

INTRODUCTION

The use of synthetic ion exchange resins and polymeric adsorbents in medicine and pharmacy has been varied and diffuse.

Natural ion exchangers and adsorbents (e.g. kaolin, bentonite, alginates, alumina, charcoal) have been used historically within the medical and pharmaceutical industries. The development of synthetic ion exchangers and adsorbents for medical applications is a relatively recent development, but, due to their flexibility, stability and specificity, their use has become integral within these industries, and new applications are continually being developed.

Pharmaceutical applications for ion exchange resins and polymeric adsorbents, for which Purolite resins can be used (besides their application as active pharmaceutical ingredients and excipients, and as water treatment media) include extraction and purification of enzymes, hormones, alkaloids, viruses, antibiotics (streptomycin, penicillin), and treatment of fermentation products, etc.

Purolite resins used in drug formulations as API's or excipients. They meet the demands of the American (USP), European (Ph.Eur.), British (BP) and Japanese (JP) pharmacopoeias. Drug Master Files are held for each, single, listed pharmaceutical product manufactured in Purolite's facilities, while resins used in extraction and purification processes, or for the production of water for injectables, meet the requirements of both the US Food and Drug Administration (FDA) and the European Union.

Purolite Technical Support, located at each of our Corporate Offices and Business Centers, provides total assurance in correct resin selection, and can assist in products design and trouble shooting.

1. ION EXCHANGE RESINS AS ACTIVE PHARMACEUTICAL INGREDIENTS

Polymeric ion exchange resins are totally insoluble, and, when taken orally, pass through the human digestive system without being adsorbed. Ingestion of specific resins, therefore, has no side effects on the human body (that is, they are non-systemic). The properties of ion exchange resins used specifically as active ingredients are well documented, and their characteristics are clearly defined in various pharmacopoeias.

1.1. Sodium / Calcium Polystyrene Sulphonate

The kidneys continuously remove potassium. When kidney function is failing, it may be necessary to remove potassium from the intestinal tract by artificial means. This can be achieved by using Polystyrene Sulphonates, in either the sodium or calcium form. Sodium Polystyrene Sulphonate is listed in the US, EU, British and Japanese pharmacopoeias, while Calcium Polystyrene Sulphonate is listed only in the British and Japanese pharmacopoeia. As the resins pass through the intestinal tract they exchange the sodium or calcium on the resin for potassium. The adsorbed potassium cannot pass into the blood and continues through the body without being released. Introduced into clinical use in the early 1950's, such resins are now widely used in the treatment of acute and chronic hyperkalaemia, in addition to controlling serum potassium levels in patients undergoing renal dialysis.

Purolite C100NaMR and **Purolite C100CaMR** are the **Purolite** names for Sodium and Calcium Polystyrene Sulfonates resins produced in Purolite's FDA clean rooms. The powder resin is subsequently flavored by the pharmaceutical company and prepared in doses to be taken orally.

1.2. Cholestyramine

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.

The advantage of Cholestyramine over other drugs is that there are no 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 D3 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.

1.3. Antacid

Purolite A830EMR is an antacid used to control gastric acidity in the treatment of peptic ulcers. It is a powdered weak base anion exchange resin, in free base form. **Purolite A830EMR** is an ideal antacid as: it is insoluble; it is neutral in aqueous suspensions; it does not irritate the stomach or intestine; it does not alter the acid-base equilibrium of the body; it does not alter mineral metabolism; it has no side effects; and it does not cause diarrhea or constipation.

2. ION EXCHANGE RESINS AS EXCIPIENTS

Ion exchange resins have been used for many years as excipients. There are a number of examples of such applications, the most common being: use as tablet disintegrants; use in taste and odor masking; and use in controlled drug release.

2.1. Polacrillin Potassium

Polacrillin Potassium is typically used as a tablet disintegrant. The resin, in the dry powdered state, is incorporated into tablets containing drugs. On wetting, the resin swells by approximately 150%, thereby causing the tablet to disintegrate. Introduced many years ago into tablet formulations as a disintegration aid, it is still widely used either alone or, synergistically in conjunction with other products. In addition, the use of Polacrillin Potassium renders the tablets physically stronger and, therefore, easier to press.

Listed in the USP as “**Polacrillin Potassium**”, **Purolite C115KMR** is a dried, powdered, weak acid, polymethacrylic cation resin in the potassium form. **Purolite C115KMR** has a regulated Drug Master File with the FDA.

2.2. Taste & Odor Masking

A number of ion exchange resins and adsorbents can be used to mask the taste and /or the odor of medicines. The selected ion exchange resins or adsorbents are loaded with the active ingredients, which, following ingestion, are then desorbed.

For example, **Purolite C102DR** is a special, dried, carboxylic resin, which is used to mask the extremely bitter taste of certain cardio-tonics and anti-depressants

2.3. Controlled Drug Release

The controlled release of drugs is a vital factor in the treatment of many diseases, and the selection of drug carrier to ensure a steady, uniform, controlled release is dependent on the kinetics of drug adsorption and desorption, which, in turn, are influenced both by chemical and physical factors. Ion exchange resins and adsorbents have found use in desired drug release profiles. There are examples of cation and anion resins used not only for solid preparations and syrups for oral consumption, but also for lotions, ointments and powders for topical application.

Purolite C115HMR is a dried, powdered, weak acid, polymethacrylic cation resin in the hydrogen form that has found particular application in the controlled, uniform release of nicotine when incorporated into “quit smoking” aids. Nicotine is adsorbed onto the powdered resin, which, when combined with the gum, is released slowly and uniformly by chewing.

Purolite C100HMR is a dried, powdered, strong acid cation resin in the hydrogen form that has been grinded into a fine dry powder for taste masking and pharmaceutical carrier applications. **Purolite C100HMR** can also be used in some controlled release and drug stabilization applications. For example, it can be used for controlled release of codeine, noscapine, dextromethorphan or norephedrine.

Cholestyramine (**Purolite A430MR**) and Sodium Polystyrene Sulfonate (**Purolite C100NaMR**) are also two APIs used for controlled release.

Both of these **Purolite** products have Drug Master Files annually regulated by Food and Drug Administration.

3. ION EXCHANGE RESINS FOR PHARMACEUTICAL PRODUCTION

The production and purification of pharmaceutical products, including the treatment of water involved in the process, is one of the most important application areas for ion exchange resins and polymeric adsorbents.

3.1. Demineralisation of Water

Many pharmaceutical processes require softened, or demineralized, water in their manufacturing process. Purolite produces the whole range of cation and anion exchange resins required to soften, or totally demineralize, water. These resins are produced to meet FDA and EU regulatory requirements, which specify permitted chemicals used in their manufacture, maximum release of TOC and other chemicals to the product water, together with analytical methods for their detection and the conditions of use of the resin products.

Disinfection of water produced by the ion exchange process for pharmaceutical manufacture is often treated by UV radiation, immediately following ion exchange or at the point of use.

3.2. Drug Purification

Ion exchange resins and adsorbents can be used in many different drug-processing applications, from extraction, isolation and purification to immobilization and stabilisation. Purification alone, for example, may consist of different stages and processes: chromatographic separation; decolorization; deashing; metals removal; and conversion. The process may also take advantage of heterogeneous catalytic reactions in the presence of specific ion exchange catalysts.

The use ion exchange resins and selective adsorbents results in the advantage of higher purity of the final product, together with minimization of losses, due the high capacity and selectivity of the resins.

The most suitable ion exchange resins and adsorbents for a given application are selected on consideration of functional groups (weak or strong, acid or base, neutral), porosity, pore diameter, hydrophilic / hydrophobic nature, and ability to resist fouling. Often, the final resin selection is a compromise between the capacity, selectivity and elution profile.

Industrial antibiotics production from fermentation broths is a significant area of both ion exchange and synthetic adsorbent use.

3.2.1. Cephalosporin-C

The manufacture of Cephalosporin-C typically takes place in a number of sequential steps.

A fermentation broth is produced containing 5 to 15 g/l cephalosporin, together with impurities, which is then passed through a weak base anion exchanger to remove residual ions and to decolorize. Decolorization is completed using an adsorbent resin, prior to completely adsorbing Cephalosporin-C onto a second adsorbent resin. The Cephalosporin-C is eluted from the adsorbent resin using isopropyl alcohol, and converted to the sodium form using a strong acid cation resin. Purolite manufactures all resins and adsorbents for these processes.

3.2.2. Streptomycin Sulphate Production

The manufacture of Streptomycin is typically carried out in the following sequential steps. A fermentation broth is produced containing Streptomycin in the presence of impurities. The fermentation broth is filtered, and the clear extract passed through a weak acid cation bed to extract the Streptomycin. The Streptomycin is eluted using hydrochloric acid, decolorized and converted to the sulphate form using a strong base anion resin. Freezing and drying achieve purification.

3.3. Other Processes and Applications

The extraction of opium alkaloids, enzymes (such as, lysozyme from albumen), heparin, together with the extraction and purification of amino acids, and the decolorization and stabilization of vitamins, are further examples of the application of ion exchange and adsorbent technology in pharmaceutical production.

Sodium form strong acid cation exchangers are used to remove calcium ions from collected blood to inhibit coagulation without the use of additional chemicals.

Carboxylic resins are used to remove zinc ions from blood plasma.

Strong acid cation exchangers are also used in the analytical determination of sodium levels in blood, and in the analysis of urine.

Purolite offer hydrophobic adsorbent products for adsorption and reversephase chromatography to separate proteins, insuline, peptides, nucleonic acids, targeted antibiotics and many more specific pharma ceutical compounds and solutions.

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