

Carbon cartridges and their use as a purification step in pharmaceutical API processes

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Abstract

The use of carbon powder to remove impurities can result in difficult and time-consuming charging and cleaning procedures due to the dusty nature of the carbon. In this paper the use of flow-through carbon cartridges is demonstrated to (i) be effective, (ii) improve operability and (iii) reduce the carbon loading. This technology can yield a significant process improvement for the carbon treatment step in pharmaceutical applications.

Carbon cartridges from suppliers 3M CUNO™ and PALL have been tested in two pharmaceutical API processes. In process 1, the aim was to reduce an impurity (A) from ~3% to at least less than 2%. In process 2, the aim was to reduce an unidentified low-level, red coloured impurity (B) to such levels that the Active Pharmaceutical Ingredient (API) would be white to off-white in colour.

Keywords: carbon treatment; carbon cartridges; impurity removal; colour removal; scale-up

1. Introduction – Why use carbon cartridges?

In the pharmaceutical industry powdered carbon is frequently used as a method to remove impurities. Impurities may be those present at unacceptable percentage levels or those that may be almost undetectable in quantity, but still affect the colour of the API. The handling of powdered carbon leads to operational difficulties due to its dusty nature and the difficulty in cleaning equipment in which carbon powder is used. Carbon cartridges have been developed to overcome these problems (Jansson 2002). This paper describes (i) the development of processes using carbon cartridges and (ii) two case studies.

2. Equipment and cartridge description

Cartridge systems supplied by 3M CUNO™ and PALL are designed to operate in a similar manner. Figure 1 is a schematic of a carbon cartridge system. It is essentially a stack of hollow discs, each constructed from a plastic frame, covered on both sides with a filter cloth containing activated carbon (figure 2). The cartridges can be ordered in different plastic materials to suit a range of solvents. The filter area differs slightly between the manufacturers but is basically dependent on the diameter of the cartridge, which is usually 12" or 16", and the number of discs within a cartridge. 3M CUNO™ also supply 8" cartridges suitable for pilot scale. The largest standard housing from PALL and CUNO contains four 16" modules and has a total area of 13 m² and 14 m² respectively, but non-standard housings containing more modules can also be ordered.

The cartridge housing can be constructed with or without a jacket and can be ordered in stainless steel or hastelloy. The housing is built to contain a number of filter cartridges and thus a certain filter area. PALL recommend always using the maximum amount of cartridges the housing can accommodate whereas CUNO add flexibility by suggesting a variable number of cartridges in a single housing (e.g. the plant housing in Process 1 can accommodate 1 or 2 cartridges).

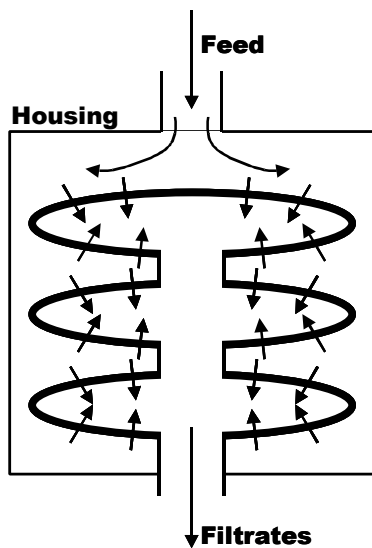


Figure 1: Schematic of cartridge housing and internals



Figure 2: Example of CUNO ZetaCarbon discs for three different scale filters (~80 mL, ~32 L, ~300 L)

3. Carbon Cartridge Operation

To apply a carbon treatment process, the fluid in the feed vessel is directed into the cartridge housing where it flows through the disc cloth into a central column. The filtrate then drains, via the outlet into a receiving vessel.

In a typical operation the cartridge requires (i) a flush to remove extractable material in the filter cloth, followed by (ii) passing through of the process liquors, and finally (iii) the filter is washed. Usually, only the filtrate of the process liquors is used for further processing, but if product yield is important the wash might also be included.

Use of carbon cartridges replaces the difficult charging of dusty carbon powder by the relatively simple installation of a new cartridge. Used cartridges are removed and disposed of. This is not necessarily an easy operation when dealing with hazardous material but is an improvement on the equipment cleaning required when using carbon powder.

4. Mechanistic understanding

Figure 3 shows a cross section of filter cloth (left) and process scheme (right) (Muller 1996). The latter is a stratified representation depicting the various transport mechanisms and compound interactions between the carbon phase and process fluid. The figure shows the compounds being forced down by convection (flow). In competition with convection is mass transfer. This transports molecules (impurity, A and product, P) towards the carbon surface. Both desired product and impurity species adsorb onto the carbon and there is competition between them for adsorption sites. Clearly the operation temperature is important, as it will change the adsorption behaviour (isotherms) of the adsorbed species.

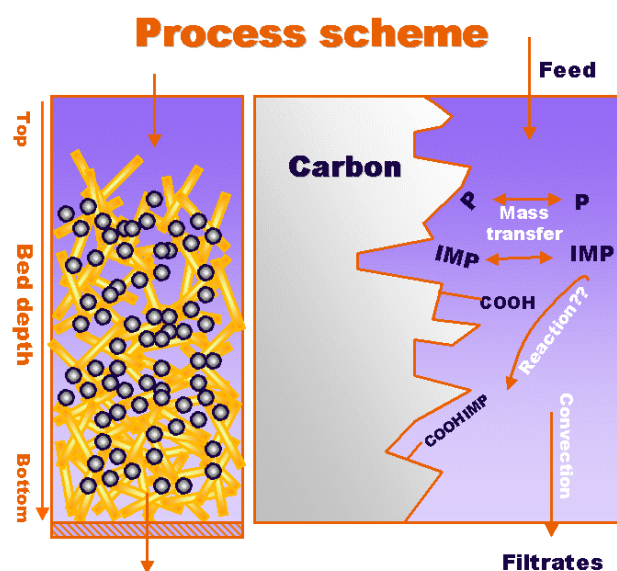


Figure 3: Diagrammatic representation of section through a disc

Breakthrough Curves

When the mass transfer to the carbon surface is high compared with convection, we can see a breakthrough curve. At the start of the transfer, the concentration in the filtrate is very low (zero) and the majority of molecules in the process stream are adsorbed. With time, the carbon surface becomes saturated (first near the top); the filtrate concentrations will thus increase. Eventually, all carbon is saturated and the filtrate concentrations reach those at the inlet. Note: the carbon in the cartridge is in equilibrium with the concentration of impurities in the feed. This is in contrast to carbon treatment by addition to a batch, where the mass of impurity adsorbed is

determined by the final concentration of impurities in solution. As a result, the amount of carbon required per kg of product is significantly less.

An example of a measured breakthrough curve from the first case study (Process 1) is shown in figure 4. The curves were generated by taking spot samples of the filtrate and using HPLC area counts as a measure of concentration. This was done at laboratory scale (~80 mL) and pilot scale (~8 L). The resulting curves show clearly that the product breaks through well before the impurity. This is most likely due to the fact that the product concentration is high, so surface saturation is achieved for a lower volume of liquors passed through.

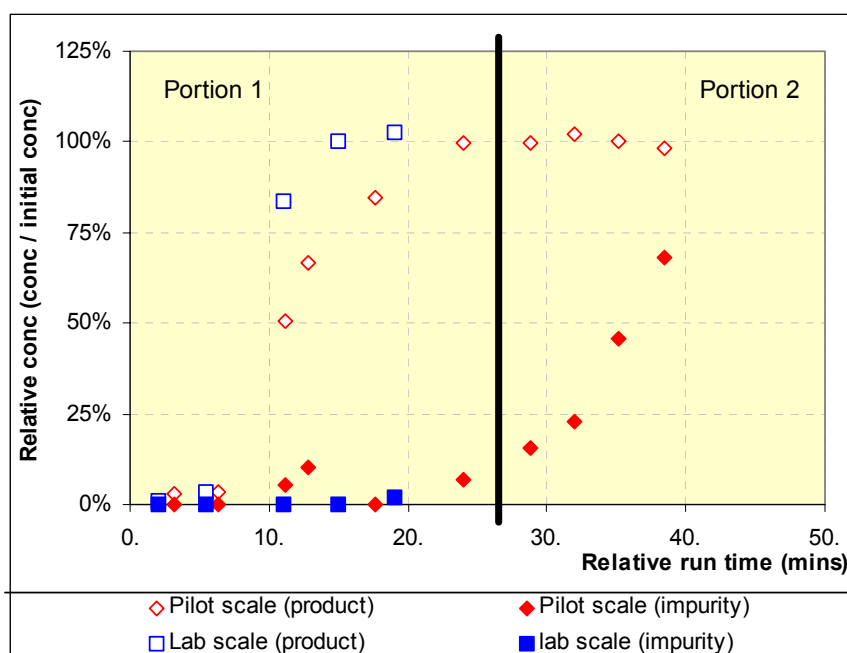


Figure 4: Experimental breakthrough curves for 8% initial impurity concentration at pilot (~8 L) and lab (~80 mL) scale, [impurity] ~ 0.8 g/L, [product] ~ 13 g/L, flux ~ 3 L/min/m²

5. Development and scale up/down of carbon cartridge processes

The development of carbon cartridge processes is often a scale down since normally there is already a large-scale process using bulk carbon or a large-scale process with a need for carbon treatment in place. Alternatively, the need for carbon treatment can also be identified during the early stages of process development and then the carbon cartridge process needs to be scaled up from small volume laboratory work. The scale up and scale down of carbon treatment can be approached in the same way.

The following parameters are considered during the development of a carbon cartridge process step:

Fixed by manufacturers recommendation

- Flush – The cartridge filter cloth is based on a resin bound cellulose fibre. To prevent product contamination with ‘extractables’ from the resin the system requires a flush prior to processing. This requires a substantial volume of liquid ($\sim 50 \text{ L/m}^2$ filter area) and can involve significant analysis effort pre-manufacture to prove that “extractables” will not contaminate the product.
- Flux – Flow rate through housing per unit area of cartridge (L/min/m^2). Both Pall and 3M CUNO™ recommend a flux of about 3 L/min/m^2 .
- Cartridge Wash – a wash with the process solvent after the process fluid has passed through the filter to wash the lines and also recover some retained product and improve the yield (N.B. impurity could also be recovered by the wash). 3M CUNO™ recommend a wash of 50 L/m^2 .
- Carbon density in the filter cloth – The mass of carbon per m^2 disc area. This information can be considered proprietary information by the manufacturers, but is very helpful if obtained. The manufacturers generate discs with constant carbon density. It is thus not an option to change this.

Degrees of freedom for development

- Feed concentration (e.g. g/L). This is often fixed on scale down.
- Loading – Total mass of product at 100% strength charged per unit area of cartridge (g/m^2).
- Cartridge Area – The effective filtration area (disc surface area available to the process flow).

In order to develop a flow through process, laboratory scale systems are made available, see figure 7. These laboratory filters do not contain a filter cartridge, but merely a disc of the filter cloth. The diameters of the CUNO and PALL laboratory filter discs are 47 mm and 60 mm respectively. However the diameters available to the process stream are 41 mm and 51 mm respectively as part of the disc is obstructed by the disc housing. The key elements of development work are described in the sections below.

Selection of carbon

When no previous knowledge of suitable carbon exists, one typically screens powdered carbon or the discs provided. Alternatively, given information on the molecule(s) to remove, such as molecular mass or size, the supplier can suggest which filter discs to use.

When scaling down an existing process with a carbon type known to be effective, one would use a disc containing the same carbon type. Although both CUNO and PALL are reluctant to disclose which carbon type is used in each disc, they can usually advise as to which discs contain a similar or better carbon type.

In all cases an initial experiment should be done to establish the suitability of a carbon type.

Process conditions

For new processes the experimental study should assess the breakthrough curve at a constant liquid flux ($\sim 3 \text{ L/m}^2/\text{min}$) for a range of concentrations and temperatures. Analysis of the breakthrough curves allows one to set the maximum volume of process liquors (V_{process}) that can be processed, as well as the maximum loading the carbon disc can sustain before the quality of the material in the filtrates is no longer acceptable.

When evaluating a disc for use in an established process, V_{process} and the concentration are fixed by existing processing conditions, and hence only the temperature can be varied to affect the breakthrough curve. In such cases an estimate of the loading can be made from the amount of powder used in the current batch addition carbon treatment process. Since carbon treatment using cartridges is more efficient, typically 70% of the carbon is needed when cartridges are used. The loading can then be calculated providing one knows the carbon density of the cloth.

Aside from testing the removal efficiency, it is also advisable to measure the breakthrough curve for the product, and to assess product stability over the duration of the filtration period in addition to heat up and cooling times (typically about 2 hours).

Area selection

The area required by the process can be estimated from

$$A_{\text{disc}} = \frac{V_{\text{process}} \cdot \text{Concentration}}{\text{Loading}}$$

The area required by the process has to be matched with the area available in the cartridge housing. There are two options: (i) one installs the size and number of cartridges that provides an area just greater than the required size, or (ii) one installs a certain area and adjusts the processing volume to give the same loading as determined in the laboratory.

Another aspect determined by the area is the time required to filter. The filtration time is given by

$$\text{Filtration time} = \frac{V_{\text{process}}}{\text{Area} \times 3 \text{ L/min m}^2} (\text{min})$$

If the product degrades with time at the conditions of the carbon treatment, a higher flux could be chosen to minimise filtration time. Both CUNO and Pall fix the

filtration rate at about 3 L/min/m² to prevent excessive pressure drop, but this can potentially be increased.

An example of a scale down procedure: Carbon cartridges are to be introduced into a process currently using powdered carbon.

- The process volume is 3000 L and the amount of carbon powder used is 10 kg. Assuming 70% is needed when using cartridges this results in 7.0 kg of carbon.
- Two PALL 16” AKS 1 modules have a total area of 7.0 m², assuming a carbon density of 1 kg/m², that results in 7.0 kg of carbon.
- The filtration time is to be kept short, so 60 min is selected.
- The flow rate per area is calculated as 3000 L / (60 min * 7.0 m²) = 7.1 L/min*m². This is about twice the recommended value and close to the upper limit given by the manufacturer.
- The volume per unit area is calculated as 3000 L / 7.0 m² = 429 L/m² which for a 60 mm laboratory disc results in a laboratory volume of 0.0020 m² * 429 L/m² = 0.875 L (assuming the same carbon density).
- This volume can then be filtered in the laboratory over 60 min to prove the process.

6. Case Studies

Two case studies are presented to show how carbon cartridge technology has been used successfully in pharmaceutical processes.

6.1 Process 1 – Reduction of a quality threatening impurity

In Process 1 the purpose of the carbon treatment was to reduce a high level impurity from ~3% to at least less than 2%, prior to a “Pures” crystallisation step producing the Active Pharmaceutical Ingredient (API).

3M CUNO™ carbon cartridges were selected. The process was scaled up from ~80 mL in the laboratory to ~300 L in the development plant. A 47mm diameter laboratory scale CUNO test rig (shown in figure 7 in section 6.2) was used for process development.

In this case the process concentration was fixed to ensure a good crystallisation yield. The process temperature was also fixed, at just below the solvent boiling point, to ensure the solids stayed in solution during the CUNO transfer. Earlier trials using the test rig confirmed the most effective carbon type for reduction of the impurity. This carbon type was used in the work reported here. The key objective was therefore to identify the batch volume and carbon cartridge area combination for development plant manufacture to ensure sufficient impurity reduction whilst minimising yield loss.

To assess the performance of the filter discs a system mass balance was completed. HPLC analysis of the feed and filtrates enabled calculation of the mass of product and

impurity adsorbed during the transfer. From this the process could be scaled up to the development plant by assuming equal adsorption efficiency (i.e. g of impurity / m² filter area) of the cartridges.

Scale up strategy

The scale up strategy described below was used to set the conditions for five development plant batches. Batches 1 and 5 had a higher initial impurity level of ~8%, compared with a typical level of ~3% for batches 2, 3 and 4.

1. The initial product concentration of batches 2, 3 and 4 was fixed to optimise the crystallisation step. The product concentration for batches 1 and 5 was then decreased in order to maintain a constant impurity concentration for all batches.
2. The impurity adsorption (g/m²) determined from the 47mm test rig trials was used to predict the plant CUNO performance. When the feed product concentration was decreased (higher, ~8%, impurity level runs) the impurity adsorption was seen to increase significantly at all scales, this is shown in figure 5.
3. The batch volume was set to give a suitable loading relative to the available CUNO area (3.2m² or 6.4m²) to ensure a sufficient reduction in impurity level.

Table 1 shows the results from the 5 batches. In batch 1, the impurity level was not reduced sufficiently and led to the discovery that the plant discs had a lower carbon density than the laboratory discs. After this was taken into account, by reducing the batch loading the expected impurity level shows reasonable agreement with the measured values for batches 2 to 5. These batches successfully pass the specification of <2% impurity level.

The difference between the expected and actual impurity levels is attributed to errors in the mass balance arising from estimated values for the significant volume of process fluid held up in the lines and / or cartridge housing.

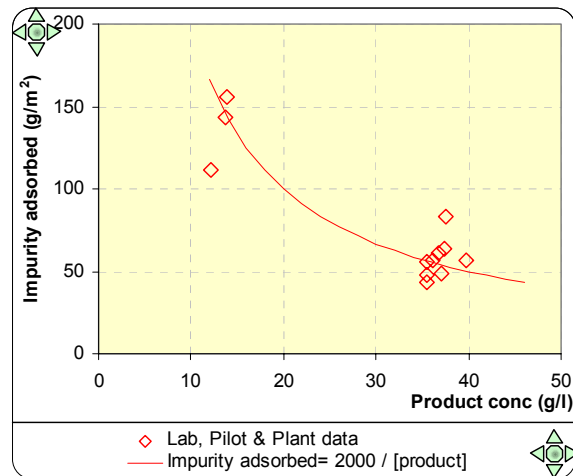


Figure 5: Impurity adsorption versus product concentration (initial impurity concentration ~ 0.9 g/l)

Table 1: Development plant results

Batch	Initial impurity level (%)	Impurity adsorption specified from lab data (g/m ²)	Expected impurity level based on lab loading (%)	Actual impurity level pre-crystallisation (%)	Comments
1	~8	150	0.58	2.7	Batch failed specification; plant CUNO did not adsorb 150 g/m ² impurity as expected.
2	~3	40*	0.85	0.7	Batches easily met specification using corrected impurity adsorption.
3				0.6	
4				0.5	
5	~8	93*	0.80	1.0	

* corrected for lower carbon density in plant discs (plant adsorption = 0.7 × lab adsorption)

For Process 1, the impurity seemed to be bound irreversibly to the carbon (perhaps due to chemisorption to acid groups on the carbon surface), so a cartridge wash could be applied to recover product from fluid in the lines. Even though a line wash was applied and added to the batch, approximately 20% of the product was lost during the filtration step. If the nature of adsorption is different, washing may release the impurity from the filter and hence should not be combined with the filtrates, leading to additional product loss.

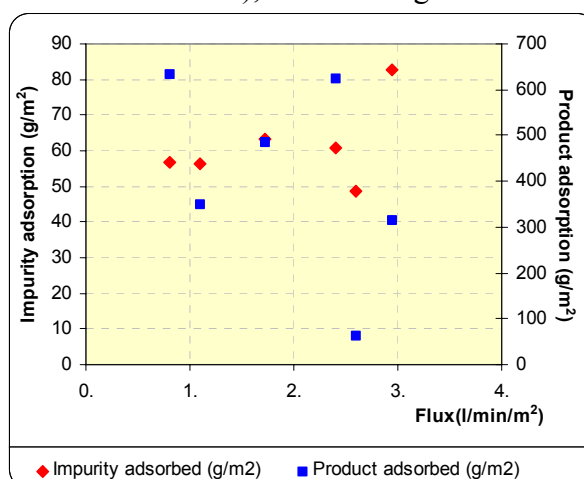


Figure 6: Effect of Flux on CUNO adsorption (initial product concentration ~ 37 g/l)

During the trials, the flux used was within the range 0.5 to 3 L/min/m². Figure 6 shows that within this range there is no apparent relationship between transfer flux and product / impurity adsorption.

The conclusions from Process 1 were as follows:

- Completing a carbon cartridge mass balance allowed successful scale up of the process. Scale up was based on constant process volume to cartridge area ratio (at constant feed concentrations and using the disc impurity adsorption determined in the laboratory).
- Retention of process fluid in the lines and / or housing led to significant errors in the mass balance.
- Transfer flux did not affect the impurity adsorption within the range tested (0.5 to 3 L/min/m²).

- Increasing feed product concentration led to reduced impurity adsorption for this particular system.

6.2 Process 2 – The pink API

Process 2 had historically always produced API that fulfilled the specification “white to off-white”. When moved to a new production facility the API came out pink. Immediately several activities were started; investigation of the cause, identification of the impurity and development of a rework method.

To rework the coloured material a range of carbon powders were screened and several possible carbon types were identified. The rework method, consisting of dissolving the API, charging carbon powder, stirring, filtering off the carbon, crystallizing, isolating and drying the API, was quickly developed.



CUNO



PALL (jacketed)

Figure 7: Laboratory housings for filter cloth discs

It was decided to investigate the replacement of carbon powder by carbon cartridges. Laboratory scale filters from CUNO and PALL were obtained (see figure 7). Discussion with the cartridge manufacturers helped to identify suitable carbon filter cloths. These were then evaluated in the laboratory.

Table 2 shows the redness of a typical failed batch, the acceptance limit of redness, the redness of a batch treated with powdered carbon and the redness of isolated API that has been filtered through different CUNO filter discs in solution. It can be seen that there is a variation in redness, with one batch outside the acceptance limit. The R54SP-disc gave the lowest redness, which is about half that of the batch treated with powder carbon. The colour was analysed by a HunterLab ColorQuest XE instrument.

Table 2 - Redness of reworked API

Batch	Filter disc	Redness (a*) ¹
Typical failed batch	N.A.	2.06
Batch just on limit of acceptance	N.A.	1.13
Batch treated with powder carbon	Powder carbon	0.65
Lab batch 1, CUNO	R53SP	0.74
Lab batch 2, CUNO	R50SP AC03	0.41
Lab batch 3, CUNO	R50SP AC01	1.54
Lab batch 4, CUNO	R50SP AC02	0.37
Lab batch 5, CUNO	R54SP	0.32

¹Analysed by HunterLab ColorQuest XE instrument

Meanwhile the rework process had seen additional development and it was decided to re-evaluate the use of filter discs. CUNOs R54SP-disc was tested again since it gave the best results in the previous experiment. In addition several discs from PALL were quickly screened and AKS 6 was chosen for further testing. Table 3 shows the results of the new process treated with carbon discs.

Table 3 – Redness of reworked API by the new process

Batch	Filter disc	Redness (a*) ¹
Typical failed batch	N.A.	2.06
Batch just on limit of acceptance	N.A.	1.13
Lab batch 6, CUNO	R54SP	-0.60
Lab batch 7, CUNO	R54SP	0.19
Lab batch 8, PALL	AKS 6	-0.63

It can be concluded that both CUNO and PALL technology can reduce the coloured impurity to well below the acceptance limit.

It was found that the pink colour consisted of several impurities at very low levels and the investigation into the cause of the colour took longer than expected. It was decided to try and incorporate carbon powder treatment into the original process in order to avoid the rework entirely. The powder treatment was successful and the next step was to evaluate the cartridges (table 4).

Table 4 – Redness of API with carbon cartridges incorporated into the process

Batch	Filter disc	Redness (a*)
Typical failed batch	N.A.	2.06
Batch just on limit of acceptance	N.A.	1.13
Batch treated with powder carbon	Powder carbon	0.46
Lab batch 9, CUNO	R54SP	0.32
Lab batch 10, PALL	AKS 6	0.23

It can be concluded that the tested filter discs from both CUNO and PALL reduce the coloured impurity to well below the acceptance limit and also below the batch treated with carbon powder.

The process was then scaled up to 4 m³ and a jacketed four module 16” cartridge housing was bought from PALL, see figure 8.

Four 4 m³ batches were run (see Table 5) using AKS 1, which had replaced AKS 6 in PALL’s selection.

**Figure 8: Jacketed PALL filter housing containing four 16” modules****Table 5 – Redness of 4 m³ production batches**

Batch	Filter disc	Redness (a*)
Typical failed batch	N.A.	2.06
Batch just on limit of acceptance	N.A.	1.13
Production batch 1	AKS 1	-0.19
Production batch 2	AKS 1	-0.04
Production batch 3	AKS 1	0.02
Production batch 4	AKS 1	-0.20

It can be seen that the colour has been successfully reduced to well below the acceptance limit and that the variation between batches is small.

The large-scale cycle time was 4h for carbon powder and 1h for the carbon cartridge treatment. In addition, cleaning carbon powder from the equipment would require significant time compared to exchanging the carbon cartridge.

7. Conclusions

This work demonstrates that using flow through carbon cartridges rather than the conventional batch wise powder addition has significant operational benefits (no dusty powder, no cleaning issues) as well as reducing the amount of carbon required. Using cartridge technology does give rise to two new issues, namely (i) contamination by extractable impurities in the filter cloth and (ii) no established scale up methodology.

A good understanding of the cartridge technology has been developed. From a process engineering perspective they may be described as a packed bed, albeit with a large diameter and a very small height. This work demonstrates that concentration and the amount of material charged per unit area (the loading) are the key parameters that should be kept constant on scale up. This assumes that the manufactures cartridges have a consistent carbon density (g of active carbon per unit area). The loading can be determined by measuring the breakthrough curve of the impurity under scrutiny. Temperature may also be important, but was not studied in this work.

We presented a development methodology in three steps: (i) carbon selection, (ii) establishing of process parameters and product stability and finally (iii) area selection. Two case studies applied this methodology and demonstrated successful scale up of cartridge technology to pilot and plant scale.

Operationally, at scale a cartridge operation does take a significant time (the CUNO related activities took ~ 8h in Process 1, and ~2h for Process 2) as the filter requires a flush and a wash which both require vessel time similar to the process fluid. The flush can be done off the critical time line and if the wash liquids are not processed further, the same applies to them. Carbon waste removal and cleaning is however much simpler for the cartridge based operation.

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