This paper summarizes the selection of material for heat exchangers for a recently constructed Pharmaceutical plant used for synthesizing the active organic chemicals in development Pharmaceutical products. Materials issues, and consideration of the life-limiting processes formed a key part of this analysis and decision-making process. Lifecycle costing was used to help choose between tantalum shell and resin-impregnated graphite block heat exchangers.

INTRODUCTION

The manufacturing of pharmaceuticals is carried out in three parts: the manufacture of the bulk chemical (the active ingredient), followed by the purification process, and then formulation.

Relatively small amounts of very expensive active ingredients (e.g. £1000 per kilogram) are manufactured in the Pharmaceutical industry, and so process vessel volumes are generally less than 10 cubic meters. Heat exchangers are used in four main ways:

1. Process vessel condensers.
2. Heat-cool-chill packages, supplying indirect heat transfer to reaction masses. These are small plate or shell and tube heat exchangers, made, for example, from 316L stainless steel.
3. Small (e.g. "Helicoil"-type) heat exchangers are used to heat nitrogen to dry isolated product on pressure filters.
4. Active ingredient formulation into products. The type of heat exchanger used depends on the formulation process.

This paper covers their application as process vessel condensers, which are used for solvent containment during processing or clean-outs, and less frequently for distillation. They are in intimate contact with reactants and products, and have, in the past, been made from resin-impregnated carbon (graphite) block.

CHOICE OF MATERIAL FOR CONDENSERS IN A PURIFICATION PLANT

Plant Conditions

Three fairly small (3-30 square meters) condensers were required to condense solvents in a Pharmaceuticals purification plant, dedicated to manufacture of possible new active ingredients. The plant was designed to handle a wide variety of processes (about 12 each year), and many changeovers were envisaged. Plant cleanliness is essential in the Pharmaceutical industry, particularly during the purification stage, and therefore thorough cleanout between products was important. This is traditionally achieved by a number of hot solvent boil-outs of all process vessels and associated equipment. The condenser duties were varied and severe, e.g. condensation of a variety of organic solvents at up to 150 degrees Celsius, and handling strong acids, such as HCl at elevated temperatures. On the cooling side of the condenser, water, glycol, or synthetic oil will be used.

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Material Requirements and Options

Candidate materials were selected primarily on the basis of corrosion resistance. However, other key issues were ease of cleanout, resistance to damage ease of repair, short delivery time after placing the order with the manufacturer, ease of fabrication and ease of installation. Cost was also important: traditionally, capital costs alone have been considered for this type of component. Although resin impregnated graphite block condensers, and Hastelloy C276 and Tantalum shell and tube condensers were initially considered, the Hastelloy condensers were rejected as they had poor resistance to boiling HCl.

Graphite Condensers

Traditionally furan resin impregnated graphite blocks have been used for condensing duties in the pharmaceutical industry. The benefits of this material are that it is cheap, possesses a wide corrosion resistance, and has good heat transfer characteristics. Widespread use enables short delivery times after ordering. However, there are several problems with these condensers: graphite is susceptible to mechanical damage, and failures have occurred during installation and cleaning, and as a result of frost damage and water hammer. Damage is often extensive. In addition, contamination of the product from minute particles of graphite has caused problems, and chemicals can be absorbed onto resin/graphite structure, necessitating lengthy cleanouts to satisfy GMP (Good Manufacturing Practice) and external regulatory standards. There are also concerns about the absorption of synthetic oils into graphite.

Tantalum Condensers

Process vessels used in this plant were glass-lined mild steel. Tantalum has a very similar chemical resistance compared with glass (1), so enabling it to be used in all the processes in these vessels. Tantalum has a very high cost per kilogram, together with a very high density compared to other materials. To make it economic, the section thickness must be kept to a minimum. To improve the strength of the tantalum in such thin sections the addition of about 2% tungsten is made to the tantalum providing a yield strength of 35-45 kpsi. However, care needs to be taken on installation and cleaning, as the tubes are less than 0.4 mm thick. However, damage is much less likely than for a graphite condenser.

Tantalum has a melting point twice that of steel, and so welding must be kept away from contacting steel, and because it is a reactive metal, welding must be carried out under a completely inert gas purge, usually argon, including the reverse side of the weld and heat affected zone. The exchangers are straight shell and tube employing 0.015” (0.4 mm) wall thickness tube. The units are mounted vertically and so the top tube/tube plate weld is of a flush design to avoid hold up of liquors. The tubes are expanded into a double groove in the tube plate and then welded to a thin tantalum cladding on the front tube plate face and silver brazed at the edge of the cladding. A vent hole in the mild steel tube allows purging behind the weld during welding, but also allows testing of the weld and acts as a "tell-tale" site in the event of leakage. It is possible to distinguish which side is leaking from an analysis of the liquors.

ZENECA, and its former parent company, ICI, have had over 25 years' experience using tantalum for heat exchangers in the manufacture and concentration of sulfuric acid operating at temperatures up to 170 degrees Celsius. Moreover, many pharmaceutical plants in the U.S.A. are using tantalum rather than graphite condensers.

In summary, the advantages of tantalum over graphite/resin condensers are chemical resistance, high thermal conductivity, relative robustness compared with graphite, ease of cleanout and cleanliness and low fouling. The disadvantages are high capital cost, and the requirement to fabricate using specialized suppliers.

LIFECYCLE COSTING

To choose between resin-impregnated graphite (low capital cost), and tantalum shell and tube condensers (high capital costs), a lifecycle cost analysis was performed. Possible failure modes and consequences of failure were assessed for both materials, using Works' data about repair costs and downtime. This is given in figure 5.

CAPITAL COST

To achieve the same cooling capacity, a smaller cooling area was required in a tantalum condenser compared with graphite. The tantalum condenser was, however, more expensive. To minimize downtime in the event of condenser failure, a spare was included in the capital cost.
**RUNNING COSTS**

Inspection of condensers made from tantalum or graphite would be required every 2 years, or so. The marginal costs of doing this are zero, as inspections would take place during a planned shutdown, and are not the rate-determining step in the shutdown.

The main expenditure in terms of running costs will be repairs and replacements of failures. Two costs are associated with this: the materials cost of repair or replacement, and the downtime cost, as in the event of failure, 2 days production would be lost on the plant, even if a replacement spare were installed immediately. The downtime cost was estimated as £10,000/ day. This includes projected loss of sales of these development products, resulting from longer time to market, asset depreciation and plant running costs.

To obtain the average annual running costs, the cost and probability of an average failure were assessed. To do this, operational data were collected for both types of condensers in ZENECA’s plants. Data was obtained for 5 tantalum shell and tube heat exchangers on an acid concentration unit on a Fine Chemical plant. Over an 8-year period, no failures had occurred. To make a more conservative estimate, it was assumed that a failure would occur once every 50 operational years on each item (2% annual probability of a failure), and also, a new condenser would be required rather than a cheaper repair. This gave an annual averaged expenditure on running costs of approximately £547/ annum for each condenser.

Operational data for 28 graphite/ resin heat exchangers on a pharmaceutical plant were examined over a 20-month period. During this time 6 repairs / replacements were made, with an average materials cost of £2714 per failure. The average annual expenditure per condenser is therefore £2920.

The annual repair costs can then be expressed in £NPV (net present value), by using the appropriate discount factor, and are tabulated in figure 1. These are added to the capital costs to determine the cumulative expenditure in £NPV for the first 10 years of asset life. It can be seen that the break-even time for using tantalum rather than graphite is about 18 months.

This analysis showed the importance of minimization of downtime: in the past, the projects had considered capital costs alone (which would have ruled out the tantalum heat exchanger), or capital costs, and materials repair costs alone, which also could not allow the cost of tantalum to be justified. The present analysis is a more accurate assessment of true costs.

**COST OF CLEANOUT**

The choice of tantalum also had another advantage: faster cleanout between product changeovers. Because the plant would be used for many products, to satisfy GMP/ external regulatory standards, good inter-product cleanout is essential. As product is more readily absorbed into the graphite/ resin condenser, longer cleanout is required for the relatively smooth tantalum surface. Condenser cleanout can often be the fate-determining step on a changeover on this type of plant. Moreover, the cleanliness of the tantalum condensers can easily be validated (for example, by opening up the condenser for inspection). This is not possible with a one-piece graphite condenser.

An analysis of the potential savings from routine cleanout is shown in figure 2. The cost savings result from a tantalum heat exchanger only needing, for example, 2 x 8 hour solvent washes / solvent boil-ups to decontaminate, rather than the 3 for graphite block condensers, and with 12 product changes per year (as given in figure 2). It can be seen that the cost savings from use of tantalum rather than graphite / resin condensers could be realized in a few months.

**SUMMARY AND CONCLUSIONS**

In conclusion, for this particular heat exchanger application, only two materials were appropriate for the range of chemical and physical conditions required. The choice between tantalum and carbon block was made using lifecycle costing rather than capital cost alone. Tantalum should prove an economic choice, not just because of better reliability than carbon block, but also because of faster and validated inter-product cleanout.

**REFERENCES**

For more information on the application of tantalum condensers into the pharmaceutical industry please contact:
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