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Open Access Journal | Volume: 4.1

Current Trends in Vaccines and Vaccinology

ISSN 2631-8970

The Potential of Dry Powder Vaccines for Intranasal Immunization

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Abstract

The nasal mucosal administration route constitutes a proven alternative and promising strategy for vaccine delivery. Historically, vaccination has proven to be a cost-effective weapon for disease prevention and has dramatically reduced or even eliminated several diseases that were once responsible for significant mortality and morbidity worldwide. The intranasal route for vaccine administration offers an attractive alternative to injection, due to the ease of administration as well as potentially better patient compliance due to some of the population, which suffer from 'needle phobia'. The first contact with inhaled pathogens happens in the nasal cavity and the upper respiratory system, so mucosal vaccine administration here would seem logical.

Article Highlights

- intranasal vaccines offers an attractive alternative to injection, due to the ease of administration, potentially better patient compliance & circumnavigates patients 'needle phobia' and needle cross contamination issues
- first contact with inhaled pathogens happens in the nasal cavity and for respiratory infections, a nasal vaccine response could offer better protection than a systemic vaccine and in addition mucosal antibody responses are broader than systemic immune responses
- Dry powder nasal vaccines have several inherent advantages – superior physical, chemical, & thermal stability, do not require preservatives or buffers, avoid cold-chain for storage and transport
- One should target the nasopharyngeal region of the nasal cavity where one finds the NALT (nasal associated lymphoid tissues) & the 'Waldeyer's Ring'
- Targeting the nasal spray to the optimal area may need device fine-tuning, many device options are available as well as industrial filling equipment

Keywords

Vaccines; Nasal; Dry powders

Background

Although there are several liquid intranasal vaccines commercially available, e.g. FluMist®, Nasovac® and Ultravac®, immunization with dry powder vaccines are also progressing in development. Dry powder nasal vaccines, although not commercially available today, have several inherent advantages, one of which is being relatively more stable at ambient temperatures compared to liquid vaccines. Challenges remain but progress is being made towards developing effective powder vaccine formulations and this coupled to novel devices for nasal delivery could lead to them being the next-generation of intranasal vaccines.

The anatomy of the nasal cavity, see Figure 1, is well documented and it has been suggested that it may of interest to target the nasopharyngeal region of the nasal cavity in order to deposit the vaccine particles. It is in this area that one finds the NALT (nasal associated lymphoid tissues) which form part of what is called the 'Waldeyer's Ring' comprising the adenoids as well as the tubal, palatine and lingual tonsils [1].

Any particles or droplets will need to be efficiently deposited on the respiratory epithelium and reside long enough to interact with dendritic or antigen presenting

Article Information

DOI:	10.31021/CTVV.20214115
Article Type:	Review
Journal Type:	Open Access
Volume:	4 **Issue:** 1
Manuscript ID:	CTVV-4-115
Publisher:	Boffin Access Limited
Received Date:	01 February 2021
Accepted Date:	19 February 2021
Published Date:	22 February 2021

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Citation: Williams G, Suman J, Marx D. The Potential of Dry Powder Vaccines for Intranasal Immunization. Curr Trends Vaccine Vaccinol. 2020 Feb;4(1):115

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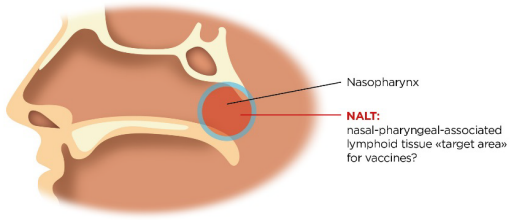

Figure 1: The anatomy of the nasal cavity

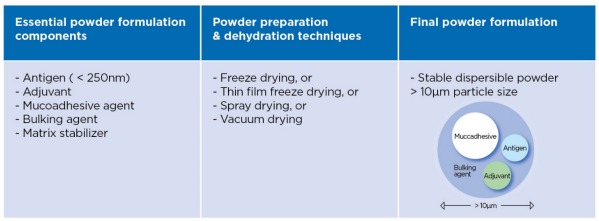

Figure 2: Typical components of a formulated powder particle for nasal vaccination

cells. Nasal mucociliary clearance will also transport the deposited particles towards the nasopharynx and the NALT region. The minimum prerequisites for mucosal or nasal vaccination will be a particle containing the antigen, adherence to the mucosal surfaces, the simulation of an innate response and a resulting appropriate adaptive immune response.

Specifically with regard to powder particles formulated for vaccination, they should comprise an antigen, an adjuvant, some mucoadhesive agents and a bulking agent in order to form a stable particle, see Figure 2. The ideal nasal vaccine powder formulation would have particles of <250 nm, consists of a component enhancing the antigenicity of the antigen and would have hydrophilic surface reducing properties to prevent aggregation, so that the particles can be taken up individually. Such particles should be able to bind to receptors mediating an interaction between the particle, mucosa, M-cells and antigen presenting cells, be capable of protecting the antigen and could release the antigen and adjuvant simultaneously.

Various powder formulation strategies involving dehydration during drying have been successfully exploited including freeze-, spray- and vacuum-drying leading to much improved storage stability while avoiding aggregation, physical or chemical degradation and loss of immunogenicity during storage. There has been significant progress in studying excipients for use in formulating nasal powders for vaccination, with matrix stabilisers, mucoadhesives and adjuvants drawing particular attention from researchers [2].

Nasal drug delivery device and the road to commercial scale production

The pathway towards developing a nasal vaccine will have many decision points along the development journey related to either device or potential large scale production viability. One of the first selections to be made are whether the vaccine formulation is best served in a liquid or powdered form. Depending on the vaccine therapy being considered the advantages of a single, bi-dose or multi-dose nasal application will need to be addressed. The compatibility of the formulation with the primary packaging will drive what type of contact materials that may be considered and this will have to be reconciled with what kind of spray, liquid or powder, that is to be delivered. Targeting the nasal spray to the optimal area of the nasal cavity to ensure suitable deposition and uptake may also take some fine tuning of the selected device, of which there are numerous choices available, see Figure 3. The availability of industrial filling equipment and processes as well as commercial large-scale access to the preferred device should also drive some of the key decisions around device selection.

Negotiating the regulatory pathways

Although today, only one of the 26 vaccines' approved in the US market is in a nasal form, the regulatory pathway for a nasal vaccine will be the same as an injected form and will initially involve non-clinical safety studies followed by clinical phases I to III. Some differences can be anticipated in that specific toxicology and safety data may be expected for risks associated with local dosing in the nasal cavity. In addition, some of the excipients that may be proposed for liquid or powder vaccines may be new or different to those previously used and well known to the regulators and these may need more detailed information behind them to successfully navigate the regulatory requirements.

Specific consideration should be given to clinical trials since injected vaccines will induce circulating antibodies which is well known and understood by regulators whereas following mucosal immunization the response is much broader and T-cell response may be triggered which needs to be assessed in the clinical phases. Specific nasal drug delivery devices will probably be associated with new nasal vaccines and like other combination drug/devices they will be subject to the existing regulatory expectations for submissions associated with such combination drug products.

In vivo progress of nasal powder vaccines

A range of dry powder nasal vaccines have been developed and investigated in vivo, both in preclinical and clinical studies. Vaccines including Diphtheria [3,4], Influenza [5], Meningitis [6], Anthrax [7], Tetanus [8] and Viral Gastroenteritis [9] have been successfully tested in animal or human studies with positive outcomes and therefore hold promise as potential commercial nasal vaccines in the future.

Typically, the dry powder vaccines investigated to date in the above clinical studies have comprised the usual formulation components, i.e., antigen and adjuvant, in addition to stabilizers, bulking agents and mucoadhesives. The powders used in the above studies were prepared in an array of different ways with spray drying and freeze-drying being the most commonly used pharmaceutical processes to produce dry powders of biologic compounds. Other alternative processes were also investigated such as thin-film freeze-drying and the encapsulation of the vaccine components in mucoadhesive particles, which were then converted into a dry powder.

Some challenges associated with nasal vaccination

There are a lack of specific antigens developed and approved for intranasal vaccination today, and they are less well understood than systemic vaccinations with responses that tend to be variable due to multiple factors (adhesion, penetration, clearance etc.) which may need investigation. Attention should also be paid to the risk of entry to the CNS during nasal vaccination due to their proximity to the olfactory region in the nasal cavity and steps should be taken to ensure deposition in the correct regions of the nasal cavity. Attention should be paid to the potential for dry nose symptom as a result of altered mucociliary clearance activity but this could be mitigated by the co-administration of nasal saline sprays.

Figure 3: A range of nasal drug delivery devices are available which are capable of dispensing liquids or powders and which can deliver single, dual or multiple doses as required.

Dry powder formulations need to be protected from humidity and specific protective packaging system are key elements in order to maintain the chemical and physical stability of dry powder vaccines. However, suitable containers for protection of nasal powder formulations are currently available and used successfully on commercialized products such as Basqimi®, a glucagon nasal powder.

The advantages of nasal vaccines

Unlike liquid vaccines, powders should not be as susceptible to physical, chemical, and thermal instability that can affect their potency and efficacy by undergoing degradation, aggregation, and/or hydrolysis. Stable powder formulations would not need certain stabilizers such as preservatives or buffers, and could avoid cold-chain for storage and transport which would be very attractive for mass vaccinations campaigns in challenging field environments. Data from several studies have indicated superior storage stability of powder vaccines at different temperatures and humidity, as compared to liquid vaccines, with some demonstrating stability and efficacy for up to 2 years at room temperature [7].

For respiratory infections, a nasal vaccine response could offer better protection than a systemic vaccine and in addition mucosal antibody responses are broader than systemic immune responses and can offer cross-protection [10]. The nasal administration route is pain free compared to injection and there are no risks of disease transmission often associated with needles. Nasal vaccination is already a safe well established pathway to disease management in the veterinary domain.

Future Outlook

Some challenges and opportunities remain for nasal powder vaccines, for example, the lack of nasal antigens and suitable adjuvants, but a lot of progress has also taken place with regard to successful clinical in vivo studies. Several liquid nasal vaccines have reached the marketplace and although regulators are less familiar with nasal as opposed to injected vaccines, the pathway to successful approval is well understood. One significant opportunity presented by mucosal nasal powder vaccines is that they could offer broader immunological responses with additional cross-protection than traditional systemic vaccines. Advantages such as painless nasal administration coupled with potentially better patient compliance should encourage both physicians and patients to consider the use of nasal vaccinations in future. Nasal vaccines could also have a clear advantage during pandemics as they can be self-administered. On the practical side, avoidance of cold chains, the plentiful availability of nasal drug delivery devices and packaging solutions in addition to industrial powder filling process offer attractive and potentially rapid product development pathways, which could well lead to the nasal powder approach becoming the next generation of nasal vaccines.

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