Tales of The Unexpected

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Introduction

- Discuss Plant problems.
  - Issues perhaps not expected in the lab, or even pilot plant.
  - May seem very simple but can cause major hold ups.
  - Processing as well as chemistry.
  - Equipment selection.

Batching up

- Quite normal for safety to add solids, then add solvent, then reagents.
- Case where this was carried out.
- Concentrated reaction.
- As soon as solvent/ water added stirrer wouldn’t move.
- Solution – add water, solid, then solvents.
- High melting liquids: Acetic acid, t-butanol. Can be melted, but can you use an aqueous solution.
- Can have similar issues with carbonate solutions, caustic, sulphuric acid viscosity

Reaction

- Simulation of plant conditions.
- Is lab always comparable to plant?
- Not always, particularly with certain plant, eg. Hydrogenations, distillations, temperature control, agitation
- Example of user trial for hydrogenation starting material – change of supplier, spec. identical.
- Lab user trial comparable to original material as control.
- On plant hydrogenation characteristics quite different. Reaction rate, impurity profile, reduced yield.
- Solution – re-crystallise material as per standard process for site “crude” material.
- Issues- vessel dynamics – agitation, mass transfer, cooling, hydrogen flow rates, very different from lab hydrogenator.

Batch work up

- DCM solution of batch.
- Required wash with K_2CO_3 (aq).
- Severe emulsions resulted.
- 2 – 3 days for separation to complete!!
- Solution – reduced reactor agitator speed from 90rpm to 50 rpm.
- Separations within 2 hours.
- Stirrer speed not recorded in lab.
- This has been used successfully on other processes where additional salt etc. was being considered.
- Can carry out modelling/ power calculations from lab to plant, but observation is often the best.
- Has been observed that applying pressure (2 bar) can help break emulsions.

Batch work up

- Coupling reaction that was catalysed with Copper Iodide.
- Copper removal down to 10ppm essential.
- Copper had been successfully removed in lab and small scale equipment (50L) using oxalic acid, ammonia, and subsequent work up, Dilute HCl, NaHCO3 (aq), brine, water.
- Scaled up to 1000L on different site and had severe issues removing copper.

Batch work up

- In attempts to remove copper several additional reagents were investigated including EDTA washes, ion exchange resin, dil. 10% NH4OH washes.
- To progress batch finally used up to 8 NH4OH washes to get pass grade material.
- 2nd Campaign entered after much labwork & “improved” simplified process.
- Did not work.

Batch work up

- Why did plant process fail & lab didn't
- The samples were turning coloured once in the sample bottles. Samples taken from batch/ NH_4OH washes look brown initially, but turn green/ blue over time?
- Why was batch retaining the copper?
- On the larger scale equipment nitrogen blankets were used. Total exclusion of air – standard safety design.
- Was air effecting batch washing?

Batch work up

- Chemist postulated effect could be due to oxidation state of Cu.
- Cu(I) less soluble in NH4OH washes
- Cu(II) more readily removed/ soluble.
- Cu(I) can readily be oxidised to Cu(II).
- Would explain colour changes in sample jars.
- Put air into vessels? Peroxide wash?
- Solution – risk assessment, fortunately non-flammable DCM as solvent. Set up control to bubble small amount filtered air through dip pipe during ammonia wash stir out & switch off during settle. Took 2 hours to set up.
- SUCCESS!

Crystallisation

- Can be lots of issues, cooling rate, mobility of batch, filtration rates, best equipment to use, cooling rate, stability of slurry, polymorphism, seeding, pumping characteristics.
- A plant example:
- Plant had been significantly upgraded to new single fluid system, new process control, millions spent.
- Hydrogenation was problematic in terms of reaction rate/ kinetics.
- Major process investigation.

Crystallisation

- Equipment, starting materials, process control, analytical methods all investigated.
- Crystal structure of intermediate was inspected.
- “Old” material had fine crystals.
- “New” material had much larger crystals.
- Better control of cooling and ramp rates had produced much larger crystals
- Heterogeneous hydrogenation, larger crystals affecting reaction rate/ kinetics
- Solution – 12 hour stir in batching vessel smashed up crystals to provide comparable/ consistent particle size.

Isolation of product

- Pilot process used standard equipment at 500L scale, used gravity fed small scale centrifuge. Product centrifuged very well.
- “Semi works” scale for larger scale at 3000L scale, similar equipment, manual plant, centrifuge, tray dryer.
- Major problems in isolation, each load was taking 2-3 days to isolate

Isolation of product

- Investigation looked at crystal form.
- Plant operators/ chemists saw product slurry turning into “pancake batter”.
- Was due to a single issue- the semi works centrifuge used a pumped loop centrifuge.
- Normally ok, but this product had fragile needle type crystals, smashed up with centrifugal pump.
- Solution – isolate on pressure filter, flick stir product slurry.

Isolation of product

- Product isolated on Nutsche filter, then dried in tray drier.
- Equipment upgraded to filter drier.
- Batch degraded rapidly.
- Process investigation, using jacket and batch temperature trends.
- Paddle on drier had been pushed onto cake & left running.
- Friction from paddle had initiated thermal decomposition.

Cleaning

- Major issue in pharma plants.
- Days, weeks, of production can be lost.
- Traditionally solvent reflux for cleanouts.
- Development chemist needs to look at cleanout procedure as part of scale up, process introduction.
- Plant engineer/ production controller needs to implement correct equipment for cleanout.
- Process engineer needs to look at “best” technology for process & cleanout.

Cleaning – process equipment example

- Carbon treatment.
- Celite/ GAF bag usage.
- Successfully introduced CUNO filtration.
- Can be used for depth filtration & avoid celite/ filter aid being added to vessels.
- Carbon filter elements good as single pass/ recycle, avoids carbon dust in reactors- “clings” to surfaces & is unreactive/ insoluble to cleaning solutions.
- Major advantage in terms of cleaning
- Also more control in terms of containment (dust), transfer rates.

Cleaning – cleaning equipment

- Alternatives to reflux.
- CIP?
- Intermediate plant solution to CIP
- Correct sprayballs – pumps/ flow rates/ pressures
- Detergents/ cleaning agents.
- Choose the correct (cheap!) solvent – labwork required.
- Training and documentation.
- Ensure corrective actions are captured for next time.
- IPPC impact – reduce waste/ cost.
- Listen to the operators, what works?

Scale up

- Heat transfer – cooling rates
- Temperature control – tight temperature ranges, single fluid systems required, plc cooling profiles.
- Condensers – now the norm to fit tempered loops, even have to heat trace & lag reflux flow & return lines
- Containment – normal now to design new plant, or retrofit old plant with gloveboxes, downflow booths, for powder, solvents, reagents, products to contain up to 1ug/m3.
- Purified water now the norm. brings its own issue off cost, validation, maintenance
- Material compatibility
- Stability of intermediates/ stages – cold storage?
- Polymorph/ particle size control – seeding/ cooling profiles/ mills.

Summary

- What equipment will it be run in.
- What control is there.
- Selection of reagents
- Think about the plant when doing investigations.
- Reproducibility of plant in lab
- Cleaning