DuPont Water Solutions
Life Sciences and Specialties

Heparin Extraction

DuPont™ AmberLite™ FPA98 Cl Ion Exchange Resin for Crude and Fine Heparin

Heparin is a sulfated glycosaminoglycan (GAG) anticoagulant that binds to antithrombin III to form a heparin-antithrombin III complex. This complex binds to and irreversibly inactivates thrombin and other activated clotting factors, such as factors IX, X, XI, and XII, thereby preventing the polymerization of fibrinogen to fibrin and reducing the formation of clots and extension of existing clots within the blood.

Nowadays, heparin is mainly extracted from porcine intestinal mucosa via enzymatic digestion, followed by heparin capture with a strong base anion exchange resin. The extracted heparin ingredients are further fractionated into various low molecular weight heparins (LMWH) that can be used in the manufacture of LMWH salts.

The heparin molecular structure (Figure 1) is a sulfated polysaccharide that contains negative charges. As a result, it can be adsorbed to anion exchange resin with quaternary amine functional groups. DuPont™ AmberLite™ FPA98 Cl ion exchange resin has been applied widely for crude heparin capture and purification into fine heparin [1-5]. As shown in Table 1, AmberLite™ FPA98 Cl ion exchange resin possesses a macroporous matrix with crosslinked acrylic structure.

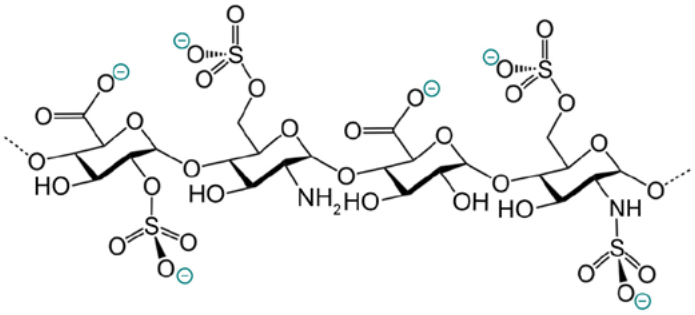

Figure 1. General structure of heparin

The porous matrix has an open pore structure that provides high adsorption capacity for the large heparin molecule. The acrylic polymer matrix has a low tendency for organic fouling, which helps with elution/regeneration efficiency. This resin can be used in a wide pH range to help manufacturers selectively extract heparin from complex crude feeds. AmberLite™ FPA98 Cl (shown in Figure 2) consists of large beads with a Gaussian distribution that can handle fairly crude organic feed stocks without fouling or breaking.

Table 1: Typical properties of DuPont™ AmberLite™ FPA98 Cl resin product

Copolymer	Crosslinked acrylic
Matrix	Macroporous
Type	Strong base anion, Type I
Ionic Form as Shipped	Cl-
Total Exchange Capacity	≥ 0.8eq/L
Water Retention Capacity	66-72%
Particle Diameter	630-850 µm

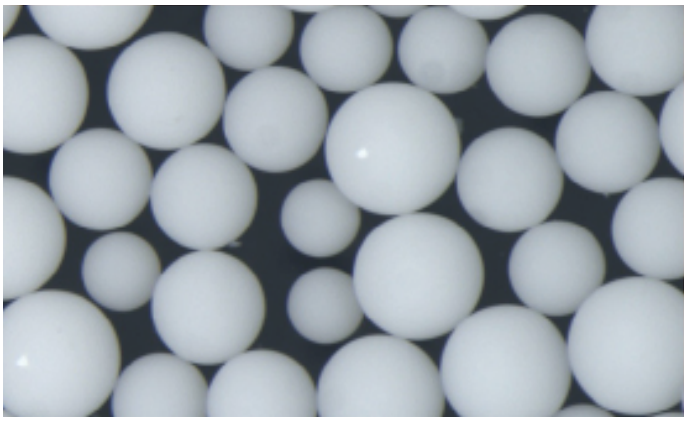

Figure 2. DuPont™ AmberLite™ FPA98 Cl ion exchange resin

The procedure for crude heparin harvesting starts by soaking the intestine in a salt solution and then scraping the mucosa from the intestines. The cleaned mucosa is then enzymatically hydrolyzed using a protease at alkaline pH (Figure 3). After enzyme heat-inactivation and filtration, a strong base anion exchange resin captures heparin from the hydrolysate, usually in a stirred-tank configuration. The loaded resin will be initially washed with a NaCl solution with a relatively low concentration (~3-8% NaCl) at 1-2 bed volumes to eliminate unbound materials. After this rinsing step, the heparin-loaded resin can be shipped to other locations for further processing, or the heparin can be desorbed on site for final precipitation, depending on facility design and value chain structure. Heparin is recovered from the resin by rinsing with a high salt concentration (~15-26% NaCl at 1-2 bed volumes) and then precipitating to form crude heparin.

Some heparin streams may require addition purification to reach the higher purity demands for heparin ingredients (Figure 4). In that case, manufacturers may run the crude heparin through a second ion exchange step, usually via ion exchange chromatography. In these column processes, heparin adsorbs onto the resin and undergoes further rinsing and processing to generate a high-purity heparin stream that can be precipitated and shipped to drug manufacturers as a starting ingredient.

DuPont has more than 50 years of ion exchange manufacturing and application expertise. As a large resin manufacturer with a global manufacturing and customer support footprint, the company is positioned to serve customers around the world. We have teams in China, North America, Europe, and South America to help manufacturers with their heparin purification processes. Contact us at https://www.dupont.com/water/contact-us.html to reach a commercial or technical service representative in your area.

References:

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2. Tong, Y.G., Tang, B.C., Ma, Q.Q., Zhao, Q., & Pan, W.C. (2015). Optimization of absorbed technology in crude heparin sodium. *Applied Chemical Industry, 44(12),* 2289-2292.
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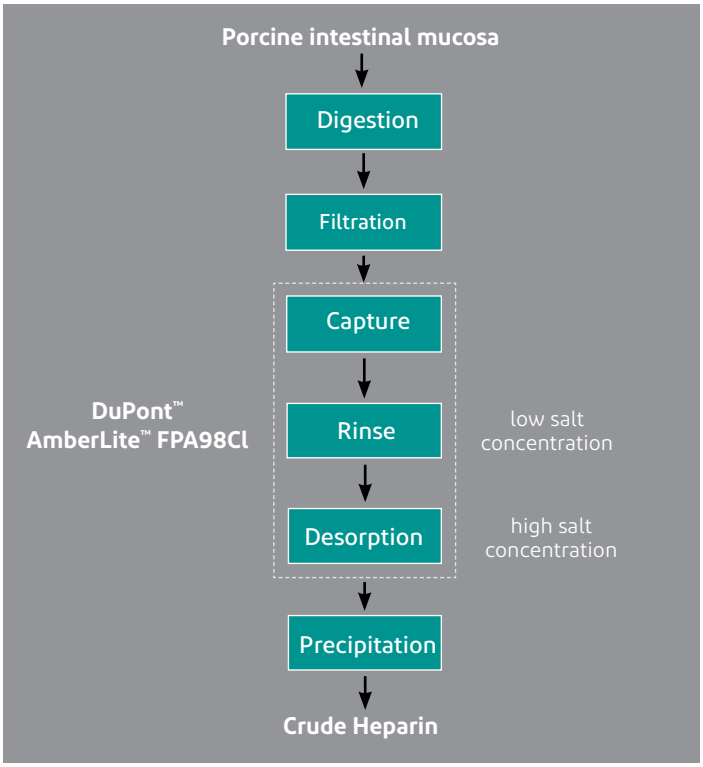

Figure 3. A typical process for crude heparin production.

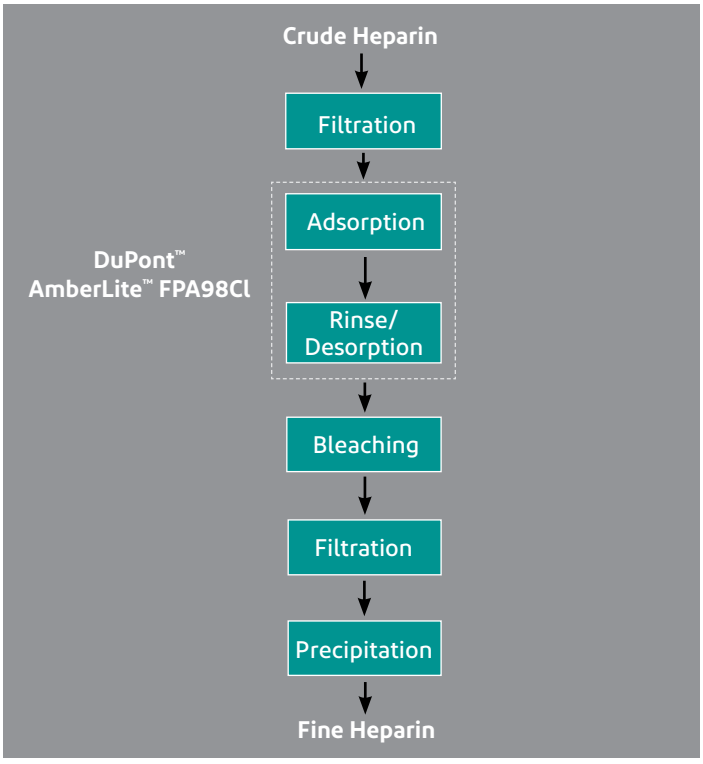

Figure 4. A typical process for fine heparin API production.

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