During the course of developing a shelf-stable, ready-to-inject liquid formulation technology (1), the need arose for a process whereby large quantities of highly polished spherical glass microspheres of known density could be manufactured. The process needed to be inexpensive, scalable, GMP-compliant and capable of sterile manufacture for parenteral drugs. Methods such as emulsion drying, freeze drying and spray-freeze drying were all investigated, but spray drying was finally chosen as the process of choice. This article reviews how the aseptic spray drying process was developed and future therapeutic applications of stable liquid technology.

GLASS MICROSPHERE STABILISATION

The formulation technology developed by Cambridge Biostability Ltd (CBL) consists of stabilising actives in water-soluble glass microspheres which are suspended in biocompatible and density-matched anhydrous liquids in which they do not dissolve, thus forming two-phase liquids. When injected, the glass microspheres dissolve in body water releasing potent vaccines or drugs, and the anhydrous liquids are either exhaled in the breath or rapidly metabolised. These stable liquid formulations can be stored at high ambient temperature for at least three years, are completely resistant to freeze damage, and can be injected without any 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, $T_g$) of the glass, which is well over 70°C with more recent 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 a process to manufacture large quantities of highly polished spherical glass micro-particles of known density. 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 generated water-soluble glasses when spray dried under appropriate conditions, but required careful selection so as to avoid the so-called
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‘shell drying’ commonly seen with spray drying (Figure 2). This produces particles with irregular gas-filled voids, many of which collapse. The effect is random and seems to be especially marked when polymers are included in the formulation. The careful control of density required for this technology is thus precluded; however, a variety of formulations have been developed which produce exclusively solid particles which are ideal. In addition, a process has been developed whereby precisely calibrated volumes of biocompatible gases are generated and trapped within the spherical particles, yielding particles of predetermined low density matched to that of injectable oils.

HIGH DENSITY FORMULATIONS

These suspensions of glass microspheres are indefinitely stable on storage; the particles have neutral buoyancy and neither settle nor float (Figure 3). This enables great simplification of the manufacturing method as the particles do not need to be particularly small in order to stay in suspension. The highly polished glassy spherical particles roll past each other with an inherent lubricity, enabling very high solids contents of up to 80% to be achieved in viscous creams. Preferred concentrations of 5-35% yield highly mobile, water-like injectable liquids. Because both the soluble glass particles and the HFE (hydrofluoroether) 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 is around 0.85-0.95kg/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. The 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. The combination of amino acid aerospheres and metabolisable oils yields formulations that avoid most regulatory problems, being composed entirely of GRAS (Generally Recognized As Safe) 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, for example, insulin. The microscopic appearance of the particles produced by various amounts of blowing agent in the spray dryer is shown in Figure 4.

These studies confirmed that the volume of the aerospheres increased as the concentration of blowing agent was increased, but gave no information about the distribution of the gas bubbles within the microspheres – that is, whether the gas bubbles were dispersed as a honeycomb or concentrated as a single gas-filled void. This question was...
addressed 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 (Figure 5a) while the blown microspheres showed classical ring fluorescence (Figure 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 (Figure 5c).

In these studies, the aerospheres had a range of densities; those made with more than 0.3M blowing agent floated in oil, whereas the ideal concentration was found to be between 0.2 and 0.3M under these drying conditions (Figure 6). This would then, of course, be 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 >2.0kg/l. In addition, multiple applications can be addressed ranging from vaccines administered by injection into infants and children on just 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.

A new aseptic spray dryer (ASD1) was developed in association with GEA Niro A/S (Copenhagen, Denmark) who provided the design and fabrication expertise. The 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 for six hours to ensure sterility; this requires ancillary heating in certain sites and also a considerable increase in insulation. The smaller de-mountable elements are designed to be autoclaved and re-mounted under sterile conditions.

The ASD will be housed in a sterile Class 100 plastic film isolator (Figure 7) designed and operated under contract by Nova Laboratories (Leicester, UK) who are expert in the production of small batches of sterile pharmaceuticals under cGMP conditions in plastic film isolators (Figure 8). The aseptic spray dryer being installed for CBL at Nova Laboratories will be housed in a large two-storey film isolator located in a separate class 100,000 room to fully quarantine vaccine manufacture from all other pharmaceutical production in the facility.
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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 two-fluid nozzle spray head and directed into the hot dry gas stream.

This ensures that the product remains well below the gas temperature until it has dried to a glass when the temperature rapidly rises to the outlet temperature (Figure 9, page 56). In addition, the typical residence time of the droplets in the drying chamber is around three 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.

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.

The striking advantage of stable liquid technology is obvious in that it provides 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 has the potential to remove vaccine production bottlenecks

Sterile spray drying is an unfamiliar technique within the pharmaceutical industry and so there tends to be a degree of resistance to its introduction. For applications other than stable liquid technology, the product is in the form of a bulk powder; for final dosage packing, this requires either sterile powder-handling methods or temporary suspension in a volatile vehicle which is then evaporated from the final container. The equipment for sterile spray drying is only now becoming available – indeed the CBL 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 the 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 for years at high or low temperatures, 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 only remain in suspension as a result of thermodynamic forces. Consequently, inexpensive, gentle processing equipment – such as spray dryers – can replace expensive, harsh milling operations in drug production.

FUTURE IMPACT

The introduction of stable liquid vaccines – even though they may be slightly more expensive to produce than existing 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 (2)). This saving could enable 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 the 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, elimination of the need for refrigeration and expiry dates on pharmaceuticals could dramatically reduce healthcare costs. For long-term storage, such as the biodefence stockpiles of vaccines and therapeutics, stable liquid technology will enable great savings to be made 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 associated with emergency distribution.

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