# REDUCING THE HAZARDS ASSOCIATED WITH SPRAY DRYING FROM LABORATORY THROUGH TO LARGER SCALE INCLUDING CONSIDERATIONS FOR OUTSOURCING AND SECONDARY CONTAINMENT

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The safety, health and environmental (SH&E) issues associated with spray drying of potent materials in flammable solvent solutions from laboratory to commercial scale have been reviewed. In particular the challenges and solutions in developing spray drying processes to safely manufacture amorphous solids for early stage development compounds where little material and data is available are considered. Details are also given on how this data can be transferred to outsourcing partners so that they can understand the potential risk within their processing equipment and the necessary containment levels at each scale.

## INTRODUCTION

Spray drying (see Figure 1) is the production of a dry powder from a concentrated solution in a single step. The fluid is finely dispersed at the top of the main drying cylinder which is then brought into immediate contact with a hot drying gas. The evaporation and drying is very rapid and the droplet remains at a lower temperature than the drying gas (its wet bulb temperature) for most of the process. The process takes place in a number of stages:

1. Production of a fine mist via a nozzle at the top of the drying chamber (Fig. 1, step 1)
2. Addition of a hot drying (preferably inert) gas (Fig. 1, step 2)
3. Contacting of the spray with the high temperature gas and evaporation of the solvent (Fig. 1, step 3)
4. Separation of the powder produced from the drying gas (Fig. 1, step 4)
5. Removal of fines using a bag filter (Fig. 1, step 5)
6. Condensation of the solvent and potential recycling of the drying gas (Fig. 1, post step 6)

Spray drying can be used for a number of reasons driven by product requirements such as;

- manufacturing amorphous materials.
- isolation of compounds with high solubility at low temperatures.
- high throughput and low contact time to retain primary particle shape (the production of spherical particles is possible).
- isolation of materials under specific conditions: heat sensitivity, pH, etc.
- production of particles of a specific size or size range.

Manufacture in the pharmaceuticals industry requires ensuring all the safety, health and environmental issues are considered appropriately, especially where the complex issue of solids processing is concerned. Recently the number of development compounds that are poorly soluble has increased and has caused a resurgence in the need to manufacture amorphous material to enhance bioavailability. In some cases this is to increase the absolute solubility of the drug for therapeutic reasons or to give increased blood levels for toxicity assessment only.

## SAFETY

### EXPLOSION HAZARD

Most commercial spray drying operations involve handling aqueous solutions of material. The over-riding explosion hazard then tends to that of a dust explosion due to the nature of the fine particulate material formed in the drying chamber and sections of the system in which the material is collected (be that a cyclonic separator and/or a fabric filter, etc.). This aspect of spray drying has been covered extensively in numerous publications[1–4] and it is not considered necessary to cover this aspect in significant detail.

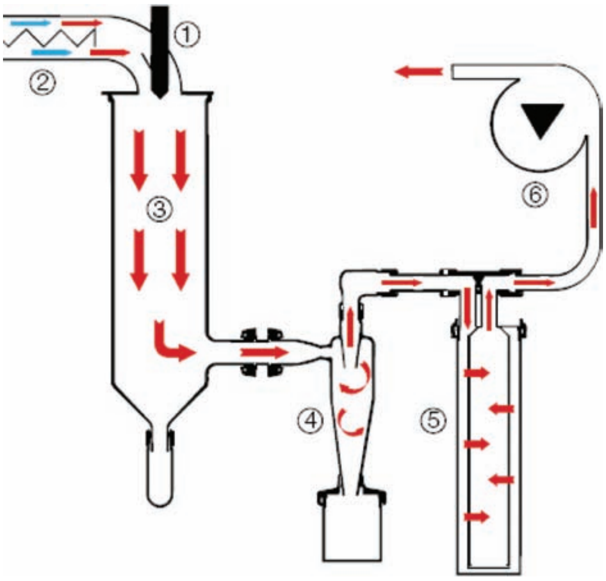


**Figure 1.** General flow diagram of the co-current spray drying process.

As stated early emphasis has shifted recently to generation of amorphous active pharmaceutical ingredient (API) in early stage development, and spray drying has proved a useful production method. The potential to use this separation technique at commercial scale has also proved viable provided all the SH&E hazards are recognized and mitigated.

In the vast majority of cases it is only feasible to use a solution of the API in an organic solvent, and although this tends to go against the principles of inherent safety there tends to be little option of avoiding this and still achieving the desired solubility of the API. With the majority of organic solvents tending to be highly flammable it inevitably gives rise to a significant explosion risk, not only in the primary drying chamber but also potentially throughout the whole spray drying system. The minimum ignition energy of the solvent vapour, or solvent / powder 'hybrid' mixture is usually significantly lower that that of the respective 'pure' dust cloud, thus increasing the probability of explosion. This aspect of operation will be discussed in more detail with regards to the individual parts of a general spray drying system.

General procedures for avoiding ignition sources during the handling of flammable solvents and powders, specifically whilst generating the solution, are well documented and should obviously be followed[5–9].

## MITIGATION OF THE EXPLOSION HAZARD IN THE COMPLETE SPRAY DRYING SYSTEM

The major issue in spray drying from a flammable solvent solution of API is that a significant proportion of the complete spray drying system could potentially be flammable during operation. One could use the comparison of spraying fuel into the cylinder of a combustion engine in readiness for ignition. This is somewhat different to the hazard created when using an aqueous solution, as here it is usually a relatively low fraction of the main drying chamber and a proportion of the collection system that can contain a flammable concentration of dust.

## EXPLOSION VENTING, CONTAINMENT AND SUPPRESSION AS PROTECTION METHODOLOGIES

In theory it is feasible to design the system to incorporate appropriate explosion venting devices. The unfortunate downside of such passive devices is that inevitably containment is lost within the system and material (both burnt, part burnt and un-burnt) will be emitted to the environment. Such material can have environmental impact and be a significant health risk on exposure to personnel. Therefore, passive explosion vents are losing favour generally and are definitely not acceptable for materials that pose significant environmental and/or health impact. It is generally much more practical to design a system with product containment in mind.

Complete explosion containment of a spray drying system although potentially feasible can in practice be very difficult, as it requires all the ancillary equipment on the system to be either explosion resistant or explosion shock resistant by design. This will need to be a decision prior to design and fabrication of such a system. Generally, this mode of protection is only feasible to relatively small and simple spray dryer systems, it tends to become impractical at significant scale. Business interruption risk assessment may be necessary to decide between explosion resistant and explosion shock resistant design. One would tend towards an explosion resistant design for use with flammable solvent systems if no other protection method were considered in mitigation of the significant explosion risk.

It can be feasible to fit explosion suppression systems to spray dryer chambers and ancillary attachments (and this is a fairly common practice for aqueous spray drying systems) but this would need careful consideration and expert design installation, and then subsequent maintenance. (The author is not aware of a 'solvent' spray dryer that has explosion suppression systems as a primary protection method).

## OPERATION UNDER NON-FLAMMABLE CONDITIONS (FUEL OR OXIDANT)

By far the most appropriate method of achieving safety in a spray drying system handling flammable solvent systems is to operate under non-flammable conditions. This can be achieved either by operating outside the flammable range by virtue of control of the concentration of fuel or oxidant (or potentially both) (see Figure 2).

On a relatively small scale it can be feasible to control the feed-rate of solution with respect to drying gas flow so as to maintain the overall fuel loading below the lower flammable limit (LEL). (Note: It is feasible to operate above the upper explosible limit (UEL), however, this has significant disadvantage, as loss of control tends to cause the system to become potentially flammable). The mode of operation below the LEL has been achieved in small-scale spray drying within AstraZeneca. It requires knowledge of the powder loading in the solution, the LEL of the solvent and strict control of the flow rates (i.e. large drying gas flow with respect to a small solution feed-rate). A value of 25% of the LEL was adhered to as closely as practically possible to allow for nominal perturbations in drying gas flow. This can be somewhat restrictive as a significant number of flammable organic solvents have extremely low LELs and to operate at 25% of this value could be very difficult to achieve. An attempt was made to make one particular solvent mixture (in ethanol) less flammable to some extent by adulteration with a solvent regarded as being effectively non-flammable, i.e. dichloromethane (DCM). It was considered that this would potential provide an inherently safer mode of operation. As a rapid evaluation of the level of reduction in flammable nature of varying DCM levels in the mixture flash point measurement were undertaken (see Figure 3). It was considered that the flash point would rise significantly with increased DCM content. However, it was noted that the flash point showed quite a marked

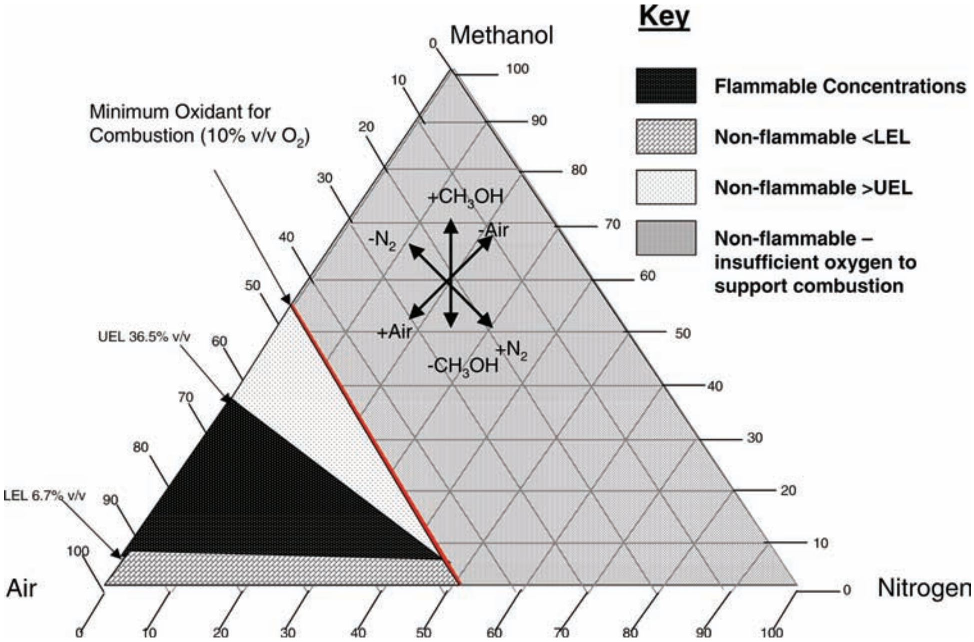


**Figure 2.** Flammability diagram for methanol/air/nitrogen mixtures.

decrease for relatively high proportions of DCM content before rising significantly on significant DCM concentration. This would suggest an adulterated solution with a certain amounts of this relatively inert solvent actually could make increase the flammability risk to some extent in the system. No further work was undertaken to determine the precise LEL of this mixture as it was considered to have no benefit over the pure solvent mixture. Obviously operating with just DCM as the solvent would be beneficial with respect to vapour flammability but would have potential environmental impact (effective VOC abatement would be needed to meet emission consents, and indeed the use of this solvent is restricted considerably in certain countries).

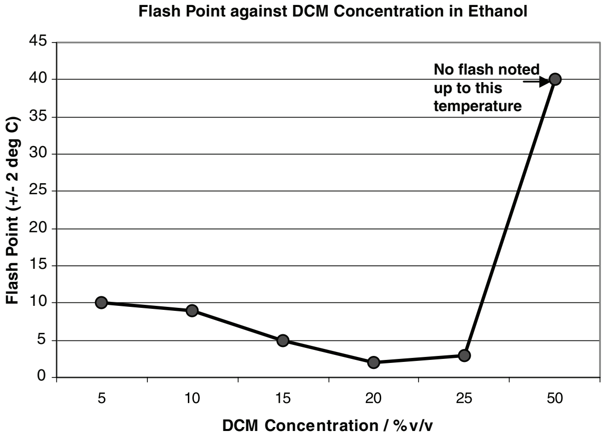


**Figure 3.** Flash point against DCM concentration in ethanol.

The more desirable and flexible option is to operate below the minimum oxidant for combustion (MoC), i.e. by inerting the system. This may not be practical for very large spray dryers where a significant 'once-through' gas flow is primarily used, but for relatively small units it is achievable with relative ease. The most practical method is to use a pure inert gas flow, but there is the potential to use any sufficiently oxygen depleted gas stream, e.g. flue gas. The general mode of operation is to engage the inert gas flow and upon achieving the desired depletion of oxygen and operating temperature then activate the spray. On relatively small systems the flow of nitrogen on a once through basis will generally maintain the desired oxygen reduction with relative ease, provided there is no significant leakage into the system. However, if it is known that oxygen can be entrained, or potentially generated by the material by say possible decomposition under high temperature conditions then continuous oxygen monitoring will be a prerequisite for the system. An alarm and trigger at a designated oxygen level will need to stop addition of solution and/or increase the input of inert gas. In some systems it is possible to recycle the carrier gas and continuous oxygen analysis is implicit. Increase in oxygen level will need to trigger additional input of inert gas to counter the oxygen increase, at an alarm state the system should shut down with maintained inert gas input.

## THERMAL DECOMPOSITION RISKS

In some location within a spray dryer there will inevitably be a build up of deposited powder material, usually on the drying chamber wall. In spinning disk atomizers with counter-current flow there tends to be a risk of material adhering to the upper part of the drying chamber where it may be hottest. In spray nozzle dryers with co-current flow then the deposits tend to adhere to the lower and cooler sections of the dryer chamber. If the material is susceptible to thermal decomposition at or around the inlet drying gas temperature then it may cause decomposition. This may cause smouldering in the material layer or if it dislodges and falls into the bulk dry material it may initiate decomposition in the mass. This may not be a hazard in an inerted dryer but it may be a risk once the powder is removed from the dryer as it may inflame on subsequent exposure to air. Some information is required on the thermal stability of the material considered for drying prior to operation so that the drying temperature can be optimized to minimize the risk suitably. In early development of material it may be difficult to supply sufficient material to carry out an appropriate 'drying' test, i.e. there may not be enough material to do a large scale test simulating hot gas flow through a material layer. Small-scale tests such as Differential Scanning Calorimetry (DSC) may give a useful insight into the thermal instability of the material from only milligram samples. It is not exactly ideal and the test will need to be carried out using high-pressure crucibles and an appropriate safety factor for the scale and sensitivity of the test method applied. It will highlight any major exothermic events that may occur in the material from relatively low temperature though, and if this could occur below the drying gas temperature then there may well be issues in acquiring the desired product via this isolation method.

### ELECTROSTATIC ISSUES

The powder product formed will generally constitute a potential dust explosion risk when dispersed in air. This is not an issue in the system if it is inert gas blanketed, but may be when the product is handled in secondary formulation operations. The general trend with APIs is that their minimum ignition energy (MIE) is towards the lower end of the scale, i.e. more materials appear to have MIEs in the range 1–3 mJ. This has potential implications for packaging the materials and their subsequent handling, i.e. in formulation and tabletting operations. If the material is known to have an MIE of 1–3 mJ then static dissipative packaging should be a pre-requisite.

The issue of residual solvent in the powder products will have potential implication in subsequent handling operations involving the material and the packaging will need to take account of this, i.e. static dissipative packaging may be required due to the residual solvent level alone. This issue of flammable atmospheres potentially arising from residual solvents has been reviewed in a previous publication[10].

## HEALTH

APIs are generally highly potent and toxic on exposure at relatively low levels. Containment of material to avoid exposure is important within any manufacturing operation of such materials, let alone spray drying. There has also been increasing legislative drivers away from protection through the use of personal protective equipment (PPE). The potency/toxicity of new materials is therefore requiring a move away from traditional 'open' manufacture towards a range of strategies and specific hardware systems to maintain material segregation from the operator, usually defined simply as 'containment'.

Containment system design and operation has to take into account all aspects of the operation from initial introduction of materials to the cleaning of equipments and the safe removal of the containment system. A significant aspect of the design is the avoidance of contamination of un-cleanable aspects of equipment. Specifically the machines drive and control system.

### DEFINITION OF CONTAINMENT

Any processing system can be considered as consisting of three elements: the process material, the operating staff, and the surrounding environment. For multi-product facilities, there is the additional quality risk of cross contamination with other products in the facility. Containment is the separation of any one of these items from the others. For example, the use of PPE is the separation of the operator from the other elements (note that the environment will potentially still be exposed and hence contaminated by the process material, as will other products within the facility). Engineered containment involves the separation of the process material from the operator, the environment, and other products, and is also known as containment at source.

### CONTAINMENT TECHNOLOGY

A range of containment technologies and solutions can be either bought off the shelf or adapted to given the necessary containment requirements. The majority are 'hard engineered' solutions and require significant levels of capital investments and usually a number of modifications to the operating equipment. This can be an issue for existing facilities and equipment. The validated status of operating equipment has to be considered. An alternative technology is "flexible isolation" that uses clear PVC and Polyurethane film to create a containment enclosure. These systems are designed specifically for the equipment and operation. When designed correctly they will avoid contamination of the machine. Most systems are fabricated intentionally to be disposable.

### CONTAINMENT PERFORMANCE

The containment capability or performance of containment equipment needs to match the Exposure levels (OEL and MEL) of the pharmaceutical active drug materials being handled. Containment technologies will state a designated range of containment capability. This enables the user to select the appropriate equipment for the material in

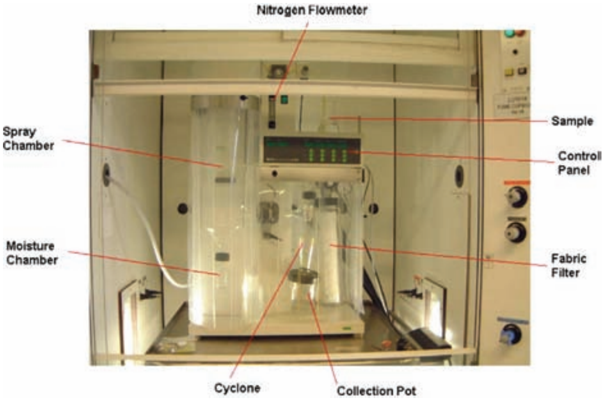


**Figure 4.** Buchi B290 Laboratory spray dryer in a fume cupboard in the Chemical Engineering Learning Laboratory.

question. However hygiene monitoring of the equipment is advisable.

## SPRAY DRYER REQUIREMENT

When considering the containment requirements and the operational aspects of a small scale laboratory spray dryer then use of a fumecupboard with a flexible containment solution was determined to be the most appropriate solution within AstraZeneca for highly potent materials. Scale up from this was also given some consideration, and flexible containment is being applied to a range of spray dryers of various sizes and plant configurations.

## TYPICAL DESIGN CRITERIA FOR A CONTAINMENT SYSTEM ON A SPRAY DRYER (FIGURE 4)

- Enclosure to provide a containment level of $\leq 1\ \mu g/m^3$
- Minimize contamination of machine.
- Operator access to all parts of the machine. For assembly, operation and strip down. (Note: all parts are glass and safe handling is essential).
- Full strip down of equipment inside enclosure and contained removal for cleaning required.
- Safe clean down, and removal of enclosure.
- Enclosure one off use to avoid cross contamination.
- Spray dryer to be operated on existing support table and in inside fume cupboard.
- Spray dryer guards can be removed and layout of machine components adjusted.

## CONTAINMENT

The parts of the spray dryer that must be contained, accessible and may be hot are summarized in Table 1.

**Table 1.** Summary of the issues to consider

| Component | Containment | Accessibility | Hot |
|---|---|---|---|
| Main chamber metal connector | ✓ | | ✓ |
| Spray chamber | ✓ | | ✓ |
| Cyclone | ✓ | | ✓ |
| Collection pot | ✓ | | ✓ |
| Fabric filter | ✓ | | ✓ |
| Control panel | | ✓ | |
| Sample feed | | ✓ | |
| Nozzle gas flowrate | | ✓ | |

Similarly, due to the accumulation of powder, the parts of the spray dryer that must be cleaned after use are generally the same as those that require containment. Usually all of these parts are dismantled and removed separately, transported across the room in a plastic bag to a sink unit housed in a fume cupboard where the gross decontamination takes place prior to the units being washed in a dishwasher to remove any residual contamination. When water is not appropriate, the units are solvent washed in an attempt to remove gross contamination to a visually clean level before dishwashing. The cleaning process is difficult and time consuming at present. It would be helpful if some of the gross decontamination could potentially be carried out within the flexible containment. This would significantly reduce the risk of exposure to the operator.

A cleaning system to ensure gross decontamination of the spray chamber and potentially the cyclone without the risk of exposure to toxic particles is planned for later in 2009. When visibly clean, the glassware could then be transported to a sink or dishwater to be sterilized with a reduced risk of emitting toxic particles.

The collection pot must be removed and the highest possible yield of product must be removed from it. This is difficult to clean as a layer of particulate solid builds up on the glass walls of the jar. In addition, when the collection pot is unscrewed, the inside of the lid is highly contaminated with a layer of powder and this is exposed to the operator.

The filter bag must be removed and washed after every cycle to prevent blockages. In addition, a layer of solid could build up on the glass housing of the filter bag so this must also be cleaned. In order to do this the glass housing must be unscrewed leaving the inside of the lid exposed to the operator.

The parts of the dryer that must be accessible during operation of the dryer are not directly connected to the glassware that must be contained; therefore it might be wise to limit the containment to the glassware to maintain easy access to the control panel.

Parts of spray dryer that get hot during operation that could be potentially problematic when considering flexible containment as the inlet gas can be heated to more than 200°C, giving a resultant glass temperature of 100°C or more in the spray chamber and similar temperatures in the cyclone, collection pot and glass connections. This could potentially limit the type of material out of which the flexible containment can be made.

## APPLICATION OF FLEXIBLE CONTAINMENT DESIGN ON A LABORATORY SCALE SPRAY DRYER (FIGURES 5 AND 6)

- A new attachment spool was designed and supplied to insert above the spray chamber. This was fitted with a Silicone ring with two grooves.
- A new clamping system was designed to fix the spray chamber to the new insert. This would be inside the enclosure and enable contained strip down of the spray chamber.
- The machine components were lowered by the length of the new insert. This forced an adjustment of the support brackets; the new support consists of a post and is also located inside the enclosure. It is removable with out tools for strip down and cleaning.
- The fabric filter container was relocated to the front of the machine from the back. This gives easy access to all components from the front glove sleeves.
- The enclosure attaches to the new insert with a tapered sleeve and encapsulated O ring.
- There are two glove sleeves at the front of the enclosure that reach all machine parts.
- There is one 300 mm dia material removal sleeve for all components. A sleeve tie or twist/ tie/ tape/ cut system is used for the safe separation of the sleeve.
- There are two service sleeves for instrument/control cables and one sleeve for the vacuum hose off the Fabric Filter.

## ENVIRONMENTAL

The major issue with spray drying solvent solutions is the potential to emit copious volumes of VOCs to atmosphere. Inevitably some form of VOC abatement system needs to be incorporated into such systems. The options usually are adsorption, absorption, thermal oxidation or condensation (usually cryogenic). It may be necessary to use more than one technique in sequence to achieve the desired emission levels.

It may be feasible to absorb certain VOCs in an aqueous solution, but this may simply move a potential flammability hazard to another part of the system (i.e. absorption column collection tank).

It may also be feasible to use a thermal oxidation system. These need careful design and control to ensure they meet the desired oxidation to non-hazardous by-products.

Condensation is good for low vapour pressure VOCs but may require a secondary abatement back up in case of coolant failure.

The most common approach on commercial spray dryers is to incorporate an activated carbon adsorption system, whether one-use or regeneration. The potential fire risk in such systems should be acknowledged in their design especially if multiple dryers (or other VOC emitting vessels vent via a single unit.

## OUTSOURCING/CONTRACT MANUFACTURE

Particularly for API manufacture by this method it is imperative that the potential toxicity and the level

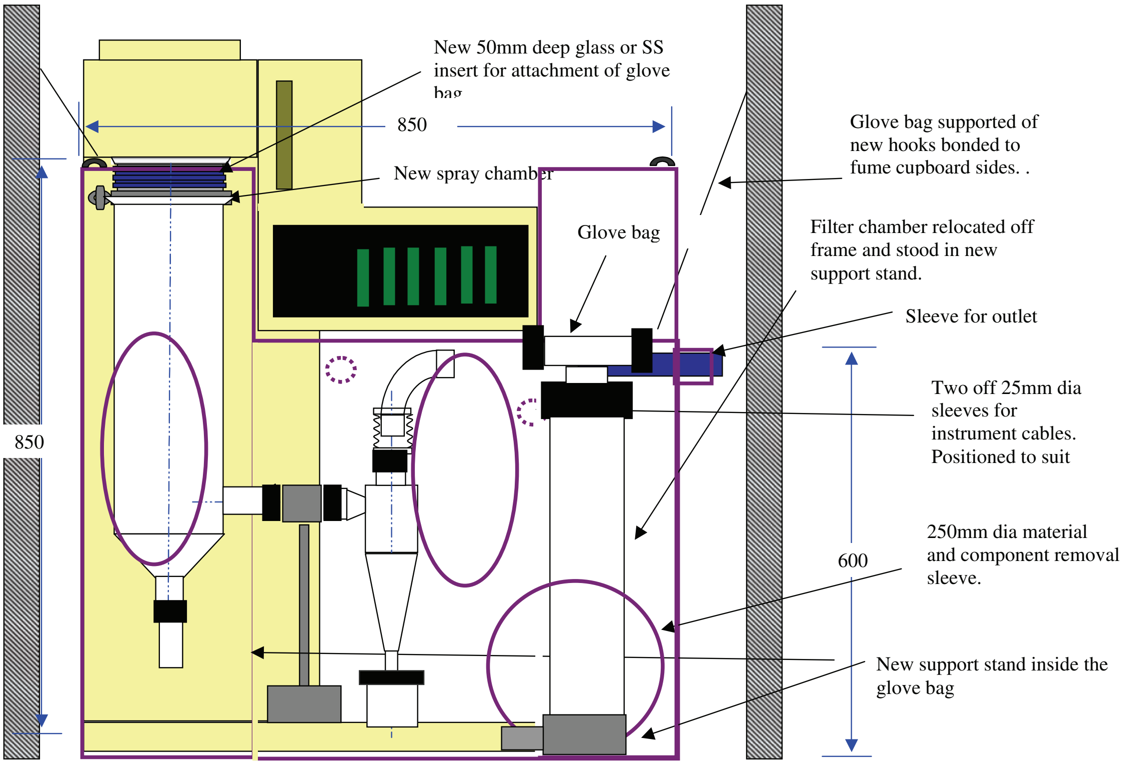
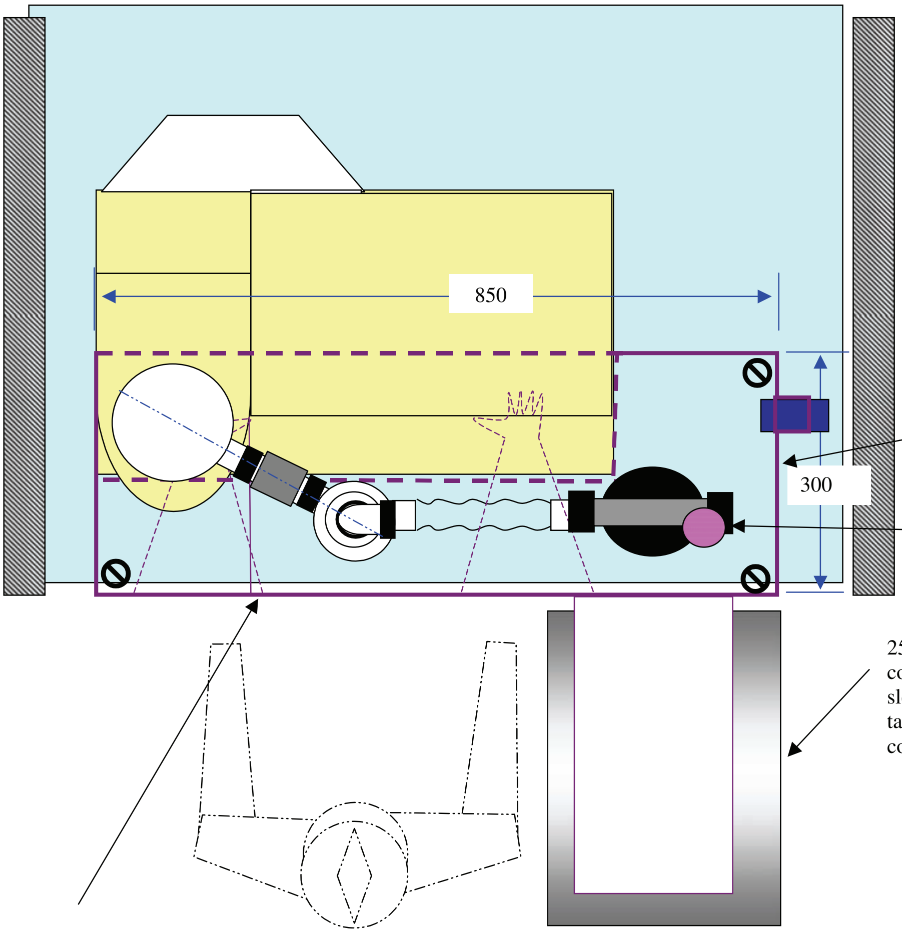


**Figure 5.** Flexible containment of the Buchi Laboratory Spray Dryer



250mm dia material and component removal sleeve. Used with mobile table for supporting components

**Figure 6.** Ergonomics of the operation of the Buchi Spray Dryer with glovebag containment.

of containment needed in the manufacturing operation is specified by the company that is outsourcing to the Contract Manufacturer. This will enable them to consider the likely exposure levels and the measures that they may need to take in applying additional exposure containment philosophies on their particular plant system.

Any thermal stability data on the material being dried should be shared with the Contractor. If none is available then it is likely that the Contractor will need to either request this information or carry out appropriate test procedures themselves.

Any specific flammability hazard data or environmental impact information on the materials in use should be provided to or sought by the Contract Manufacturer.

When a Request for Contract Proposal is generated by the customer then it standard practice to include the information that is available on potential hazard, health and environmental risks.

Sharing the laboratory spray drying containment work with the Contract Manufactures and involving them in discussions has allowed a number of designs to be elaborated with flexible containment on large scale spray driers and an example is given in Figure 7.

Note: It is not practical to provide a single Flexible enclosure for the larger Spray Dryer systems. The approach

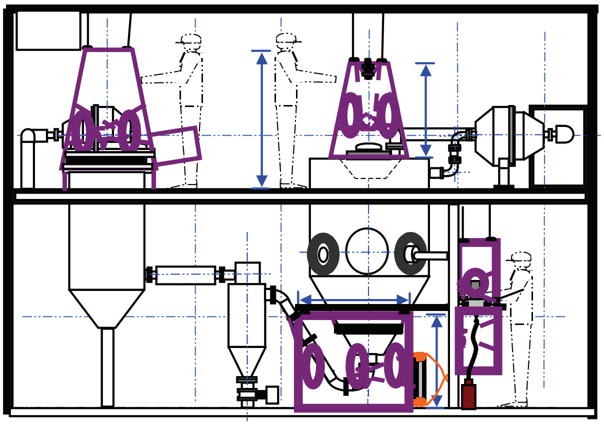


**Figure 7.** Scale up for Spray Dryer systems.

to take on these systems from a containment view point is to risk assess the equipment and its process. From this it will be possible to identify the areas on the system where exposure levels could be exceeded either during operation or break in scenarios and then provide containment specifically for those areas. Flexible containment has proved suitable for these areas, typically:

- The Top of the spray dryer enclosing the spray head.
- The base of the spray dryer, usually for potential pipe work removal.
- The top of the Filter unit for filter sock change and removal.
- Safe filter changes.

## CONCLUSION

Scaling up spray drying processes from a safety, health and environment point of view can be achieved by considering the main hazards and risks in each area. For spray drying using solvents the basis of safety is to use inert gas blanketing following a check on the thermal stability of the isolated powder.

Containment of a laboratory scale spray drier in a fumecupboard by totally enclosing the equipment within a single flexible containment bag has been developed. For larger scale equipment the main exposure points only need to be considered however the same containment principles apply as those for the laboratory spray drier.

Environmentally there are a number of solutions for dealing with the VOCs and fine dust. On the laboratory scale the use of condensation for the control of VOCs is effective whilst dust control is via a simple bag filter.

Finally it has been demonstrated that by closely working with Contract Manufacturers in the area of spray drying it is possible to modify existing assets at low risk to perform to the acceptable SHE standards and still supply customer needs efficiently and effectively.

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