

ENVIRONMENT: SELECTING A PROCESSING TECHNOLOGY TO TREAT SECONDARY PHARMACEUTICAL MANUFACTURING EFFLUENT STREAMS

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Details are given of the selection methodology to establish a treatment method for aqueous waste containing active ingredient from a Secondary Pharmaceutical Manufacturing Plant. The technology selected combines: collection, filtration and reverse osmosis with incineration of concentrated retentate and purge streams.

BACKGROUND

A new tabletting, primary and secondary packing facility will provide for a wide number of different sales products, which contain a range of active pharmaceutical ingredients (API). The Secondary Manufacturing Plant will be built at an industrial site in Egypt. The location of the site is in semi-arid desert, therefore water is in short supply and is generally provided by local rivers and aquifers, and by recycle. Locally there is a municipal waste water treatment plant (WWTP) that treats the local domestic and industrial aqueous waste.

A brainstorm of all the possible treatment technologies for aqueous effluent containing API was carried out. The major selection criteria were as follows: achieve internally agreed aqueous effluent concentrations, use commercially available technology, easy to use (for non-specialists), easy to maintain (remotely), minimum requirement for process development, minimum capital cost, minimum revenue cost and acceptable to local regulatory authorities. Fourteen APIs were considered as part of this process.

SCREENING TECHNOLOGIES

Aqueous effluent treatment technologies considered are listed in Table 1 below along with an evaluation. From Table 1 it can be observed that the best option from this decision analysis is molecular filtration. To test out this decision, it was decided to carry out evaluation trials on a cross section of active ingredients. Not all active ingredients were chosen and the following selection criteria were used to reduce the amount of technology evaluation required. The selection criteria used were as follows: manufacturing quantity, comparatively the lowest acceptable aqueous effluent concentration, molecular weight and molecular shape. This shortened the list for testing to five APIs.

Table 1. Technologies considered and evaluation

Technology	Target concentration	Commercially available	Complexity	Maintenance/support	Development cost/time	Capital	Revenue	Regulation
Incineration	Yes	Yes	Medium	Medium	Low	Medium	High	High
Evaporation to dryness	Yes	Yes	Medium	Low	Low	High	High	Low
Chemical Oxidation	No	Yes	Medium	Low	Low (if not enhanced)	Low	Low	Low
H.P. wet Air Oxidation	Yes?	Yes	High	High	Medium	High	High	Low
L.P. Wet Air Oxidation	Yes?	Yes	High	High	Medium	High	High	Low
Biotreatment	No	Yes	Low	Low	Low	Low (existing system)	Low	Low
Enzymatic Treatment	Unknown	Limited	Low	Low	Medium	Low	Low (assuming availability)	Low
Molecular Filtration	Yes?	Yes	Low	Low	Low	Low	Low	Low
Adsorption	Yes	Yes	Low	Low	Low	Low	Medium (regeneration)	Low
Precipitation	No	Yes	Low	Low	Low	Low	Low	Low

Table 2. Membrane rejection for various APIs using reverse osmosis membranes

API	API(1)	API(2)	API(3)	API(4)	API(5)
Rejection % (Supplier 1)	91.7	99.9	99.8	89.0	98.1
Rejection % (Supplier 2)	97.41	99.9	91.5	98.5	99.1

EXPERIMENTAL

The actives were tested in a dead-end 50 cm^3 membrane cell using nanofiltration and reverse osmosis membranes for the degree of rejection[1]. A dead end target rejection of 90% was agreed upon as the minimum acceptable. Nanofiltration membranes were discounted as giving unacceptable performance with rejections 80% or lower. The membrane rejection results are given in Table 2.

API (1) was chosen as the compound for further scale-up testing of the membrane technology. Two sets of pilot plant trials have been carried out on simulated API (1) effluent. Crushing tablets and mixing the crushed tablets with purified water produced this effluent. The objectives of the pilot plant trials were to prove the following;

- Confirm the final permeate concentration is within an acceptable range after the appropriate volume concentration and record the API rejection achieved under flow conditions
- Establish the feasibility of maintaining a constant permeate flux rate at ambient temperature with an inlet pressure in the range 20 to 30 bar whilst achieving a volume concentration factor (VCF)[2] in the range 20–40.
- Verify the cleaning performance using an appropriate cleaning agent.

Supplier 1 used their own in-house pilot plant facilities. The summary results from the Supplier 1 trial on the RO membrane are shown in Table 3.

The clean water flux for a virgin membrane is 55 $dm^3\ m^{-2}\ hr^{-1}$. Post Run 1 the flux-rate is 25 $dm^3\ m^{-2}\ hr^{-1}$. The clean water flux after cleaning is 40 $dm^3\ m^{-2}\ hr^{-1}$. The clean water flux after Run 2 was 37 $dm^3\ m^{-2}\ hr^{-1}$. As observed in no case has the API rejection dropped below 99.5%.

For Supplier 2, the pilot plant facilities used were those within PR&D (Macclesfield) Development manufacturing. The results from the trial on the RO membrane are shown in Table 4.

The clean water flux-rate for the membrane is 90 $dm^3\ m^{-2}\ hr^{-1}$. During operation flux-rates in the range 18 to 82 $dm^3\ m^{-2} hr^{-1}$ were experienced depending on the VCF used.

[1]% rejection = (1 – Permeate concentration/Retentate concentration)*100.

[2]VCF = Initial volume/Retentate volume.

Table 3. Rejection of API(1) using the supplier 1 RO membrane with various VCFs

Run 1				Run 2			
VCF	Feed API (ppm)	Permeate API (ppm)	Rejection (%)	VCF	Feed API (ppm)	Permeate API (ppm)	Rejection (%)
1	120	0.56	99.5	1	120	0.53	99.6
1.5	160	0.70	99.6	15.3	1300	3.3	99.7
2	220	1.1	99.5	19.5	1700	3.8	99.8
6.1	640	2.4	99.6	35.8	2200	5.9	99.7
10.4	1000	3.5	99.6				

From Tables 3 and 4 it can be observed that both membranes have a very similar performance. It was observed during the trials that Supplier 2 membrane was more prone to fouling, however, it was possible to return the membrane close to its original performance by cleaning with hot water.

SOLUTION

The design for the membrane wastewater treatment for the new secondary manufacturing facility is based on the following criteria:

Wastewater produced is 20000 litres per week.
Wastewater will contain approximately 120 mg dm^{-3} of API either dissolved or undissolved.
The design has been based on the pilot plant API trial.

The waste water treatment solution that will be installed is as follows. The process waste water will be collected in a sump. The waste water from the sump will be fed through a contained bag filter to remove excess solids and then to a bulk storage tank. The waste water is further filtered via a tighter contained bag filter and is then fed to the reverse

Table 4. Rejection of API(1) using the supplier 2 RO membrane at various VCFs

Run 3				Run 4			
VCF	Feed API (ppm)	Permeate API (ppm)	Rejection (%)	VCF	Feed API (ppm)	Permeate API (ppm)	Rejection (%)
1	90	0.36	99.6	1	120	0.71	99.4
2.8	222	0.49	99.8	3.7	410	1.6	99.6
8.7	390	3.1	99.6	10	930	1.2	99.8

osmosis system with approximately a 10% take-off as permeate. The recycled retenate is then fed back to the main bulk storage tank. The permeate is collected in a bulk storage tank. The permeate is then further filtered via a contained bag filter before passing through a second reverse osmosis plant. The retenate from this second plant is fed back into the second plants bulk feed tank. The permeate (approximately 10% of feed) is then sent directly offsite via the drains. When the bag filters become full of solid material

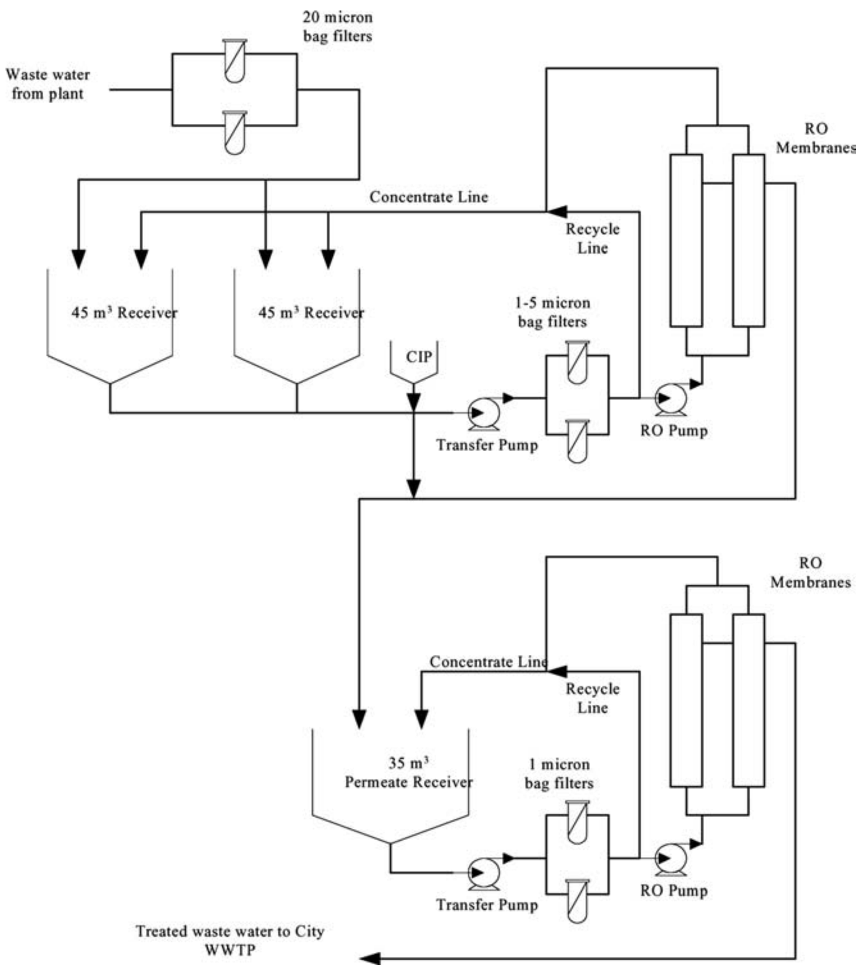

Figure 1. Typical flow diagram for new RO membrane plant

they are removed for on-site incineration. To avoid accumulation of API in the process liquors a purge will be implemented. These concentrated purged liquors from the first pass reverse osmosis plant will be mixed with sawdust in a drum and incinerated (see Figure 1).

Table 5 below summarises the predicted levels in the environment of API(1) for a range of operating criteria. It should be noted that this data is supplied based on laboratory and large-scale trials that have been carried out on the performance of membrane plants. These trials have used an idealised wastewater (i.e. simulated) sample. Table 5 is also based on theoretical calculation/predictions of what a full-scale treatment plant could produce. The predicted performance in Table 5 also indicates that the RO membrane technology can tolerate a range of initial active concentrations and a limited variation in membrane rejection performance.

There are a number of risks with the performance of the plant that could give rise to higher API levels than those predicted. These risks are perceived as minor and do not entail a redesign or providing additional equipment to meet a yet unknown actual requirement. However, it is reasonable to consider these risks and identify what is possible should the full-scale plant be unable to meet the levels predicted in the table below.

Table 5. Typical calculated membrane performance criteria

Inlet API conc. to membrane plant. (ppm)	Rejection rates, 1st pass and 2nd pass. (%)	Bulk permeate API conc. leaving site. (ppm)	API conc. after dilution.* (ppb)	% of Target#
60	99.00 & 99.0	0.082	0.004229	2.115%
60	99.5 & 99.5	0.021	0.001083	0.542%
60	99.7 & 99.7	0.008	0.000413	0.207%
120	99.0 & 99.0	0.164	0.008458	4.229%
120	99.5 & 99.5	0.041	0.002114	1.057%
120	99.7 & 99.7	0.015	0.000774	0.387%
240	99.0 & 99.0	0.327	0.016864	8.432%
240	99.5 & 99.5	0.083	0.004281	2.141%
240	99.7 & 99.7	0.030	0.001547	0.774%

*Once the permeate leaves site it is further diluted by mixing with the cities WWTP flow. For the purpose of this table the dilution factor used is based on the half the capacity of the WWTP as stated within the Environmental Impact Statement (EIS), which is 100000 m^3/day. The actual dilution figure used is half the WWTP capacity per week divided by the bulk permeate discharged from site per week. The figures do not take credit for biotreatment of the API in the WWTP.

This is comparing the calculated levels of API expected from the wastewater treatment plant after dilution with the acceptable aqueous effluent concentration as a percentage of the acceptable aqueous effluent concentration.

The design does allow for additional membrane area to be fitted such as a third pass if required at a later date. Also a convenient removable pipe section will be fitted, which could allow retrofitting of other technologies such as carbon, peat or sawdust adsorption.

The membrane unit does generate a concentrate stream after the first pass, which effectively contains the API. This can either be recycled into the next "batch" for treatment or can be partially or fully removed for incineration. From an incineration point of view the worst case is that it is all removed and incinerated after each batch. Typically this would equate to some 1000 litres per week or approximately 50 tonnes per year. The site incinerator is therefore designed to cope with some 1000 litres of wastewater for incineration. This is in addition to the any solid waste already identified as needing to be incinerated.

The figures in red in the Table 5 above are the stated design as in the suppliers quote.

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