALE FOR RESINATES AS CONTROLLED RELEASE DOSAGE FORMS

• Ion-exchange resinates of drugs can help in reducing the dose.

• Reduced fluctuations in blood and tissue concentrations.

• Fewer administrations and maintenance of drug concentration below toxic levels.
• GENERAL PREPARATION OF DRUG RESINATES

The foremost step in the preparation of drug resinates is to purify the resins carefully.

Loading of drugs:
Loading of drugs is done by two ways.

Column process: A highly concentrated drug solution is eluted through a bed or column of the resin, until equilibrium is established.

Batch process: The resin particles are stirred with a large volume of concentrated drug solution.

    subsequently the resin is to be washed to remove adhering free and un-associated drug and thereafter it is air dried.
EVALUATION OF DRUG RESINATES

• In vitro tests:
• The in vitro tests demonstrate the release pattern of a drug from a resinate preparation dosage form which depends on:
  ✓ Size of resinate,
  ✓ Degree of crosslinkage,
  ✓ Ionogenic groups of resins,
  ✓ Nature of drug,
  ✓ The test conditions e.g. ionic strength of dissolution medium.
A variety of methods are described for drug resinates evaluation by in vitro dissolution testing. However, commonly employed methods to test drug resinates include the on-column and the batch exposure of the resinates to simulated gastric juice and intestinal fluids.

In vivo tests:
In vivo procedures used for estimating drug activity of resinates include serum concentration level determination, urinary excretion, and toxicity studies.
APPLICATIONS OF ION EXCHANGE RESINS

• With the development of modern synthetic IER pharmaceutical industry adapted the ion exchange technology to achieve sustained release of drug.
• Keating listed the following advantages of adsorbing basic nitrogen containing drug onto strong acid cation exchange resins and using them in dosage forms:

  ✓ Prolonged release of drug from the complex for 8-12 hours in the gastrointestinal tract;
  ✓ Reduced toxicity by slowing drug absorption;
  ✓ Increased stability by protecting the drug from hydrolysis or other degradative changes in the gastro-intestinal tract;
✓ Improved palatability;
✓ Availability of formulation in liquid and solid sustained release dosage forms.

• **Sustained release tablets:**

  • The release of drug from IER depends upon a series of ionic reactions between various body fluids and the drug resin complex. The first two factors control the diffusion of active ingredient through resin particles and third factor controls the equilibrium of drug resin complex and electrolytes in body fluids.
• Schliching has done a complete and detailed study of an antihistaminic drug carbinoxamine using weak acid and strong acid cation exchange resins to develop a sustained release tablet of carbinoxamine.

• Wolf compared the duration of antitussive effect of Noscapine Hydrochloride in a commercial resinate of Noscapine and sulfonated cross-linked polystyrene resins.

• Another study showed that microencapsulated tramadol-resin complex gave slow release.

• Resinates of propanolol Hcl, chlorpheniramine maleate and phenyl propanolamine have been described to show sustained release. Manek and Kamat evaluated INDION® CRP-244 and CRP254 resins as sustained release and taste masking agents.
• **Sustained-Release Capsules**
  • Absorbing an ionic drug on an ion-exchange resin and administering it in a capsules or tablet dosage is an alternative for controlled-release dosages.
  • Biphetamine, a capsule containing equal quantities of amphetamine and dextroamphetamine complexed to a sulfonic acid cation exchange resin, has been used for several decades as an antiobesity agent and for behavior control of children.

• **Sustained-Release Liquids**
  • The best application of ion exchange resins as drug carriers is their use in sustained- or controlled-release liquids.
• In liquid form, the ion exchange resins can bind the drug in a liquid suspension by keeping the liquid free of counterions. When ingested, the ions in the body initiate gradual release from the resin.

• If the properties of the drug-resin complex do not give the desired sustained-release rate, coating the particles with a rate-controlling membrane often achieves the target bioavailability.

• Dextromethorphan (Delsym Polystirex)

• Delsym is a liquid suspension product designed to provide 12-h relief of coughs caused by minor throat and bronchial irritation.

• The active agent is dextromethorphan bound to a sulfonic acid ion exchange resin which is partially coated with ethylcellulose.
• Penntuss (Codeine and Chlorpheniramine polistirex)
  • It is combination product of two drugs are in the form of resinates bound to a sulfonic acid cation exchange resin; the codeine-resinate particles are coated with ethylcellulose whereas the chlorpheniramine-resinate particles are uncoated.
  • It is intended for 12-h cough and cold relief.

• Tussionex (Hydrocodone and Chlorpheniramine Polistirex)
  • Similar to penntus, this is a combination product intended for 12h cough and cold relief. Both drugs are in the form of resinates bound to a sulfonic acid cation exchange resin.
• Liquifer (Controlled-Release Iron)
• Liquifer is a controlled-release suspension containing iron in the ferrous state bound to a sulfonic acid ion exchange resin. It is designed to provide supplemental iron as a once-a-day dosage in a pleasant tasting liquid form.

• **Drug stabilization:**
• A component of the API is fixed onto the IER. This prevents harmful interaction with other components. E.g., The stability of vitamin B12 (that deteriorates on storage) can be improved by complexing it onto a weak acid cation exchange resin(Indion-264). This complex is as effective as free form of vitamin.
• **Taste masking:**
  • Taste masking in chewable tablets containing drugs with amino groups like dextromethorphine, ephedrine, pseudoephedrine has been successfully carried out using weak acid cation exchange resin.
  • Avari et al. reported taste masking of highly bitter antibiotic, sparfloxacin with Indion 204 weak cation exchange resin.

• **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.
• **Tablet Disintegration (Improved tablet Disintegration properties)**

• Many tablet disintegrants owe their action to capacity to absorb water and swell up. Fine particle size ion exchange resins have shown superiority as disintegrating agents due to their considerable swelling pressure upon hydration.

• Because of their unusually large swelling capacities polymethacrylic 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.
• **Bioadhesive system for treatment of gastric mucosa.**
  • Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions.
  • 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 amoxycillin and cimedine.

• **Chewing gum for glycol absorption**
  • Nicorette gum 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 flavoured chewing gum base, which provides gradual drug release through glycol mucosa as the gum is chewed offering fresh saliva as solvent for elution.
CONCLUSION

• Ion-exchange resinates prepared from suitable drugs and ionic polymers can help in alteration of physicochemical and biological properties of drugs.
• Improved therapeutic efficiency and reduced toxicity is the beneficial performance of these resinates.
• Drug-resin complexes are promising controlled delivery systems and can come to market with a manufacturing feasibility, as these can give better tolerance, more uniform delivery of the drug, and for a longer period.
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