PREPARATION OF A PHARMACEUTICAL INTERMEDIATE : AN EXAMPLE OF HOW INHERENT SAFETY CAN BE MAXIMISED DURING THE EARLY STAGES OF PROCESS DEVELOPMENT

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An inherently safe process has been defined as one which by virtue of its design will not generate a hazard if a fault occurs. Whilst inherent safety has traditionally been pursued by working with the principles of substitution, minimisation, attenuation and simplification [1], it is often very difficult, if not impossible, to make all processes inherently safe. In this situation the goal then becomes one of making the process as inherently safe as possible. The purpose of this paper is to show, by reference to the synthesis of a pharmaceutical intermediate, how it is possible to make very significant increases in the level of inherent safety within a process providing thermal stability and kinetic data is available.

Keywords: Inherent Safety

INTRODUCTION

It would obviously make life much simpler if every chemical process was inherently safe, ie no matter what went wrong, there would be no hazard. In reality this would be impossible to achieve and we are in fact often faced with the task of making processes as inherently safe as possible.

Within AstraZeneca, a potential new drug comes into Process Research and Development Department (PR&D) usually only after having been made on a very small scale. The process will not have been designed for plant scale operation but rather to produce material for initial screening tests, ie toxicological, efficacy etc. The development of the compound passes to a team of chemists whose aim is to devise a synthesis that is appropriate to the scale of manufacture. The initial campaign is usually carried out within the Large Scale Laboratory (LSL), which is equipped with glass reactors. Subsequent campaigns, where an increasing quantity of material is required, are usually carried out in conventional multi-purpose chemical plant.

When a compound first comes into PR&D a meeting is held between representatives of the Development, LSL and Process Safety teams, the purpose of which is to try and identify any potential problems before any significant development work is carried out. The following is an example of how beneficial this procedure can be in increasing the inherent safety factor within a chemical process.

OUTLINE OF PROCESS

The process under investigation involved the formation of hydroxylamine free base by the addition of aqueous sodium hydroxide to a mixture of hydroxylamine hydrochloride and water at ambient temperature. The batch temperature was then increased to 50°C and reagent X added. After acidifying with hydrochloric acid the batch is concentrated via distillation, the product isolated as a solid and finally dried. A more detailed description is given below.

1. Hydroxylamine hydrochloride and water are charged to the reactor.

2. Aqueous sodium hydroxide is added in a controlled manner, the batch temperature being maintained at 20°C.

3. On completion of the addition the batch temperature is raised to 50°C.

4. A solution of reagent X is added in a controlled manner.

5. On completion of the addition the batch is stirred for a further 2 hours at 50°C before cooling back to 20°C.

6. Hydrochloric acid is added to adjust the batch pH to 3.

7. The batch is concentrated by distilling under vacuum at a maximum batch temperature of 30°C.

8. The residue is extracted with toluene and re-distilled under vacuum at a maximum batch temperature of 34°C.

9. Cyclohexane is added and the product filtered off and dried.

FORMATION OF HYDROXYLAMINE FREE BASE

The literature contains many references to incidents involving hydroxylamine free base [2], including two recent incidents at Concept Chemicals in Allentown, Pennsylvania [3], and at Nissin Chemical in Japan [4]. In these two incidents nine people were killed and at least thirty eight were injured. The hazardous nature of hydroxylamine free base, which was highlighted at the initial meeting between development, production and safety representatives, resulted in a decision to evaluate, at the earliest opportunity, the kinetics of the reaction as well as the thermal stability of the various mixtures generated in the process.

The addition of aqueous sodium hydroxide was carried out in a power compensation calorimeter. The addition was exothermic, the overall heat of reaction being determined as -11 kcal/mol hydroxylamine hydrochloride. Subsequent calculation indicated that the associated adiabatic temperature rise was 30K. Heat was evolved immediately on starting the addition, a maximum power output equivalent to 34 watts / mol hydroxylamine hydrochloride being recorded after 4 minutes, before falling gradually back to 13 watts / mol hydroxylamine hydrochloride by the end of the addition. On completion of the addition the power output fell quickly back to the baseline indicating no significant accumulation. It was therefore possible to conclude that the heat of reaction was controllable via the rate of addition and that the process could be operated safely on a large scale. Unfortunately even though the heat of reaction would not give rise to any hazard a thermal stability test (Carius tube) carried out on a sample of the batch after the addition of sodium hydroxide had been completed, showed the presence of a large exotherm from 58°C. It should be noted that all the thermal stability tests reported in this paper were carried out in the presence of very small quantities of mild steel, cast iron and stainless steel. This is done in order to simulate the presence of materials of construction.

This test is only used for screening and requires the incorporation of a scale factor if the onset temperature is to be related to operation on the plant scale. Application of the scale factor gave a potential plant onset temperature of below ambient and as the process called for the batch to be heated to 50°C there was obviously a potentially serious problem. In order to

accurately determine the decomposition onset temperature under adiabatic conditions a Dewar experiment was carried out. This showed clearly that the hydroxylamine free base reaction mixture did self-heat from ambient temperature, the batch temperature reaching reflux after just over 15 hours, with approximately 5% of the batch being distilled from the reactor. It was therefore recommended that the batch temperature was not raised to 50°C following the addition of sodium hydroxide.

The adiabatic Dewar experiment clearly showed that the hydroxylamine free base reaction mixture would self heat from ambient temperature to reflux in the absence of cooling. Ejection of material and / or overpressurisation of the reactor was also a possibility. Consequently even though the batch was no longer going to be heated to 50°C, the consequences of loss of cooling at 20°C still needed to be addressed. The obvious way forward was simply to increase the heat capacity of the batch and the decision was taken to increase the initial water charge by 60%. A second adiabatic Dewar experiment carried out on the more dilute process still showed that the batch would self heat from ambient temperature but importantly that the rate of temperature rise was much slower, ie 25 hours to reach 96°C and that reflux would not be attained.

ADDITION OF REAGENT X
Discussions with the development chemists confirmed that reaction of the hydroxylamine free base with reagent X did not go to completion at ambient temperature and that it was necessary to increase the batch temperature to 50°C. They were also able to confirm that the reaction proceeded in two steps, an initial condensation followed by a cyclisation. It was therefore decided to carry out the addition of reagent X at 20°C and then, following subsequent thermal stability testing, to decide what processing conditions were most appropriate.

The addition of reagent X was carried out in a power compensation calorimeter and shown to be exothermic. The overall heat of reaction was determined as -29 kcal/mol hydroxylamine hydrochloride, the associated adiabatic temperature rise being calculated as 55K. Heat was evolved immediately on starting the addition, a maximum power output equivalent to 28 watts / mol hydroxylamine hydrochloride being recorded after 3 minutes. The power output then remained fairly constant at around 21 watts / mol hydroxylamine hydrochloride for the remainder of the addition before falling quickly back to zero on completion of the addition, ie no accumulation. Analysis of the batch however confirmed that the reaction had not gone to completion and that only the initial condensation had taken place.

A thermal stability test carried out on a sample of the batch after the addition of reagent X showed the presence of an initial exotherm from 61°C with a second from 152°C. Subsequent thermal stability testing of the batch after heating to 50°C showed that the exotherm at 61°C was no longer present. Analysis of the reaction mixtures both before and after heating to 50°C clearly showed that the exotherm seen from 61°C was associated with the cyclisation. The heat evolution associated with the cyclisation was not excessive and a gradual warming of the batch following addition of reagent X was acceptable from a chemical reaction hazard standpoint.

WORK-UP AND ISOLATION
In the originally submitted process the work-up involved the addition of hydrochloric acid followed by a distillation and isolation procedure that resulted in the final product being isolated as a solid. The addition of the hydrochloric acid was evaluated by power compensation calorimetry and shown to be exothermic. The overall heat of reaction was determined as -8 kcal/mol hydroxylamine hydrochloride, the adiabatic temperature rise being

calculated as 14K. The heat was evolved immediately on starting the addition, ie no delayed onset and there was no significant accumulation on completion of the addition. It was therefore concluded that the heat was controllable via the rate of addition and that as thermal stability testing of the batch showed no exothermic activity at anywhere near the proposed operating temperatures, that this stage of processing would be free from chemical reaction hazard.

A thermal stability test (Carius tube) carried out on a sample of the final product showed the presence of an endotherm associated with melting from 59°C, followed by a very large exotherm from around 110°C. It is very difficult to determine the onset temperature when an endotherm runs directly into an exotherm and further larger scale stability work would have been necessary in order to determine safe operating and drying temperatures. Another potential problem was that the rate of pressure rise was too fast for the standard equipment to record. Further testing using a modified Carius tube high rate apparatus did confirm that the compound would not be classifiable as an explosive but the exotherm associated with its decomposition was certainly large and fast enough to cause structural damage if accessed.

Subsequent discussions with the development chemists centred around ways of avoiding the isolation of the final product as a solid. It was agreed that the most appropriate way forward was to try and devise a work-up where the final product was obtained as a solution which could then be telescoped into the next stage of the synthesis. Continued process development resulted in a work-up where the batch, after the addition of hydrochloric acid, was extracted with butyronitrile, washed and then concentrated to approximately 9%w/w.

Thermal stability testing (Carius tube) of the solution after extraction into butyronitrile and after distilling to the desired concentration showed the presence of exotherms from 162°C and 166°C, which even after making an allowance for scale, were still well in excess of the proposed 60°C distillation service temperature.

SUMMARY OF CHANGES

1. The amount of water used during the formation of hydroxylamine free base has been increased

2. The batch temperature is not increased to 50°C after the addition of sodium hydroxide.

3. Reagent X is added at 20°C and then the batch temperature is raised to 50°C.

4. The product is not isolated as a solid, rather it is obtained as a solution which is telescoped into the next stage.

CONCLUSIONS

The initially submitted process could not have been operated safely on the plant scale.

The modified process was evaluated by the development chemists and shown to be acceptable both from a product quality and yield standpoint.

This paper illustrates both the need for process development chemists to be aware of the potential hazards that could be associated with their processes and the advantages that can be gained from the early involvement of Process Safety Groups, both in terms of inherently safer processes and the reduction in abortive effort.

REFERENCES
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