Dow Advanced Release Technologies
for improved present and future pharmaceutical formulations
**Sodium Polystyrene Sulfonate USP Resin**

**AMBERLITE™ IRP69**

is used to treat hyperkalemia. Hyperkalemia occurs when the level of potassium in the bloodstream is higher than normal. The most common cause of hyperkalemia is kidney (or renal) disease.

The kidneys normally excrete excess potassium from the body.

In case of severe hyperkalemia, the patient can be given a cationic resin to bind potassium ions. The functional polymer remains in the intestines, where it absorbs potassium and forms a complex of resin and potassium. Eventually this complex is excreted in the feces.

Typical dosage amounts are 15-60 g per day for extended periods of time.

**Cholestyramine Resin USP**

**DUOLITE™ AP143**

is used for the treatment of hypercholestesterolemia. Low Density Lipoprotein (LDL) favors fatty deposits called plaques that clog the arteries and thus impede the flow of blood. Elevated levels of LDL cholesterol are an important factor in the likelihood of cardiac arrest.

During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption. It increases the fecal loss bile acid-bound low density lipoprotein (LDL) cholesterol.

To reduce elevated serum cholesterol, cholestyramine is administered as chloride salt. It binds bile acids, exchanging chloride for bile acid. Cholestyramine is a quaternary ammonium anion exchange resin with a polystyrene polymer skeleton. The cholestyramine resin is not absorbed from the digestive tract and the resin combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces.

Typical dosage amounts are 8-24 g per day for extended periods of time.
Dow has recently developed know-how including some patents. Advanced Released Technologies improve the manufacture of drug resinates (resin/drug complex) and expands the uses of functional polymers into new areas.

AMBERLITE™ IRP ion exchange resins can be used for different types of oral dosage forms (liquid such as syrups, solid such as tablets, capsules or melt-in-the-mouth forms). It is not recommended to use these materials for injectable formulations or medical devices.

Taste Masking

Drug-Resin complexes “Resinates” are insoluble. Hence, the bitter taste of the drug is not sensed as the drug is not released during quick passage through the mouth, but is rapidly released in the gastro-intestinal (GI) tract. This technique has been successfully used for bitter drugs such as ranitidine and paroxetine. Moreover, Dow Water & Process Solutions has designed new equipment for buccal dissolution that allows the selection of taste masking formulations. This technology was specially developed to help formulators to optimize their taste masking formulations in vitro and show differences between formulations.

Tablet Disintegration

Numerous drugs are formulated in the form of tablets. Their efficiency depends on the speed at which the tablet disintegrates in the stomach. AMBERLITE™ IRP88 swells easily in an aqueous medium and thus rapidly disintegrates the tablet by creating internal pressure. The use of AMBERLITE™ IRP88 offers advantages in term of tablet hardness when it is submitted to a high level of compression, preventing them to break or dust during packaging and shipping. Carboxymethyl cellulose and alginates are adhesive in nature and thus not very efficient in overcoming the bonding of particles in compressed tablets whereas AMBERLITE™ IRP88 shows a minimal adherence rate and is therefore more effective for such formulations.

Controlled and Modified Release

A way of formulating a drug so that it is released into the body steadily over a long period of time, thus reducing the dosing frequency. With AMBERLITE™ IRP69 or DUOLITE™ AP143, a controlled rate of drug release allows sustained release up to several hours or the site and timing of release of the drug. Further control can be obtained by applying a coating to the resinate.

Reduced Abuse

One interesting potential of controlling the release rate of drugs is in the specific case of drug abuse where a high and rapid release from high dose formulations of certain drugs is sought by abusers. The use of drug resinates make this process more difficult than with simple drugs themselves and can be one of a number of possible strategies used to reduce the instance of formulation abuse.

Nicotine Polacrilex USP

The Nicotine resinate is the principal ingredient of the nicotine chewing gums currently marketed by a variety of companies. Dow Water & Process Solutions manufactures the key starting material—AMBERLITE™ IRP64—for the production of the Nicotine Polacrilex USP resinates.

Deliquescence

By the use of a resinate, it is possible to eliminate deliquescence, a property of a drug that dissolves in water adsorbed from contact with moist air. Loading a drug onto a functional polymer imparts some of the characteristics of the polymer onto the resulting resinate, in particular, the physical properties of a fine free flowing powder. It has been shown that the amount of moisture uptake by the drug is significantly reduced and even at elevated moisture content, the resinate remains a free flowing powder which is easily formulated.

Stabilization of Molecules

The stability of certain pharmaceutical preparation can be affected by environmental conditions such as moisture, light, pH, etc., and therefore needs protection. Molecules such as Vitamin B12, are adsorbed onto the resin and thus can be protected from the action of gastric juices. The molecule passes practically unchanged through the gastric system into the intestinal tract where it is released. Shelf life can be extended well beyond the 3-6 month typically seen with Vitamin B12.

Poor Soluble Drugs

Many modern drugs are poorly soluble due to slow dissolution and/or low solubility. The rate of release of a poorly soluble, ionisable drug from a resinate can be improved over the rate of dissolution of the pure drug. A functional polymer avoids the reticular or crystal energy of the active ingredient, the principal barrier to a rapid dissolution in aqueous phase. The use of resinate, where applicable, does not necessitate to grind the drug in ultrafine particles, nor to add lubricants or surfactants to the dosage form.

Polymorphism

Drugs are often available with more than one crystal form: each with distinct properties in terms of solubility, melting temperature, etc. which often results in a difference in bioavailability. Polymorphs are difficult to control at large scale, especially during storage. A drug resinate is an amorphous solid, and therefore cannot alter its form. Knowing that the release of a drug is independent from its crystal form during manufacturing, it is sufficient to load drugs onto functional polymers, to obtain reliable and consistent drug properties.
FloVitro™ Dissolution Testing offers a new approach to dissolution testing. It can be used to determine how quickly and how efficiently tablets or other dosage forms dissolve and so make the drug available to the human body or in the development of new formulations to control the quality of the formulations.

The technology gives excellent In Vitro / In Vivo Correlation (IVIVC) results leading to greater confidence in the quality assurance of drug formulations.

**Buccal Dissolution Testing** is used to measure the efficiency of an excipient used for taste masking. This is of particular interest with liquid and dissolve-in-the-mouth dosage forms.
Recent Investment
More than 4 Million euros over 2 years.

Manufacturing According to Full cGMP Standards
• Smooth walls, filtered air, stainless steel equipment.
• Separate process zones with airlocks.
• Production process flow designed to minimize cross contamination risk potential.

Personnel
Fully trained and dedicated technical operating staff assisted by Quality Control and Quality Assurance department.

Quality Assurance
• Complies with cGMP (current Good Manufacturing Practices) regulations and ISO 9001 certified.
• Quality management system that involves the management and the personnel.
• Personnel regularly trained to cGMP.
• Quality controls at each step.
• Evaluation of suppliers of raw materials and packagings.
• Stability studies.

Bulk Pharmaceutical Quality Control Laboratory
The dedicated Pharmaceutical Quality Control Laboratory tests batches of pharmaceutical resins and checks their stability.
Final batches are released by the Quality Assurance group according to their analytical conformity and production review.
Both our Quality Control and Assurance groups assist customers by exchanging information on analytical methods and help them when they have difficulties in implementing them in their own laboratories.
They use qualified equipment and validated methods.

Dow Chauny
The largest ion exchange resin production site worldwide
• AFSSAPS (2006)
Certifications:
• Quality : ISO 9001
• Environment : ISO14001
• Health and Safety : OHSAS 18001
Site classified Seveso 2 “high threshold”
### AMBERLITE™ IRP AND DUOLITE™ AP143
### ION EXCHANGE RESINS
Bulk Pharmaceutical Chemicals for Finished Dosage Forms

<table>
<thead>
<tr>
<th>Compendial Name</th>
<th>Commercial Name</th>
<th>Function in the Dosage Form</th>
<th>Active For</th>
<th>Exciplient For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polacrilex Resin(1)</td>
<td>AMBERLITE™ IRP64</td>
<td>Taste masking agent</td>
<td></td>
<td>Drug stabilising agent Nicotine</td>
</tr>
<tr>
<td>Polacriline Potassium</td>
<td>AMBERLITE™ IRP88</td>
<td>Tablet desintegrant</td>
<td></td>
<td>Taste masking agent</td>
</tr>
<tr>
<td>Sodium Polystyrene Sulfonate</td>
<td>AMBERLITE™ IRP69</td>
<td>Potassium reduction</td>
<td></td>
<td>Sustained release</td>
</tr>
<tr>
<td>Cholestyramine Resin(2)</td>
<td>DUOLITE™ AP143</td>
<td>Cholesterol reduction</td>
<td></td>
<td>Drug stabilising agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Taste masking agent</td>
</tr>
</tbody>
</table>

(1) Refers to Nicotine Polacrilex monograph  
(2) Cholestyramine resin is available in several grades which vary only in their particle size

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If you have any specific requests in terms of particle size or other polymer characteristics, please visit [www.theartofformulation.com](http://www.theartofformulation.com). We are interested in expanding our product line in partnership with pharmaceutical companies.

For applications such as deliquescence, polymorphism, controlled or modified release and poor soluble drugs, please call us at 1-800-447-4369.

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### Regulatory Compliance and Support
Dow Water & Process Solutions is committed to manufacturing bulk pharmaceutical chemicals of consistent and uniform quality in compliance with current good manufacturing practice (cGMP) standards and complying with the latest requirements of the regulatory authorities. The processing, packaging, labelling and control operations in the production of all our pharmaceutical grade resins are carried out by Dow Water & Process Solutions France SAS facility located in Chauny.

Assistance is also provided to customers with preparing regulatory submissions. Chemistry, Manufacturing and Controls (CMC) Documentation is available for each of our pharmaceutical grade resin for your review and/or inclusion in your Marketing Authorisation Applications.

For US applications, Dow Water & Process Solutions has filed with the Food and Drug Administration appropriate Drug Master Files (Type II and Type IV DMF). Letters of Authorisation and CMC will be issued and provided upon request.

To contact our nearest local representative or to obtain more information, visit [www.theartofformulation.com](http://www.theartofformulation.com)
Warning: Oxidizing agents such as nitric acid attack organic ion exchange resins under certain conditions. This could lead to anything from slight resin degradation to a violent exothermic reaction (explosion). Before using strong oxidizing agents, consult sources knowledgeable in handling such materials.

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