Pharmaceutical Aspects of Intranasal Delivery of Vaccines Using Particulate Systems

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ABSTRACT: The nasal route offers a promising opportunity for the delivery of vaccines. This review analyses the opportunities and novel delivery strategies based on particulate systems for the nasal delivery of vaccines, including liposomes, proteosomes, virosomes, nano- and microparticulate systems, with and without adjuvants. The influence of pharmaceutical aspects of the particulate formulations on nasal delivery is analysed. Recently developed delivery devices for nasal vaccination are also described. Potential barriers to clinical and commercial success of some novel intranasal vaccines are critically evaluated. Although particulate systems may offer potential in the nasal delivery of vaccines by enhancing uptake by antigen-presenting cells, the real success in enhancement of vaccine delivery can only be achieved by careful design and manipulation of physicochemical properties of particulate vaccine delivery systems. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:812–843, 2009

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INTRODUCTION

The continuous emergence of new pathogens and evolution of resistance of micro-organisms towards conventional drugs make it mandatory to continue to develop efficient vaccination strategies capable of producing acquired immune response, which is both antigen specific and possesses memory. The two important aspects of any successful vaccination strategy are to increase the potential to generate a potent defence against diseases that evade the immune system, and to develop long-lasting effective immunity after a single administration of vaccine. Consequently the development of vaccines has always been focused on effective induction of both humoral (antibody) and cell-mediated immunity (CMI).[1] Recent developments show that effective vaccination can not only protect mass population from life threatening infectious diseases, but also provide potential applications in the prevention and treatment of noninfectious diseases such as cancer, allergy, autoimmune disease and AIDS.[2,3]

Recent technological advances have permitted fast identification of potentially useful antigens and safe production of subunit vaccines in bulk, in a reproducible manner.[2] However, the full potential of vaccines still relies on the development of effective delivery systems and adjuvants. This is because, in many instances, purified antigens are poorly immunogenic and induce only an

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antigen-specific T-helper 2 cell-dependent (Th2-polarized) antibody response but not a CMI response (Th1-polarized and/or cytotoxic lymphocytes activating) and require a delivery system with either an appropriate adjuvant or a CMI-indicator cytokine to enhance immunogenicity.[4] Although it can be argued that live attenuated vaccines, in general, can provide long-lasting humoral and cell-mediated immunity, they do bear the potential risk of reversion to virulence. This concern is also reflected by the fact that stringent regulatory requirements need to be satisfied before evaluation of their safety and efficacy in humans. In addition, there are considerable logistical and bio-safety problems associated with their storage, particularly in the developing world.

There is an increasing body of evidence demonstrating that the success of vaccination is not only dependent on the nature of the vaccine's immunogenic components, but also on the delivery system.[5–9] Therefore, the search for an effective vaccine formulation or delivery system is of paramount importance in modern vaccine development.

In this review, we analyse the opportunities and challenges in mucosal, more specifically, intranasal vaccine delivery and how these have been considered in the rational design of intranasal vaccine delivery systems and their relationship to the generated immune response. Emphasis is placed on the influence of pharmaceutical aspects of the formulation of nasal delivery systems and the advances in delivery devices for nasal vaccinations which have been recently developed. Furthermore, the potential barriers to clinical and commercial success of some novel intranasal vaccine systems are critically evaluated.

OPPORTUNITIES AND CHALLENGES IN MUCOSAL VACCINE DELIVERY

Most significant viral and bacterial infections are acquired through the mucosal membranes of the respiratory, intestinal, lachrymal, or urogenital tract.[10] Immunization *via* mucosal routes has been reported to induce both mucosal and systemic immune responses at least in some monogastric species including human,[6] hence the potential usefulness of this strategy in the prevention of initial colonization of the mucosa by pathogenic microbes. The antibody-mediated protection at the mucosal surfaces offered by secretory immunoglobulin-A (sIgA), in co-operation with other innate defence factors, has been termed "immune exclusion."[11] In contrast, parenteral administration of vaccines generally fails to induce comparable mucosal immune responses.[12] Mucosal immunization may offer advantages in the immunity generated and provide a noninvasive needle-free option for antigen delivery. If suitable delivery strategies can be developed, there is the potential for acceptable and safe modes of administration suited for self or mass administration of vaccines. Table 1 summarizes the opportunities for mucosal vaccine delivery.

The delivery of an antigen to the mucosal surface can be achieved by several routes including oral, rectal, intranasal, pulmonary, or vaginal. Organized lympho-epithelial structures associated with the gut, upper respiratory tract and nasopharyngeal tissue are termed gut associated lymphoid tissue (GALT), bronchus-associated lymphoid tissue (BALT) and nasopharynx associated lymphoid tissues (NALT) respectively. These are the prime inductive sites for mucosal immunity.[13–17] Of these mucosal sites, the oral and nasal routes of administration are considered to be the most accessible and acceptable if effective.

The mucosal immune system is represented by lymphoid tissues in mucosae and external secretory glands.[18] IgA antibody isotype is primarily produced locally in mucosal lymphoid tissue and is

Table 1. Opportunities for and Advantages of Mucosal Vaccine Delivery

Mucosae are the main entry ports for pathogens and microbes
Humoral defence is largely provided by antibodies produced at mucosa tissues. Presentation of antibodies in systemic circulation by parenteral administration does not necessarily prevent infections at different mucosal sites[241]
Mucosal tissues are rich in T cells, B cells and plasma cells, far exceeding those in systemic circulation[242,243]
Mucosal tissues possess both antigen-processing and antigen-presenting cells with potential ability to initiate specific B cell and T cell-mediated immune responses including immunological memory[15,244]
Vaccination at one site of mucosae induces immunity at several distant mucosal sites[245]
Mucosal immunization is able to provide both local and systemic immunity
Mucosal vaccine delivery is needle-free, eliminating the possibility of injection-related infection and side effects