

Using deposition modelling and air-stream technology to target specific tissues in the nose.

Using the nasal passages as a route for drug delivery is not a new concept; the nose has been used for the administration of anti-inflammatories and decongestants for years. Nasal devices are increasingly being considered for the non-invasive delivery of active substances for systemic effect; offering therapeutic advantage as well as ease of use.

The nasal cavity provides several benefits as a drug delivery route; drug uptake through its highly vascularised sub-epithelial layer enables therapies to pass quickly into the bloodstream for rapid onset of action. The nasal route bypasses the body's first-pass metabolism, reducing the likelihood of drug degradation and hence the opportunity to deliver delicate biological molecules such as proteins. Nasal delivery also provides a non-invasive means of delivery for drugs that suffer poor oral bioavailability and it offers patients obvious advantages over parenteral administration.

The nasal passage can be split into several distinct regions based on tissue types. The turbinate region in particular has been highlighted as an area of interest, with a highly permeable layer and a good blood supply close to the surface. This region is believed to be ideal for systemic delivery of drugs.

Additionally, it has been postulated that drugs depositing in the olfactory region of the nasal passages can reach the brain directly bypassing the blood brain barrier. This could be highly desirable for pain management, or for drugs treating diseases of the brain. Currently the nasal drug delivery community is split as to whether this is proven, with an active debate ongoing and a lack of conclusive evidence. Either way, it is difficult to get material to deposit in this region.

It is clearly desirable to "target" these different tissues and regions. To this end, Bespak has developed an extensive computer modelling capability to help design devices capable of targeting the different regions.

Methods

3D anatomically correct computer models of the nasal airways were created using magnetic resonance imaging (MRI) and computed tomography (CT) data from medical scans. A finite element mesh of brick-shaped elements was constructed using the commercial meshing software Gambit (Fluent, Inc., Lebanon, NH).

Anatomical regions were identified and tagged on the model. This process required identification by geometry alone, as the medical scans do not differentiate between tissue types. The regions identified were the turbinates (inferior, middle and superior), the olfactory region and nasal associated lymphoid tissue (NALT). The turbinates were easily identified as structures protruding into the air spaces. The olfactory region and the NALT tissue however had to be identified based on medical knowledge alone. Tissue on the walls surrounding the turbinates was also tagged, as this tissue contains the same respiratory epithelium cells as the turbinates.

Computational Fluid Dynamics (CFD) techniques were used to calculate steady state, inspiratory airflow streams through the nose using the commercial CFD software FIDAP (Fluent, Inc., Lebanon, NH). A uniform velocity profile (plug flow) was imposed at the nostrils and the velocity set to zero at the airway walls (no-slip condition). Proprietary particle transport code was used to predict particle deposition. Particles were assigned an aerodynamic particle size, an initial velocity, and a release point. Each particle was then followed until it either deposited on one of the nasal walls, or exited the model. The method is deterministic, so only one prediction is required for each release point.

The computer model allows experiments to be run very quickly, looking at the effect on deposition on each of the target tissues by varying relevant parameters such as particle size, spray speed, cone angle, nozzle insertion depth and inspiratory airflow. Very quickly a database can be constructed plotting deposition for each tissue against a matrix of these parameters. This provides very useful information on the basic characteristics that a nasal drug delivery device should have for optimum performance. Additionally, a sensitivity analysis can determine the characteristics of a device that not only gives a high deposition fraction on the tissues of interest, but that will also produce a consistently high deposition despite changes that are likely to occur in the operation of the device. For instance, it is likely that inspiratory airflow will vary considerably from person to person, whereas particle size will most likely be fixed for a particular device. It would therefore be important to design a device that is fairly insensitive to changes in inspiratory airflow more so than one which is insensitive to particle size.

This idea of a matrix of simulations is very useful, but it does not exploit the full potential of the computer models. One way in which Bepak has pushed the modelling further is to look at very specific targeting of tissues using airstreams.

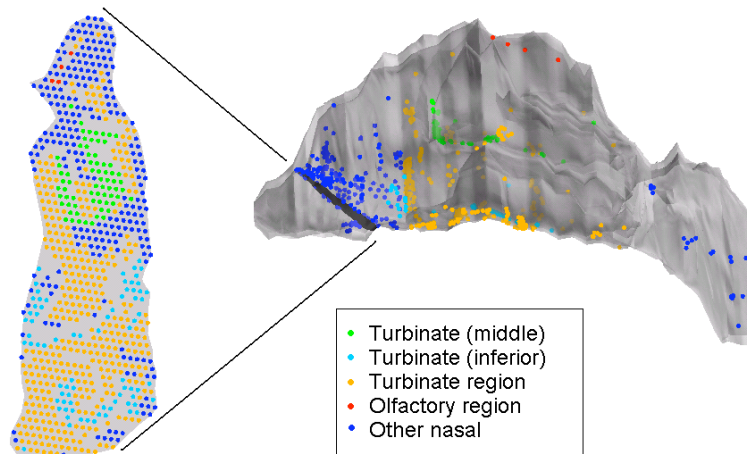
Airstreams describe the way that air moves through the model. If you take an element of air at the nostril and follow it through to the back of the nose, the path it takes is an airstream. Airstreams that passed next to target tissues were back calculated to the nostril. It was observed that for each target tissue the back-calculated airstreams originated from clusters in the nostril opening. It was then postulated that particles released at these cluster points would approximately follow the predetermined airstreams and so increase the probability of depositing on the target tissue.

To test this, a release plane was defined in the nostril opening that represented a possible position and orientation for a nozzle inserted into the nose. This plane was then divided into a grid of release points and particles of various sizes were released from these points. The initial speed of the particles was also varied to represent different spray conditions. The deposition site in the model nose was calculated for each particle released. To make the data easier to analyse, the site of deposition was grouped into four major regions of interest; the middle turbinate, the inferior turbinate, the lateral wall, and the olfactory region. The lateral wall was defined as the nasal passageway surrounding the turbinates, which has the same tissue type as the turbinates. Particles that did not deposit onto any of these regions were further defined as depositing somewhere else in the nose, or exiting the nose through the nasopharynx.

Results

Figure 1 shows an example data set, where the release points on the nozzle plane have been colour coded to represent the related site of deposition. Similar pictures were created for different particle sizes and particle release speeds, and all were very similar to Figure 1. From this figure it can be seen that there are obvious clusters of release points that land on the same target tissues. It is also noticeable that the shapes of these clusters bare some resemblance to the target tissue. For instance, the release points which related to deposition on the middle turbinate, labelled as light green in this figure, have a characteristic horseshoe shape which is the shape of the airways running over the middle turbinates when looking into the nose from the nostril. This mirroring of anatomical shapes is a sign that the airstreams are actually fairly well behaved when they travel into the nose. Because most noses have similar shapes for the internal airways, this also gives hope that common release points can be found for all noses.

Figure 1 – Side view of nasal anatomy and deposition map of nozzle insertion plane



To examine the possible benefit of targeted release, nine circular release regions were defined on the nozzle plane, to represent nine possible positions for a targeting nozzle. These were chosen to encompass the release points that targeted the middle turbinate. Particles were released from each of these regions separately to determine their effect on turbinate deposition. When releasing particles over the whole of the nozzle plane, 15% were calculated as depositing on the turbinates (both middle and inferior). When using each targeting nozzle, the deposition fraction ranged from 50% to 0%.

These data show that it is possible to enhance deposition on target tissues by controlling where in the nostril particles are released. However, it also shows that if the release region is too narrow or misplaced, there is a potential for decreasing deposition below levels seen with no targeting. Because nasal anatomy changes from person to person, any nozzle design will have to take into account expected variation in the population by releasing particles over fairly large release regions in the nostril. This will have the effect of reducing any effect of anatomy, but also reducing the potential increase in deposition on the target tissue.

Although much of the modelling work so far has been focused on enhancing deposition on the turbinates, simulations have also been run to examine targeting of the olfactory region. The olfactory region is much harder to reach, with airstreams naturally avoiding it,

probably as a way of protecting the very sensitive cells, which line this part of the nose. Under normal inspiratory conditions as little as 1.5% of particles released into the nostril will land on the olfactory region, even when carefully choosing the particle size. However, examination of the airstreams shows that the particles that do land in this region originate from a very tight region in the nostril. This gives an excellent opportunity to create a nozzle that can target the olfactory region of the nose, and so potentially allow drugs to

be targeted at a region that can bypass the blood brain barrier. Early tests indicate that the fraction depositing on the olfactory region could be increased from 1.5% up to 15%.

There is also another use for the very close clustering of release point that target the olfactory region, and this is in the delivery of vaccines to the nose. Vaccines are typically composed of bioactive material, which you definitely do not want to reach the brain. By designing a nozzle that releases particles in the nostril a long way from the airstreams that would carry the particles to the olfactory region, we can therefore have a safe way of delivering vaccines without the risk of the vaccines reaching the brain through the olfactory bulb.

Summary

Airstreams have been back calculated from the turbinates in the nose to a plane representing the nozzle of a device inserted into the nostril opening. When releasing particles at the intersection of each airstream and this plane, deposition onto the turbinates is enhanced compared to releasing particles over the entire plane. In practise this would be achieved by ensuring that the particle-releasing nozzle of a device was always located in the same part of the nostril. If you imagine a pepper pot, with many holes, but only one of these holes released particles, then you have a very easy way of controlling where particles are released. Another important feature of any device would be to minimize disruption of the airflow into the nostril. If the airflow is disrupted the airstreams will not follow predicted paths, and the targeting potential will be lost. Bepak is designing nozzles that allow unrestricted air to enter the nose through an outer open nozzle, with particles released from a smaller inner nozzle positioned to pickup specific airstreams.

Bepak is currently testing such 'air-stream targeting nozzles' using physical models of the nose and hopes that these will be seen on future advanced nasal drug delivery systems.