Product Data Sheet

AMBERLITE™ IRP64 Ion Exchange Resin

Pharmaceutical Grade Cation Exchange Resin (Polacrilex Resin)

Description

AMBERLITE™ IRP64[1] resin is an insoluble, weakly acidic, hydrogen form, cation exchange resin supplied as a dry, fine powder. AMBERLITE™ IRP64 is suitable for use in pharmaceutical applications, primarily as a carrier for certain basic (cationic) drugs and related substances. It can also be used to mask objectionable tastes associated with certain basic drugs. Commercial examples of its use include:

- Stabilization of Vitamin B12
- Sustained Release of Nicotine

A Drug Master File for this product is maintained with the United States Food and Drug Administration. Letters of authorization granting access to the file by FDA in support of NDA and ANDA submittals will be provided upon request. Similar assistance can also be offered in support of the registration of formulations containing AMBERLITE™ IRP64 in many other countries.

[1] The use of AMBERLITE™ pharmaceutical grade ion exchange resins as components of drug formulations is subject to the Food, Drug, and Cosmetic Act as amended.

Typical Properties

Physical Properties	
Copolymer	Crosslinked-acrylic
Type	Weak acid cation
Functional Group	Carboxylic acid
Physical Form	White to off-white fine powder, free of foreign matter and any agglomeration
Chemical Properties	
IR identification	Conforms to reference spectrum assay
Ionic Form as Shipped	H^+
Exchange Capacity (as is)	≥ 10.0 meq/g, on dried basis
Purity testing	
Sodium	≤ 0.20%
Heavy metals	≤ 0.001%
Iron	≤ 0.01%
Methacrylic acid	≤ 300 ppm
Water extractable impurities	≤ 2.0%
Physico-chemical testing	
Loss on drying	≤ 5.0%
Particle Size §	
< 0.150 mm	≤ 1.0%
< 0.075 mm	15.0-30.0%
> 1.180 mm	≤ 70.0%
Microbial Purity	
Total bacterial count	≤ 100 cfu/g
Total mold count	≤ 100 cfu/g

§ For additional particle size information, please refer to the Particle Size Distribution Cross Reference Chart (Form No. 177-01775).

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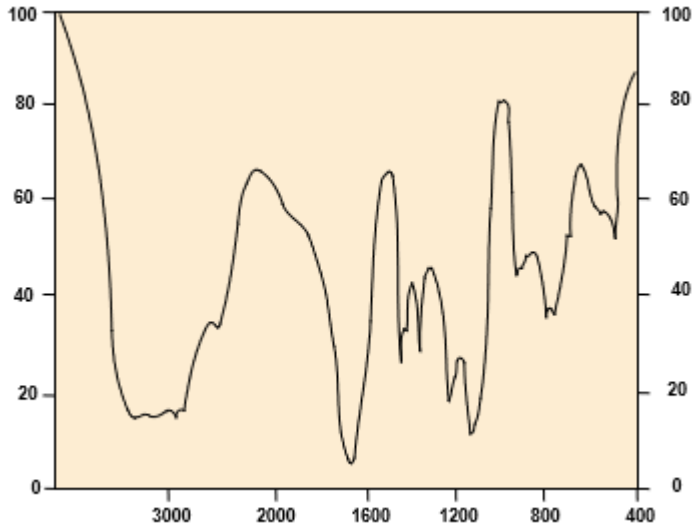
IR Spectrum

AMBERLITE™ IRP64 is manufactured in accordance with Good Manufacturing Practices (cGMP) for bulk pharmaceutical chemicals.

Identification AMBERLITE™ IRP64 can be identified by infrared spectroscopy, as shown in the sample spectrum in Fig. 1.

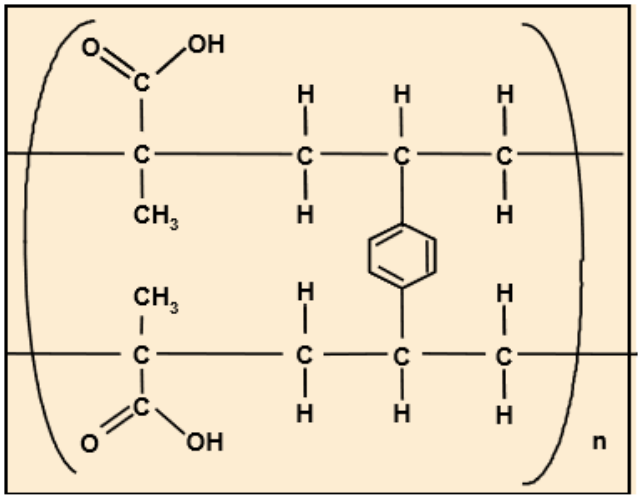
Figure 1. AMBERLITE™ IRP64 Resin IR Spectrum



Chemical Structure

AMBERLITE™ IRP64 is derived from a porous copolymer of methacrylic acid and divinylbenzene. The chemical structure of AMBERLITE™ IRP64 is shown in Figure 2.

Figure 2. AMBERLITE™ IRP64 Chemical Structure



Applications

Applications for AMBERLITE™ IRP64 include:

- Taste Masking
- Drug Stabilization
- Carrier for Cationic Drugs
- Controlled Release Formulations

AMBERLITE™ IRP64 provides a means for binding medicinal agents onto an insoluble polymeric matrix. This affords an effective technique for overcoming

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problems of taste and odor in oral dosage formulations as well as providing a matrix upon which a sustained or controlled release formulation can be developed.

The high affinity of AMBERLITE™ IRP64 for the hydrogen ion results in ready desorption of adsorbed species by exposure to an acidic environment, such as that exhibited in the stomach. This accounts for the higher desorption efficiencies versus a strong acid cation resin like AMBERLITE™ IRP69.

Chemical instability problems can sometimes be resolved by adsorption on to AMBERLITE™ IRP64. For example, complexes of AMBERLITE™ IRP64 with cyanocobalamin (Vitamin B12), a nonionic material, have been used for many years as a means of providing a stable oral dosage form of this vitamin.

Drug Loading

Batch equilibration is the preferred practice when loading a drug or other sorbate into finely divided ion exchange operations normally used with ion exchange resins.resin powders. Due to its fine particle size, AMBERLITE™ IRP64 does not lend itself to conventional columnar operations normally used with ion exchange resins.

The mobile, or exchangeable, cation in this resin is the hydrogen ion. In acidic environments (generally below pH 4) AMBERLITE™ IRP64 exists as the free acid in an essentially nonionic state. Adsorption (loading) onto this cation exchange resin is usually carried out at pH 6 or higher.

The amount of drug loaded onto AMBERLITE™ IRP64 will be influenced by such factors as:

- the inherent affinity or selectivity between the ion exchange resin and the drug.
- the concentration of the drug in the loading solution.
- the concentration and selectivity of competing cations.
- the pH of the loading solution.

The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

When utilizing a batch or equilibrium contact to load a drug or other anionic sorbate onto AMBERLITE™ IRP64, it may be desirable to load as much as possible of the substance of value onto the resin. Complete transfer of the drug from the loading solution is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the resin. The use of two or more loading stages, separating the resin from the liquid phase between stages, is an effective means of achieving maximum loading of the drug onto the resin while maintaining minimum loss of drug from the liquid phase of the final stage.

Carefully controlled laboratory experiments are required to establish precise loading and elution conditions.

Drug Release

The rate and completeness of drug desorption in vivo will be controlled by the diffusion rate of the drug through the polymer phase of the resin, (usually a function of molecular weight), the selectivity of the drug for the resin, and the concentration of electrolytes particularly in the hydrogen ion, in the desorption environment.

More hydrophobic drugs will usually elute from the resin at a lower rate, as will drugs with a relatively high selectivity for the carboxylic acid functional structure in

the resin. Other resinsorbate interactions are possible, and these can have a pronounced effect upon loading capacities and rates.

An example of this might be the presence of a transition metal in the structure of the sorbate molecule which can result in considerable selectivity through the formation of a coordination compound with the resin.

Applications Reference List

Controlled/Sustained Release

Leo Corporation, 1973. Smoking substitutes and method of production. Patent GB 1,325,011.

Taste-Masking

Douglas, S.J. Glaxo Group Research Ltd, 1990. Process for the preparation of a ranitidine resin absorbate. US 5219 563.

Astruc, J., and A. Sambot, 1970. Ion-exchange resin: spiramycin compositions. Patent GB 1,180,233.

Borodkin, S., and D.P. Sundberg, 1971. Chewable tablets including coated particles of psuedo-ephedine-weak cation exchange resin. Patent US 3,594,470.

Wilding, I.R., S.S. Davis, K.P. Steed, R.A. Sparrow, J. Westrup, and J.M. Hempenstall, 1994. Gastrointestinal transit of a drug-resinate administered as an oral suspension. Int. J. Pharm. 101: 263-268.

Other

Fretland, D.J., 1974. Use of ion-exchange resins for removing prostaglandins from human urine prior to radioimunoassay. Prostaglandins 6 (5): 421-425.

Miles Laboratories, Inc., 1970 Detection device for enzymes and other factors in body fluids. Patent US 3,616,251. Kunin, R., S. Vetrano, and B. L. Libutti, 1990. A novel approach to the use of ion exchange and adsorption media for the processing of pharmaceutical and biological substances. Reactive Polymers 13: 291-298.

Pogocki, D., T. Ruman, M. Danilczuk, M. Danilczuk, M. Celuch, and E. Walajtys-Rode, 2007. Application of nicotine enantiomers, derivatives and analogues in therapy of neurogenerative disorders. Eur. J. Pharm. 563: 18-39.

Product Stewardship

DuPont has a fundamental concern for all who make, distribute, and use its products, and for the environment in which we live. This concern is the basis for our product stewardship philosophy by which we assess the safety, health, and environmental information on our products and then take appropriate steps to protect employee and public health and our environment. The success of our product stewardship program rests with each and every individual involved with DuPont products—from the initial concept and research, to manufacture, use, sale, disposal, and recycle of each product.

Customer Notice

DuPont strongly encourages its customers to review both their manufacturing processes and their applications of DuPont products from the standpoint of human health and environmental quality to ensure that DuPont products are not used in ways for which they are not intended or tested. DuPont personnel are available to answer your questions and to provide reasonable technical support. DuPont product literature, including safety data sheets, should be consulted prior to use of DuPont products. Current safety data sheets are available from DuPont.

Please be aware of the following:

- **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.

Regulatory Note

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