

PHARMACEUTICAL AEROSOLS – ENHANCING THE METERED DOSE INHALER

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INTRODUCTION

Pharmaceutical aerosols have been playing a crucial role in the health and well being of millions of people throughout the world for many years. These products include pressurized metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebulizers, sublinguals, skin sprays (coolants, anesthetics, etc.) and dental sprays. The technology's continual advancement, the ease of use, and the more desirable pulmonary-rather-than-needle delivery for systemic drugs has increased the attraction for the pharmaceutical aerosol in recent years.

Since the mid 1950s, aerosol forms of pharmaceuticals have played an important role in treating respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD), and MDIs and DPIs have become an important part of that treatment. But administration of drugs by the pulmonary route is technically challenging because oral deposition can be high, and variations in inhalation technique can affect the quantity of drug delivered to the lungs. Therefore, there have been considerable efforts to provide more efficient and reproducible aerosol systems through improved drug delivery devices and through better formulations that disperse more readily during inhalation.

Traditionally most pharmaceutical aerosols have been propelled with chlorofluorocarbons (CFCs), but current global regulations require pharmaceutical aerosols to be reformulated to contain non-ozone-depleting propellants. In the process of reformulation for this transition, there is the opportunity to improve today's pulmonary delivery technology and to create new systems to treat a wide array of infirmities and afflictions.

Alternatives to CFC propellants must satisfy many other criteria in addition to environmental acceptability. Most importantly, they need to have acceptable toxicity profiles given their use in the delivery of medicaments. For the sake of patient safety, it is also important that they are nonflammable. Finally, their physical properties must allow workable formulations within the available technology. The two current alternatives to CFC propellants for pharmaceutical aerosols are hydrofluorocarbon (HFC) 134a (also known as hydrofluoroalkane (HFA) 134a or 1,1,1,2-tetrafluoroethane), and HFC-227ea (HFA-227ea or 1,1,1,2,3,3,3-heptafluoropropane).

While HFCs are more environmentally friendly compounds, eliminating chlorine from these molecules has added a significant solvency challenge.



Addressing these reduced solvency characteristics has been a major element of pharmaceutical reformulation programs for replacing CFCs and has amplified the need for new technology.

The lower solvency of the pharmaceutical HFC fluids, by comparison with their CFC predecessors, is not easily overcome; it is an even tougher technical hill to climb since the group of FDA acceptable solubility enhancing excipients is relatively small. So, with the advent of HFC propellants, recent attention has turned more and more to suspension MDIs.

In a suspension MDI, the drug is relatively insoluble in the propellant and hence drug particles are maintained as a slurry inside the can. While the drug substance itself is usually more chemically stable in the solid-state than in the dissolved-state, there are still quite complex dispersion and device related challenges in formulating a stable microcrystalline suspension MDI. In particular, for suspension MDIs, the interfacial chemistry of the suspended drug particles tends to be a dominating factor. Surfactants are required to disperse the particles in their biologically preferred aerodynamic size of 1–5 microns. In many instances, the surfactants that are permissible for inhalation drug formulation are better suited to the interfacial chemistry of CFC products, and there is a lengthy road to approval of new surfactants. Hence, the formulator's task is constrained to reformulations with the standard CFC MDI surfactants, and therefore has had to look for assistance in other technology. Some of this technology has come via new developments in aerosol valves and can coatings to cope with the challenges of metering small precise volumes of slurries, which are more prone to block the orifice of a metering valve and lead to poor dose uniformity. This article discusses a research program that DuPont began recently to assist pharmaceutical formulators with developing suspension MDIs based on HFCs. The concept of this research has been to better understand surfactant chemistry and combine that understanding with new processing techniques that could help provide stable dispersions of asthma medicaments in liquid HFC propellants.

INTEGRATING CHEMISTRY AND PROCESS

Recognizing a need for better understanding of the dispersion chemistry, and that HFC propellant technology alone would not provide a full solution to MDI reformulation issues, the DuPont Dymel[®] propellants group sponsored a research program with the DuPont Particle Science and Technology group. This research program seeks to tackle HFC reformulation challenges from two aspects:

1. Characterizing the surface interaction between the formulation components, and
2. Introducing process benefits by integrating chemistry with new milling techniques to improve HFC dispersions of MDI medicaments.



The ultimate goals are:

- To use a fundamental understanding, rather than a trial-and-error, reformulation approach
- Integrate formulation and process development, and
- Accomplish HFC performance equivalent to CFC performance in MDIs

Research has proceeded in two phases. The first phase evaluates chemistry of formulation components with various asthma medicaments. The second phase advances optimized formulations to processing in a high-pressure media mill.

PHASE 1: FORMULATION CHEMISTRY

In phase 1, experiments were conducted to understand interactions of the basic MDI formulation components:

- Drug active
- Surfactant
- Co-solvent
- Propellant

In doing so, each formulation component was characterized by certain physical properties judged to be important to the surface interactions.

The MDI medicaments were characterized by:

- $\log P_{OW}$ (octanol-water partition coefficient)
- density
- particle size
- surface energy
- morphology

The propellants were characterized by:

- density
- dielectric constant

The surfactants were characterized by:

- head/tail structure
- molecular weight
- chemistry

The following tables summarize characterization properties for the formulation components that were considered in the program.

**TABLE 1
PHYSICAL PROPERTIES FOR THE DRUG ACTIVES**

Drug Active	Log P _{ow}	MW	Density (g/cc)	Critical Surface Tension (mJ/m ²)	Particle Size (µm)
Budesonide	2.55	431	1.26	29	2.6
Albuterol (Salbutamol)	0.11	239	1.14	29	15
Albuterol Sulfate	1.83	409	1.31	36	11
Ipratropium Bromide	-	412	1.37	41	6

**TABLE 2
PHYSICAL PROPERTIES FOR THE PROPELLANTS**

		HFC 134a	HFC 227ea
Boiling Point	°C	-26.1	-15.6
Vapor Pressure @ 25°C	Bar	6.7	4.5
Liquid Density @ 25°C	g/cc	1.2	1.4
Dielectric Constant	-	9.5	4.1
Dipole Moment	D	2.1	0.9

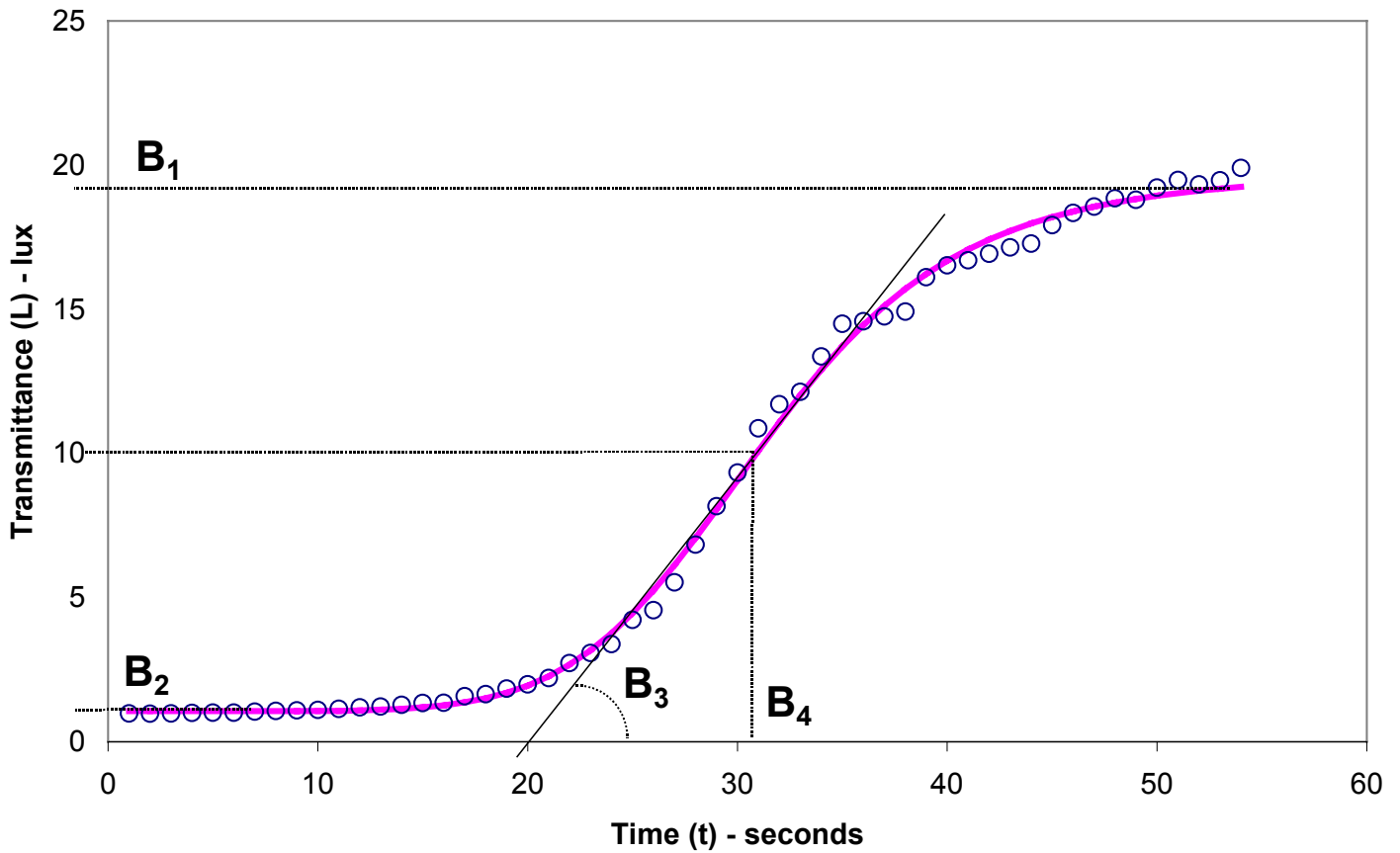
**TABLE 3
PHYSICO-CHEMICAL PROPERTIES FOR THE SURFACTANTS**

Head Group	Tail Group	Surfactant
Acidic	Aliphatic	Aerosol OT
EO	Fluorinated	Zonyl® FSO
EO	PPO	Pluronic® 25R4
Basic	Fluorinated	Zonyl® UR
Acidic	EO	
Basic	PPO	Propomeen T/12
Basic	PPO	Armeen 12D
Basic	EO	Ethomeen C/15
Acidic	Fluorinated	Zonyl® FSD
EO	Aliphatic	Neodol 25-7
EO	EO	

Using these characteristic properties, a matrix of test formulations was developed to evaluate different component combinations at different concentrations. The test formulations were prepared in glass aerosol bottles and evaluated for the optimum dispersion stability using two methods to allow rapid screening of a large number of samples.

The first method was a simple direct visual evaluation to qualitatively rate dispersion stability against a set of yes-no criteria. Promising formulations were then quantitatively evaluated using an internally developed method that measures light transmittance through the dispersion versus time. Measuring light transmittance versus time provides quantitative data that can be mathematically related to dispersion stability. Figure 1 illustrates an example of the data collected.

Figure 1 - Sample of Light Transmittance Data Set



The light transmittance data (L) versus time (t) from agitation is fitted to an equation (Equation 1), which can be used to design experiments that identify the optimum combinations for stable dispersions.

$$L = B_1 + \frac{B_2 - B_1}{1 + e^{B_3 * (\log t - \log B_4)}} \quad (\text{Equation 1})$$

Coefficients B_1 through B_4 describe parameters of the L versus t curve. B_2 describes the fully dispersed state immediately after shaking and B_1 describes the final equilibrated state after a long period of time. B_4 is the time for the L to reach halfway between B_1 and B_2 . And B_3 is the slope of the L versus t curve at B_4 .

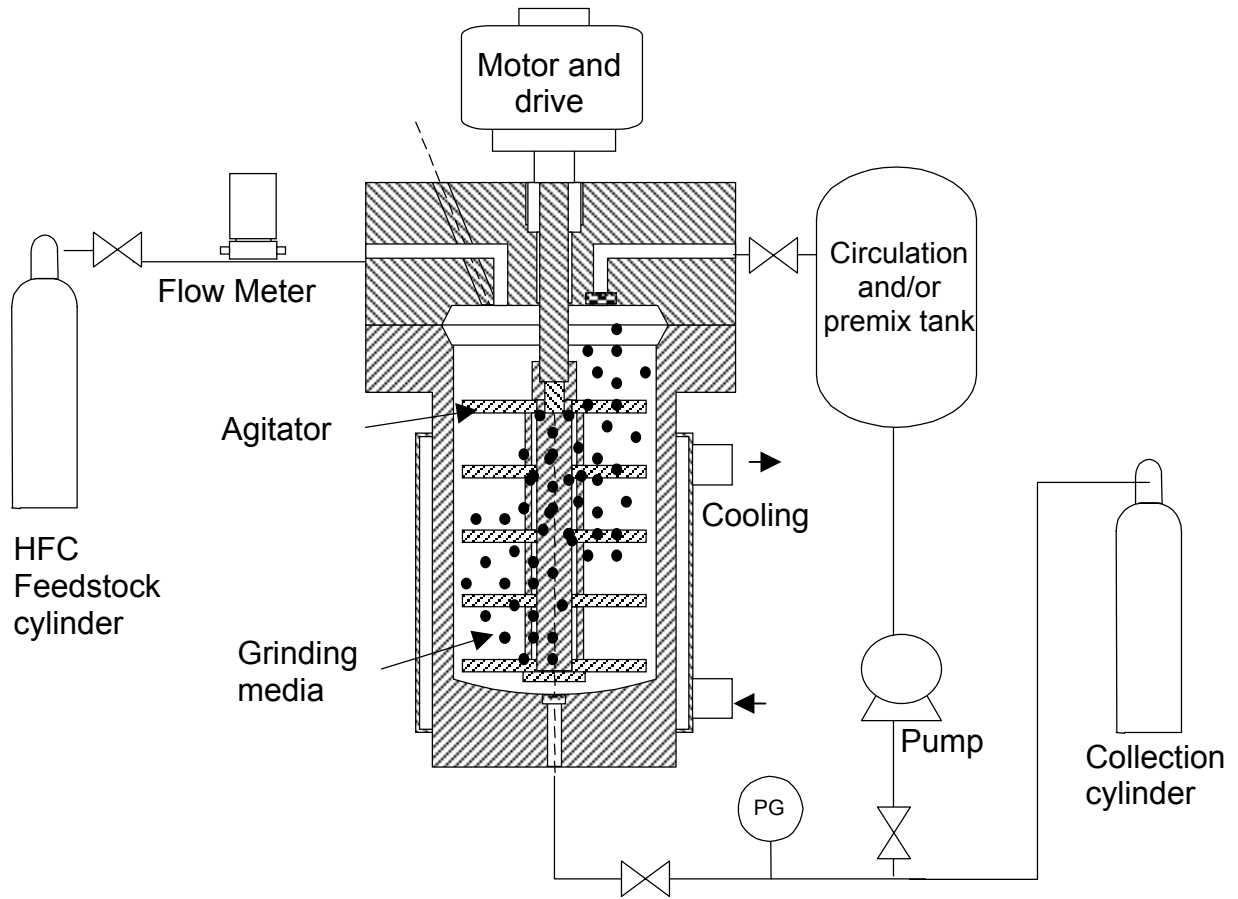
Using this relationship, experiments can be designed to identify formulations that exhibit optimum parameters for stable dispersions. In this way, a large number of combinations can be evaluated for the optimum chemistry. Optimum formulations identified in phase 1 are carried forward to phase 2, to evaluate impact of process.

PHASE 2: PROCESSING

Slurry media milling is an important unit operation in various industries for fine and ultra-fine grinding of materials, like minerals, paints, inks, pigments, food, agricultural products and pharmaceuticals. In these mills, the feed material particles are reduced in size between a large number of small grinding media that are usually sand, plastic, glass, steel, or ceramic beads. Internal agitation, coupled with very small grinding media and the liquid medium, produce sub-micron or nano-size particles.

The specific media milling processing developed for this research was designed to operate at high pressures, allowing preparation of dispersions using the propellant itself as the milling medium. This high-pressure media milling (HPMM) process yields stable, fine particle dispersion of medicament in liquid HFC propellant. The milling is performed with the entire MDI formulation so that surfactants and co-solvents are available to the drug actives during the milling process. "In-situ" milling is believed to increase dispersion stability because having the surfactant available during milling results in improved deposition or adsorption onto the surface of the medicament particles as they are milled.

Figure 2 - Schematic of the High Pressure Media Mill (HPMM)



A second advantage for HPMM process using HFC propellant as the medium is that, when milling is complete, it is the final formulation that is available. Conceptually, the batch in the mill can be filtered and directly packaged to the MDI container, offering a potential improvement in commercial processing productivity, cost and quality.

The HPMM process produces medicament dispersions in liquefied HFC propellant that are stable for long periods of time and that are easily re-suspended if they do settle. Figure 3 shows the light transmittance data from a prototype budesonide formulation optimized by the interaction studies and processed in the HPMM. Note that the formulation shows some slight initial flocculation, but equilibrates and remains stable for a long period of time. The photographs in Figures 4 and 5 show the prototype formulation with and without milling, demonstrating the impact of the HPMM process. Figure 5 is a milled prototype budesonide formulation undisturbed for about 2 weeks.

Figure 3 - Data for Milled Prototype Budesonide Formulation

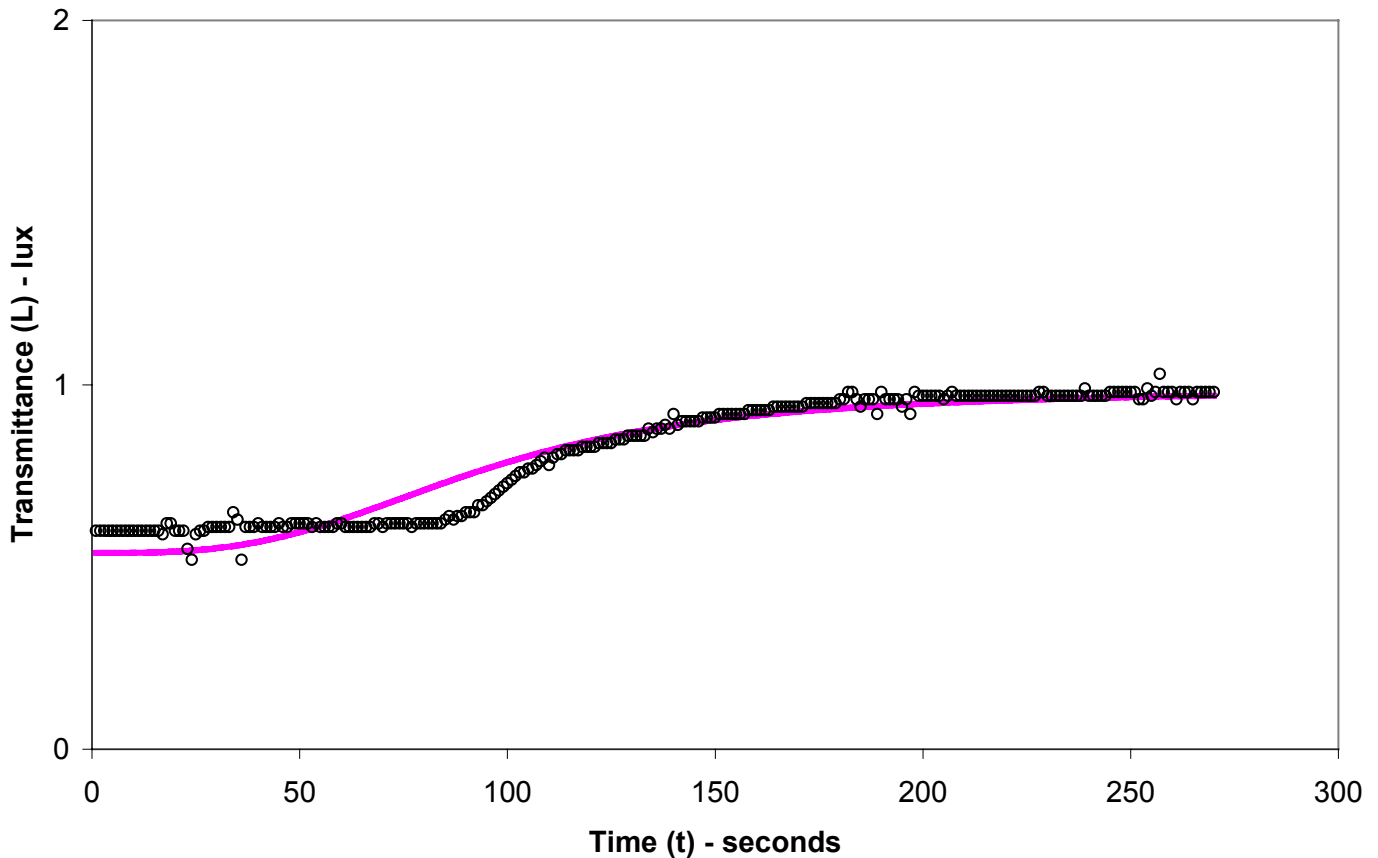


Figure 4 – Unmilled Budesonide Prototype Formulation after 30 minutes

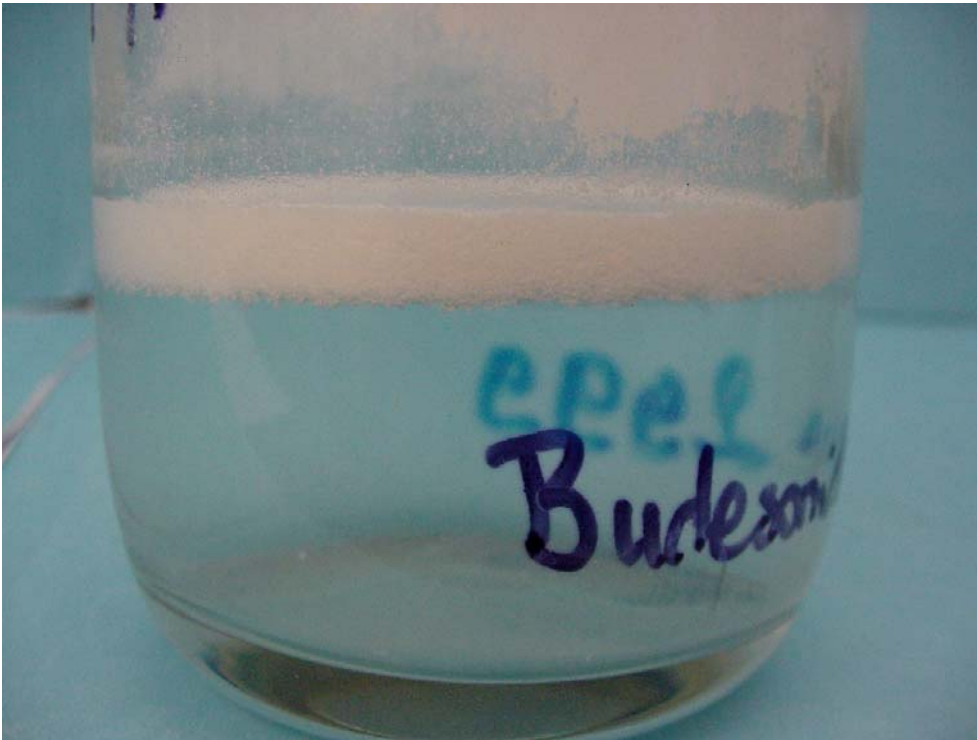


Figure 5 – Milled Budesonide Prototype Formulation Undisturbed for about 2 Weeks



SUMMARY

In recent years, much attention and research has been devoted to drug delivery via the lungs, which enable tremendous mass transfer from the gas phase to the blood stream. While oral dosage forms are typically preferred by patients, in many cases they lack efficient bioavailability – especially for newly discovered drugs that have very low solubility in water. Meanwhile, parenteral products (injectibles) are least preferred by patients, yet they deliver the highest bioavailability. Aerosol delivery of drugs via the lung can provide the benefits of both, without discomfort, efficiently delivering drugs that might otherwise be metabolized before reaching the intended treatment site. Research efforts, as those described above, continue to provide opportunities for new patient-friendly treatments using the pressurized MDI despite the additional challenges from non-medically related issues.

Optional Photographs

