Effect of Micromeritics Properties and Static Charge on the Performance of Dry Powder Inhaler
Kapileswar Swain1, Mahesh Giri1, Pranabkumar Patra1, Jairam Gosavi2

1D-4 Wockhardt research centre, Chikhalthana MIDC, Aurangabad
2 D.S.T.S Mandal’s college of pharmacy, Solapur

ABSTRACT
A drug product combines pharmacologic activity with pharmaceutical properties. Desirable performance characteristics are physical and chemical stability, ease of processing, accurate and reproducible delivery to the target organ, and availability at the site of action. For the dry powder inhaler (DPI), these goals can be met with a suitable powder formulation, an efficient metering system, and a carefully selected device. This review focuses on the Effect of micromeritic properties and static charge on the performance of Dry powder inhaler. Most DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways.

Key words: Dry powder inhaler, micromeritics, static charge

INTRODUCTION:
Dry powder inhalers are becoming more and more attractive since they possess many advantages over MDI and Nebulisers. Without use of propellant dispersion and entrainment of drug particles in DPIs are caused by the inhalation efforts of the patient alone. Thus DPIs are environmentally friendly and very easy to handle overcoming the problems associated with the required synchronization of actuation and inhalation often required to operate MDI successfully.

The main advantage of the inhalation route compared to other delivery methods is its fast onset of action. It can be used to deliver APIs to the target sites much faster than the oral route, which is the most common non-invasive delivery route. For example, short-acting bronchodilators such as albuterol start acting within minutes after inhalation. This advantage is of particular importance for the relief of asthma crisis where the fast effect of a drug can be vital. Conversely, orally administered Bronchodilators must pass through the digestive system to reach the intestines where they are absorbed into the bloodstream. As a result, the drug has its peak effect between 45 minutes and 90 minutes after absorption.

Treatment of lung diseases by inhalation also requires a lower amount of API than other delivery routes. Contrary to orally absorbed drugs; inhaled drugs avoid the first pass metabolism in the liver, which destroys small
molecules. Big molecules such as proteins are also destroyed by acid and enzymes in the gastrointestinal tract. Systemically delivered drugs are distributed through the entire circulatory system whereas inhaled drugs are administered directly to the site of action in the lungs. As a result, much greater doses of API must be delivered orally in order to obtain the same therapeutic effect as that of inhaled drug.

Advantages of DPI over MDI
1) Minimal extra–pulmonary loss of drug due to low Oropharyngeal deposition, low device retention and low exhaled loss.
2) Stability is more as compared to MDI as the formulation is present in dry state.
3) Breath actuated hence no hand-mouth coordination is required.

Principles of Operation
Most DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. The dispersion of a dry powder aerosol is conducted from a static powder bed. To generate the aerosol, the particles have to be moved. Movement can be brought about by several mechanisms. Passive inhalers employ the patient’s inspiratory flow. When the patient activates the DPI and inhales, airflow through the device creates shear and turbulence; air is introduced into the powder bed and the static powder blend is fluidized and enters the patient’s airways. There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared. Thus, deposition into the lungs is determined by the patient’s variable inspiratory airflow. Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPIs.

Objectives
The objectives of the study are as follows:
1. To investigate the effect of micromeritic properties on the performance of dry powder inhaler.
2. The micromeritic properties which are to be studied in this are particle size analysis
   - Particle morphology
   - Surface area
   - Surface energy
   - Static charge

Methods used for the evaluation of Micromeritics properties
1) Particle size analysis
   Particle size analysis is done by dry method by using the Malvern Mastersizer 2000. 1 gm of sample is added to the dry accessor and measured the particle size distribution. The particle size distribution is calculated and represented as a volume distribution, and also characterized by the 10th, 50th and 90th percentile of the cumulative particle undersize frequency distribution. Similarly the particle size analysis can also be done on the basis of wet dispersion method by the use of solvent provided the sample should not be soluble in it and it should get easily dispersed in it.

II) Particle morphology
   The surface appearance and shape of the Lactose and API particles were investigated by the Morphology by G3-ID. Morphology G3-ID integrates automated size/shape analysis of particles from 0.5μm – 10mm with chemical identify cation provided by Raman microscopy. Multiple shape parameters calculated for each particle and distributions generated on each parameter.
   Parameters include: Circle equivalent diameter, Length, Width, Perimeter, Area, Aspect ratio, Circularity, Convexity, Solidity, Elongation, and Intensity
III) Particle surface area
The surface areas of drug and carrier particle are determined by Nitrogen adsorption method with a single point BET (Brunner, Emmett, and Teller) method using Monosorb Surface area analyzer. The 1 gm of sample is taken and kept in Dewer cell, the pre adsorbed gas and vapors must first be removed from surface of a solid using a gas flow. Once the sample is out gassed the solid sample is cooled to boiling point of adsorbed gas until surface is covered by the gas. The liquid nitrogen Dewer is then removed from the sample cell and amount of previously adsorbed gas is measured by the detector.

IV) Surface energy
The inverse-gas chromatography is a technique for studying particulate or fibrous solids or films using the gas chromatographic principles. The IGC experiments are carried out using an IGC 2000 with a flame ionization detector. The lactose samples are packed into standard columns (30*0.3 cm) using a tapping machine. Columns are filled with 2-3 gm of material and then conditioned in-situ for hours at 30 degrees to remove the absorbed water. Measurements are performed with a range of Alkanes (Decane, nonane, octane and Heptane) and ethanol as a polar. Probe Injections are made in duplicate using a range of different vapor concentrations via a vapor sample loop with 0.25 ml volume at 30 degrees and 10 ml/min flow rate of Helium carrier gas.

V) Static charge on drug and carrier particles
The JCI Faraday pail is used for the determination of Static charge on drug and carrier particles. Before determination of Static charge the Faraday pail is cleaned with ethanol (95%) to remove any contaminants present on the surface of Faraday pail, then exactly 1 gm of material of which we have to determine the static charge is placed in the Faraday pail, the value of static charge which the API possess is denoted on the digital display.

Effect of Micromeritic properties in the performance of Dry powder inhaler
Effect of Particle size distribution on the performance of Dry powder inhaler
It is argued that each dry powder inhaler has a working range within this range it does its job a substantial part of dry powder inhalation research has been directed to the dilute systems i.e. formulations consisting of lactose carriers with very low percentages of drugs. In this range, the surface properties of carrier tend to dominate the behavior. The performance of dry powder inhaler depends mostly on the particle size of the carrier particle used during the formulation of dry powder inhaler.

It has been noted that, smaller carrier particles possess smoother surfaces relative to the larger carriers. It is then proposed that, most drugs are sheltered within asperities on larger carrier surfaces and are thus less susceptible to detachment by the flow stream. So, the fine particle fraction of the Dry powder inhaler gets increased when the particle size of the carrier particles decreased. Additionally the surface area of carrier particle gets decreased when the particle size of the carrier particle is increased and thus there will be less attachment in between the drug and carrier particles resulting in the decrease in the performance of the dry powder inhaler with increase in the particle size of the carrier particle.

Effect of Particle morphology on the performance of Dry powder inhaler
The particle morphology consist of following parameters
a) Particle shape
b) Particle smoothness
c) Nature of the particle

a) Particle shape
The performance of dry powder inhaler varies according to the particle shape, the carrier particles having pollen shape have more performance as compared to that of having circular shape, this occurs due to the pollen shape carrier particles have more surface area for drug carrier attachment as compared to carrier particles having the circular shape so more drug – carrier particle attachment leads to greater performance of the formulation which leads to increase in Fine particle fraction.

b) Particle smoothness
Particle surface smoothness is an important factor in determining particulate interaction either via cohesion or via adhesion. A drug particle will have a higher contact area if it is adhered to uniform flat surface however if the surface contains indentations or gaps the drug particle will have a lower contact area due to the increased void spaces. This affects how strongly the drug particle adheres to the surface of carrier particle. A minimum level of adherence is desired to enable drug particle to be removed from the carrier particle during respiratory deposition. Most commercially available carrier particles have undergone processing such as the mechanical milling. During mixing some drug particles are likely to be entrapped within these surface asperities. The portion of drug particles entrapped into the carrier surface asperities is
likely to become detached from the carrier particles under normal inhalation conditions since they may adhere to carrier particles via mechanical interlocking. The more asperities the particle surface has the more drug particles are likely to be entrapped and the few drug may be detached from the carrier particle, resulting in decrease in Fine particle fraction of the Drug. For carriers with minimal surface roughness, the drug is readily exposed to the flow stream and detachment by flow is the dominant mechanism with increasing carrier surface roughness and drug detachment is more reliant on mechanical forces. Hence the carrier particles, which are to be used, should have less roughness, as it requires more efforts to detach the particles from carrier surface.

c) Nature of the particle
The performance of dry powder inhaler depends on the nature of carrier particle used during the preparation of Dry powder inhalation i.e. (Crystalline, Amorphous, Spray-dried.) The crystalline particles have more numbers of sites of attachment and have less adhesive forces of interaction as compared to that of amorphous particles, so the drug detachment will be much rapid from carrier particles having crystalline surface as compared to that of particles, which are amorphous, or spray dried. The amorphous carrier surface have more surface energy than the crystalline particles hence there will be more adhesive forces of interaction in between drug and carrier particles which results in the decrease in fine particle fraction of the drug. The respirable fraction obtained from spray dried carrier particles is less as compared to that of micronized particles. The reduction in flowability and respirable fraction of the spray dried drug particles may be partly due to the stronger interparticulate forces brought about as a result of greater deformation at contact sites due to hollow and amorphous nature of Spray-dried particles. Moreover the amorphous content will render spray-dried particles more sensitive to the changes in RH of surrounding atmosphere than the micronized particles.

Effect of Surface area on the performance of dry powder inhaler
The surface area of a solid material provides the information about the void spaces or surfaces of individual particles or aggregates of particles. The addition of fine particles in the dry powder inhalation formulation causes the increase in surface area and the carrier surface due to surface roughness enhancements provided carrier fines exhibit another size, shape, surface, energetic charge than that of drug particles.

Effect of Surface energy on the performance of dry powder inhaler
The increase in surface energy has negative impact on the performance of dry powder inhaler. The increase in surface energy causes increase in the adhesive forces between drug and the carrier particles which leads to increased forces of adhesion between the drug and carrier particles which causes increase in the tensile strength of drug-carrier particle complex and result in the increased inertial properties of the drug-carrier complex, due to this increase in inertia, the resistance of drug particle to detach from the carrier particle gets increased and Fine particle fraction of it gets decreased.

Effect of Static charge on the performance of dry powder inhaler
The increase in surface area of the micronized particles offers greater opportunity to develop charges .The electrical charges developed on the particle play a key role in the increase in adhesive property as well as increase in the deposition of drug particle. Fraser showed that Deposition of particles (0.4-3.5 micron size range) in the respiratory systems was significantly increased as the particles were charged.

Effect of micromeritics properties on the stability of dry powder inhaler
The micromeric properties play a key role on the stability of dry powder inhalation formulation. The micromeric properties explained above have an impact on the stability of DPI formulation. The increase in the surface area, surface energy, and static charge causes increase in the rate of aggregation as well as rate of degradation due to increase in the absorption of moisture because of increase in surface area.

CONCLUSION
Interest in DPIs has increased in the last decade due to its numerous advantages over other pulmonary drug delivery dosage forms. Currently, the inhalation performances of DPIs are being improved by changing formulation strategy, drug and carrier particle engineering. Regarding formulation development, micronized drug particles are cohesive with poor flow properties. Addition of large carrier particles into powders to enhance their flow characteristics has been an appropriate approach. The main goal in
the inhalation field is to obtain reproducible, high pulmonary deposition, which can be highly effected by physico chemical characteristics of carrier. This could be achieved by successful carrier selection and careful process optimization. Technologies for engineering carrier particle shape, density, size and static charge will continue to develop to enhance the effectiveness of pulmonary drug formulations. This approach may enable more drugs to be delivered through this route for local treatment of lung diseases or systemic therapy.

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