



Graver Technologies

Ensure...
Purity, Productivity & Profits



ECOSORB® Products for Pharmaceutical Purification



Introduction

Many Active Pharmaceutical Ingredients under development today will be produced by multi step synthetic processes requiring extensive downstream purification. Recognizing that re-crystallization is often not efficient for the removal of certain contaminants pharmaceutical companies are rediscovering the use of adsorption processing as adjuncts to re-crystallization purification and other expensive purification methods. With today's increasing demands for purity, productivity and profits many PHARMA companies have found that ECOSORB® products provide a simple, cost effective means to remove and or recover catalysts, reaction by-products and color from API's and intermediates.

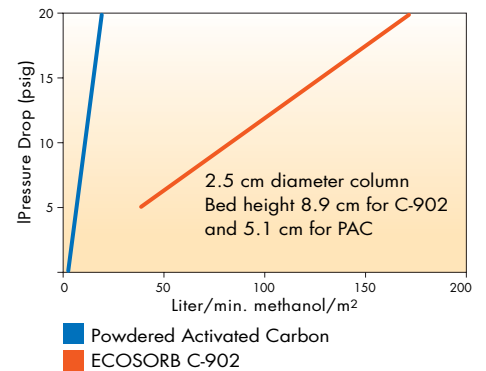
For over 20 years Graver Technologies has developed innovative products for the purification of industrial fluids. Today Graver provides standard and custom adsorption products helping companies around the world meet their requirements for high purity processing. This bulletin reviews the use of ECOSORB multifunctional adsorption products in pharmaceutical processing and provides a guide for evaluation and use.

ECOSORB products are specifically designed to improve on the kinetic and hydraulic limitations encountered in adsorption processes. Those familiar with adsorption theory understand that adsorption processes are to some extent all rate limited, that better kinetics translates to increased processing speed and that the simplest way to increase rate is to increase the surface area with smaller particles. However, as one quickly discovers the use of small particles comes with the downside of an exponential increase in hydraulic pressure drop which quickly reaches levels impractical for industrial operations. To improve on this situation Graver developed a family of proprietary immobilized fine particle adsorption products with significantly lower pressure drop and high adsorption capacity. This technical advancement allows ECOSORB products to be used in industrial adsorption processes as deep beds, precoat or batch operations where ordinary fine particle adsorbents would prove less than satisfactory.

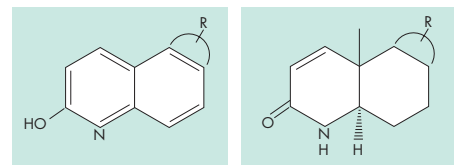


Photo on left shows laboratory filter used for filtration sizing. Photo on right shows industrial horizontal plate filter. ECOSORB products in batch operations provide significant benefits in handling, selectivity and faster filtration.

HYDRAULIC COMPARISON ECOSORB C-902 VS POWDERED ACTIVATED CARBON



Powdered activated carbon Vs ECOSORB C-902 in a deep bed operation/ hydraulic and removal efficiency



By passing a reaction mixture through a deep bed of ECOSORB C-941 the compound on the right is successfully separated from reaction by-product on the left with > 99% efficiency.



ECOSORB Sample Kits: Pre weighed micro tubes, above; 250 cc jars, below. To request samples please send request to info@gravertech.com or call toll-free in USA only 800-249-1990, outside USA call 302-731-1700



Lab Evaluation/Adsorbent Selection

Generally the first step in evaluating adsorption purification is to test series adsorbents at the bench under controlled batch conditions. The objective is to find an adsorbent with suitable capacity and selectivity to effectively adsorb the contaminant(s) and leave the target compound largely unchanged using the same solvent and conditions as the targeted process step. It is important to note however that minor changes to solvent conditions can result in marked changes in adsorbent performance.

Similar to the way chromatography methods are optimized with modification to the mobile phase adsorption capacity and selectivity can be tuned for optimal function. Additional performance for removing poorly adsorbed compounds is also gained by using ECOSORB products in deep beds with equipment capable of providing columnar plug flow. Although not commonly investigated ECOSORB products with their much improved hydraulic properties are also suitable for capture and release methods.

To make it faster and more convenient for clients to evaluate ECOSORB products Graver now offers test kits for bench top evaluations. Each kit consists of an array of commercially available ECOSORB pharmaceutical products pre-weighed into micro tubes. For larger scale testing Graver also provides bulk quantity samples. For additional information on the selection of adsorbents see: Welch et al, Organic Process Research & Development 2005, 9, 198-205.

Pilot and Full Scale Operation

Batch, Precoat or Deep Bed

Based on their overall simplicity batch adsorption methods are often used in commercial API processes. The scale-up of batch processes is highly predictable and is easily calculated by linear extrapolation from laboratory data. The most challenging part of scaling up a batch process will normally be sizing the filtration at the end of the process to remove the spent adsorbent.

Adsorption processes utilizing precoat and or deep bed operation offers advantages over batch operations in the form of reduced reactor cleanup and improved compound recovery. The schematic below shows a typical single pass operation.

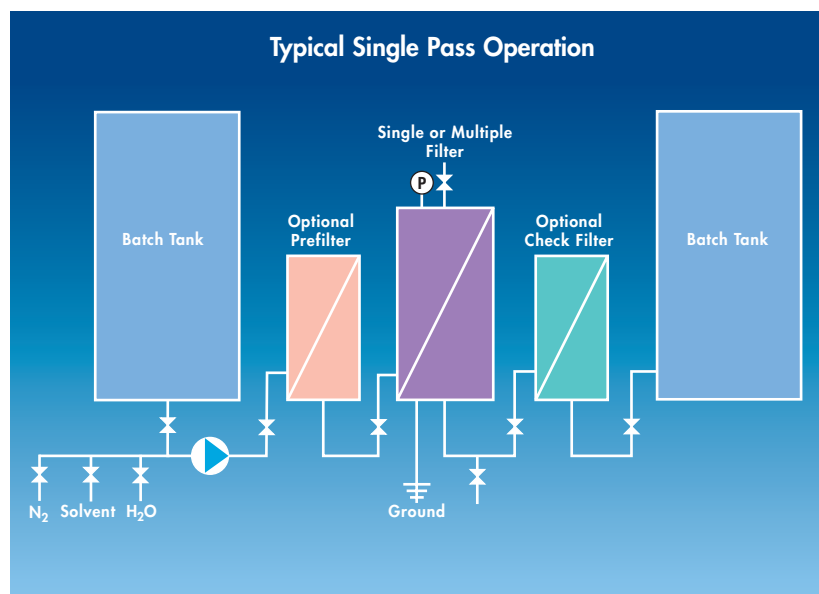
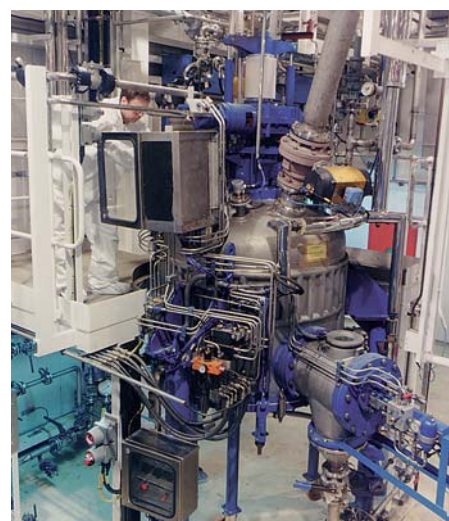


Photo above shows laboratory column and typical setup for deep bed pilot test. Photo below shows industrial scale single plate filter used for deep bed operation with ECOSORB Product.



Typical Single Pass Operation

1. Initiate recirculation of process solvent between slurry tank and plate filter.
2. Add adsorbent in increments until adsorbent bed forms on filter plate.
3. Pass API reaction mixture to be purified through adsorbent bed and collect purified product in receiver tank.
4. Rinse adsorbent bed with process solvent, sometimes followed by water and blow down filter bed with Nitrogen
5. Drop and Drum Spent Adsorbent Cake
6. Clean slurry tank, pump and piping.

ECOSORB Products for Pharmaceutical Applications

Product #	Process Mode*	Ash on Incineration	Commercial Applications, Removal and Recover	Form
C-902	B & P	Low	Color, Reaction By-Products	Dust Free Moist Cake
C-905	B & P	Low	Color, Reaction By-Products	Dust Free Moist Cake
C-908	B & P	Low	Chelated Pd & Pd ⁰	Dust Free Moist Cake
C-941	B, P & DB	Low	Homogenous Rh	Low Moisture, Free Flowing Powder
C-945	B, P & DB	Low	Homogenous Pt & Pd	Low Moisture, Free Flowing Powder
C-947	B, P & DB	Low	Homogenous Pt, Pd & Rh	Low Moisture, Free Flowing Powder
C-971	B, P & DB	Low	Cationic Contaminants	Dust Free Moist Cake
C-981	B, P & DB	Low	Organic Contaminants Fermentation Broth	Dust Free Moist Cake
GL-988	B & P	high	Color, Reaction By-Products	Low Moisture, Free Flowing Powder

* B = batch, P = Precoat, DB = Deep Bed

A precoat is defined as a layer of the product on a filter screen at about 3 cm thick. A deep bed can be operated at up to 1 meter in height.

Note: Custom products are available upon request including individual adsorbents and specific moisture levels.

For precoat and deep bed applications it is important to conduct hydraulic testing that closely approximates the targeted full scale processing conditions and requirements. In particular note that for deep bed applications compression effects with ECOSORB products are not linear across a wide range of bed heights and pressures and for best results testing should be done using a close approximation of the the bed height, linear velocity, fluid viscosity and insoluble solids of the full scale process.

Heat of Adsorption: When added to polar and non polar solvents ECOSORB products will release heat energy. In deep bed operations with high plate count devices and non polar solvents the temperature rise can exceed the boiling point of some solvents. For more information and solutions to this problem contact Graver Technologies.

Chemical Compatibility: ECOSORB products are chemically stable with most organic solvents including methanol, IPA, toluene, DCM, THF, hexanes. ECOSORB products are stable at pH of 1-13 for the majority of applications up to 24 hours. *"Do not use ECOSORB Products with strong oxidizing agents such as Nitric Acid"*

To request samples please send request to info@gravertech.com or call 800-249-1990 in USA only, outside USA 302-731-1700.

Superior Products & Global Reach

Whether your business is around the corner or around the world, Graver Technologies can support you with superior products and services. Our ion exchange, adsorbent, filtration, and membrane products deliver exceptional performance in some of the harshest process environments in North America, Europe, Asia, the Pacific Rim, South America, and Africa.

Graver Technologies, LLC is a member of The Marmon Group of companies, an international group with more than \$6 billion in annual sales. Graver Technologies is a fast-growing company with the technical resources and financial strength that make us the perfect partner for your business.

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