

# ZetaCarbon® Evaluation & Scale-up for Pharmaceutical Applications

## INTRODUCTION:

Activated carbon in the pharmaceutical industry has been used for many years to reduce impurities derived from the reactions that create active pharmaceutical ingredients (API's). The adsorptive properties and very large surface area of activated carbon make it ideal for filtering impurities from API's, with de-colorization being the most common pharmaceutical application.

CUNO's ZetaCarbon® cartridge system immobilizes the activated carbon within a resin-cellulose matrix to alleviate the disadvantages of bulk activated carbon usage in granulated or powdered form. These disadvantages include:

- Operator exposure to carbon dust
- High cost of maintaining and cleaning process equipment
- Inefficient removal of the carbon from the process stream
- Costs associated with batch and solvent re-work.

Additional information on issues related to the use of bulk carbon and the benefits of a ZetaCarbon system can be found in CUNO Application Brief LITCABZC1, "A Review of the Practices of Using Carbon in the Production of Fine Chemicals".

This CUNO Application Brief describes how the ZetaCarbon system is evaluated for use in pharmaceutical applications and how the optimal carbon type and media grade are chosen for a given application. In addition, the brief describes how a process is scaled-up in order to determine the requisite ZetaCarbon filter area for manufacturing and production of an active pharmaceutical ingredient.

## ZETACARBON FILTER EVALUATION

Upgrading a process to ZetaCarbon filtration from bulk activated carbon relies on several factors. For a typical pharmaceutical process, the type of carbon being used was selected at some time in the past (often many years) and based on limited data and information. The resulting process is therefore not optimized for carbon type or the amount of carbon being used.

ZetaCarbon filters are designed to optimize the process by eliminating the disadvantages of bulk carbon usage and to provide the best carbon that most efficiently produces a product with the highest quality.

ZetaCarbon filter evaluation testing is done in order to determine:

- The optimal carbon type used for a given process
- The optimal media porosity
- Optimum flux rate to determine scale-up parameters

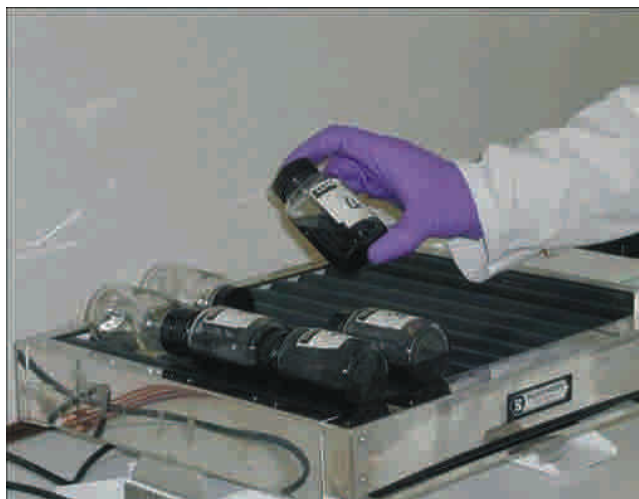
The laboratory scale methods used to evaluate an application for ZetaCarbon filters are: 1.) *Carbon Shake Test Screening*, and 2.) *ZetaCarbon Filter Disc Trials*. Carbon Shake Test Screening provides a method to determine the optimal activated carbon for a given application. ZetaCarbon filter disc trials are used to generate the data that is required to scale-up a process for production and to determine the number of ZetaCarbon cartridges required for the process volume. There are cases where the type of carbon is licensed or locked into a process and cannot be changed. The evaluation process in this case begins with disc trials using the specified carbon.

## CARBON SHAKE TEST SCREENING

Carbon Shake Test Screening is a laboratory method to determine the optimal carbon for use with a pharmaceutical de-colorizing application. Shake testing is a relatively simple, qualitative method that gives quick, visual results. The method is scaled-down from actual process conditions and it compares a panel of carbons to the current powdered carbon used in the application to determine the activated carbon that best de-colorizes the API solution.

A typical shake test screening protocol is listed as follows:

- Activated carbon of various grades is measured at a fixed quantity (e.g. 0.1, 0.5 or 1.0 gram) into a lab jar or bottle.
- An aliquot of process fluid (e.g. 100 mL) is added to each bottle; the bottle is then capped and placed onto a mechanical shaking device.
- All bottles are uniformly shaken at constant temperature for a 30 minute period (Figure 1).
- After the 30 minute shake, an aliquot of a mixture from each jar is filtered through a syringe filter into individual test tubes, with care taken to ensure no cross-contamination between samples.
- Test tubes are visually compared (or measured for color using a spectrophotometer) to determine which carbon was most effective (Figure 2).



*Figure 1: Shake testing*



*Figure 2: Visual comparison*

If all of the color or impurities are reduced by more than one type of carbon, the test should be repeated using less carbon or more process solution until the most effective carbon type is identified.

CUNO's ZetaCarbon filter is available in five standard types of activated carbon to cover a broad range of applications. The five standard carbon types have been selected based on their properties to meet the requirements of the pharmaceutical industry. Additional "a la carte" grades are also available in order to cover the widest range of carbon applications in the pharmaceutical industry. In summary, 19 types of carbon are available for shake testing, with custom grades available as required. Shake testing represents a simple cost effective way to select the best carbon available for a given pharmaceutical application.

## ZETACARBON FILTER DISC TRIALS

Once the optimal type of carbon is determined, bench-scale disc trials are used to determine the porosity of the ZetaCarbon media and the flux rate of a ZetaCarbon filtration process. Determination of flux rate is required in order to calculate the number and size of ZetaCarbon cartridges required for a production scale operation. The value of the

filter flux is defined as a fluid flow rate per unit of effective filter area (milliliters/minute/cm<sup>2</sup> at lab scale, or liters/minute/ft<sup>2</sup> at process scale). Once identified, the flux rate is held constant regardless of operating scale and is used to calculate the theoretical filtration area requirement at process scale for a given batch volume.

Successful ZetaCarbon filter disc testing begins with the selection of how the contaminant removal will be evaluated. De-colorization performance can either be visually evaluated or by measuring the absorbance of the product solution at a specific wavelength using a spectrophotometer. Contaminant removal can be evaluated with any analytical method that determines the contaminant level of interest in the product solution.

A typical test set-up for ZetaCarbon filter disc testing can be viewed in Figures 3 & 4:

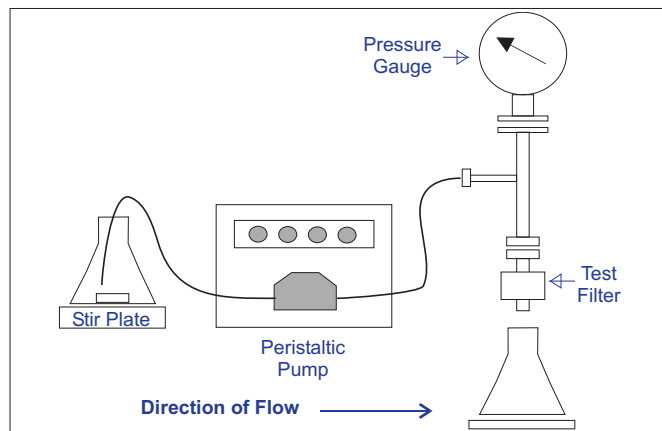


Figure 3: Test set-up schematic



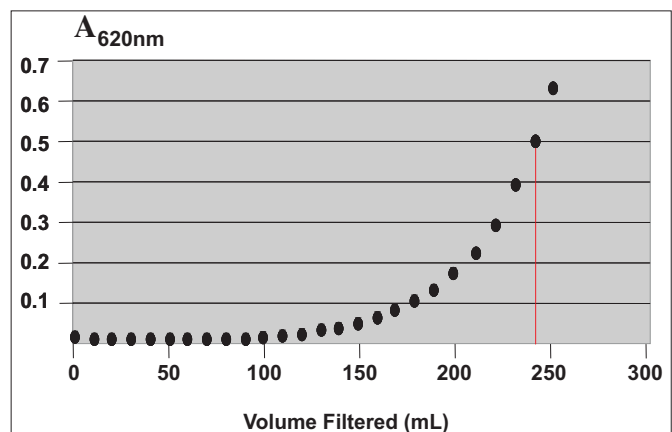
Figure 4: Actual

Assuming the use of 47mm discs (effective filter area = 13.0 cm<sup>2</sup>), the testing sequence is:

1. Install the appropriate ZetaCarbon filter disc into the test housing and attach the housing to the peristaltic pump.

2. Rinse the filter and housing with filtered deionized water or solvent at a flow rate of 10 mL/min for 10 minutes to wet the filter and flush out any residual carbon fines.
3. Measure and record the initial color or level of contaminant of interest in the product solution.
4. Pump the product through the 47 mm ZetaCarbon filter disc at an initial flow rate of 3 mL/min (flux rate = 3 mL/min ÷ 13.0 cm<sup>2</sup> = 0.25 mL/cm<sup>2</sup>/min). Collect filtrate fractions at various time intervals, then measure and record the color or contaminant level of each sample.
5. Prepare a graph of throughput vs. absorbance or contaminant level.

A typical absorbance breakthrough curve is presented in Figure 5:



From this graph, we can observe that a total volume of approximately 240 mL was filtered before the color absorbance of the effluent was equivalent to the original influent.

The test sequence should be repeated at various flow rates (e.g. 6 mL/min or twice the flow rate of the initial experiment) until the fastest process flow rate is found that still produces the desired de-colorization or contaminant reduction.

The end point of the test can be defined in one of two ways: When the required product or other contaminant reduction has been achieved for a pooled sample of fractions or when the equivalent process batch throughput is reached.

## DETERMINATION OF PRODUCTION-SCALE FILTRATION AREA EXAMPLE

Data from ZetaCarbon filter disc testing is routinely used to determine the filtration area for a production scale process. In order to provide an example of how the test data is used to determine the requirements of a production process, the following assumptions are made:

Batch size: 2,000 liters  
Filtration time not to exceed: 2 hours (120 minutes)

Using 47 mm discs, ZetaCarbon filters were evaluated and found to have optimal color removal at a flow rate of 6 mL/min, which equates to a flux rate of 0.5 mL/cm<sup>2</sup>/min (6 mL/min ÷ 13.0 cm<sup>2</sup>), or 0.43 liters/ft<sup>2</sup>/min.

1.5 liters of fluid were processed in 120 minutes to a final color reading just below the highest acceptable level. The throughput was calculated at 0.12 liters/cm<sup>2</sup> or 107.1 liters/ft<sup>2</sup>.

Using the batch volume of 2,000 liters and dividing it by the throughput of 107.10 liters/ft<sup>2</sup>, the calculated filtration area required for the application is:

$$2,000 \text{ liters} \div 107.10 \text{ liters/ft}^2 = 18.7 \text{ ft}^2$$

The calculated filtration area should be increased by an engineering safety factor to account for real-world constraints, and unforeseen variables that occur at larger scale. Using a typical engineering safety factor of 10-15%, the recommended filtration area is between 24-36 ft<sup>2</sup>.

A single, 16", 13 cell ZetaCarbon cartridge has 34.4 ft<sup>2</sup> (3.2 m<sup>2</sup>) of effective filtration area, making this an acceptable choice for this application.

The filter housing to accommodate the single 16", 13 cell cartridge is the 16ZPB1 or 16ZPC1.

### SUMMARY OF SCALE-UP DATA

Process Variable	Units of Measurement	47 mm disc	Calculated production requirement	Recommended System	Safety factor
Area	ft <sup>2</sup>	0.014	18.70	34.40	47%
Flux	Liters/min/ft <sup>2</sup>	0.43	0.43	0.43	—
Throughput	Liters/ft <sup>2</sup>	107.10	107.10	107.10	—
Volume	Liters	1.50	2,000.00	2,000.00	—
Time	Minutes	120.00	120.00	<120.00	—

The increased filter area of the 16", 13-cell ZetaCarbon cartridge would enable the recommended system to process the 2,000 liter batch in less than 120 minutes. Additional scale-up testing with 90 mm discs or BioCap 1000 or 2000 capsules should be done to establish an additional data point for estimating the requirements at process scale conditions.

## SUMMARY

ZetaCarbon filters present an economical option for producers of active pharmaceutical ingredients over the traditional method of using bulk activated carbon. Evaluation and scale-up is easily achieved using laboratory-scale shake test evaluation and 47 mm disc testing. These methods have been proven in a variety of pharmaceutical applications including the de-colorization for morphine, penicillin and ethyl acetate, for example. Consult your CUNO sales representative to learn more about the benefits of ZetaCarbon filters in pharmaceutical applications or to schedule evaluation testing.

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