ASEPTIC SPRAY DRYING FOR STABLE LIQUID 21ST CENTURY PHARMACEUTICALS

INTRODUCTION

Cambridge Biostability has developed completely shelf-stable, ready-to-inject liquid formulations of vaccines and drugs. The process consists of stabilising actives in soluble glass microspheres which are suspended in biocompatible and density-matched anhydrous liquids in which they do not dissolve (Fig. 1). When injected, the microspheres dissolve in body water releasing potent vaccines or drugs and the anhydrous liquids are exhaled in the breath or rapidly metabolized. These formulations can be stored at high ambient temperature for at least three years, are completely resistant to freeze damage and can be injected without preparation at the point of use. Because of the mechanism of stabilisation, the product, which is in solid solution in the dry glass, is stable up to the softening point (glass transition temperature - Tg) of the glass. This is well over 70°C with our new glass formulations. This is true even of products which are extremely unstable in aqueous solution in their native form.

These products promise to radically improve the way vaccinations and therapeutic drugs are delivered worldwide. The anhydrous liquids used in these preparations are of two types: high density fluorocarbon liquids and low density metabolisable oils. In order to produce physically stable suspensions that do not separate into two phases, the formulations must contain density-matched high density or low density glass microsphere particles.

Crucial to this technology was the development of an inexpensive and scalable process to manufacture large quantities of highly polished spherical glass micro-particles of known density. This process obviously also required to be GMP-compliant and capable of sterile manufacture for parenteral drugs.

Although emulsion drying, freeze drying and spray-freeze drying were all investigated, spray drying was finally chosen as the process of choice. The glass-forming excipients used in the process generate water soluble glasses when spray dried under appropriate conditions but required careful selection so as to avoid the so-called “shell drying” commonly seen in spray drying (Fig. 2).

This produces particles with irregular gas-filled voids, many of which are collapsed. This effect is random and seems to be especially marked when polymers are included in the formulation. This precludes the careful control of density required in this technology. However, a variety of formulations have been developed which produce exclusively solid particles ideal for this technology. In addition, a process has been developed which generates and traps within the spherical particles, precisely calibrated volumes of biocompatible gases yielding particles of pre-determined low density matched to that of injectable oils.

Fig. 1 Soluble glass microspheres forming a monodisperse suspension in anhydrous fluorocarbon liquid. Because the microspheres are solid their density can be precisely controlled to match that of the surrounding liquid. Such suspensions are physically stable. The particles neither settle nor float in the liquid phase.
Fig. 2 Collapsed hollow particles typically produced by conventional spray drying. While this type of particle maybe found in many spray dried powders they are specially frequent in preparations made from feed mixes containing polymeric compounds such as proteins, polysaccharides etc. Because of the random presence and persistence of the gas voids they cannot be reproducibly density matched with any liquid phase of the formulation.

HIGH DENSITY FE FORMULATIONS

These suspensions are indefinitely stable on storage; the particles have neutral buoyancy and do not settle or float (Fig. 3). This allows for a great simplification in the manner of manufacture as the particles need not be particularly small to stay in suspension. The spherical particles roll past each other with an inherent lubricity, enabling very high solids contents of up to 80% in viscous creams to be achieved. Preferred concentrations of 5-25% yield highly mobile, water-like injectable liquids. Spherical particles are made by spray-drying. Irregularly shaped particles made by grinding have a tendency to “bind” together, inhibiting free-flow. Because both the soluble glass particles and the HFE liquid are dry and environmentally stable there is no degradation due to light, heat or oxygen.

The density of injectable oils approved by regulatory authorities are about 0.85-0.95 kg/l. The only practical way to density-match glass microspheres with these oils is to add precise quantities of gas bubbles into the microspheres as they are formed. This has recently been achieved by adjusting process conditions in the spray dryer and by the use of a “blowing” agent. This agent decomposes into biocompatible gases at the precise stage when the drying droplets are sufficiently viscous to trap the gas bubbles but before they have dried to a brittle glassy solid.

This technology also capitalises on alternative soluble glass forming amino acids that reach the required viscosity at the correct stage in the spray dryer. These are also already approved by the regulatory authorities for injection. This combination of amino acid aerospheres and metabolisable oils yields formulations that avoid most regulatory problems, being composed entirely of GRAS materials normally found in the body. They are suitable for frequently repeated injections of parenteral pharmaceuticals and can be used for stable liquid formulations of insulin for example. The microscopic appearance of the particles produced by various amounts of blowing agent in the spray dryer (Fig. 4).

Fig. 3 Solid high density mixed glass microspheres are density matched with the anhydrous fluorocarbon liquid (Left). Typical amino acid glass particles sediment in injectable oils (Middle) but float in fluorocarbons (Right).

Fig. 4 - Bar = 10 μm - Phase contrast photomicrographs of “blown” microspheres in oil showing the effect of increasing amounts of blowing agent from nil to 0.6 Molar. There is a reproducible enlargement of the spheres with increasing amounts of agent. The degree of inflation of the aerospheres and hence their density, is controllable within tight limits and is a reproducible function of both the drying conditions and the quantity of agent used.

These studies confirmed that the volume of the aerospheres was increased as the concentration of
blowing agent used increased but gave no information on the distribution of the gas bubbles within the microspheres i.e. whether the gas bubbles were dispersed as a honeycomb or concentrated as a single gas-filled void. This was approached by spray drying microspheres containing a fluorescent compound together with increasing amounts of blowing agent and examining them by confocal microscopy. Solid microspheres containing no blowing agent showed uniform fluorescence as expected (Fig 5a) while the blown microspheres showed classical ring fluorescence (Fig 5b) indicating that the gas was in the form of a single central bubble. This was further confirmed by freeze-fracture scanning electron microscopy which clearly showed these objects to be hollow spheres (Fig 5c).

In these studies the aerospheres have a range of densities; those made with more than 0.3 M blowing agent float in oil; the ideal concentration being between 0.2 and 0.3 M with these drying conditions (Fig. 6). This is, of course, accurately titrated for the final formulation.

Density matched formulations can now be made with a range of injectable liquids varying in density from <0.8 to >2.0 Kg/L. In addition multiple applications can be addressed ranging from vaccines injected into infants and children on only a few occasions to insulin and other drugs injected multiple times per day. Only spray drying technology provides the flexibility of processing conditions required to address all these opportunities. To manufacture marketable injectable products requires the development of a new aseptic spray drying process operating under current Good Manufacturing Practice (cGMP) conditions.

**ASEPTIC SPRAY DRYER FACILITY**

A new aseptic spray dryer (ASD1) was developed in association with GEA Niro A/S of Copenhagen, Denmark who provided the design and fabrication expertise. This equipment depends on Clean in Place (CIP) and Sterilise in Place (SIP) technology being used between runs. CIP is obtained using conventional spray ball equipment and standard pharmaceutical cleaning protocols. SIP is achieved by attaining temperatures of 180°C, using super-heating of the drying nitrogen gas throughout the drying chambers and maintaining the temperatures in excess of 6 hr to ensure sterility. This has required ancillary heating in certain sites and also a considerable increase in insulation. The smaller demountable elements are designed to be autoclaved and remounted under sterile conditions.

The ASD will be housed in a sterile Class 100 plastic film isolator (Fig. 7) designed and operated under contract by Nova Laboratories of Leicester UK who are expert in the production of small batches of...
sterile pharmaceuticals under cGMP conditions in plastic film isolators.

This ensures that the product remains well below the gas temperature until it has dried to a glass when their temperature rapidly rises to the outlet temperature (Fig. 9). In addition the typical residence time of the droplets in the drying chamber is ~3 seconds and since the particles also spend only a few seconds in the cyclone before being separated into the much cooler collection vessel, there is little time for thermal damage to occur to the product.

**SPRAY DRYING AS A PHARMACEUTICAL PROCESS**

It is surprising to many in the Pharmaceutical Industry that fragile biomolecules such as vaccines can be spray dried at gas inlet temperatures of over 150°C without any damage to the product. This apparent anomaly is explained by the extreme evaporative cooling of the very small droplets produced by the 2 fluid nozzle spray head (Fig. 8) and directed into the hot dry gas stream.

The last stage of the production process is the addition of the sterilised biocompatible anhydrous liquid to the powder collection vessel and the dispersion of the powder in the liquid to produce a homogeneous, density-matched suspension. This is the final sterile product which is vialled, labelled and packaged in conventional sterile bottling equipment in a separate isolator.

**ADVANTAGES**

The striking advantages of stable liquid technology are obvious in giving instantly injectable vaccines and drugs which never require refrigeration and are also fully resistant to freezing damage. This enables such a dramatic simplification of storage and delivery logistics that these agents can now reach even the most remote parts of the world without harm.

The advantages of sterile spray drying as a production process are equally remarkable:

- Spray drying is very fast and gentle
- Product dries in seconds rather than days
- It avoids freeze damage to the product
• It is a continuous rather than a batch process
• It is cheap
• Capital cost is comparable with freeze dryers
• Running costs are about 1/10-1/5 of freeze drying
• Glass-forming formulations are simple
• It could remove vaccine production bottlenecks
• Spray drying machines are fully scalable from grams per hour to tonnes per hour scales

DISADVANTAGES
Sterile spray drying is an unfamiliar technique in the Pharmaceutical industry and can experience resistance to its introduction as a result.

For applications other than stable liquid technology the product is a bulk powder. For final dosage packing this requires either sterile powder handling methods or temporary suspension in a volatile vehicle which is evaporated from the final container.

Finally the equipment for sterile spray drying is only now becoming available - indeed the Cambridge Biostability plant in Leicester is the world’s first Aseptic spray drying plant for the cGMP production of sterile vaccines. However, the design problems and scale up issues are all being collaboratively addressed in this facility so that validated equipment will then be available from the manufacturer.

OTHER APPLICATIONS
Stable liquid technology was originally developed solely to address problems of inadequate vaccine thermostability. With the recent development of simple aerosphere production techniques in the same spray drying equipment it has now become possible to produce stable injectable liquid formulations of essentially any vaccine or pharmaceutical under sterile conditions suitable for cGMP manufacture. These formulations are not only chemically stable at high or low temperatures for years but are also physically stable due to density matching. Properly formulated microsphere preparations show no tendency to phase separate over several years at room temperature. They do not even require shaking before use.

Stable liquid technology can now be applied to essentially any parenteral drug. Of course the same density matching principle also enables the production of oral, optic, otic, nasal, rectal and other suspensions with indefinite physical stability.

This avoids the need to produce particularly small colloidal scale particles which remain in suspension by thermodynamic forces only. This means that inexpensive, gentle processing equipment like spray dryers can replace expensive, harsh milling operations in drug production.

FURTHER IMPACT
The introduction of stable liquid vaccines, even though they may be slightly more expensive to make than current vaccines, has the potential to save $200-342 million per year according to a working group of the Global Alliance on Vaccines and Immunisation (GAVI ). This saving could allow vaccines to be purchased and delivered to some of the 20 million new children not protected each year by full vaccination and perhaps save a significant proportion of the 2-3 million that die each year from vaccine preventable diseases.

Since up to 70% of vaccines used in WHO outreach programmes are damaged by freezing in improperly set-up cold boxes, many of the patients actually reached by vaccination campaigns are administered damaged vaccines. Fully thermostable liquid vaccines will completely remove this risk adding greatly to the efficacy of the campaigns.

The expansion of stable liquid technology to encompass all unstable pharmaceuticals completely removes the need for refrigeration for this class of product. This could enable even the most labile of modern drugs, diagnostics and biologicals to be transported, stored and used anywhere on earth. Even people in the remotest areas could have access to the benefits of modern medicine. The savings in refrigeration, cold boxes and the logistics of transportation could help fund the provision of this higher quality healthcare.

In the developed world the elimination of the need for refrigeration and expiry dates on pharmaceuticals can dramatically reduce health care costs. For long term storage such as the Biodefence stockpiles of vaccines and therapeutics, stable liquid technology will enable great savings in renewal costs and dispersal into smaller stockpiles at the local level. This is more efficient and cost effective than central refrigerated stocks with their inherent expense of logistical turnover of expired components and the delays and difficulties of emergency distribution.

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