

APPLICATION GUIDE

Pharmaceutical and Biotechnology

This Application Guide highlights the use of ion exchange resins and polymeric adsorbents in a variety of pharmaceutical and biotechnology applications.

PHARMACEUTICAL & BIOTECHNOLOGY

Inside this Application Guide you will find an overview of usages for Purolite products within pharmaceutical and biotechnology applications. For more detailed information on any product or to find a product for an application not mentioned, visit www.purolite.com or contact the closest Purolite regional office, listed on the back cover.

INTRODUCTION

Founded in 1981, Purolite is a leading manufacturer of ion exchange, catalyst, adsorbent and specialty resins. With global headquarters in the United States, Purolite is the only company that focuses 100% of its resources on the development and production of resin technology.

Responding to the needs of our customers, Purolite has built the largest technical sales force in the industry, the widest variety of products and five strategically located Research and Development groups. Our ISO 9001 certified manufacturing facilities in the U.S.A, Romania and China combined with more than 40 sales offices in 30 countries ensure complete worldwide coverage.



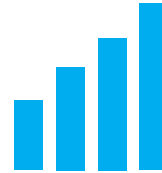
PREMIER PRODUCTS

The quality and consistency of our products is fundamental to our performance. Throughout all Purolite plants, production is carefully controlled to ensure that our products meet the most stringent criteria, regardless of where they are produced.



RELIABLE SERVICE

We are technical experts and problem solvers. Reliable and well trained, we understand the urgency required to keep businesses operating smoothly. Purolite employs the largest technical sales organization in the industry.



INNOVATIVE SOLUTIONS

Our continued investment in research & development means we are always perfecting and discovering innovative uses for ion exchange resins and adsorbents. We strive to make the impossible possible.



In addition to their application as active pharmaceutical ingredients, excipients and water treatment media, ion exchange resins and polymeric adsorbents can be used in a number of pharmaceutical applications—including extraction and purification of enzymes, hormones, alkaloids, viruses, antibiotics, treatment of fermentation products, etc.

Purolite® resins used in drug formulations, such as APIs 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 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 U.S. Food and Drug Administration (FDA) and the European Union.

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 APIs listed in this brochure.

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 1950s, such resins are now widely used in the treatment of acute and chronic hyperkalemia, in addition to controlling serum potassium levels in patients undergoing renal dialysis.

Cholestyramine

Although cholesterol is essential for human and animal life, an excess of cholesterol in the blood is one of the most significant risk factors for cardiovascular disease.

Cholesterol is converted by the liver into bile acids, which, when discharged into the duodenum, emulsify ingested fats to assist digestion. The bile acids absorb through the intestine and are returned to the liver, where they convert to low density lipoprotein (LDL) cholesterol through a chain of reactions.

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, it precipitates as cholesteryl esters on the walls of blood vessels and restricts flow. As this can lead to heart attack, it is advantageous to reduce cholesterol levels in such cases.

Purolite® A430MR is a non-absorbable, non-metabolizable anion exchange resin that complexes bile acids and prevents their re-absorption so they can pass through the body. The reduction of bile acids causes a depletion of hepatic cholesterol. This, in turn, stimulates the transformation of LDL cholesterol into hepatic cholesterol, reducing LDL cholesterol levels and lowering the total cholesterol level in the blood.

The advantage of pharmaceuticals containing cholestyramine over other treatments 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.

Purolite APPLICATION GUIDE

USAGE FOR PHARMACEUTICAL AND BIOTECHNOLOGY APPLICATIONS

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.

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.

Ion exchange resins as excipients

Ion exchange resins can provide effective solutions to problems that arise during pharmaceutical formulation. Resins can mask unpleasant taste, facilitate extended and controlled release, stabilize active ingredients and serve as a disintegration aid. In some cases, the resin can provide multiple benefits. For example, a select resin will not only mask bitter taste, but also stabilizes ingredients. Purolite manufactures many pharmaceutical-grade resins for excipient use.

Tablet Disintegrant

Polacrillin Potassium is typically used as a tablet disintegrant. The resin, in the dry powdered state, is incorporated into tablets containing pharmaceutical ingredients. On wetting, the resin swells by approximately 150%, which causes the tablet to disintegrate. Introduced many years ago into tablet formulations as a disintegration aid, it is still widely used either alone or 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, and polymethacrylic cation exchange resin in the potassium form. Purolite C115KMR has a regulated Drug Master File with the FDA.



Taste & odor masking

A number of ion exchange resins and adsorbents can be used to mask the taste and/or odor of medicines. For example, Purolite® C108DR is a special, dry, carboxylic resin used to mask the extremely bitter taste of certain cardio-tonics and anti-depressants.

Controlled release

Controlled release of medication 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 in solid preparations, syrups for oral consumption, 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 is commonly used for controlled, uniform release of nicotine and incorporated into products that aid smoking cessation. Nicotine is adsorbed onto the powdered resin, which, when combined with the gum, is released slowly and uniformly by chewing.

Table 1 – Purolite Range of API and Excipients

CHEMICAL NAME	RECOMMENDED RESIN	APPLICATION
Sodium polystyrene sulfonate	C100NaMR	Used in the treatment of hyperpotassemia, sustained released, taste masking, stabilization of final dosage
Calcium polystyrenesulfonate	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
Polacrilin potassium	C115KMR	Used as a high-performance tablet disintegrant
Polacrilex	C115HMR	Used as carrier for sustained release

Purolite® C100HMR is a dry, powdered, strong acid cation exchange resin in the hydrogen form that is grounded into a fine dry powder for taste masking and pharmaceutical carrier applications. Purolite C100HMR can also be used in some controlled release and 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.

Ion exchange resins for pharmaceutical production

The production and purification of pharmaceutical products are important applications for ion exchange resins and polymeric adsorbents.

Demineralization

Many pharmaceutical processes require softened or demineralized water for manufacturing. Purolite produces a full range of cation and anion exchange resins to effectively soften or demineralize water, all of which meet FDA and EU regulatory requirements.

Purolite UltraClean™ UCW resins quickly produce water of extremely high purity with resistivity >18.2 MΩ·cm and TOC levels < 1ppb resulting in reduced downtime and rinse water costs.

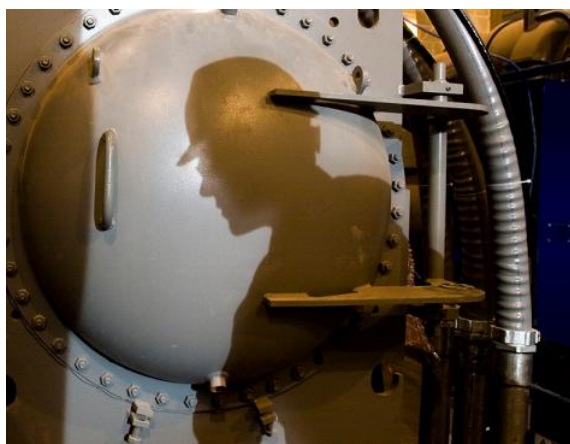
Purification

Ion exchange resins and adsorbents can be used in many different 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, de-ashing, 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 result in higher purity of the final product and minimized loss due to the high capacity and selectivity of the resins.

When choosing the most suitable ion exchange resins and adsorbents for a given application, consideration should be given to 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 production of antibiotics from fermentation broths is a significant area for both ion exchange and synthetic adsorbent use.



Cephalosporin-C

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

A fermentation broth is produced containing 5 – 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.

Streptomycin sulfate production

The manufacture of Streptomycin is typically carried out in multiple 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.

Other processes and applications

The extraction of opium alkaloids, enzymes (such as, lysozyme from albumen) and 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 offers 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.

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

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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Americas

150 Monument Road
Bala Cynwyd, PA
19004
T +01 800.343.1500
T +01 610.668.9090
F +01 484.384.2751
Americas@purolite.com

Europe

Llantrisant Business Park
Llantrisant
Wales, UK
CF72 8LF
T +44 1443 229334
F +44 1443 227073
Europe@purolite.com

Asia Pacific

Room 707, C Section
Huanglong Century Plaza
No.3 Hangda Road
Hangzhou, Zhejiang, China 310007
T +86 571 876 31382
F +86 571 876 31385
AsiaPacific@purolite.com



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