Next-Generation Nasal Drug Delivery Exploiting Non-Newtonian Fluids and Smart Thermoresponsive Materials

Hessam Rasooli Nia
School of Life and Medical Sciences, University of Hertfordshire, Hertfordshire, UK

1. Background

- Systemic nasal drug delivery (NDD) as an alternative to oral and parenteral routes has been an area of interest due to its rapid and effective systemic absorption, reduced risk of contamination and infections (1).
- Additionally, NDD allows for systemic drug delivery via the respiratory region, nose-brain delivery via the olfactory region and immunisation via the nasopharynx (1). Fig. 1 [A] Illustrates drug delivery to the regions of interest for NDD, [B] Depicts absorption mechanisms at the olfactory region, [1] transcellular, [2] paracellular and [3] intracellular. [C] Illustrates absorption mechanisms at the respiratory region, [1] transcellular, [2] paracellular and [3] Active transport.

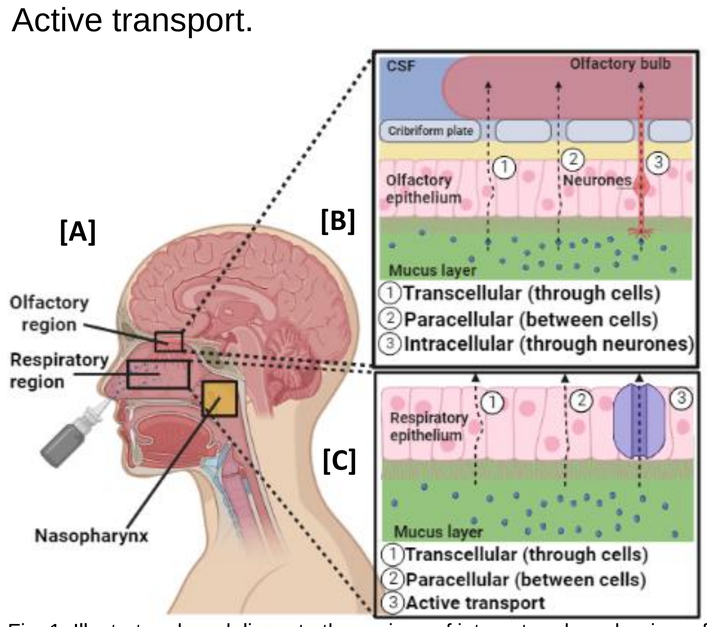


Fig. 1. Illustrates drug delivery to the regions of interest and mechanism of absorption at the sites (BioRender).

2. Statement of Problem

- As shown in Fig. 2, the nasal epithelium consists of a layer of mucus and cilia that clears administered drugs in ~20 minutes by mucociliary clearance (MC); this reduces drug-nasal cavity contact time and absorption of drugs (2).

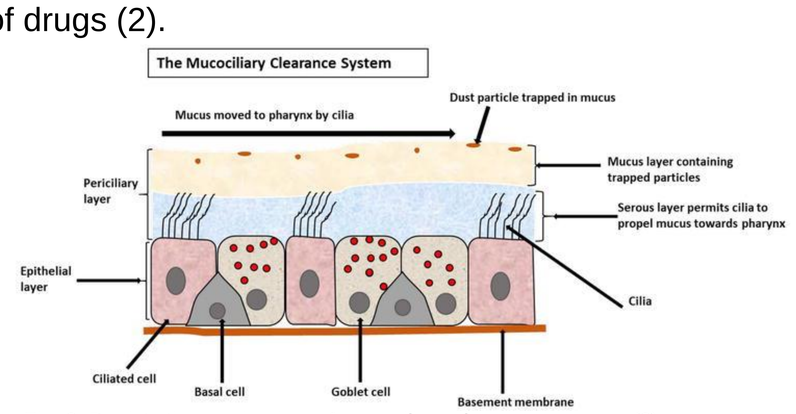


Fig. 2. Depicts the mechanism of mucociliary clearance process (3).

- Thus, overcoming MC prolongs contact time at the absorption site and improves drug absorption. One way of doing this is the addition of viscosity modifiers. These increase the viscosity of formulations, leading to stronger drug-nasal cavity interaction (2).
- However, high viscosity will negatively impact the characteristics of the generated spray [Fig. 3] (4).

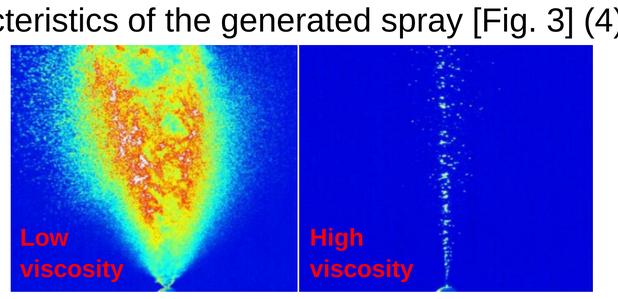


Fig. 3. Illustrates the effect of viscosity spray characteristics (4).

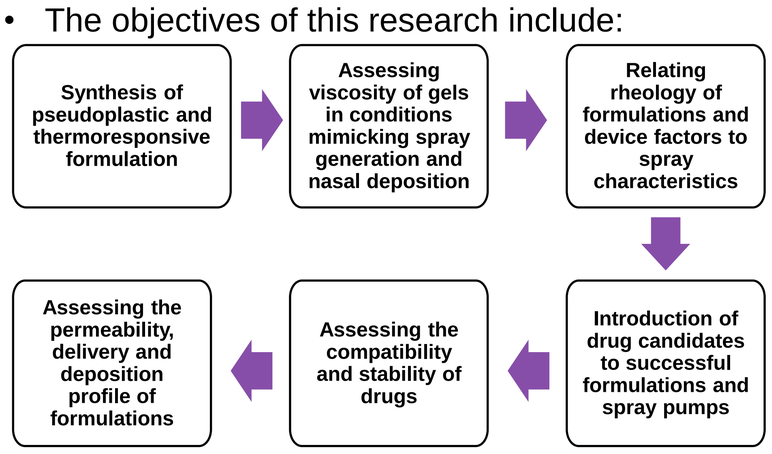
- Additionally, spray generation is also dependant on nasal spray pump device factors such as orifice shape and size (4).

3. Aims and Objectives

- The primary aim of this project is to develop a novel nasal formulation that exploits pseudoplastic materials and smart thermo-responsive gels (TGs).
- Favourable formulations are in a low viscosity state during spray generation to improve spray characteristics, and a high viscosity state when deposited in the nasal cavity to prolong the contact time [Fig. 4]. Thus prolonging the duration of local effects and drug absorption (2, 4).

Fig. 4. Illustrates the effect of temperature on viscosity of a thermoresponsive gel.

- The objectives of this research include:



4. Methodology

- **Synthesis and formulation analysis:**

1. Large library of pseudoplastic and thermoresponsive formulations will be prepared.
2. The viscosity of formulations will be assessed using a rotational rheometer [Fig. 5].

- **Spray characterisation:**

1. Formulations with favourable rheology will be aerosolised in various inexpensive single-dose spray pumps [Fig. 6].
2. The spray pattern and plume geometry will be assessed using the Proveris Sprayview instrument [Fig. 7].
3. Droplet size distribution will be assessed using laser diffraction techniques [Fig. 8].
4. Finally, the spray characteristics will be linked to the rheology of formulation and the device factors.

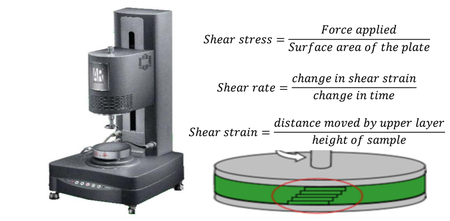


Fig. 5. Depicts a rotational rheometer, a schematic of how the equipment works and the equations used to calculate viscosity (VLABS, Malvern).

Fig. 6. Depicts a few example of spray pumps (Aptar Unidose).

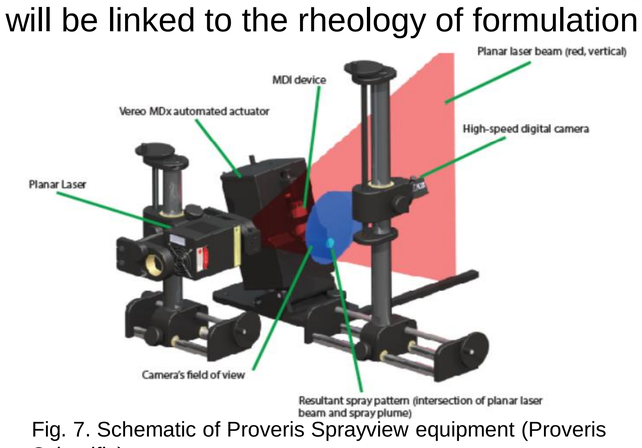


Fig. 7. Schematic of Proveris Sprayview equipment (Proveris Scientific).

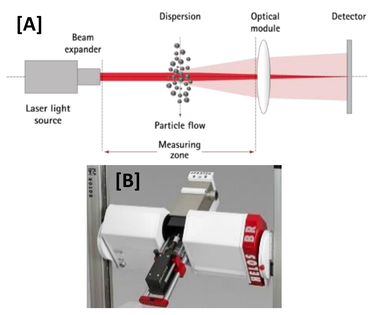


Fig. 8. Illustrates [A] the schematic of laser diffractor components. [B] An example of a laser diffractor equipment (Sympatec).

- **Compatibility and stability testing:**

1. Compatibility and stability of the drugs within formulations and spray pumps will be assessed during storage, atomisation and nasal deposition.
2. The physical stability of formulations will be tested using visual, pH and viscosity testing.
3. Chemical stability will be assessed using high-performance liquid chromatography.

- **Permeability, delivery and deposition profile analysis:**

1. Inertial impaction techniques will be used to ensure the atomised droplets are within the 10-20 µm size range, thus ensuring delivery to the nose [Fig. 9].
2. 3D-printed nasal cast coupled with dye-based imaging will be used to evaluate the fraction of the formulation deposited in the respiratory, olfactory or nasopharynx region [Fig. 10].
3. Finally, cell cultures like RPMI 2650, will be used to study the drug permeability through epithelium and biocompatibility of formulations by detecting toxicity to the cells.

Fig. 9. Depicts a next generation impactor (TSI).

Fig. 10. Illustrates a deposition profile examine using dye-based imaging on a nasal cast (Upperton).

5. Responsible Innovation

- Although the polymers used are considered safe, these formulations are preliminary and there is a lack of knowledge on biological compatibility. Thus, there is a chance of harm during clinical trials. This will be mitigated by biocompatibility testing using cell cultures.
- Given the potential of drug delivery to the brain, these formulations may become harmful in the wrong hands. For example, they could be exploited for delivery of illicit substances. However, it is very unlikely to effectively manufacture these formulations, without expertise and equipment.

6. Scientific/ policy Innovation

- By linking rheology, device factors and spray generation, this research will bring together the expertise of polymer scientists, aerosol scientists and engineers to enhance NDD.
- This research can trigger a transition in immunisation policy from parenteral administration by healthcare professionals to self-administered nasal vaccines.

7. Challenges

- It is likely that simple pseudoplastic formulations cannot be sprayed effectively if spray pumps fail to generate a shear stress that triggers reduced viscosity. However, TGs are being assessed to overcome this hurdle.
- Reliability of comparing in-vitro data from nasal casts and cell cultures to in-vivo human trials. However, many studies suggest the use of these methods in early formulation studies.

References:

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