Vancomycin purification and extraction of other natural products used as pharmaceuticals

The case for substituting ion exchange resins with specialty activated alumina

Dr. Mark Moskovitz and Gary Witman, MD

Peptide fermentation broths yielding useful antibiotics are an integral mainstay of the pharmaceutical industry. Vancomycin remains the most important antibiotic in the treatment of methicillin resistant staphylococcus aureus (MRSA). Given the increasing prevalence of MRSA in the community setting, and it's presence in previously healthy individuals, the role for this drug in controlling both the spread and disease eradication is gaining global recognition. As the antibiotic is no longer protected by patent rights, and generic competitive pricing is intense, the most cost effective production methods must be achieved to assure product profitability. To that end the production process should be as automated, reproducible and efficient as possible.

Vancomycin is the product of a fermentation broth. It is one of the glycopeptide antibiotics produced by the genus Actinomycetes, such as the strain Amycolatopis orientalis (ATCC 19795). Glycopeptide antibiotics are classified into four groups based on their chemical structure. Group I, or the vancomycin type has aliphatic amino acids at positions 1 and 3. Vancomycin is a branched tricyclic glycosylated non-ribosomal peptide. The drug is effective in growth inhibition of gram positive bacteria such as Streptococci, Staphylococci, Clostridium difficile, as well as organisms which are resistant to penicillin and cephalosporin class antibiotics. The drug can be administered in either an oral or intravenous form. The impurities in the fermentation of vancomycin tend to be polymeric species containing one of several carboxylic acid groups. The preferred vancomycin strain is Vancomycin B, with the desired adsorbent used to select out this strain being either a cation exchange resin such as Dowex 50 WX2, or Amberlite XAD-16, a non functional resin, with both these products available from Dow Chemical.

The term decolorization as used in the pharmaceutical industry is a misnomer. It does not mean to literally remove color. That would be too simple, too literal. Rather, to decolorize means to remove impurities of one sort or another. In the decolorization of a fermented product process stream one often uses ion exchange resins. However, a superior solution lies in the use of specially designed DAI activated alumina.

Steps for purification of the drug via fermentation are well characterized. The initial purity of vancomycin in a fermentation broth is around 34%, and the purity must be driven up to greater than 95% for pharmaceutical application. The colors which are present in the fermentation process tend to be similar to the colors seen in the sugar industry, as the carbon source for the fermentation process tends to be rapeseed oil or molasses. The fermentation broth is adjusted through a series of pH changes with the filtrate traditionally passed through either a silica or a polymeric chromatography packing. Vancomycin is subsequently eluted from an adsorbent resin using reverse phase column chromatography. After repeating the process a basic salt of vancomycin is crystallized with a solvent and the crystals are acidified at a low pH. The acidified product is precipitated in an organic solvent such as acetone or alcohol to produce vancomycin HCl.

To control costs in some of the processes for the production of vancomycin, the agent used for decolorization is activated carbon rather than ion exchange resins. Up to 10% of the volume of the vancomycin can be activated carbon. However, activated carbon has limitations which include absorption of the final product, which dramatically decreases yields. Activated carbon is not pure, and colloidal carbon requires further filtration downstream, which can slow down the flow rate. Additionally, there is the possibility of contamination with metals when using activated carbon.

Decolorization of crude filtered vancomycin improves the purification of vancomycin with subsequent reversed phase chromatography. The decolorization also diminishes fouling of the reversed phase packing material, and

allows an effected single reverse phase step approaching the purity level of 95%, which would be acceptable for use as a pharmaceutical agent.

Many pharmaceutical firms traditionally use basic anion exchange resins (such as Dow Amberlite FPA98 CL) for decolorization of the crude vancomycin broth. Such basic anion exchange resins were introduced because they had proven more effective and economical than carbon or bore char based technologies for sugar solutions. However, the argument is made that activated alumina provides that ability and much more. Furthermore, due to its amphoteric character, and the ability to manipulate pore sizes, activated alumina can do so much more. The basic ion exchange resins were promoted because they offered a pore structure allowing high molecular weight organics to be easily adsorbed. These ion exchange resins were felt to exhibit good resistance to physical breakdown by attrition and osmotic shock.

There is no material which offers the endurance, the amphoteric properties, the heat and pressure stability of DAI activated alumina. The molecular metallurgists at Dynamic Adsorbents are able to manipulate the pore size of the specialty alumina to accommodate virtually any high molecular weight organic material, and provide both a decolorizing and polishing for many bio-processing applications such as natural product extraction and the recovery of antibiotics from fermentation broths.

Update your manufacturing competitiveness.

Think Alumina - Think Dynamic.