Dispersible powders for inhalation applications

The poor powder dispersibility found with current DPI and pMDI formulations of micronised drugs can be overcome through the use of PulmoSphere™ technology.

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The colloidal domain is where physics, chemistry, biology and technology meet. Nowhere is this more important than in the field of biotechnology, where small particles are being engineered to achieve attributes such as cell-specific targeting, sustained release and enhanced protein stability. PulmoSphere™ technology relies on particle engineering principles to achieve powders with improved dispersibility - an attribute which is critical in achieving reproducible delivery of drugs to patients via the lung (1-4).

The challenge

The two most important aerosol delivery devices for the pulmonary administration of drugs are metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). All of the currently approved formulations for pMDIs and DPIs utilise micronised drug. The micronisation process is equivalent in many ways to throwing a crystal ball against a steel wall. Upon contact, the crystal splinters into millions of pieces with little control over the distribution of sizes, their morphology, density, surface energy or rugosity. However, all of these factors affect the dispersibility of a drug, and efficient dispersion is the key to achieving patient-reproducible delivery.

Powder dispersibility is controlled by inter-particle cohesive forces, which are proportional to the area of contact and average separation distance between particles. Micronised drugs often have flat particle surfaces, thereby promoting large contact areas (Figure 1). In addition, cohesive forces gain in strength with decreasing particle size, and are very strong for the aerodynamic particle sizes required for efficient delivery to the lung (that is, less than about 5µm). The strong cohesive forces have two important effects on fine powders. First, they lead to poor powder flow characteristics, necessitating blending of the micronised drug with lactose carrier particles; this effectively limits the dose that can be delivered from a DPI to less than about 10mg. Second, strong cohesive forces lead to poor powder dispersion from small, passive DPI devices. Powder dispersion in these DPIs is controlled by the physics of the device and, more importantly, by the patient’s inspiratory effort. Dramatic differences in powder dispersion and subsequent lung deposition are observed as a function of variations in patient inspiratory flow rate.

For patient-reproducible delivery in pMDIs, the dry powder must be dispersed in a hydrofluoroalkane (HFA) propellant. The classic approach to stabilising suspensions of drugs in propellants is to add a small amount of a propellant-soluble surfactant to increase electrostatic repulsive forces between particles. Charge stabilisation in non-aqueous suspensions is effective only at large inter-particle separation distances - that is, at particle volume fractions much less than are typically found in pMDIs. As a result, suspensions are susceptible to flocculation and generally tend to “cream” rapidly (creaming times of the order of a minute or less). Rapid creaming can have profound effects on the
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A unique spray-drying process

Powder dispersibility is designed into PulmoSphere particles through a combination of novel formulation design and processing. PulmoSphere particles are manufactured by spray-drying an emulsion-based feedstock. Accordingly, a submicron fluorocarbon-in-water emulsion is prepared by high pressure homogenisation. The emulsion is stabilised by a monolayer of a long chain phospholipid, such as dipalmitoylphosphatidylcholine - the principal component of endogenous pulmonary surfactant. Active drug is incorporated in the emulsion by solubilisation in the lipid acyl chains, or by dissolution or dispersion of micronised drug in the continuous water phase. The fluorocarbon serves as a blowing agent, resisting droplet shrinkage during the spray-drying process (4). As the process continues, the fluorocarbon outgases leading to pore formation and a hollow particle core (Figure 1).

Improved dispersibility - pMDIs

It was hypothesised that improved suspension stability in pMDIs could be achieved through particle engineering, whereby penetration of the propellant inside the hollow porous particle leads to the formation of a new type of suspension termed a homodispersion™. The prefix “homo” refers to the fact that the continuous and dispersed phases are now identical, separated by a porous particle wall comprised of drug and phospholipid. Homodispersion formation improves suspension...
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stability by, first, minimising the difference in density between the particle and the medium, thereby decreasing particle creaming, and second, decreasing inter-particle attractive forces due to the fact that much of the inter-particle contact is propellant on propellant.

In contrast to traditional pMDI suspensions, PulmoSphere suspensions have long creaming times, of the order of minutes to hours (1). This is illustrated in Figure 2, where a typical albuterol sulphate PulmoSphere suspension is compared with the commercial Proventil HFA product (Schering-Plough), the first HFA pMDI formulation to be approved in the US. The Proventil HFA® product is completely sedimented within 30 seconds following shaking, whereas little change is noted in the PulmoSphere formulation over a 4-hour period. The improved suspension stability leads to improvements in dose uniformity (1,3). This is illustrated in Figure 3, where data for the emitted dose across the contents of the canister is presented. In this shake-pause-fire experiment, a period of 30 seconds was taken between shaking and actuation of the canister. This leads to dramatic variations in the emitted dose for Proventil HFA (relative standard deviation, RSD = 91%), whereas little variation in emitted dose is noted for the PulmoSphere formulation (RSD = 3%). PulmoSphere formulations typically have RSDs of less than about 5%, making them well suited for meeting the newly proposed FDA guidelines for content uniformity, where - from a statistical standpoint - an RSD of about 6% or less is necessary.

The efficient dispersion of particles from the pMDI device leads to enhanced lung deposition relative to currently available commercial products. This was shown for an albuterol PulmoSphere formulation, where 40% of the emitted dose was deposited in the lungs of human volunteers, versus only 17% for the Ventolin Evohaler® (Glaxo-Wellcome) (5).

**Improved dispersibility - passive DPIs**

The PulmoSphere design also has a significant impact on the dispersibility of dry powders. Compared with the flat surfaces noted for micronised crystals, PulmoSphere particles are nearly spherical, thereby minimising the area of contact between flocculated particles. In addition, the points of contact are often very weak (for example, particle on a pore). Particle size distributions of PulmoSphere formulations are narrow with few fine particles; this leads to decreased inter-particle coordination numbers for PulmoSphere formulations, and a decreased tendency towards flocculation.

The micronisation process often leads to patches of surface with high surface energy; by contrast, the hydrophobic lipid acyl chains lead to surfaces for PulmoSphere particles that have low surface energy. Variations in surface rugosity can also be engineered into PulmoSphere particles through variations in the particle drying rate. The presence of asperites on the particle surface increases the inter-particle separation distance, thereby decreasing the resulting cohesive force. All of these factors contribute to the improved powder flow and dispersibility properties noted with PulmoSphere formulations.

The free-flowing nature of PulmoSphere powders means that they need not be blended with lactose carrier particles for effective loading into capsules. This boosts the maximum dose that can be delivered from small, passive, capsule-based DPIs. For example, about 25 mg of PulmoSphere powder can be effectively emitted and dispersed from a No 2 capsule.

**Figure 3.** Plot of the emitted dose across the contents of the canister for the Proventil HFA and PulmoSphere suspensions shown in Figure 2. The canisters were shaken and then held in the inverted position for 30 seconds prior to actuation.

**Figure 4.** Plot of the fraction of particles of less than 3.3µm as a function of flow rate observed for a budesonide PulmoSphere formulation delivered from the Turbospin device versus the Pulmicort Turbuhaler®. The PulmoSphere formulation exhibited a decreased flow rate-dependence relative to the micronised drug formulation.
The improved dispersibility of PulmoSphere formulations relative to traditional micronised drug is illustrated for the corticosteroid, budesonide, in Figure 4. Plotted in the figure is the fine particle fraction (FPF) of particles of less than 3.3µm as a function of flow rate measured by in vitro impaction techniques. The comparator is the current gold standard for budesonide delivery, the Pulmicort Turbuhaler® (Astra-Zeneca). The budesonide PulmoSphere formulation is delivered from the PH&T Turbospin device. Both are medium-resistance devices and can, therefore, be compared at comparable flow rates. For these devices, a flow rate of 60 litres per minute (LPM) is equivalent to that generated by a patient when asked to breathe forcefully, while a flow rate of 28.3 LPM is equivalent to that at a comfortable breathing rate.

Emitted doses for PulmoSphere formulations are typically between 80% and 95%, and are independent of inspiratory flow rate. A dramatic dependence of FPF with flow rate is noted for the Pulmicort Turbuhaler; the dependence is much less marked for the budesonide PulmoSphere formulation. A small dependence of FPF on flow rate is needed, however, to achieve flow rate-independent deposition of drug in the lungs of patients, since deposition is dependent not only on the aerodynamic particle size, but also on the inspiratory flow rate. Calculations suggest that drug deposition for PulmoSphere formulations will exhibit little dependence on inspiratory flow rate. Clinical trials are in progress to confirm this hypothesis.

**A platform technology**

A wide range of drugs have been incorporated in PulmoSphere formulations, including hydrophilic small molecules (albuterol sulphate, cromolyn sodium), hydrophobic small molecules (budesonide, triamcinolone acetonide), peptides (calcitonin, haemaglutinin peptide), proteins (insulin, hIgG) and viruses (influenza virus). As shown, the hollow porous morphology achieved with the spray-drying process employed allows for excellent dispersibility and highly efficient delivery from small, inexpensive pMDI and passive DPI devices - making PulmoSphere formulations an ideal platform technology for aerosol drug delivery.

**References**