Learn the role of Purolite® ion exchange resins as active pharmaceutical ingredients (APIs) and excipients, including drug carriers.
About Purolite

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

Responding to our customers’ needs, Purolite has a wide variety of products and the industry’s largest technical sales force. Globally, we have strategically located research and development centers and application laboratories. Our ISO 9001 certified manufacturing facilities in the USA, United Kingdom, Romania and China combined with more than 40 sales offices in 30 countries ensure complete worldwide coverage.

Purolite has been part of Ecolab since 2021. A trusted partner at nearly three million commercial customer locations, Ecolab (ECL) is the global leader in water, hygiene and infection prevention solutions and services. Ecolab delivers comprehensive solutions, data-driven insights and personalized service to advance food safety, maintain clean and safe environments, optimize water and energy use, and improve operational efficiencies and sustainability for customers in the food, healthcare, hospitality and industrial markets in more than 170 countries around the world.

PREMIER PRODUCTS
The quality and consistency of our products are 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 team in the industry.

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

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Ion Exchange Resins as Active Pharmaceuticals</td>
<td>3</td>
</tr>
<tr>
<td>Ion Exchange Resins as Excipients</td>
<td>8</td>
</tr>
<tr>
<td>Examples of Resins Used in Controlled Release</td>
<td>13</td>
</tr>
<tr>
<td>Regulatory Support</td>
<td>16</td>
</tr>
</tbody>
</table>
Introduction

A resinate consists of an active pharmaceutical ingredient (API) in which excipients are added to improve the taste and effectiveness of the drug. The resinate may be prepared so that the API is either released into the body immediately or gradually in a controlled manner.

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

This document addresses different uses of ion exchange resin in the pharmaceutical industry, the applications, the resins, their properties and the role of Purolite ion exchange resins as APIs and excipients, including drug carriers.

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) pharmacopeias. Drug Master Files (DMFs) 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 Pharmaceuticals

Polymeric ion exchange resins used for APIs and excipients are insoluble and, when taken orally, pass through the human digestive system without being adsorbed. Therefore, ingestion of specific resins 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 pharmacopeias.

Purolite has DMFs for all three APIs listed in this brochure: sodium polystyrene sulfonate, calcium polystyrene sulfonate and cholestyramine. Sodium and calcium polystyrene sulfonate are used to control blood potassium to prevent hyperkalemia. Cholestyramine is orally administered to reduce blood cholesterol. Purolite provides value to these mature markets in many ways, including investment in the expansion and maintenance of cleanroom operations and provision for and quality-related systems.
**TABLE 1** Active Pharmaceutical Ingredients

<table>
<thead>
<tr>
<th>Active Pharmaceutical Ingredient</th>
<th>Product Name</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Polystyrene Sulfonate</td>
<td>Purolite C100MRNS</td>
<td>Strong acid cation-exchange resin with sulfonic acid groups in sodium form; exchange resin is purified, dried, milled and is used to control blood potassium for the treatment of hyperkalemia.</td>
</tr>
<tr>
<td>Calcium Polystyrene Sulfonate</td>
<td>Purolite C100CaMRNS</td>
<td>Strong acid cation-exchange resin with sulfonic acid groups in calcium form; resin is purified, dried, milled and is used to control blood potassium for the treatment of hyperkalemia.</td>
</tr>
<tr>
<td>Chloestyramine</td>
<td>Purolite A430MR</td>
<td>Special strong base anion-exchange resin in chloride form; resin is purified, dried, milled and is used for reducing blood cholesterol.</td>
</tr>
</tbody>
</table>

Note: The products listed above are produced in an FDA inspected, cGMP certified facility.

Purolite has cleanrooms for API manufacturing in Victoria, Romania and opening in 2022 in King of Prussia, Pennsylvania, in the United States of America.
**Polystyrene Sulfonate, Purolite C100MRNS and Purolite C100CaMRNS: Treatment of Excessive Potassium Levels in Blood**

Hyperkalemia is one of the most common complications in end-stage renal disease patients. It could cause serious abnormality in the heart, such as cardiac arrhythmias, thereby being involved in heart failure and sudden death in patients with advanced chronic kidney disease (CKD).

Polystyrene sulfonate resin, a cation-exchange resin, is the most commonly used drug to treat hyperkalemia. The resin can be used in calcium (Ca) form and sodium (Na) form polystyrene sulfonate. Thus, hyperkalemia can be treated with Purolite C100MRNS or Purolite C100CaMRNS. The sodium or calcium in the resin is exchanged for the potassium in the body.

Purolite C100MRNS and Purolite C100CaMRNS are powdered, fully synthetic, polystyrenic, cation-exchange resin in sodium and calcium form, respectively, fully conforming to the monographs found in the USP/Ph. Eur./BP/JP of sodium and calcium polystyrene sulfonate.

The resin is an odorless buff powder. Loss on drying (residual humidity) is less than 10%, and the particle size NMT 1% over 150 microns (100 US mesh). The body does not absorb the resin.

Both alternatives Purolite C100MRNS and Purolite C100CaMRNS exchange their bound cations for potassium in the lumen of the proximal and distal colon and consequently reduce serum potassium levels through the excretion of potassium into the stool.

---

**FIGURE 1**

Typical Structure of Main Repeating Units

Purolite C100MRNS

\[
\begin{align*}
\text{SO}_3\text{Na}^+ & \quad \text{CH} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_2 \quad \text{CH} \quad \text{CH}_2 \quad \text{SO}_3\text{Na}^+ \\
\end{align*}
\]
Purolite manufactures Sodium Polystyrene Sulfonate and Calcium Polystyrene Sulfonate which are used to treat hyperkalemia.

Cholestyramine, Purolite A430MR: Reduction of Cholesterol and Treatment of Cardiovascular Disorders

Clinical studies have demonstrated that the formation of cholesterol in the liver is in equilibrium with biliary cholesterol acids.

The cholesterol level in the blood and liver can be reduced by adsorption of the biliary acids and formation of an insoluble complex. A strong base anion-exchange resin in powdered chloride form is used for this purpose. Purolite A430MR is a milled, fully synthetic, polystyrenic, Type I quaternary ammonium anion-exchange resin in chloride form, fully conforming to the monographs found in the USP/Ph. Eur./BP/JP of cholestyramine.

Purolite A430MR cholestyramine resin is an active pharmaceutical ingredient that decreases plasma levels of total cholesterol and LDL cholesterol. It is indicated for the treatment of type II hyperlipoproteinemia. Bile acids are formed in the liver through the metabolism of cholesterol. They are adsorbed by cholestyramine in the intestine, thus lowering the level of LDL cholesterol in the body.
This product is a white or almost white, fine powder hygroscopic. Loss on Drying (residual humidity) is of NMT 12%, usually between 5% to 12%, and particle size is NMT 1% max. over 150 microns (100 US mesh).

The organism does not adsorb the drug, and the resin-biliary acid complex is excreted with the feces.

**Diarrhea Treatment with Purolite A430MR**

During bile acid malabsorption (BAM), patients may suffer from bile acid diarrhea (BAD). This can happen by instance to people who undergo a cholecystectomy (gallbladder removal). They can develop chronic diarrhea after an excess of bile acids spill into the colon and trigger loose and watery stools. The medication has the effect of reducing diarrhea symptoms.

For persons with BAD, a larger amount of bile acids gets passed to the colon, increasing motility and stimulating water secretion, resulting in diarrhea. Cholestyramine is used to remove the bile acids, thereby minimizing this effect.
Grave’s Disease Treatment with Purolite A430MR

A low dose of cholestyramine is an effective and well-tolerated adjunctive agent treating hyperthyroid Graves’ disease, an autoimmune disorder that overproduces thyroid hormones. Cholestyramine is used to treat people with severe thyrotoxicosis, a high level of thyroid hormones in the blood.

The medication helps to bind thyroid hormones in the intestine, increasing their excretion so that blood levels of the thyroid hormones are reduced.

Purolite A430MR for Veterinary Uses

Cholestyramine may be prescribed to help eliminate drugs or toxins from an animal’s body. This medicine may also be prescribed to lower the animal’s high cholesterol level or treat certain types of diarrhea.

Ion Exchange Resins as Excipients

Pharmaceutical excipients are substances other than the API that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Ion exchange resins are the ideal excipients when the goal is one of the following:

- Reduce side effects and conceal the taste of the drug
- Stabilize the drug
- Increase its solubility by neutralizing the effect
- Improve tablet disintegration properties by a physical effect on the tablet
Taste Masking

Taste is a key organoleptic factor in the development of oral dosage forms. Taste can affect the patient’s acceptability of a drug. Whether the drug is bitter or acid, when dissolved in saliva, a taste is quickly developed. Drug molecules interact with taste receptors on the tongue to give a taste that can be bitter, sweet, acidic, alkaline, or salty.

For example, many alkaline drugs can be very bitter. Thus, the drug system required an excipient with the ability to mask the taste while in the mouth. Weak acid cation ion exchange resins such as Purolite C115KMR/5100 can be used because of their pH they are not dissociated in the mouth under the alkaline conditions of the saliva, thus masking the taste and releasing the drug once in the acidic environment in the stomach.

Drug Stabilization

Some APIs have reduced effectivity because of their poor stability under storage conditions. Stability can be improved by complexing the drug with a carboxylic ion exchange resin such as Purolite C115HMR without reducing the therapeutic effect of the API. One example is vitamin B12. The resinate complex formed in this way is just as effective as free vitamin B12.
**FIGURE 3**

Typical Structure of Main Repeating Units

Purolite C115KMR

Purolite C115HMR
**Improvement of Dissolution of Poorly Soluble Drugs**

The dissolution of a drug has a direct effect on the bioavailability of such a drug. The presence of ion exchange resins can increase the solubility of some APIs. Drug resinate complexes have a faster rate of dissolution. Some ion exchange resin matrices are relatively hydrophilic and can allow aqueous solutions to penetrate the dimensional resin structure, increasing the dissolution rate.

**Tablet Disintegrants**

A tablet disintegrant is an excipient incorporated into the formulation of tablets to promote their disintegration when they come into contact with liquid or fluid matter, in this case with saliva and gastric fluids. This property is inherent to most dry ion exchange resins because of their ability to absorb water and swell. This property is also enhanced when fine particle mesh is used. Among all ion exchangers, carboxylic ion exchange resins such as Purolite C115HMR have substantial swelling capacity without causing secondary reactions with the drug.

**Controlled Release — Drug Carriers**

The delayed, extended or sustained release action technique is prevalent in the pharmaceutical market. It permits a controlled quantity of the active substance to be released gradually into the body (over several hours), thus reducing the number of doses and increasing the acceptability of the drug.

Additionally, and on the contrary, it can also improve the slow dissolution of poorly soluble drugs having poor bioavailability. The release of such medicines from the resin-drug complex is much faster than the dissolution rate of the pure drug.

The rate of release of an API from the ion exchange resin depends on the resin properties such as the exchange capacity, the degree of cross-linkage, particle size, chemical structure, functional group pK, porosity, swelling and purity.

The exchange capacity limits the total amount of drug to be fixed in the resin. In most cases, because of the high total weight capacity of the weak acid cation resins derived from acrylic acids polymers, they have higher exchange capacity.

The divinylbenzene (DVB) cross-linking can vary from 2–16%. The DVB level will strongly affect the shrinking and swelling of the resin. The swelling will affect the hydration, and this property can, in many cases, be used for tablet disintegration.

In general, a basic (alkaline) API will be adsorbed on a cation exchange resin, either by a sulfonic group or weak carboxylic acid group, i.e., carboxylic groups. The acidic API, they will be fixed in anion resin with strong functional, i.e., quaternary anion groups or with weak functional, i.e., tertiary amine groups.
The ionization of the attached functional group depends on the self-functional group, the pH of the media, and the water content in the resin. In aqueous media, strong acid cation and strong base anion are fully hydrated. The counter ions associated with the functional group are fully available for exchange with ions from the solution (i.e., saliva or gastric fluids).

The value at which ionization becomes effective depends on the pKa of each resin. Resins containing sulfonic or carboxylic acid exchange groups have different pKa values. Anionic exchangers are quaternary and tertiary ammonium groups that have different pKa values. The pKa value of the resin will significantly influence the rate at which the drug will be released in the gastric fluid.

Drugs fixed to the resin are released by an ion exchange mechanism when reaching the rich ionic environment in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins to the body.

The reactions for the formulation of the resinate complex (R-SO$_3^-$drug) and the drug release in the body are described here below for a strong acid cationic resin and weak acid cationic resin:

**Resin Loading**

Cationic Resin R SO$_3^-$ – Na$^+$ + Drug (+) Cl $\rightarrow$ + R SO$_2^-$ Drug + Na Cl

Cationic Resin R COO- H$^+$ + Drug (+) Cl $\rightarrow$ + R COO Drug + H Cl

And their respective release in the body once in contact in the intestine environment.

**Drug Release**

R SO$_3^-$ Drug + Na Cl $\rightarrow$ Drug Cl + R SO$_2^-$ Na

R COO Drug + Na Cl $\rightarrow$ Drug Cl + R COO Na
Examples of Resins Used in Controlled Release

Antitussive Agents

Ion exchange resins can be used for the extended release of antitussive agents. During the extended release, the drug is released slowly over time. The benefit of this is taking pills less often and potentially may be fewer side effects.

Both sodium polystyrene sulfonate and weak acid cation carboxylic resins can be used.

Sodium polystyrene sulphonate, Purolite C100MRNS is used to fix the active antitussive principles of codeine or hydrocodone. Pharmaceutical companies will then offer in the market in capsule or oral suspension form. The extended release into the intestinal tract takes place over 12 hours, which reduces the number of doses.

Appetite-Reducing Drugs

Another application of ion exchange resins as drug carriers consists of a resin, particularly a strong acid cation resin such as sodium polystyrene sulphonate, Purolite C100MRNS, which supports an active principle called “phentermine.” This drug is used under medical prescription to suppress appetite in combination with other therapies.

The medicament is available in capsule form. The active principle is gradually released into the gastro-intestinal region over 10 to 12 hours, which increases its acceptability.

Nicotine Replacement Products for Cessation of Smoking

Purolite C115HMR weak acid cation resin is used for the sustained release of nicotine. The resinate complex known as polacrilex nicotine is essentially nicotine drug bound to an ion-exchange resin (polymethacrylic acid resin).

The resinate complex is added to flavored chewing gums and hard lozenges used for nicotine in therapy for smoking cessation programs. The use of the polymer for controlled release maximizes the amount of nicotine released and absorbed by buccal mucosa during chewing when saliva act as a solvent for elution of the drug from the resinate complex.

Purolite C115HMR can be offered in different grades depending on the formulation and chewing product.
Other Drug Delivery Applications

Ion exchange resins are also used in several controlled drug release applications such as nasal and ophthalmic drug release or the sustained release of antidepressants.

Loading the Drug

Once the proper resin has been selected as a drug carrier because of its properties, the next step is to fix the drug in the resin and prepare the resin drug complex called resinate. This process needs to be optimized to load the right amount of drug in the resin. The steps include the preconditioning of the resin, if necessary, and the self-loading through various procedures. Drug manufacturers are using their own procedures to load the drugs on the resins.

Preconditioning

The resin as received has already been preconditioned by the resin manufacturer by washing with ethanol or ethanol-water mixtures followed by final rinsing with purified water. The API manufacturer may elect to provide additional cleaning on-site.
Regulatory Support

When applying for a new drug application or changing your primary supplier to Purolite, we will provide all pertinent regulatory information available for our APIs and excipients, as well as samples to support your application.

Available documentation includes GMP certification, ISO certification, FDA inspection reports, FDA Product and Facility Registrations, Applicant’s Part of the DMF (Drug Master File) or ASMF (Active Substance Master File), a series of contaminant declarations and other necessary documents.

Purolite’s factories and cleanroom facilities have been and will continue to be audited by pharma and biotech companies located worldwide. We typically host audits weekly.
Purolite, a leading manufacturer of quality ion exchange, catalyst, adsorbent and specialty high-performance resins, focuses 100% of its resources on the development and production of resin technology.

We’re ready to solve your process challenges. For further information on Purolite products and services, visit www.purolite.com or contact your nearest Technical Sales Office.

The statements, technical information and recommendations contained herein are believed to be accurate as of the date hereof. Since the conditions and methods of use of the product and of the information referred to herein are beyond our control, Purolite expressly disclaims any and all liability as to any results obtained or arising from any use of the product or reliance on such information; NO WARRANTY OF FITNESS FOR ANY PARTICULAR PURPOSE, WARRANTY OF MERCHANTABILITY OR ANY OTHER WARRANTY, EXPRESSED OR IMPLIED, IS MADE CONCERNING THE GOODS DESCRIBED OR THE INFORMATION PROVIDED HEREIN. The information provided herein relates only to the specific product designated and may not be applicable when such product is used in combination with other materials or in any process. Nothing contained herein constitutes a license to practice under any patent and it should not be construed as an inducement to infringe any patent and the user is advised to take appropriate steps to be sure that any proposed use of the product will not result in patent infringement.