

Pharmaceutical and Biotechnology Application Summary

Pharmaceutical & Biotechnology

Just ask Purolite.

PUROLITE[®]
ION EXCHANGE RESINS



Pharmaceutical applications of 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, and treatment of fermentation products, etc.

Purolite® resins used in drug formulations as API's or excipients 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.

1. ION EXCHANGE RESINS AS ACTIVE PHARMACEUTICAL INGREDIENTS (API)

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. Purolite has Drug Master Files (DMF's) for all three API's listed in this brochure.

1.1. Sodium / Calcium Polystyrene Sulfonate

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 Sulfonates, in either the sodium or calcium form. Sodium Polystyrene Sulfonate is listed in the USP, Ph.Eur, BP and JP, while Calcium Polystyrene Sulfonate is listed only in the BP and JP. As the resins pass through the intestinal tract they exchange the sodium or calcium on the resin for potassium. The potassium fixed by the resin 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 Polystyrene Sulfonate APIs produced in Purolite's FDA approved and cGMP compliant clean rooms. The powdered resin may subsequently be flavored by the pharmaceutical company and prepared in doses to be taken orally.

1.2. Cholestyramine

Cholestyramine is listed in USP, Ph. Eur. and BP. 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.

Purolite® A430MR 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 containing drugs over other drugs is that there are no side effects. Besides the treatment of hypercholesterolemia, Cholestyramine has other medical applications, such as: improving diarrheal states by significantly reducing the activity of endotoxins, treating vitamin D3 overdose and, as recent studies indicate, regression in arteriosclerosis.

Listed in USP, Ph. Eur. and BP 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 dry, powdered, weak acid, polymethacrylic cation exchange 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. For example, **Purolite® C108DR** is a special, dry, 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. The selection of the drug carrier to ensure a steady, uniform, controlled release is dependent on the kinetics of drug adsorption and desorption, which, in turn, are influenced by both chemical and physical factors. Ion exchange resins 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, also known as Polacrilex, is a dry, powdered, weak acid, polymethacrylic cation exchange 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 dry, powdered, strong acid cation exchange resin in the hydrogen form that has been grounded 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 regulated by Food and Drug Administration.

Table 1 – Purolite Range of API and Excipients

Chemical Name	Recommended Purolite® Resins	Application
Sodium Polystyrene Sulfonate	C100NaMR	Used in the treatment of hyperpotassemia, sustained released, taste masking, stabilization of final dosage.
Calcium Polystyrene Sulfonate	C100CaMR	Used in the treatment of hyperpotassemia.
Hydrogen Polystyrene Sulfonate	C100HMR	Used as carrier for sustained released, taste masking, stabilization of final dosage.
Cholestyramine	A430MR	Used for cholesterol reduction, taste masking, sustained release.
Polacrillin Potassium	C115KMR	Used as a high performance tablet disintegrant.
Polacrilex	C115HMR	Used as carrier for sustained release.



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. Demineralization 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 total organic carbon (TOC) and other chemicals to the product water, together with analytical methods for their detection and the conditions of use of the resin products.

When Ultra Pure Water is required, Purolite **UltraClean™** resins help producing water of extremely high purity, with resistivity >18.2 MΩ•cm and very low levels of < 1bbp TOC. This is of particular advantage to the pharmaceutical industry, by reducing the volume and cost of rinse water when installing new resin beds and reducing outage times of operating plants. The availability of high purity water for the process soon after resin changes

translates into highly reliable and consistent production.

Disinfection of water produced by the ion exchange process for pharmaceutical manufacture is often treated by UV radiation, immediately following ion exchange or at 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 stabilization. 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 to 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 (**Purosorb™ PAD 900**), prior to completely adsorbing Cephalosporin-C onto a second adsorbent. The Cephalosporin-C is then eluted from the adsorbent 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 Sulfate 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 sulfate 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 reverse phase chromatography to separate proteins, insulin, peptides, nucleonic acids,

targeted antibiotics and many more specific pharmaceutical compounds and solutions.

4. Adsorbent Technology

Purolite[®] specialty adsorbents, **Purosorb**[™] and **Hypersol-Macronet**[®], are solid copolymers with highly porous structures designed to adsorb and desorb a wide variety of complex molecules and structures in a range of environments. The behavior and degree of adsorbent activity is a function of the hydrophobicity of the copolymer and the degree of polarity of the solvent environment it is surrounded by. Typically, non polar molecules adsorb greatest.

Some application examples are:

- Purification of antibiotics, vitamins, drugs, enzymes and chemicals
- Removal of surface-active components
- Organic acids purification.

5. Microbeads for Chromatography

Purolite supplies a wide range of microbeads for chromatographic separation. Both Chromalite[™] and Hypersol-Macronet[®] are available, on request, in microbead form. Mean diameters of, for example, 5, 10, 30, 50, 100 and 200 microns are available in a choice of functionality, according to the application. All products are specially purified, and made to narrow size range specifications. These microbeads are especially useful where separation by sorption properties control the chromatographic process.

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