Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 4; 138-148.
Published on- 15 Dec 2010

Original Article

ISSN 0975-8216

RECENT TRENDS IN ION EXCHANGE RESINS USED IN PHARMACEUTICAL FORMULATIONS-AN UPDATES

Debjit Bhowmik[1]*, K.P.Sampath Kumar[2]

Affiliated to:

1. Karpagam University, Coimbatore
2. Department of Pharmaceutical sciences, Coimbatore Medical College, Coimbatore

For Email Click Here

ABSTRACT

Ion-exchange resins are used in the manufacturing of pharmaceuticals, not only for catalyzing certain reactions but also for isolating and purifying pharmaceutical active ingredients. Ion exchange resins are polymers that are capable of exchanging particular ions within the polymer with ions in a solution that is passed through them. This ability is also seen in various natural systems such as soils and living cells. The synthetic resins are used primarily for purifying water, but also for various other applications including separating out some elements. Ion-exchange resins have found applicability as inactive pharmaceutical constituents, particularly as disintegrants (inactive tablet ingredient whose function is to rapidly disrupt the tablet matrix on contact with gastric fluid). One of the more elegant approaches to improving palatability of ionizable drugs is the use of ion-exchange resins as taste-masking agents. The selection, optimization of drug: resin ratio and particle size, together with a review of scale up of typical manufacturing processes for taste-masked products are provided. Ion-exchange resins have been extensively utilized in oral sustained-release products. Resins have also been used in topical products for local application to the skin, including those where drug flux is controlled by a differential electrical current (ionotophoretic delivery).

Keywords: Disintegrants, Ion-Exchange Resin.

INTRODUCTION

An ion-exchange resin or ion-exchange polymer 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. The material has highly developed structure of pores on the surface of which is sites with easily trapped and released ions. The trapping of ions takes place only with simultaneous releasing of other ions; thus the process is called ion-exchange. There are multiple different types of ion-exchange resin which are fabricated to selectively prefer one or several different types of ions. Ion-exchange resins are also used as excipients in pharmaceutical formulations such as tablets,

capsules, and suspensions. In these uses the ion-exchange resin can have several different functions, including taste-masking, extended release, tablet disintegration, and improving the chemical stability of the ingredients. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolyte that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stiochiometric with the displacement of one ionic species by another. Synthetic ion exchange resin has been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950 s. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol. The unique advantage of ion exchange resins is 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 drug posses 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 the 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 and with no after taste, but at the same time its Bioavailability was not affected. Sodium polystyrene sulfonate (SPS), an ion-exchange resin designed to bind potassium in the colon, was approved in 1958 as a treatment for hyperkalemia by the US Food and Drug Administration, 4 years before drug manufacturers were required to prove the effectiveness and safety of their drugs. In September 2009, citing reports of colonic necrosis, the Food and Drug Administration issued a warning advising against concomitant administration of sorbitol, an osmotic cathartic used to prevent SPS-induced fecal impaction and to speed delivery of resin to the colon, with the powdered resin; however, a premixed suspension of SPS in sorbitol, the only preparation stocked by many hospital pharmacies, is prescribed routinely for treatment of hyperkalemia. We can find no convincing evidence that SPS increases fecal potassium losses in experimental animals or humans and no evidence that adding sorbitol to the resin increases its effectiveness as a treatment for hyperkalemia. There is growing concern, however, that suspensions of SPS in sorbitol can be harmful. It would be wise to exhaust other alternatives for managing

hyperkalemia before turning to these largely unproven and potentially harmful therapies.

TYPES OF ION EXCHANGE RESINS

Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cationic or anionic exchanger. Within each category, they are further classified as strong or weak depending on their affinity for soluble counterions.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] where as 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.

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 co polymerization for crosslinking 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 polymethacryllic acids with DVB as crosslinking agents.

Four major types of ion exchange resins are available.

Table No 1: Common ion exchange

Type	Exchange species	Polymer backbone	Commercial Resins
Strong cation	$-So_3H$	Polystyrene DVB	Amberlite IR 120, Dowex 50
Weak cation	-COOH	Methacrylicacid DVB	Amberlite IRC 50, Indion 234
Strong anion	N^+R_3	Polystyrene DVB	Amberlite IR 400, Dowex 1
Weak anion	N^+R_2	Polystyrene DVB	Amberlite IR 4B, Dowex 2

EQUILIBRIUM PHENOMENON

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 absorbed on the resin as illustrated in Equation 1 & 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 [70] given in Eq. 3.

$$K_{DM} = \frac{[D]_R [M]_S}{[D]_S [M]_R} \quad \text{——— 3}$$

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 valence, hydrated size, pKa and the pH of the solutions

Borodkin and Yonker 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.

PROPERTIES OF ION EXCHANGE RESINS

1] 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 the equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern.

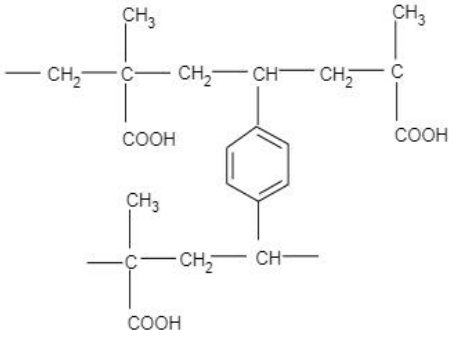
2] Porosity and swelling

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.

3] Cross-linking

The percentage of cross-linking affects the physical structure of the resin particles. Resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However resins with high DVB content swell very little and are hard and brittle. Cross-linkage has dramatic effect on loading efficiency. It affects porosity and swelling properties of resin. Low cross-linking agents remarkably upon hydration. Higher grade have finer pore structure thus reducing loading efficacy with increase in cross-linking. Low cross linkage increase loading efficacy but also increases release rates.

When the methacrylic acid crosslinked with DVB the general resins structure is shown as follows.



4] Exchange capacity

The exchange capacity refers to the number of ionic sites per unit weight or volume (meq per gram or meq per ml). The weight basis values (meq. Per gm) is much higher than the volume based exchange capacity since the wet resin is highly hydrated. The exchange may limit the amount of drug that may limit the amount of drug that may be absorbed on a resin hence the potency of a complex.

Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities (10meq. /gm) than sulfonic acid (about 4meq. / gm) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore higher drug percentages may often be achieved with carboxylic acid resins.

5] Acid base strength

It depends on the various ionogenic groups, incorporated into resins. Resins containing sulphonic, phosphonic or carboxylic acid exchange groups have approximate pka values of <1, 2-3 & 4-6 respectively. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having pka values of >13, 7-9 or 5-9 respectively. The pKa values of resin will have significant influence on the rate at which the drug will be released in the gastric fluid.

6] Stability

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

7] Purity and toxicity

Since drug resin combination contains 60% or more of the resin, it is necessary to establish its toxicity. Commercial product cannot be used as such. Careful purification of resins is required. Resins are not absorbed by body tissue and are safe for human consumption. Test for toxicological tolerance showed that it does not have any pronounce physiological action at recommended dosage and is definitely non-toxic.

APPLICATION OF ION EXCHANGE RESINS IN PHARMACEUTICAL FORMULATIONS

Ion exchange resins are used in a variety of pharmaceuticals formulations.

1] Taste masking (Chewable or Dispersible tablet of bitter drugs)

Certain drugs that have very bitter taste can be made relatively tasteless by adsorbing the drug on ion exchange resin although all the ion exchange resins can be useful for this purpose, the proper selection on ionic character of drug and release characteristics.

Weak cation exchange resins can be used to formulate chewable or dispersible tablet of bitter drugs, for example Rodec decongestant tablet containing pseudoephedrin.[65] Weak cation exchangers are most preferable for their ability to remain undissociated at alkaline pH of mouth, and thus masking the taste of bound drug and further releasing it rapidly at acidic pH of stomach.

Avari and Bhalekar reported taste masking of highly bitter antibiotic, sparfloxacin with Indion 204 weak cation exchanger. Resins have been used with success to prepare stable and tasteless dosage forms. Taste masking in chewable tablets having amino containing drugs like dextromethorphon, ephedrine, psedoephedrin, etc.have been successfully carried out by using weak cation exchange resin.[81]

2] Chewing gum for buccal absorption

Nicorette 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.

3] Sustained release formulations such as capsules, liquids, oral tablet, etc.

Gastrointestinal sustained release mechanism

Bioavailability of drug absorbed on ion exchange resins depends on both transits of the particles through the G.I. tract and drug release kinetic. Drug release or dissolution from the resin can in turn occurs only by replacement of the drug by another ion with the same charge. Since, the exchange is an equilibrium process, it depends on the body fluids, ionic constitution and fluid volume. Additionally release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. The net result of all the phenomena is a sustained release system.

If the drug resin complex is administered orally a small amount of drug may be released. This would be followed by significant and continuous release in the stomach where drug is exposed to high acid and chloride concentrations. Anionic exchange resins and strong cation exchangers release a limited amount of drug in the stomach as shown in Eq. 1& 2.

$$Re\text{-}So_3^- Drug^+ + H^+ \Longleftrightarrow Re\text{-}So_3^- H^+ + Drug^+ \quad \text{--------} \quad 1$$

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

In contrast drug bound to weakly acidic carboxylic acids released much more readily in the stomach as illustrated in Eq.3

$$Re\text{-}COO^- Drug^+ + H^+ \Longleftrightarrow Re\text{-}COOH + Drug^+ \quad \text{--------} \quad 3$$

The high effective pKa of the resin drives the equilibrium towards the formation of undissosiated acid in a low pH environment. This may promote rapid drug release. In the intestine the neutral pH should keep all ionic sites on the resins ionized and the exchange process should occur continuously. The absorption into the body of solubilised drug should drive the equilibrium further towards drug release. In the large intestine, desorption from the resin and the absorption into the body may be slow, considerably due to low fluid content, entrapment in the faecal matter and poor membrane absorption.

The highly insoluble resin is not absorbed. It is simply eliminated from the body with the counter ions that have replaced the drug. **Biphetamine**[R] a capsule containing an equal quantity of amphetamine & dextroamphetamine complexed to a sulphonic acid cation exchange resin has been used for antiobesity agent and for behavioral control of children.

Several preparations involving resinate of strong sulphonic acid cation exchange resin are marketed as well as reported in the literature. They provide more moderate release than the carboxylic acid resins.

Another example is pennkinetec system by Pennwalt corporation, USA marketed as **Penntuss**[R] where codeine and Chlorpheniramine polystyrex contains both drugs complexed with sulphonic acid cation exchange resin wherein the chlorpheniramine resin complex is uncoated and codeine resinate particles are coated with release controlling ethyl cellulose membranes [84]

Sulphonic acid type resinate containing antitussive phenyltolaxamine and dihydrocodeinone have been marketed as **Histionex**[R] and **Tussionex** [R], Wolff compared the duration of the antitussive effect of Noscapine hydrochloride (Longatin [R)], a commercial resinate of noscapine and a sulphonated cross linked polystyrene resin. In another study microencapsulated Tramadol-resin complex showed slow release.

Resinate of propranolol hydrochloride Chlorpheniramine maleate and phenyl propanolamine have been described to show the sustained release.

Microparticulates of ion exchange resin drug complex have been used for ophthalmic drug delivery of Betaxolol, an antiglaucoma

agent.A recent review describe the use of ion exchange resin microparticulates for ophthalmic drug delivery.

4] Drug stabilization

Complexing active ingredients with ion exchange resins prevents harmful interaction with other components e.g. Vitamin B_{12}. 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 by complexing it with a weak acid cation exchange resin (INDION 264). This complex is as effective as the free form of the Vitamin. Thus the introduction of INDION 264 in the formulation significantly reduces the overages. Ion exchange resin can also be used as carrier for immobilized enzymes to provide extended activity at localized sites.

5] Bioadhesive system for treatment of gastric mucosa.

Ion exchange resin may have inherent bioadhesive properties similar to those of highly charged polyanions.[94] 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 cimetidine.

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 disintegrant 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.

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 effect complete drug elution.

7] 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.

8] 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.

TASTE MASKING BY DISPERSION COATING [MASS EXTRUSION TECHNIQUE]

In this method bitter drug was mixed with nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH without affecting the drug release pattern and Bioavailability of drug.

Taste masked granules of bitter drugs oxybutynin and piperazine were prepared by using Eudragit E100 [cationic copolymer based on dimethyl amino ethyl methacrylate.] and ethanol.

Drug was mixed with powdered Eudragit E-100. Then ethanol was added to the mixture of drug with Eudragit E 100 in a glass beaker. Then gel containing the mixture of the drug and Eudragit E 100 was prepared; using this prepared gel the taste-masked granules were prepared by the extrusion method. The prepared gel was manually extruded (pressed out) using a syringe. After extrusion of the gel, ethanol was removed by evaporation overnight and subsequently the solidified gel in the shape of a stringe was crushed into granules using a mortar.

Of the various methods mentioned previously the resinate method and dispersion coating method was chosen for the taste masking because of the following advantages.

Advantages of Ion Exchange Resin and Eudragit E 100 as a Taste Masking Agent

1. These method requires few and simple equipment.
2. The numbers of excipients required are less and are easily available.
3. The Bioavailability of drug is not altered.
4. The resins and Eudragit E 100 are easy to process and has high margin of safety.
5. The manufacturing can be carried out at room temperature and no other special experimental conditions are required
6. It has low cost of manufacturing.

CONCLUTION

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 methods for taste masking is the use of ion exchange resin. As indicated by literature survey weak ion exchange resins are found to be interesting hydrophobic polymers for the taste masking of bitter drugs because of its complex forming ability, non toxicity and low economy as compared to other methods. Other methods are quite tedious and require a long time for manufacturing. An ion exchange resin reduces a solubility of the drug in the saliva and it releases the drug immediately in the stomach so the bioavailability of the drug is not affected. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and Bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor.

REFERENCE

1) Dorfner , K. " Ion Exchanger Properties and Applications" Third Edition,Ann Arbor Science Publisher, 2, 1972
2) Jain, N.K.; "Advances in controlled and Novel drug Delivery", First Edition, pp 290-306, 2001
3) Martin, G.L., "Ion Exchange and Adsorption Agents in Medicines" Little Brown, Boston 1955.
4) Borodkin , S.Ion Exchange Resin Delivery system, In "Polymers for controlled Drug Delivery (P.J. Tarcha, ed.) CRC Press, Inc, Boca Raton, pp 215-230, 1991.
5) Format given by Ion Exchange India Ltd. Mumbai.
6) Borodkin, S; Sundber, D.P. US Patent 3594470 (1971).
7) Sambhaji Pisal, Ranna Zainnudin, Praddin Nalawade, Kakasaheb Mahadik and Shivajirao Kadam. "Molecular properties of ciprofloxacin Indion 234 complexes",AAPS Pharm. Sci.Tech 2004 ; 5(4) Article 62.
8) Manek, S.P.; Kamat,V.S.; Indian Journal of Pharmaceutical Science; 43, pp 209-212(1981).

9) Kalmen, C. and Kressman,T.R.;Ion Exchange in Organic and Biochemistry, New York: Wiley interscience, 1957,502.

10) Jain, N.K.; Advances in controlled and novel drug delivery; First edition pp 290 (2001).

11) Ion Exchange Resins and Sustained release; Swarbik,J.;Encyclopedia of pharmaceutical Technology, Vol-8, pp 203-217.

12) Irwin,W.J.;Belaid, K.A.; Alpar,H.O.; Drug. Dev. Ind.Pharm, 13,1987, pp 2047-2066.

13) Bruk,G.M.; Mendes,R.W. and Jambhekar,S.S.; Drug. Dev. Ind.Pharm, 12,1986 pp 712-732.

14) Mahesh Bhalekar, J.G.Avari and S.B. Jaiswal; "Cation Exchangers in pharmaceutical formulations." Indian Journal of pharmaceutical Education,38(4), Oct –Dec. 2004.

15) Avari J.G., Bhalekar M., " Cation Exchange Resines for Taste Masking and rapid dissolution of Sparfloxacine" Indian Drugs, (41), pp 19-23, 2004.

16) Brudney,N.; US Patent 2987441 (1961).

17) Borodkin, S. sunderberg, "Polycarboxylic acid Ion Exchane Resin absorbates for taste coverage in chewable tablets," Journal of Pharmaceutical Science, 60(10), pp 1523-1527,(1971).

18) Ishikawa, T., Watanabe, Y., Utoguchi ,N. and Matsumoto M."Preparation and Evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by the compression method.", Chem. Pharm.Bull., 47 (10) pp 1451-1454.