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Development of a Dry Powder Multi-dose Inhaler using Computational Modeling

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Abstract: This paper is based on developing a new reusable multi-dose dry powder inhaler at low cost since available multi-dose inhalers are not affordable to poor. Low cost is achieved by making the inhaler reusable. Layer separation method of the blister strip was used in the new model. It is capable of holding a blister strip, having a maximum of 60 doses. Therefore the patient is able to use it at least a month before reloading. Initial geometry of the inhalation air chamber was modeled by considering the simplicity of construction. Commercially available 3D software tool named Pro/E was used to create the virtual geometrical model. Computational fluid dynamic software tool named Star/CD was used for the numerical analysis. Analyses were carried out for varying inlet diameters and outlet diameters for the inhalation air chamber at volume flow rate (60L/min). Velocity, pressure and particle track distributions were studied. Optimum values for each dimension were obtained. Other dimensions were kept constant while changing one parameter. Device resistance to the air flow through the inhaler was considered as a key factor for the inhaler model.

1 Introduction

Asthma is a chronic disease that makes it difficult to breath. It is the most common respiratory disorder encountered in clinical practice. Worldwide, according to the WHO estimation, more than 300 million people are affected by asthma. The prevalence rates of asthma have shown a progressive and a significant increase over the past few decades. According to the symposium on bronchial asthma Nov. 2002, more than 1 million people are affected by asthma in Sri Lanka while the recorded annual asthma admissions (leading cause for admissions) and the asthma deaths in the government hospitals have shown a steady increase over the past decade with the figures for 2002 being 176,206 and 800 respectively [1].

Asthma can be controlled with treatment, even though there is no permanent cure for it. Inhalation has become the most used method of therapy of asthma. Drugs are administered by inhalation for two reasons, to increase the desired clinical effect of the drug by direct application where that effect is needed and to reduce undesired side effects [2].

An inhaler is a device for administering vapor or volatilized medication by inhalation. There are two major configurations; single-dose inhalers in which the drug has to be loaded each time, and the multi-dose inhalers that could be used several times without loading and which are more practically suitable, especially when the patient is having a severe asthmatic attack and immediate drug administration is required. At present all the multi-dose inhalers locally available are imported, hence expensive. This research study is focused on developing a multi-dose inhaler to make it available for all patients at reduced cost.

2 Types of Inhalers

There are three types of inhalers available:

2.1 Metered Dose Inhalers (MDI

Metered dose inhalers contain medication in aerosol form. MDI consists of a canister of medication and an actuator with a mouthpiece. The actuator is the outer shell in which the canister sits. In the canister, medication is suspended in a mixture of a liquid propellant gas and preservatives [3]. It contains chlorofluorocarbons (CFCs) as a propellant. With the implementation

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of the 1987 Montreal Protocol and phasing out of CFCs, newer CFC-free inhaler devices using ozone-friendly hydrofluoroalkanes (HFAs) have been developed.

2.2 Nebulizers

A nebulizer is used to deliver aerosol medication rapidly to the lungs. This device is commonly used in an emergency room setting, is basically a simple system that allows rapidly flowing air or oxygen be bubbled through a solution containing the drug. The system produces a vapor that the patient inhales. They differ in terms of the size of mist particles they produce. It does not require the coordination between hand and breathing necessary for MDI use. The prime advantages of the nebulizers are their simplicity, easy generation of relatively small droplets and delivery of high dosage. However they are not historically portable devices, expensive and require more maintenance and cleaning than others. There is a greater risk of contamination with nebulizers and patients must follow a proper cleaning routine. The greater quantity of drug delivered by the nebulizer method may also result in greater side effects such as tremors, rapid heartbeat, muscle cramps, nervousness,... etc than others [3].

2.3 Dry powder inhalers (DPI)

In DPIs the drug is contained in a powder form. Upon actuation, a measured dose is entrained in the air stream and subsequently inhaled. DPIs are increasingly used for aerosol delivery to the airways for the reasons that they are easy-to-use with no requirements of co-ordination. They are convenient and are without propellants or irritants. In all DPIs the inspiratory airflow of a patient provides the energy source to disperse the agglomerates of micronized powder and to move the respirable particles from the body of the inhaler to the lung. The drug is drawn from a holding bin of pure drug, or is available as drug particles mixed in a bulking agent such as lactose, which helps dispersion. Drug is entrained by the patient's inspiratory effort.

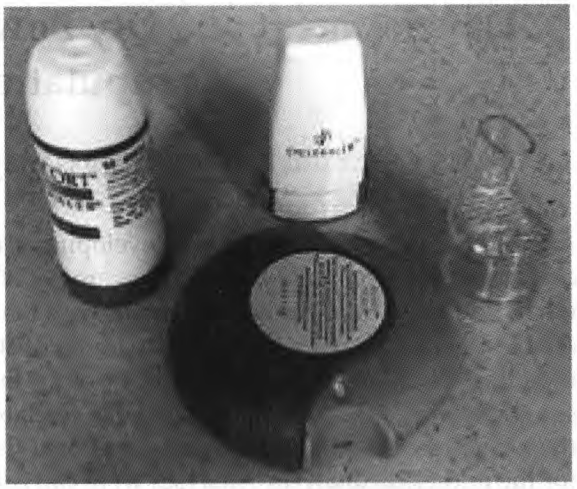

Figure 1 - Locally available Dry Powder Inhalers

There are two types of DPIs,

2.3.1 Single dose dry powder inhalers

Drug is inserted into a capsule. The patient should load the capsule into a chamber where there is a suitable mechanism to get the drug out. Then the inhaler is ready to inhale. After inhaling, the patient has to remove the residue and load a capsule again. The patient should carry the inhaler together with capsules wherever he goes.

2.3.2 Multi-dose dry powder inhalers

The blisters, which carry the drugs inside, are inserted into the inhaler. This allows patients to use the inhaler several times without loading the drugs. These are suitable for the patients who find it difficult to load drugs (children, elders) and also appropriate when the immediate drug administration is required. It is safer than that of the single dose inhalers since no hand coordination with loading the drugs is involved. All commercially available multi-dose inhalers are disposable.

3 Physical Design Considerations of Inhalers

All currently marketed DPIs are passive devices in which the energy for powder fluidization and aerosolization is derived from the patient's inspiratory effort. They should deliver the maximum possible proportion of the active particles expelled to the lungs, including a significant proportion to the lower lungs, preferably at low inhalation efforts.

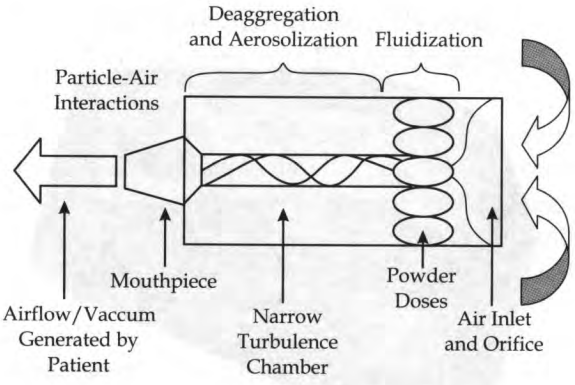

Figure 2 - Schematic of the basic components leading to aerosolization in a passive dry powder inhaler

Most important parameters in design of an inhaler are flow rate and device resistance. Increasing airflow increases drug dispersion because it increases the drag forces of the fluid acting on the particle located in the flow. Increasing inhalation flow rates usually increases the de-aggregation of the formulation, resulting in an improved fraction of small particles. Increasing the flow rates would improve particle detachment from device components, producing a higher emitted dose [4]. However, increase in flow rate will increase particles deposition by impaction, especially in the upper airways. Furthermore, increasing flow rates should enhance the turbulence of the air stream, mainly in the upper air ways, resulting in a greater contact of particles with the air way walls, thereby increasing the deposition in these regions. Increasing the air flow will also reduce the residence time of airborne particles in the respiratory tract and thereby reduce the deposition of particles by sedimentation and diffusion mechanisms in the lower air ways. Therefore, slow inhalation is desirable to obtain improved deposition of particles in the lower air ways.

Device resistances through dry powder inhalers are relatively high compared to nebulizers and metered dose inhalers. This is a result of the design, which has elements of flow constriction to increase the kinetic energy of the air flow through the inhaler. Device resistance together with the pressure drop determines the volume flow rate through the inhaler. Increasing the device resistance increases the turbulence of the air stream. Higher turbulence creates better dispersion and de-aggregation of the drug particles. An increased device resistance would require a higher inspiratory effort by the patient in order to achieve a suitable air flow rate. Increase in inspiratory effort makes difficulties in achieving necessary flow rates for the patients especially for the children and old people. Therefore an ideal inhaler would be one that generates sufficient turbulence at a lowest possible device resistance. The relationship between flow rate and pressure drop across the inhaler is given by the empirical equation

$$\Delta P^{0.5} = Q \times RD \quad \text{..... (1)}$$

Where, ΔP = pressure drop across the inhaler

Q = volume flow rate through the inhaler

R_D = Device resistance

Clark and Hollingworth (1993) noticed that resistances higher than 0.032 kPa0.5min.l-1are uncomfortable for healthy volunteers [5].

4. Cascade Impactor Testing

An important characteristic of pulmonary drug products is the aerodynamic particle size distribution (PSD) which is generated by the patient during inhalation. The cascade impactor is a complex instrument, which fractionates the dose delivered from the device into size classes that can be collected and quantified separately, so that the aerodynamic particle size distribution can be assessed.

Inhaler is attached to the apparatus by using a suitable mouthpiece in cascade testing. Air flow through the inhaler is created from the vacuum pump. Volume flow rate can be varied by using a valve and can be measured by a digital flow meter. Testing is done by keeping the constant volume flow rate through the inhaler for specified time interval which is calculated by considering the amount of air volume a patient can inhale.

5. Computational Fluid Dynamics (CFD)

Computational Fluid Dynamics has become an integral part of the engineering design and analysis environment of many companies who require the ability to predict the performance of new designs or processes before they are manufactured or implemented. CFD software can be used to analyze and optimize powder entrainment, powder dispersion, and powder delivery [6]. CFD can also be used to analyze the throat deposition patterns for specific inhaler

designs. CFD codes are structured around the numerical algorithms that can tackle fluid flow problems. In order to provide easy access to their solving power, all commercial CFD packages include sophisticated user interfaces to input problem parameters and to examine the results. In this research study, CFD was used to analyze the air flow through the new dry powder multi dose inhaler.

6. Geometrical Modeling of New Multi-Dose Inhaler

Parametric feature based 3D modeling software tool named Pro-Engineer was used to model the geometry. This tool not only unites the 3D parametric features with 2D tools but also addresses every design through manufacturing process. It is a powerful program used to create complex designs with a great precision. The design intent of any 3D model or an assembly is defined by its specification and its use. To make the designing process simple and quick, this software package has divided the steps of designing into different modules. Generally the design process consists of the following steps: [7]

- Sketching using sketch mode
- Converting the sketch into features and parts in part mode
- Assembling different parts and analyzing them in assembly mode
- Documentation of the parts and the assembly in terms of drawing views in drawing mode
- Manufacturing the final parts and assembly in manufacturing mode

The inhaler was modeled using layer separation method. Blister pack consists of two layers bonding together, carrying doses in between them. Cavities are formed in one layer to insert doses. Second layer is bonded over the first layer. A dose can be loaded to the air chamber by separating two layers. This model consists of many components namely inside pack, Mouthpiece, Rotor, Upper and Lower Covers and Gears. All the components were modeled in part mode. Then they were assembled together in assembly mode. Fully assembled and exploded views are shown in figures 3 and 4.

Figure 3 - Assembled Geometrical Model of the Third Multi-Dose Inhaler

Figure 4 - Exploded View of Assembled Model

7. Air Flow Simulation through Computational Fluid Analysis

Geometrical model which was virtually assembled together in the Pro-Engineer software package was used to simulate air flow through inhalation air chamber by computational fluid dynamic (CFD) software tool named Star-CD. It was expected to achieve best possible values for the inlet size and the outlet size by CFD analysis. Initial shape of the air chamber was geometrically modeled by considering simplicity and ease in manufacturing. Boundaries of the air chamber consist of inside pack wall, upper cover wall, mouth piece hole and two layers of the blister strip.

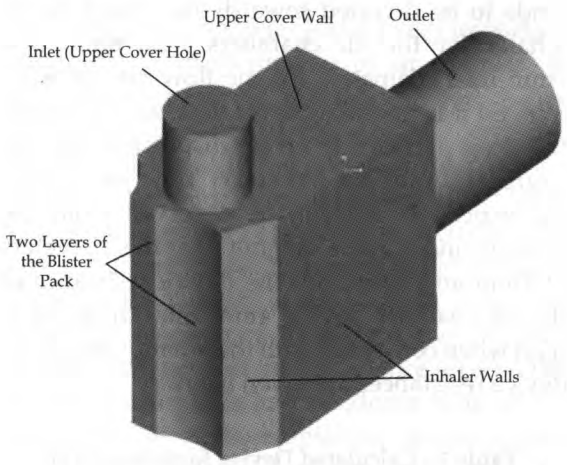

Figure 5 - Initial Air Chamber of the New Model

First step of CFD analysis was converting 3D model into IGES format. IGES data should be first processed via pro-surf before being imported into pro-amm which stands for pro-star auto mesh module. Then the pro-surf module in starCD was run in order to convert data stored in IGES format into surface mesh. Finally the surface grid data was saved in a database file. Then the file saved as a dbs format in the pro-surf module was imported into pro-amm module in order to generate volume mesh of the air chamber. Hybrid type mesh was selected. The hybrid mesh produces a high quality, fully automatic, versatile grid. The bulk of the inner domain volume is composed of hexahedral cells while surrounding is a layer of pyramid cells that form a transition into the tetrahedral cells on the outside. Rest of the analysis part was done in the pro-star module. Suitable fluid properties, boundary conditions and solution control parameters were applied within this module.

In the new design drug is concentrated at the opposite wall to the inlet. Inlet is a hole created on the upper cover. So the first target was to determine the necessary inlet diameter to create a flow jet to strike where the drug particles are concentrated. Smaller inlet diameters may produce high velocities hence required flow jet. But it may also require high pressure drop to create necessary volume flow rate through the inhaler. That creates high device resistance through the inhalers.

CFD analyses were carried out for different inlet diameters for the inhalation air chamber at volume flow rate of 60L/min. This flow rate was selected as this is the moderate volume flow rate that the patients achieve and the mostly used for inhaler testing. Pressure boundary was selected at the inlet. Atmospheric pressure was assumed at the inlet. Uniform inlet and outlet velocities, incompressible flow and constant volume flow rate were assumed. Corresponding mass flow rate was specified at the outflow boundary. A no-slip condition was assigned to all walls. Air chambers with inlet diameters of 4mm, 5mm, 6mm and 7mm were used. A diameter less than 4mm is too small for the chamber since only single inlet is used. 7mm diameter is the maximum value that can be set according to the width of the chamber.

Reynolds number was calculated based on the inlet diameter of the inhalation air chamber. Due to the higher Reynolds numbers calculated the flow was assumed turbulent. Therefore, to account for the turbulence level generated and the associated effect on the flow, it is necessary to employ a turbulence model. One of the most widely used concepts in the present day turbulence models for practical engineering applications is the "eddy viscosity" [8]. Under this concept two equation k-e model which was used in this study is the most popular for scientific and engineering calculations since its simplicity and the computational efficiency [9]. 5% turbulent intensity and the one order of magnitude less than inlet diameter for mixing length were selected at the inlet.

8. Results

8.1 Vector plots of the velocity distributions through the inhaler with different inlet diameters at flow rate of 60 L/min are shown below.

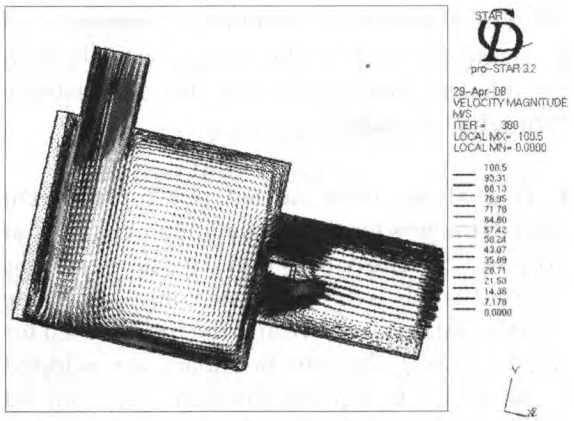

Figure 6 - Velocity distribution of 4mm inlet at an outflow rate of 60L/min

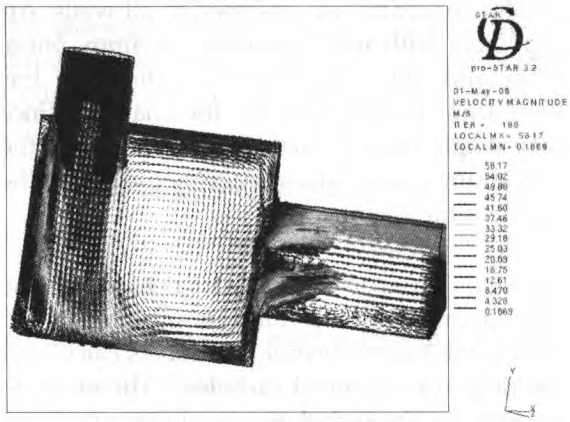

Figure 7 - Velocity distribution of 5mm inlet at an outflow rate of 60L/min

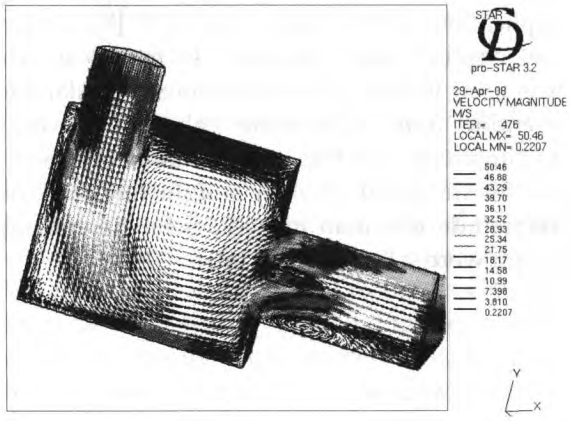

Figure 8 - Velocity distribution of 6mm inlet at an outflow rate of 60L/min

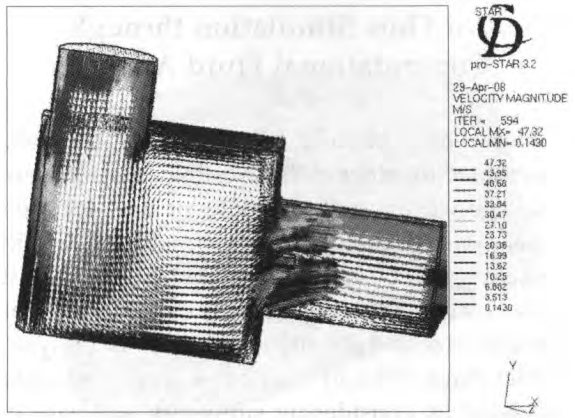

Figure 9 - Velocity distribution of 7mm inlet at an outflow rate of 60L/min

As seen in the velocity diagrams above, flow tends to be diverted towards the outlet of the inhaler for the air chambers with 6mm and 7mm inlet diameters for the flow rate of 60L/min. So it is possible the air flow will not reach the drug particles to create dispersion and de-aggregation inside. Necessary flow jet striking the expected area can be observed from the velocity and particle diagrams for the diameters of 4mm and 5mm. But the device resistance of the air chamber having 4mm inlet diameter is high when compared with the others. Calculated device resistances are given below.

Table 1 - Calculated Device Resistances for Different Inlet Diameters for 60L/min

Q=60 L/min		
Inlet Diameter (mm)	Pressure Drop (KPa)	Device Resistance ($KPa^{0.5}L^{-1}min$)
4	6.9	0.04378
5	3.3	0.03028
6	2.5	0.02635
7	2.1	0.02415

Low device resistance was calculated for the air chamber with 5mm inlet when compared with the 4mm. Therefore inhalation air chamber with 5mm inlet diameter was selected. Flow will not reach at the sharp corners smoothly as clearly seen at the lower right edge of the air chamber for every velocity diagram shown above. So there is a possibility for the drug to be trapped at that corner, preventing it from being inhaled.

Therefore some modifications were done to the inhalation air chamber. Modified chamber with 5mm inlet 8mm outlet is shown below.

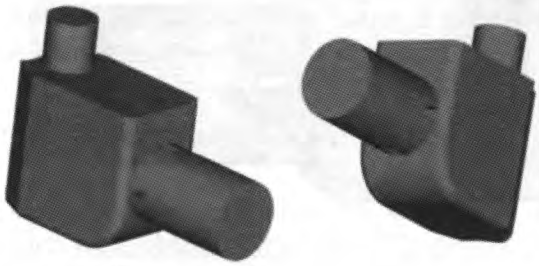

Figure 10 - Geometrical Model of Modified Inhalation Chamber

Size of the outlet diameter is also a very important factor of the performance of an inhaler. It controls the patient's inhalation effort hence the device resistance of the inhaler. Increasing diameter of the outlet would ease the patient's effort to produce the sufficient flow rates through the inhaler. Therefore it decreases the device resistance. Also increasing outlet diameter decreases the velocity of the drug particles that enters the respiratory tract from the patient's mouth. That controls the turbulence level of the air flow inside tract and residence time of the drug particles at the respiratory system hence controls the deposition of the particles at the respiratory tract.

But increasing the diameter of the outlet should be limited so that the patient has no difficulties on holding the mouth piece of the inhaler. Larger diameter of the outlet also influences the size of the mouthpiece. It controls the overall size of the final product. An inhaler should be small enough to be carried easily by the patient. CFD analysis was carried out for modified air chamber with different outlet diameters. Diameters of 7mm, 8mm, 9mm and 10mm were used with same conditions applied earlier. Velocity, pressure and particle tracks were obtained for the flow Rate of 60L/min.

8.2 Velocity diagrams and the particle tracks for the inhalation air chamber with different outlet diameters for the volume flow rate of 60L/min are given below

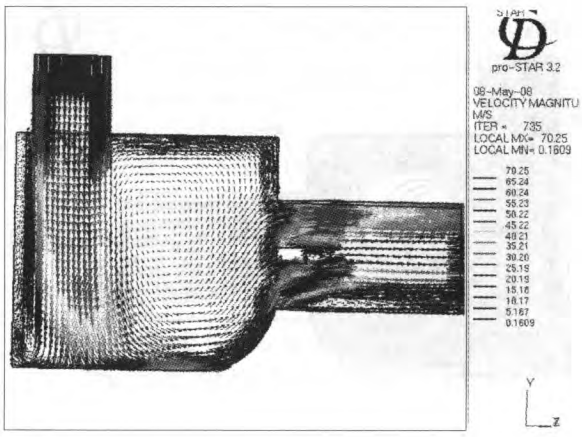

Figure 11 - Velocity Distribution for Outlet Diameter of 7mm

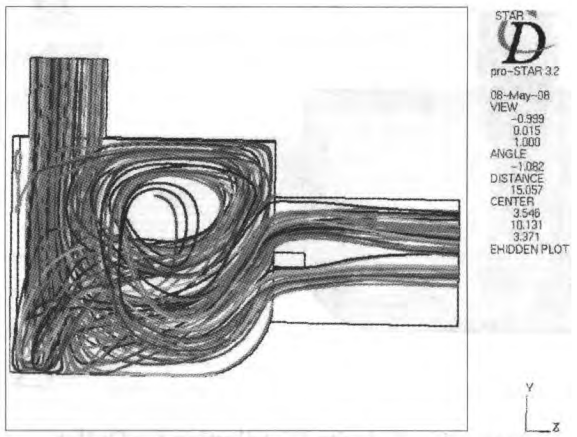

Figure 12 - Particle Tracks of the Outlet Diameter of 7mm

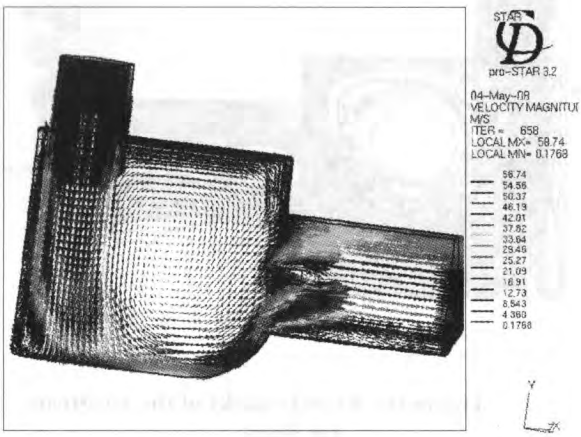

Figure 13 - Velocity Distribution for Outlet Diameter of 8mm

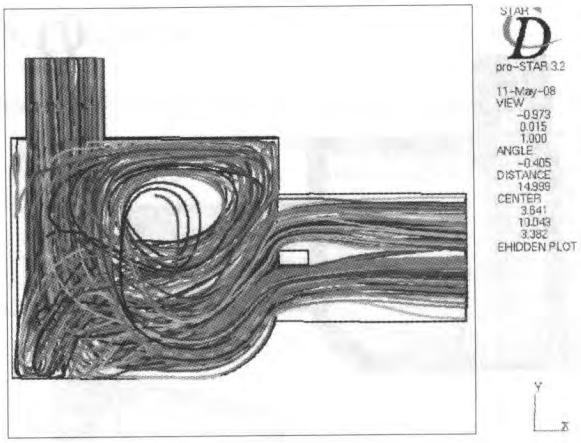

Figure 14 - Particle tracks of the air stream for 8mm

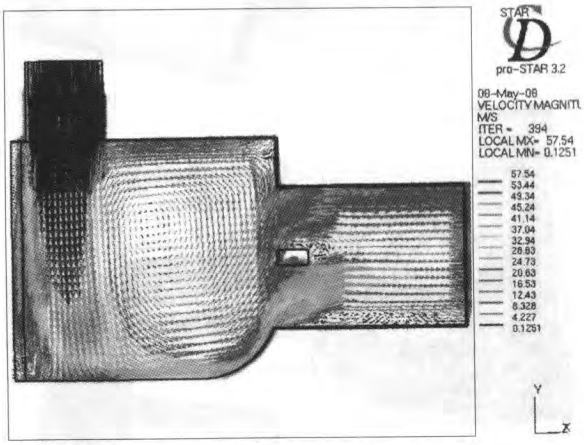

Figure 15 - Velocity Distribution for Outlet Diameter of 9mm

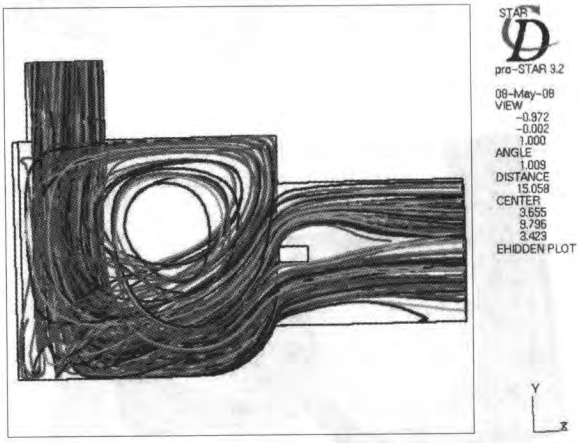

Figure 16 - Particle tracks of the air stream for 9mm.

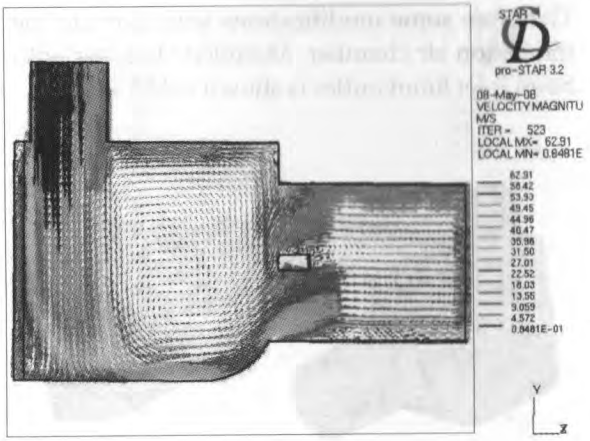

Figure 17 - Velocity Distribution for Outlet Diameter of 10mm

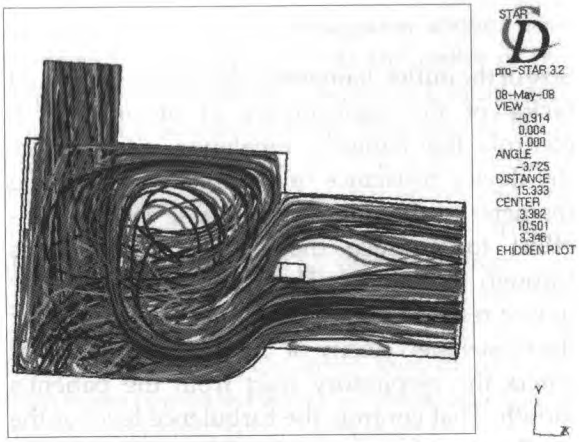

Figure 18 - Particle tracks of the air stream for 10mm

Table 2 - Calculated device resistances for Inhalation Chamber with Different Outlet Diameter for the Flow Rate of 60L/min

Outlet Diameter (mm)	Pressure Drop (KPa)	Device Resistance ($KPa^{.5}L^{-1}min$)
7	4.7	0.03613
8	3.6	0.03162
9	2.9	0.02838
10	2.8	0.02789

According to the above figures of particle tracks and velocity diagrams, higher turbulence can be observed inside the air chamber with 10mm outlet which is shown in the figure 18. Increasing the turbulence of the air stream enhance the dispersion and de-aggregation of aerosol dry powders. There are some areas that the streamlines don't exist in other three diagrams as

does in the 10mm chamber. Less particle tracks were created at the area where the drug particles are more likely to concentrate in the 9mm outlet chamber in figure 16. It was observed the device resistance of the 10mm chamber is lower with respect to the others. So the 10mm is better for the diameter for outlet of the inhaler.

9. Conclusion and Future works

Velocity, pressure and particle track distributions which were obtained from the CFD results for the inlet diameters of 4, 5, 6 and 7mm, were studied. Pressure drop vary from 4mm to 5mm. Necessary flow jet striking the expected area where the drug concentration is considered high, can be observed from the velocity and particle diagrams for the diameters of 4mm and 5mm. Low device resistance was calculated for the 5mm chamber compared with the 4mm. Therefore inlet diameter having 5mm was considered as the most favorable value.

CFD was carried out for outlet diameters of 7, 8, 9 and 10mm. Inlet diameter and the length of the outlet were kept constant. Pressure drop decreased (the device resistance) from 7 to 10mm. Therefore lowest device resistance was estimated in 10mm inhalation chamber. Also higher turbulence was observed inside the air chamber with 10mm outlet. Consequently outlet diameter of 10mm was selected.

Prototype of the new multi dose dry powder inhaler is to be constructed and be tested in the cascade impactor.

References

1. Annual Health Bulletin 2002, *Department of Health Services*

2. Christopher Marriot Xian Ming Zeng, Grey P. Martin. *Particulate Interactions in Dry Powder Formulations for Inhalation*, January 2001

3. Fracis V. Adams, M.D. *The Asthma Sourcebook.* 2004

4. Hindle, M. and Byron, P.R., *Dose Emissions from Marketed Dry Powder Inhalers, Int.J Pharmocol, 1995.*

5. Clark, A.R., Hollingworth, A.M., 1993. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers - implications for in vitro testing. *J. Aerosol Med. 6, 99-110.*

6. http://www.esi-group.com, Visited, 13th October 2006.

7. Prof. Sham Tickoo, Perdue University Calumet, Pro/*ENGINEER for Engineers & Designers*

8. Biswas G., Eswaran V., 2002. *Turbulent Flows:Fundamentals, Experiments and Modeling, 327.*

9. Reynolds, W.C. 1976. 'Computation of turbulent flows', *Ann. Rev. Fluid Mech.*, 8, pp. 183-208