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Nanovaccines formulation and applications-a review

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A B S T R A C T

When the use of the conventional methods in the field of vaccinology is not sufficient anymore, where the incorporation of live or killed microbes to produce immune response is not strong enough to face the current severe and sometimes life threatening medical conditions, nanoparticles caught the interest of many researchers with the various properties they provide such as their size, shape, charge, inertness, biocompatibility, biodegradability and many more which led to the emergence of a new attractive topic that is widely researched nowadays known as nanovaccinology. This review will discuss the development of nanovaccines and their administration into the body via different routes. As well as the applications, advantages, limitations and the types of nanoparticles used in the preparation of vaccines used for both treatment and prophylaxis of a broad range of diseases.

1. Introduction

It has been the mankind's goal since earlier ages to protect themselves against life-threatening illness, started with the Indians drinking snake venom with the idea that it would protect them from being poisoned by it. Then the idea flourished when Edward Jenner discovered that cowpox protects individuals from smallpox and ever since then the medical field became interested in improving the immunity against diseases some which can be fatal [1]. But as the infectious diseases have spread, the increased necessity of ongoing development of new effective vaccines has emerged. Most vaccines have been formulated in a way that mimics pathogens and thereby stimulate the individual's immunity towards the disease. However, vaccine development is not always such a simple task and so several studies were initiated to gain detailed knowledge regarding the immune system recognition to antigens which resulted in synthesizing many vaccines with antibody and cell mediated mechanisms for protection [2]. Mostly difficulties appear when trying to develop vaccines against viruses like HIV, HCV etc. which are known to be hypervariable where the commonly followed approach of vaccine formulation 'isolate, inactivate, inject' is unhelpful. For the past several years, high throughput technology has proven to be necessary in order to understand the complex biological systems and their immune systems and finally utilize these technologies in new vaccine development [3]. And so, in order to move forward with improving immunogenicity, the use of nanotechnology in the field of vaccinology came into the picture and brought about the term nanovaccinology. The use of nanoparticles which are of size 1–1000 nm in vaccines is mainly to help in prophylactic approaches and many are approved to use, as well as in therapeutic approaches which is used in cancer to a great extent, in addition to treatment of other diseases such as Alzheimer's, hypertension etc. Nanoparticles in vaccines can basically work by enhancing antigen processing or activating immunity to provide protection against diseases. They can be used in this field because of their size, so they can pass through cellular components by cellular endocytosis and thus are able to deliver the biologically-active compounds [4]. Earlier the particles were synthesized from poly alky-cyanoacrylate, and with the new advantages the nanoparticles brought over the ones which were used before, they still have a short half-life and thus a shorter therapeutic effect due to their elimination by phagocytes. However, with the help of techniques like surface modification, their stay in the body can be lengthened and the delivery of many drugs, vaccines, diagnostic agents and other biological compounds became possible and they can circulate longer or even achieve a targeted action on different organs [5]. With this development in the vaccinology field, challenges appear as well and so knowledge is the key to clinicians to overcome such challenges [3]. The mechanism of vaccine response is studied first in order to improve the immunogenicity. Then the efficacy of this vaccine is studied and compared in different populations. Then the clinical trials are performed and this can help assess the success of the vaccine developed [6]. This all helps to plan future prospects of the use of prophylactic nanovaccinology.

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2. Nanovaccine development 26 21

Over the years, the concept of vaccination experienced many advancements, after Jenner's successful attempt in vaccinating against smallpox, Louis Pasteur worked on isolating and attenuating the disease-causing microorganism to provide protection against diseases and was able to utilize this technique in vaccinating against chicken cholera, rabies and anthrax [7]. Vaccines used in humans were made using the disease-causing virus or bacteria which undergoes modifications in order to attenuate its pathogenicity but not affecting its antigenicity. And so they will lose their ability to cause infection but can elicit humoral and cell mediated immune response. However, certain problems arise when live attenuated bacteria are incorporated in vaccine like the possibility of its mutation and so causing diseases. In addition, there can be a need to use adjuvants with killed vaccines and protein subunits because they generally elicit a weak response and adjuvants can enhance the vaccine action [8]. Adjuvants which were in use include mineral salts, emulsions, polymers etc. which can potentiate immune response and such an action was produced by either by sustaining antigen release or cellular recruitment at injection site, by increasing antigen uptake, up-regulating cytokines or activating antigen presenting cells [9]. Then, scientists began to direct their studies towards developing newer antigenic agents and the process of their administration in order to overcome the troubles of micro-organism reactivation and anaphylactic reactions such as exhaustive purification of vaccines, genetic mutation or new subunit antigens. In addition, the lack of adjuvant formulations is a limitation in the vaccines available in which alum, the adjuvant in use, cause swelling and erythema, is unstable after freezing and can only be administered parenterally [7]. Hence, the idea of incorporation of nanotechnology in this field of medicine emerged because of the belief that when nanostructures are designed and introduced into the human body they improve health, including cellular repairs at the molecular level, as a result the application of nanotechnology played a major role in solving many troubles faced with earlier vaccines [10]. The size and surface properties that the nanoparticles are characterized with allows the uptake by the antigen presenting cells. They also provided advantages like protection of antigen against degradation, stability in body fluids and provision of a prolonged release [7].

The first studies in this area were done in 1970s, which broadened the scope of vaccination and vaccine development. Initially, polymeric micelles were experimented on and administered subcutaneously which reported the enhancement of immune response against an antigen. Following that, the study on polymeric microparticles which were administered as a single dose, brought about the idea of a controlled delivery system in vaccines. Then a Program for Vaccine Development was introduced which allowed the use of PLGA microspheres in single dose formulation [7] and was followed by the approach of encapsulating antigens in PLGA nanoparticles. It's biodegradable which can be broken down inside the body and easily metabolized, hence considered safe. Loading it with antigens to produce Antigen-loaded polymer-based nanoparticles was the one of the first steps towards a new era for vaccination. Liposomes, phospholipid bilayer, were also introduced to encapsulate or conjugate antigens. Other materials which are inorganic in nature such as gold were also proposed to be incorporated in the design of nanovaccines [11]. These carriers are capable of delivering both the antigen as well as the adjuvant enhancing their introduction to antigen presenting cells and delivery to the target cells [12]. Such techniques resulted in the ongoing development of nanoparticle based vaccine delivery systems that can induce specific antibody production.

3. Administration of nanovaccines

Different routes are associated with the administration of nanovaccines, like oral and by injection which are the most common and also transdermal, transmucosal, ocular, pulmonary, and implantation. In addition, multiple particles are studied including PLGA, PGA, PCL, and PEO [13].

3.1. Intradermal route

Drugs and genes can be administered for the purpose of immunization by intradermal route which is one of the most common routes used. These are emulsified forming depots which are injected into the skin, specifically the epidermis layer. The drug is slowly released from the formulation leading to a prolonged effect. Different adjuvants can be used for the purpose of emulsification including oil emulsions, saponins or a combined composition as these help in targeting the antigen-presenting cells. Studies were done on magnetic nanoparticles and monodispersed polyacrolein nanoparticles and this increased the response of bovine serum albumin antibody. Other formulations are tested to increase the immune response like the ones using hen egg lysozyme/cytosine-guanine tandems nanoparticles (HEL/CpG) while another used thyolated N-Trimethyl Chitosan-Hyluronic acid nanoparticles TMC/HA loaded with ovalbumin and proved the ability to improve immunogenicity increasing IgG titers [10,14].

3.2. Intramuscular route

In certain cases, the antigen may not be able to reach the Langerhans cells of the epidermis and thus intramuscular can be an alternate route used but immune response produced can be modest as it acts indirectly on dendritic cells. A needle of microscale length with nanoscale tip can be used to avoid pain and irritation and the tip is coated with drug and inserted under the skin as a small patch and thereby the drug can be delivered. The use of this approach has been reported in formulating vaccine against influenza. Intramuscular administration of virus-like particles for vaccination of H_5N_1 has reported to be effective [14].

3.3. Subcutaneous route

Several studies have been performed to evaluate the transport of particles like liposomes by injecting subcutaneously to the lymph nodes. PEGylation of liposomes can lead to steric stabilization of liposomes and increase lymphatic uptake at injection site [15] and are found to be present in larger amounts in the lymph nodes through this route as compared to other routes [4]. A nanovaccine developed against leishmaniasis, which contain recombinant Leishmania superoxide dismutase loaded onto chitosan nanoparticles has been examined and administered subcutaneously and resulted in an increase in the immunogenicity using this approach [16].

3.4. Oral route

In gene therapy, the administration of DNA vaccine is possible with the help of polymer based nanoparticles via oral route first proposed by by Bhavsar and Aniji. In light of this, the attempts of using oral DNA vaccination against diseases are initiated. However, a limitation of the use of oral route include the necessity of high concentration of the vaccine in order to achieve adequate efficacy. This is attributed to the dilution that occur in the gastrointestinal tract as the vaccine travel down [10,14].

3.5. Nasal route

To replace alum, nanoemulsion was formulated by Baker's group out of soya bean oil, alcohol, water and detergents emulsified into droplets of 40 nm and was used in hepatitis B which proved to be non-toxic, safe and effective. So, this method which don't involve any needle-borne infections was also discussed to develop vaccine for