Characterisation of medicinal aerosols

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Four commercially available medicinal aerosol products in India have been assessed for the aerosol size distribution at two different humidities using a ten stage cascade impactor device having a quartz crystal microbalance system. An indigenously made nebulizer in use in a city hospital has also been assessed for its aerosol efficiency. The size range is between 0.05 and 25 μm. Mode in the aerosol mass size distribution is between 0.4 and 1.6 μm at 30% relative humidity (RH) and between 0.4 and 3.2 μm at 85% RH for three inhalers: the mode for powder inhaler is between 3.2 and 6.4 μm at 30% RH and 2.5 μm at 85% RH. The mode for indigenous nebulizer is between 0.05 and 0.1 μm. These results are discussed in the context of the deposition of aerosols in the human respiratory system.

Recently, medication through the respiratory tract in selected diseases has gained considerable popularity due to factors such as easy application, lack of side effects, economic and efficient use of the medicine and better response. The medicine is introduced into the respiratory system as an aerosol by the use of a nebulizer or utilizing medicinal aerosol packages consisting of medicine mixed with a propellant gas and provided with a control valve for dose inhalation to a fixed quantity of aerosolised medicine. Different aspects of the use of pharmaceutical aerosols are being studied in various laboratories all over the world of understand and improve its performance.

For the effective treatment of respiratory tract ailments, it is essential to learn the mechanism and the degree of aerosol penetration in lungs and their absorption. Data on size distribution and concentration of medicinal aerosol are scarce and classified; the commercially available medicinal aerosol products need to be characterised to enable an estimation of the site and efficiency of deposition in the respiratory system. A few of the common medicines in aerosol form frequently used by physicians in India have been analysed for their particle size distribution.

Deposition in Respiratory Tract

On the basis of the structure, air flow pattern, function and sensitivity to depositing particles, the respiratory tract has been divided into different regions, i.e., Nasopharyngeal (NP), Tracheobronchial (TB) and Pulmonary (P), for modelling of deposition and clearance of airborne particles. In a recent model, the NP region has been extended to oral passage and it is called as Ex-trathoracic (ET) region. The TB region is divided into bronchi (BB) and bronchioles (bb) regions and gas-exchange region is called as alveolar interstitial (AI). The deposition of the particles in respiratory tract takes place by impaction, sedimentation and diffusion. The impaction is the primary mechanism of deposition in the large airways, sedimentation is the most efficient mechanism in the smaller airways and the alveolar region, where air velocity is low and airways dimensions are small. Diffusional deposition is the predominant mechanism for particles smaller than 0.5 μm in diameter and is governed by geometrical rather than aerodynamic size.

The deposition of inhaled particles also depends upon breathing rate, inhalation volume and the length of retention of breath. The deposition of the different size aerosols in lung's three different compartments has been drawn graphically and shown in Fig. 1. In this figure, terms AMTD and AMAD are defined as activity median thermodynamic...
Experimental Procedure

A ten stage cascade impactor device using Quartz Crystal Microbalance (QCM) system has been used to analyse the size distribution of medicinal aerosols. Fig. 2, shows a schematic of the experimental system used for this analysis. The size separation of particles is done by impaction. The apparatus directly gives a spectrum giving mass concentration of particles in 10 stages; each stage is designated by the size for which it is having 50% probability of capture of particles of a specified mass density.

Four medicinal aerosols generally used for respiratory tract therapy have been analysed (Table 1). For obvious reasons, their identities with the obtained results are not indicated. Three of these medicines are in liquid or semi-liquid form filled in pressurised can with facility for introducing them into mouth. While the fourth one is a powder. The powdered medicine comes in capsules. The medicine is inhaled with the help of rotahaler. During aerosol therapy the patient is asked to introduce the aerosolised medicine through the mouth piece of the canister and inhale slowly. As shown in Fig. 2, a two litre flask for collecting these aerosols for measurements has been used. Two sets of readings have been taken with each medicine: (i) introducing in a flask having room air of 30% humidity, (ii) introducing in the flask air which is usually moisturised to about 85% humidity. The measurements at two humidities have been carried out to study variation in size distribution due to change in RH of the inhaled air. Very large aerosols quickly deposit in the neck of the flask and whatever remain suspended are measured by the QCM. The sampling time of these aerosols for analysis by the QCM depends upon the concentration and it varies from 5 s to a few minutes.

Other systems are also used for generating the medicinal aerosols for inhalation by patients. One such system was received from a hospital at Jabalpur for characterisation of aerosols generated from its nebulizer. The system is shown in the photograph in Fig. 3. The nebulizer is operated by a pedalling pump and the medicines dissolved in distilled water are kept in the nebulizer can. Aerosols have also been produced from pure distilled water only. The same flask shown in Fig. 2, was filled with aerosols coming out from nebulizer and measured by QCM.

Results and Discussion

The results of these measurements are shown in Figs 4-7. In Figs 4a, 5a, 6a and 7a, two graphs of aerosol size distribution are shown: the lower one for room air (30% RH) in flask and the upper one for medicinal aerosol after pumping them in the flask from inhaler. The size distribution of aerosol particles in room air is not the same in each case, because it depends upon several parameters of the room air. Similarly in Figs 4b, 5b, 6b and 7b, the lower graph shows the aerosol size distribution in moist air (85% RH) in the flask and upper one after pumping the medicinal aerosols from inhaler into the same moist flask. On the abscisae the mass median diameter separated by each stage of QCM are shown.

Table 1—Medicinal aerosols tested for their efficiency

<table>
<thead>
<tr>
<th>Name of the company</th>
<th>Name of the Medicinal aerosol</th>
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<tr>
<td>Glaxo</td>
<td>Salbutamol</td>
</tr>
<tr>
<td>Cipla</td>
<td>Sodium Cromoglycate</td>
</tr>
<tr>
<td>Cipla</td>
<td>Beclamethasone Dipropionate</td>
</tr>
<tr>
<td>Cipla</td>
<td>Salbutamol Sulphate</td>
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Note: The results on the above medicines are presented in the paper without identifying the manufacturer.
Inhaler-I is in the form of thick solution and releases 5 mg of medicine in one metered dose. Most of the aerosol particles released from this inhaler are of very large size (> 25 μm) and they quickly fall in the neck and on glass body of the flask and inside of the glass tube leading to QCM. Deposition of the aerosol particles on glass surface of the flask can be observed visually. Fig. 4a shows the particle size distribution and their relative mass concentrations after 15-20 s of pumping in the flask. The graph clearly shows that the maximum concentration is around 1.6-6.4 μm size particles. There are some large size (around 25 μm) particles also. These particles must have formed by coagulation on the way during the process of collection by QCM cascade impactor for measurement. Fig. 4b shows the size distribution and mass concentration of the same medicinal aerosol particles in moisturised atmosphere. The comparison of two sets of groups shows a slight shift in size concentration but a big reduction in mass concentration. This may be due to faster growth in the moisturised air to form large size particles which quickly settle down. Major fraction of aerosols from this inhaler will get trapped in the extrathoracic (ET) region since they are of larger than 10 μm size. The particles of smaller than 3 μm size will pass through tracheobronchial region and smaller than 1 μm size will reach the pulmonary region.
In inhaler-II, the medicinal particles are suspended in an inert propellant. In each puff of inhaler 100 µg of medicine in the form of aerosol particles is released along with the propellants. The measurement of particle size and their mass distribution is again carried out in the same way after injecting the medicine in flask from the can.

The neck of the flask and the body do not show any deposition of large size particles in the first few minutes. The results are shown in Fig. 5a. This figure clearly shows that the majority of the aerosols are around 0.8 and 1.6 µm size and the concentration is also quite low as each puff consists of only 100 µg of medicine. Large size parti-
Fig. 7a—Aerosol mass size distribution in one dose of day powder inhaler and in AC room air (30% RH).

Fig. 7b—Aerosol mass size distribution in 85% RH air and in one dose of powder inhaler inflated in moisture.

Fig. 5b shows the spectrum of aerosol size distribution and their mass concentration in the presence of moisture. Moisture clearly influences the medicinal aerosols to form large size particles. Formation of large size particles leads to the reduction in the mass concentration due to faster settling as can be seen from the graph. The aerosols from this inhaler will easily reach tracheobronchial and pulmonary regions.

Inhaler-III releases 200 μg aerosolised medicine in one puff. The results of measurement of this medicine are shown in Figs 6a and 6b. Most of the aerosols produced by this inhaler are of very small size, mainly between 0.03 and 0.8 μm. There are some traces of large size particles also. Since these aerosol particles are of smaller sizes and their concentration is also low, there is not much influence of moisture on them, however the increase in the total concentration and slight change in their size spectrum can be noticed. The medicinal aerosols from this inhaler will quickly reach pulmonary regions.

The fourth medicine is a dry powder filled in capsules. Each capsule contains 200 μg of this powder. This powder in the capsule is inhaled with the help of rothahaler by the patient. The particles in the powder are of very large size (> 50 μm). Their size analysis is done by sieving technique. The powder was introduced in the flask by blowing air over the sample kept in a tube connected to the flask. A small number of particles which remained suspended in the flask are collected and measured by QCM. The results are shown in the Fig. 7a. This figure clearly shows that the particles smaller than 1.6 μm are negligible. The majority of the particles are between 3.2 and 12.5 μm size. From Fig. 7b, it can be seen that the concentration of the particles gets modified in the presence of moisture with the formation of larger size particles. The particles smaller than 1.6 μm are found to be absent. The majority of the aerosol particles in the presence of the moisture are larger than 25 μm. It is likely that these particles might have formed on the way towards QCM. Most of the particles of this medicine will get struck to throat and the left over particles will get trapped in the trachea.

The results of manually operated nebulizer using distilled water are shown in Fig. 8. The aerosols produced from this nebulizer are from 0.03 to 0.2 μm diameter. Since the aerosol produced from this system are inhaled through nose, the large size (> 12.5 μm) will get trapped in nose itself. A considerable fraction of the fine aerosol will reach tracheobronchial and pulmonary regions easily. It is observed that the paddling speed
of the pump does not change the size distribution of aerosols. It only changes the concentration.

Conclusions

The work reported here gives an idea of the size distribution of particles in aerosolised medicines being used for the treatment of the respiratory tract ailments. The study has clearly brought out instances where a major quantity of the medicine is lost in the upper respiratory ways. Medical practitioners can plan the line of treatment after knowing the size distribution of the aerosols available from the inhaler. Such studies will also help the pharmaceutical companies to adopt suitable manufacturing processes for production of appropriate size spectrum of aerosolised medicine.

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References