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# Preface for Innovative Inhalation Technologies—Special Edition

Inhalational therapy is at the cutting edge of modern drug delivery research. Over the last decade, there have been advances in the understanding for both nasal and pulmonary inhalation therapies. A substantial level of patient acceptance and compliance has been obtained with the marketing of pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI) devices. However, problems associated with formulation and aerosolization have meant that some therapies cannot be delivered using these techniques. Watts et al. report on the resurgence in the investigation of aqueous droplet systems, which may enable a precisely metered dose of active pharmaceutical ingredient (API) to the peripheral lung. Aqueous nebulization systems include air-jet, ultrasonic and vibrating mesh designs; each has been incredibly useful in addressing therapeutic needs.

Spray devices as well as formulation design play an important role in the effectiveness of nasal drug delivery. The general requirement of a corticosteroid nasal spray is the incorporation of suspended lipophilic drug particles within an aqueous medium. Most effective nasal sprays then undergo a shear thinning process (as viscosity is reduced during the spray phase), under atomization followed by pseudoplastic properties (as the viscosity increases to allow effective dose delivery in the nasal cavity). Pennington et al. describe the use of Newtonian fluids to approximate the rheological properties at the high-shear conditions of a standard nasal spray pump. This approach leads to the development of another analytical tool which can be used to better describe the viscosities generated at actual spray nozzle conditions. An obvious advantage of this is a more efficient formulation development process, which may ultimately lead to more efficient nasal drug delivery from nasal spray devices.

One of the most challenging aspects of pMDI delivery in recent times has been the change from using chlorofluorocarbons (CFCs) propellants which have environmental concerns to the use of hydrofluoroalkane (HFA) 227 or 134a propellants. The issue of chemical compatibility of APIs with these propellants presents a challenge, and additionally many previously used excipients and solutes have been shown to behave differently with the HFAs. Mogalian et al. examine the effects of moderately increased pressure in HFAs on the energetics of melting of organic solids. The research is aimed as a tool for developing predictive models for solid solute solubilities in HFA propellants. The relationship between melting point of an organic solid and the ideal crystalline solubility at various pressures is defined. This relationship may be shown to have a bearing on the dose uniformity of a given regimen.

The Staccato system represents a novel delivery device. It is a breath-actuated inhaler that may incorporate a solid thin film of pure drug on an inert metal substrate. Upon actuation, this film of pure drug is rapidly vaporized, this has been shown to generate a condensation aerosol with a high purity. Simis et al. report a modification of this method to accommodate the use of drugs which may be liquid or low-melting point solids in their pure form. The authors report that nicotine may be physically stabilized by complexation with metal halides to form a thermally reversible solid drug complex. The Staccato drug delivery system demonstrates an innovative delivery technique which has potential application in a wide range of therapeutic areas. More novel formulation work in recent years has focused on the prospect of nanoparticle drug delivery to the lung. Nanoparticle delivery to the lung represents challenges, not least of which is the dispersion of the drug-loaded nanoparticles throughout the respiratory airways. Several groups have focused on this issue in recent years, and techniques involving carrier particles which have an appropriate particle size have been investigated. In a novel formulation design approach, Azarmi et al. describe a new inhalable effervescent carrier preparation containing model nanoparticles. The group explains how spray-freeze drying was used to prepare powders containing butylcyanoacrylate nanoparticles for inhalation. An in vivo study showed the feasibility of dose administration in mice, with a high degree of tolerance.

A common thread throughout this themed issue of *Drug Development and Industrial Pharmacy* (DDIP) is the concern of variability. As McConville et al. reports, variations of interpatient and intrapatient breathing may have a profound influence over drug deposition in the lung. A common goal for an effective method of drug delivery is to minimize the impact of this patient variability. The authors go on to describe an array of delivery devices and formulation options that are specifically aimed at maximizing the therapeutic potential of DPI delivery systems. A featured delivery system which represents advancement in drug delivery to the lungs is the Taifun® inhaler. This is a reservoir-based DPI originally developed to administer salbutamol for asthma therapy. Crowley et al. describe how fentanyl citrate particles may be separated from their larger lactose carrier particles by using the turbulent flow of air in the device upon patient actuation. This represents a non-invasive delivery option and alternative means of rapid pain management that might be useful in the treatment of breakthrough cancer pain. In a continuation on the theme of delivery device performance, Birchall et al. investigate a comparison between hypromellose and gelatin capsule puncture properties, used in

DPIs. The authors describe how they have developed a valuable tool to evaluate the shell properties of capsules that are used as dose units for many delivery devices.

It is universally accepted that pharmaceutical drug product components (i.e., API and excipients) show compliance with regulatory requirements such as the pharmacopoeia. Edge et al. point out that there is a distinct lack of compendial requirements for purity and functionality for excipients that are used in DPI formulations. This is an important consideration as there could easily be consequences for end-user product quality. Edge further indicates that advances in regulatory guidance means that pharmaceutical development, processes, and materials will come under greater scrutiny. This may be evidenced by the proposed introduction of a specific USP monograph for inhalation lactose, both anhydrous and monohydrate in Europe. The importance of processing parameters that may affect product functionality by changing physicochemical properties of the input material is also considered by Hooten et al. The authors describe the effect of crystallization parameters in determining the crystal habit of the unprocessed active ingredient. The cohesive–adhesive balance (CAB) approach to colloid probe atomic force microscopy (AFM) was employed to determine the cohesive and adhesive interactions of budesonide against itself and sugar substrates often used in DPI formulation design. Ren et al. also report the importance of processing parameters and formulation design on powder characteristics for the model drug ambroxol hydrochloride.

Young et al. indicate the importance of considering polymorphism of pharmaceutical drugs and excipients. This is highlighted as a long-term problem in the pharmaceutical industry with implications that extend to formulation and therapy. The relationship between surface energy, measured by inverse gas chromatography and aerosolization efficiency, is investigated in an attempt to address the fact that variation in polymorphism may significantly affect end-user drug products and in particular those with low-dose APIs. As indicated, the surface energy of DPI formulations plays an important role in the final aerosol dispersion performance. By investigating two lactose carrier systems comprising either spray-dried or milled particles, Saleem et al. investigated the ability of surface energy measurements and rates of mixing to predict aerosol dispersion performance. Such an understanding of particle–particle interactions would undoubtedly lead to an ability to predict and optimize DPI performance.

This special edition of DDIP entitled “Innovative Inhalation Technologies” takes us through many different aspects of cutting edge inhalation research. In designing new delivery devices, one must also be cognizant of formulation design. New and improved analytical methods will undoubtedly be needed given the ever changing world of regulatory compliance and stricter control of inhalation products.

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