



DUOLITE™ API43/I083

Pharmaceutical Grade Anion Exchange Resin

(CHOLESTYRAMINE RESIN USP)

PRODUCT DATA SHEET

DUOLITE™ API43/I083^[1] resin is an insoluble, strongly basic, anion exchange resin in the chloride form supplied as a dry, fine powder. DUOLITE API43/I083 resin is suitable for pharmaceutical applications either as an active ingredient or as a carrier for acidic (anionic) drug substances. A monograph for Cholestyramine Resin USP appears in the United States Pharmacopoeia/National Formulary. DUOLITE API43/I083 resin conforms to the compendial specifications.

A Drug Master File for this product is maintained with the United States Food and Drug Administration.

IDENTIFICATION

DUOLITE API43/I083 resin can be identified by infrared spectroscopy, as shown in the example Figure 1. Letters of authorization granting access to the file by FDA in support of NDA and ANDA submissions will be provided upon request.

DUOLITE API43/I083 resin is manufactured in accordance with Good Manufacturing Practices (cGMP) for bulk pharmaceutical chemicals.

Figure 1: Duolite API43/I083 IR Spectrum

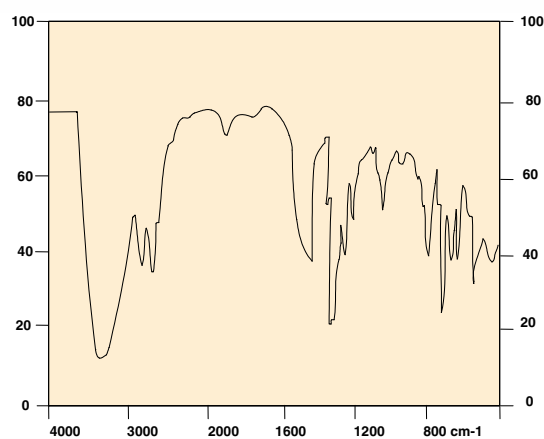


TABLE I : PROPERTIES

Ionic form _____	Chloride
Particle size ^[2] _____	100% min. < 425 microns
	85% min. < 150 microns
	50% min. < 75 microns
Loss on drying ^{[2] [3]} _____	12.0 % maximum
Heavy metals ^{[2] [3]} _____	0.002 % maximum
Identity (by IR spectrum) ^{[2] [3]} _____	Identical to USP reference standard
pH of slurry ^{[2] [3]} _____	4.0 to 6.0
Residue on ignition ^{[2] [3]} _____	0.1 % maximum
Dialysable quaternary amine ^{[2] [3]} _____	0.05 %
Trimethylamine ^[2] _____	20 ppm maximum
Chloride content ^{[2] [3]} _____	13.0 to 17.0 %
Sodium glycocholate exchange capacity ^{[2] [3]} _____	1.8 to 2.2 g/g
Organic Volatile Impurities <467> ^{[2] [3]} _____	Meets requirements

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

^[2] Contractual value

^[3] Appears in current USP/NF

TYPICAL PHYSICAL PROPERTIES

DUOLITE™ AP143/1083 complies with the compendial specifications for Cholestyramine Resin USP when tested in conformance to the compendial test methods presented in current USP/NF. The resin is described as a “White to buff colored, hygroscopic, fine powder. Is odorless or has not more than a slight amine-like odor. Insoluble in water, in alcohol, in chloroform and in ether”.

CHEMICAL PROPERTIES

DUOLITE AP143/1083 resin is derived from a copolymer of styrene and divinylbenzene with quaternary ammonium functionality. The mobile, or exchangeable, anion is chloride which can be exchanged for, or replaced by, virtually any anionic species. DUOLITE AP143/1083 resin is an insoluble salt of a strong base and a strong acid; hence, its ability to exchange anions is largely independent of pH. The chemical structure of DUOLITE AP143/1083 resin is shown below in Fig. 2.

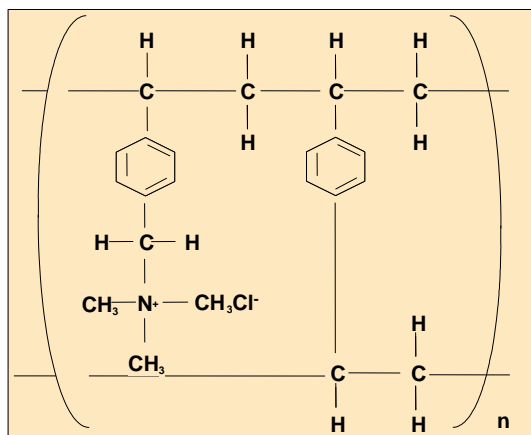


Figure 2

APPLICATION

- Taste Masking
- Drug Stabilisation
- Controlled Release
- Active Ingredient

When used as a drug carrier, DUOLITE AP143/1083 resin provides a means for binding medicinal agents onto an insoluble polymeric matrix; this can be an effective technique to minimize taste and odor problems associated with the drug.

Controlled or sustained release properties can also be imparted to oral dosage formulations through the formation of resin-drug complexes (drug resinates). The drug is released from the resin in vivo as the drug resinate reaches equilibrium with the high electrolyte concentrations typically found in the gastrointestinal tract. When used as an active ingredient, DUOLITE AP143/1083 resin binds bile acids; this leads to replenishment of the bile acids through increased catabolism of serum cholesterol, resulting in lowered serum cholesterol levels.

DRUG LOADING

Batch equilibration is the preferred practice when loading a drug or other sorbate into finely divided ion exchange resin powders. Due to its fine particle size, DUOLITE AP143/1083 resin does not lend itself to conventional columnar operations used with ion exchange resins.

The total anion exchange capacity represents the maximum achievable capacity for exchanging cations, measured under ideal laboratory conditions. The capacity which will be realized when loading a drug onto DUOLITE AP143/1083 resin will be less than this ideal; typically loadings will normally be between 5% and 50% of this maximum. The actual amount of a drug loaded onto DUOLITE AP143/1083 resin will be influenced by such factors as the inherent selectivity of the anion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing anions also present in 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 DUOLITE AP143/1083 resin, it is usually 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.

Although carefully controlled laboratory experiments are required to establish precise loading and elution conditions, a few general principles can be used. High loading capacity will be favored by high charge density in the drug, A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing anions, will also favor higher adsorption capacity.

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 in the desorption environment.

MATERIAL SAFETY DATA SHEETS

Material Safety Data Sheets (MSDS) are available for all Rohm and Haas products. These sheets contain pertinent information that you may need to protect your employees and customers against any known health or safety hazards associated with our products.

We recommend that you obtain copies of our MSDS by calling 1-800-RH-AMBER before using our products in your facilities. We also suggest that you contact your suppliers of other materials recommended for use with our products for appropriate health and safety precautions before using them.

Caution: Acidic and basic regenerant solutions are corrosive and should be handled in a manner that will prevent eye and skin contact. In addition, the hazards of other organic solvents should be recognized and steps taken to control exposure.

Nitric acid and other strong oxidizing agents can cause explosive reactions when mixed with ion exchange resins. Proper design of process equipment to prevent rapid build up of pressure is necessary if use of an oxidizing agent such as nitric acid is contemplated. Before using strong oxidizing agents in contact with ion exchange resins, consult sources knowledgeable in the handling of these materials.

Note: Ion exchange resins and polymeric adsorbents, as produced, contain by-products resulting from the manufacturing process. The user must determine the extent to which organic by-products must be removed for any particular use and establish techniques to assure that the appropriate level of purity is achieved for that use. The user must ensure compliance with all prudent safety standards and regulatory requirements governing the application. Except where specifically otherwise stated, Rohm and Haas Company does not recommend its ion exchange resins or polymeric adsorbents as supplied as being suitable or appropriately pure for any particular use. Consult your Rohm and Haas technical representative for further information.

All our products are produced in ISO 9001 certified manufacturing facilities.

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WEB SITE: <http://www.rohmhaas.com/ionexchange/Pharmaceuticals>

CHOLESTYRAMINE APPLICATIONS REFERENCE LIST

Irwin, W. J, R. MacHale, and P. J. Watts. (1990) Drug-delivery by ion exchange. Part VII: Release of acidic drugs from anionic exchange resin complexes. *Drug. Dev. Ind. Pharm.* 16(6):883-898

Sriwongjanya, Mongkol; Bodmeier, Roland; Effect of ion exchange resins on the drug release from matrix tablets; College Pharmacy, Freie Universitaet Berlin, Berlin, D-12169, Germany; *Eur. J. Pharm. Biopharm.* (1998), 46(3), 321-327

Polli, Gerald P. and Shoop, Clyde E., (Merck and Co. USA), 1976. Palatable cholestyramine coacervate compositions. Patent US 3,974,272.

Brauns H. A., Polli, Gerald P and Shoop, Clyde E., (Merck and Co., USA), 1974. Cholestyramine containing coacervate. *Ger. Offen DE 2,344,090.*

Kunin, Robert; Blood cholesterol reducing pharmaceutical composition; 1998; Patent US 5840339.

