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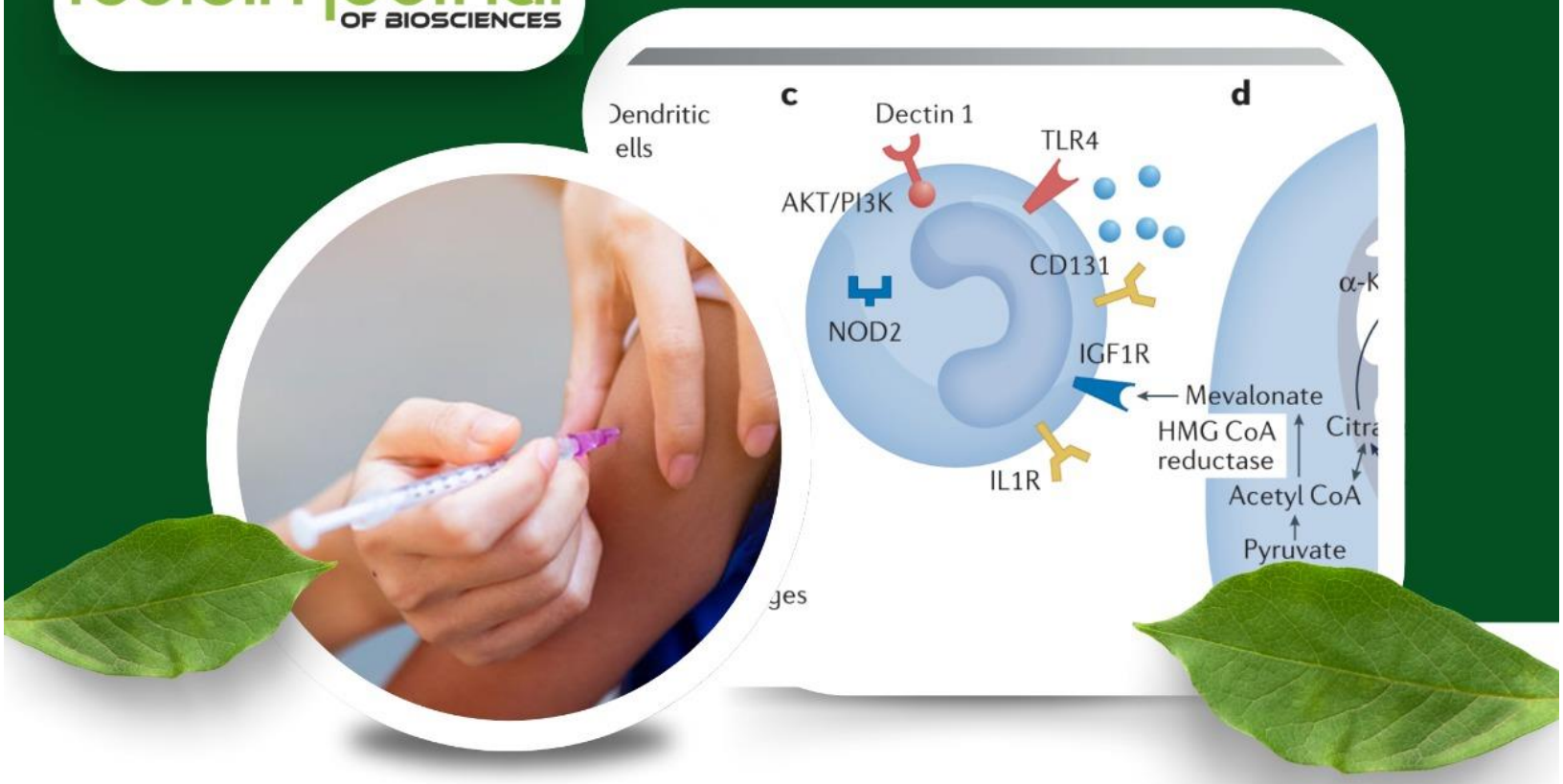
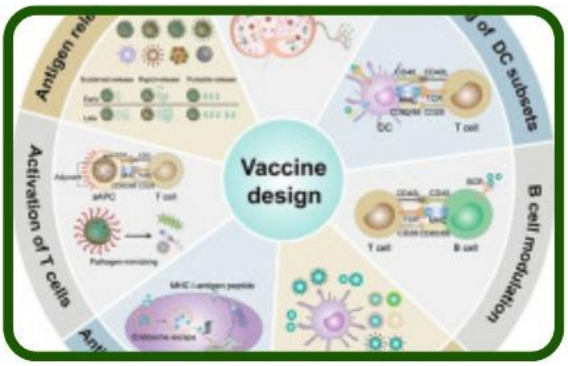
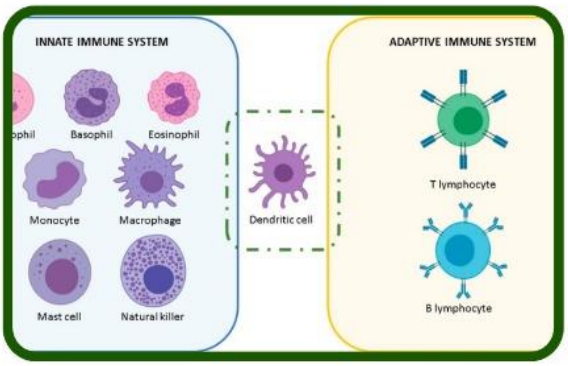


SINGLE ADMINISTRATION VACCINES:

Engineering Long-Lasting Immunity Through Advanced Release Kinetics





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Single Administration Vaccines: Engineering Long-Lasting Immunity Through Advanced Release Kinetics

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Abstract

Vaccination is the most effective method for eradicating diseases from society, yet it typically requires multiple doses. To address this, single-dose vaccine formulations have been developed to automatically deliver subsequent doses over time. Given the global shortage of vaccines and rising vaccine hesitancy, enhancing vaccination coverage has become increasingly important. Traditional vaccination schedules often involve several doses at specific intervals, and missing any of these can lead to inadequate immunity and unsuccessful immunization efforts. Therefore, there is growing interest in transforming multi-dose vaccines into single-dose formats, commonly known as Single Administration Vaccines (SAVs). One promising solution involves using injectable, controlled-release microspheres that contain the vaccine antigen. These microspheres are designed to release the antigen in a timed pulse, typically between 1 to 6 months after injection. The timing of this release depends on how quickly the polymer material degrades, which in turn is influenced by its composition and molecular weight. This innovative delivery method could offer full disease protection with just one injection.

Keywords: Single-Administered Vaccines (SAVs), PLGA (polylactic-co-glycolic acid), Scalable manufacturing,cGMP (current Good Manufacturing Practice), Aluminum-based adjuvants.

1. Vaccines

A vaccine is a biological preparation designed to prevent disease. It typically contains weakened, inactivated, or broken-down forms of microorganisms or their toxins, and can also include components like antibodies, lymphocytes, or messenger RNA (mRNA). Vaccines work by triggering the body's immune response, leading to the development of active immunity against a specific pathogen. This process involves stimulating B cells—specialized immune cells responsible for producing antibodies—to recognize and respond to the threat. Once activated, these B cells remain alert and prepared to fight off the same pathogen if it enters the body in the future. In some cases, vaccines provide **passive immunity** by directly delivering pre-formed antibodies or immune cells from another person or animal [1].

1.1 Types of Vaccines

There are several types of vaccines:

- **Live-attenuated vaccines** use a weakened form of the germ.
- **Inactivated vaccines** use a killed version of the germ.
- **Subunit, recombinant, polysaccharide, and conjugate vaccines** use only specific pieces of the germ, such as its protein, sugar, or casing.
- **Toxoid vaccines** use a toxin (harmful product) made by the germ.
- **mRNA vaccines** use messenger RNA, which gives your cells instructions for how to make a protein (or piece of a protein) of the germ.
- **Viral vector vaccines** use genetic material, which gives your cells instructions for making a protein of the germ. These vaccines also contain a different, harmless virus that helps get the genetic material into your cells [2-4].

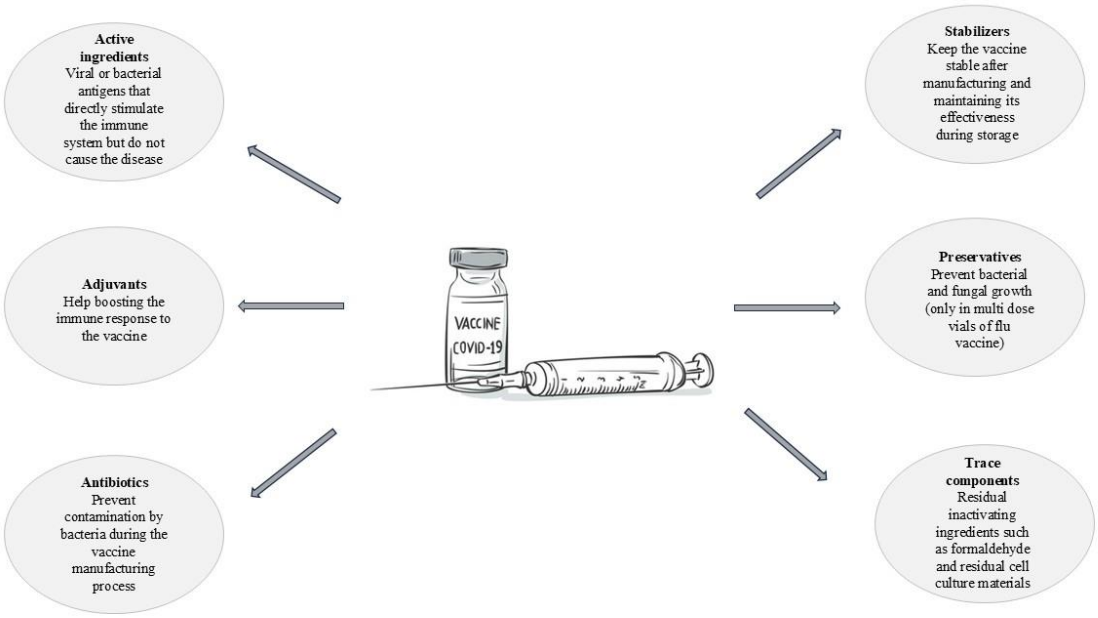

Figure 1. Basic components of a Vaccine.

1.2 Vaccine Presentations

Vaccines come in various forms, each designed for specific use and handling procedures:

- **Single-Dose Vial (SDV):**
  This type of vial contains only one dose and is meant for use with a single patient. Since SDVs lack preservatives that inhibit microbial growth, they must be punctured only once. After administering the dose, any remaining vaccine must be properly discarded. SDVs should never be used for more than one person.

- **Manufacturer-Filled Syringe (MFS):**
  These syringes are pre-filled and sealed under sterile conditions by the manufacturer, containing a single dose. Like SDVs, MFSs do not include preservatives and are intended for one-time use per patient. Once the seal is broken, the vaccine should be administered or discarded by the end of the day.

- **Multidose Vial (MDV):**
  MDVs hold multiple doses of vaccine and are typically formulated with antimicrobial preservatives to prevent contamination. These vials can be punctured multiple times but must be stored and accessed only in a designated, sanitary preparation area, away from treatment zones. The number of doses drawn from an MDV should not exceed the amount specified by the manufacturer, and combining leftover contents from different vials is strictly prohibited.

- **Oral Applicators and Nasal Sprayers:**
  Oral applicators deliver single-dose oral vaccines and do not contain preservatives. In the U.S., for example, the rotavirus vaccine is given this way. Nasal sprayers are used to administer intranasal vaccines, such as the live attenuated influenza vaccine [6-9].

1.3 Disadvantages of Multiple doses of Vaccines

1. Increased Risk of Adverse Events (AEs) and Reactogenicity

Each vaccine dose triggers an immune response, and repeated stimulation can increase the likelihood of side effects such as fever, fatigue, muscle pain, headache, and swelling at the injection site. This is particularly noticeable with adjuvanted or mRNA vaccines (such as those used for COVID-19), where repeated doses may provoke stronger systemic reactions due to enhanced innate immune memory or trained immunity responses.

2. Immunological Tolerance or Blunting

In specific situations particularly when doses are administered too closely together repeated exposure to antigens can result in the immune system becoming less responsive, leading to reduced effectiveness due to immune tolerance or T-cell fatigue. Additionally, in the case of live vaccines, if the timing is not well-spaced, maternal antibodies present in infants may hinder the vaccine's ability to trigger an effective immune response, a process known as immune interference or immunological blunting**.**

3. Compliance and Dropout Risks in Longitudinal Immunization

Multi-dose schedules require strict adherence to timing to elicit optimal immune memory (e.g., prime-boost mechanisms). Delayed or missed doses can reduce vaccine efficacy.

4. Increased Cost and Logistical Complexity

From a pharmacoeconomic perspective, every extra vaccine dose adds to both direct expenses—such as production, storage, and delivery—and indirect costs like follow-up appointments and lost work time. Additionally, managing cold-chain requirements and coordinating vaccination schedules becomes more

complicated, especially in low-resource environments, which can hinder fair and widespread access to vaccines.

6. Antigenic Drift and Vaccine Mismatch
In the case of rapidly mutating pathogens like influenza or SARS-CoV-2, receiving multiple vaccine doses may not provide comprehensive protection if the virus undergoes antigenic changes between doses, which can decrease vaccine effectiveness. Additionally, booster shots based on earlier virus strains may trigger a phenomenon known as **original antigenic sin** (or immune imprinting), where the immune system favors producing antibodies against previous versions of the virus, thereby weakening its response to newer variants [9].

2. SINGLE ADMINISTRATION VACCINES (SAVs)

A single-administration vaccine is a preventive immunization developed to provide long-lasting protection against a specific pathogen with just one dose, eliminating the need for additional booster shots within the initial vaccination schedule. The main goal of this approach is to reduce the number of required doses, which in turn enhances adherence to vaccination programs and simplifies the logistics of vaccine delivery. This type of vaccine is designed to fulfill three key objectives:

1. Increase global vaccination coverage,
2. Lower the costs linked to multi-dose vaccine regimens, and
3. Enhance convenience for patients [10]

2.1 History of attempts to develop single-dose vaccines

The concept of single-dose vaccines dates back nearly 40 years and received most attention with the WHO Special Program for Vaccine Development initiated in the 1980s. In the late 1970s Langer et al. first showed that a single vaccination with a polymer-based vaccine formulation could induce long-lasting antibody titers in animal models.The polymer was bio-erodible and allowed for slow and sustained antigen release, whilst also providing an adjuvant effect. Development of single-dose vaccines, mostly using the established biodegradable polymer, poly(lactide-co-glycolide) (PLG) nanoparticle technologies for controlled antigen delivery. O'Hagan et al. showed long-term vaccine-specific antibody responses in mice following subcutaneous immunization with ovalbumin entrapped in PLG-based biodegradable nanoparticles. Singh et al. successfully developed a way to obviate the need for encapsulation, by preparing the PLG particles separately and then adsorbing the antigen on the particles; while the surface adsorption of antigen does not allow for controlled release of antigen, such an approach does take advantage of the adjuvant properties of particulate antigen delivery. Malyala et al. developed a two-stage process in which PLG microparticles were first sterilized by γ-irradiation, avoiding the need for aseptic manufacturing, and then incubated with reconstituted, sterile antigens to allow surface adsorption; the adsorbed PLG vaccines induced potent immune responses. Most recently, Tzeng et al. showed a process for PLG encapsulation of an inactivated polio vaccine that involved the use of excipients to stabilize the formalin-fixed antigens and helped to preserve its stability [11-12].

2.2 Formulation challenges of SAV technologies

Converting a traditional vaccine into a single-administration vaccine (SAV) involves developing a controlled-release system capable of preserving antigen stability over time. The release pattern and antigen stability are crucial factors, as they play a central role in eliciting a robust and durable immune response—both of which are explored in the sections that follow.

2.2.1 Controlled Antigen Release to Mimic Multi-Dose Vaccine Schedules

Studies have shown that chitosan microspheres can provide sustained release of the tetanus toxoid vaccine for up to six months in both in vitro and in vivo models. However, the inconsistent properties of natural polymers from batch to batch and the challenges in precisely controlling their release mechanisms limit their suitability for commercial single-administration vaccine (SAV) platforms. In contrast, synthetic biodegradable materials like polycaprolactone (PCL) and polyorthoesters offer greater flexibility, allowing for better control and customization of release kinetics. PCL is a biodegradable polyester frequently used in medical devices for tissue engi neering such as sutures. Studies have demonstrated improved immune responses and survival rates in mouse models. Tomar et al. reported that Hepatitis B surface antigen (HBsAg) could be released in vitro over a span of six months, and the resulting immune response in vivo was comparable to that of the traditional aluminum-based HBsAg vaccine. Despite these promising outcomes, the application of polycaprolactone (PCL) in vaccine delivery remains limited, with only a few studies exploring its use. Over time, PCL has largely been replaced by PLGA as the preferred material for vaccine delivery systems. PLGA is a synthetic polymer allowing tuning of the release profile by changing its characteristics such as the molecular weight, lactic/glycolic acid ratio or polymer end chemistries [14-16].

➢ PLGA release kinetics for use in SAV

Hydrophilic antigens are released from PLGA microspheres through two main mechanisms: diffusion via aqueous channels and polymer erosion. This results in a triphasic release pattern—an initial burst, a steady diffusion phase, and a second rapid release phase as the polymer degrades—affecting in vivo antigen concentration and potentially influencing efficacy and safety. The release of antigens from PLGA microspheres is influenced by multiple factors, including polymer properties, microsphere size, antigen loading, and environmental conditions. Smaller particles tend to cause higher initial burst release, while larger ones exhibit more controlled, erosion-driven profiles. Antigen distribution, polymer porosity, and formulation additives like stabilizers (e.g., trehalose) also significantly affect release kinetics. Additionally, the lactic/glycolic acid ratio, molecular weight, and end-group chemistry of PLGA determine its hydrophobicity, degradation rate, and overall release behaviour.

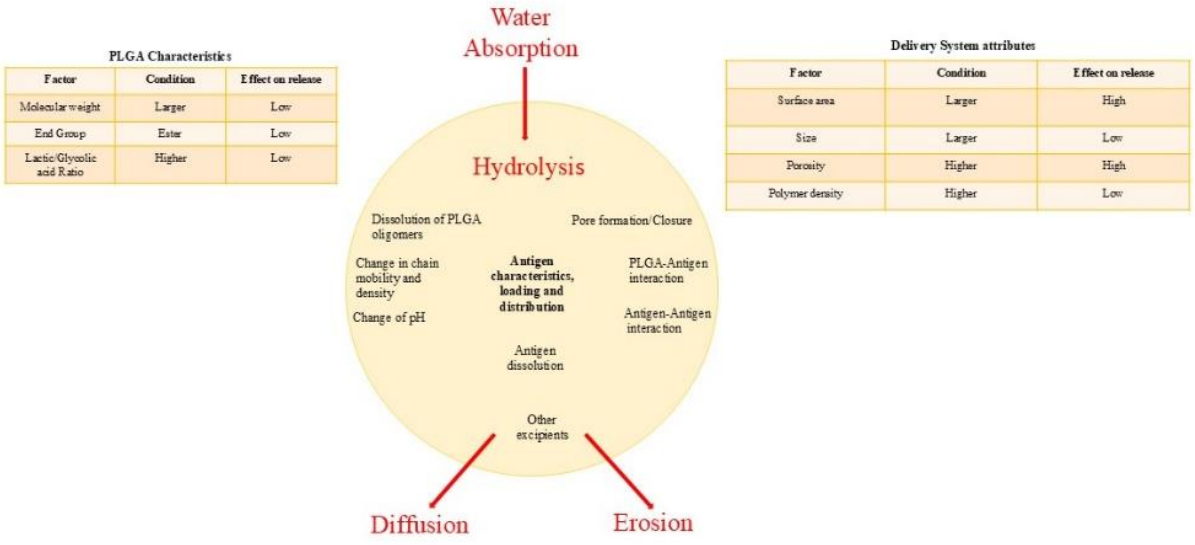

Figure 2. Factors influencing antigen release from PLGA microspheres.

2.2.2 Ensuring Antigen Stability: Physical and Chemical Integrity

Many vaccines use protein-based antigens, which must remain physically and chemically stable during preparation, storage, and after administration. Key threats to stability include denaturation (due to unfolding, aggregation, or surface adsorption) and degradation (through oxidation, hydrolysis, or acylation). Factors such as temperature, shear forces, and organic solvents during formulation can cause instability, while moisture and pH changes during storage or in vivo release can further degrade proteins. Stabilizers like trehalose, surfactants (e.g., polysorbates), and buffering agents (e.g., magnesium hydroxide) help preserve antigen structure and function. Several strategies, including co-adjuvanted microspheres, double emulsions, core-shell particles, and non-polymer coatings like alumina, have been developed to balance antigen stability with sustained or pulsatile release. Although many of these approaches show promising immune responses in animal models, scalability and manufacturing costs remain significant hurdles for commercial translation [21-22].

2.2.3 Advances in Antigen Design: From Reverse Vaccinology to Nanoparticle-Based Vaccines

The foundation of effective vaccination strategies begins with selecting the appropriate antigen. Traditionally, this selection followed an empirical approach where whole pathogens or their components were isolated, inactivated, and administered to trigger immunity—a method responsible for many current vaccines. However, over the past two decades, a more rational and innovative method known as reverse vaccinology has transformed this process. By leveraging genome sequencing, proteomics, and bioinformatics, reverse vaccinology enables the identification of ideal antigens directly from a pathogen's genetic information. This technique has led to the successful development of vaccines that were previously unattainable through conventional methods, including the licensed vaccine for serogroup B meningococcus.

Building on this, **structural vaccinology**—a discipline that applies computational and bioinformatic tools to design protein antigens for optimal immune recognition—has become a major driver of modern vaccine development. This approach focuses on enhancing the presentation of protective epitopes to B cells. It supports three key strategies:

1. **Stabilization of protective conformations**: Unstable protein structures that induce neutralizing antibodies can be stabilized through sequence modification. This method has enabled progress in vaccines against RSV, HIV, and influenza.
2. **Chimeric antigens**: Protective epitopes from different variants can be combined into a single protein, producing broad-coverage vaccine candidates such as those targeting Factor H binding protein and pilus proteins in meningococcus and streptococcus.
3. **Self-assembling nanoparticle vaccines**: These structures present multiple copies of an antigen, significantly enhancing B cell responses. Nanoparticles have already been successfully employed in HBV and HPV vaccines and are being tested in universal influenza and RSV vaccine candidates. Ferritin-based nanoparticles, for example, preserve the native structure of influenza hemagglutinin and have shown promising results in early clinical trials.

Studies have further shown that nanoparticle vaccines not only induce strong germinal center and T follicular helper cell responses but also benefit from glycan-dependent enhancements in immunogenicity. Despite their advantages, a single dose of nanoparticle-based vaccines may not suffice for long-lasting immunity in humans—especially in vaccine-naïve individuals. However, combining these advanced antigen design strategies holds great potential for creating next-generation, highly effective vaccines [28-29].

3. In vivo responses to SAV technologies

3.1 Inactivated polio vaccine (IPV): a key candidate for SAV technologies

The inactivated polio vaccine (IPV) includes antigens for all three poliovirus serotypes, each with distinct stability profiles, making its adaptation into single-administration vaccine (SAV) formats particularly challenging. While oral polio vaccine (OPV) is cost-effective and induces both mucosal and systemic immunity—ideal for low-resource settings—it carries a risk of reverting to a virulent form. IPV, although safer and widely used in developed nations, requires multiple doses, cold-chain storage, and does not induce mucosal immunity. These limitations often result in incomplete immunization, as shown by declining booster uptake. SAV technologies could address these challenges by improving coverage and compliance, but no viable IPV SAV formulations existed until recently. In a breakthrough study by Tzeng et al., pulsatile-release PLGA-based SAV formulations incorporating different cationic polymers (Eudragit E and poly(α-l-lysine) with branched polyethylenimine bPEI) were tested in animal models. Results showed that both SAV formulations produced neutralizing antibody responses comparable to two conventional IPV doses, with some variation across serotypes. Notably, both SAVs triggered earlier immune responses than the standard regimen, which could be beneficial in urgent immunization scenarios. However, questions remain regarding the longevity of these immune responses and their ability to match the protection provided by the full three-dose IPV schedule. Further investigation into the breadth and durability of the immune response is essential to fully understand the potential of IPV-based SAVs in eradication efforts [36].

3.2 Hepatitis B (HBV): A stable target for SAV technologies

Hepatitis B virus (HBV) immunization currently relies on virus-like particles (VLPs) composed of surface proteins and requires a prime followed by two booster doses to ensure protective antibody levels (>10 IU/L), as recommended by the WHO. Despite high global coverage, incomplete vaccination remains a challenge, especially in newborns. Combination vaccines (e.g., 6-in-1) have improved uptake, and the HBV antigen (HBsAg) has served as a model for developing single-administration vaccine (SAV) formulations, particularly due to its stability in acidic environments and compatibility with PLGA microspheres. Several studies have shown that SAV formulations using PLGA and techniques like double emulsion can generate antibody levels comparable to conventional multi-dose schedules. Adjustments in polymer composition, end groups, and stabilizers such as trehalose and magnesium hydroxide have further enhanced antigen stability and immune response. Comparative research on microspheres and nanospheres revealed that larger microspheres favor humoral responses, while smaller nanospheres trigger cellular immunity; however, adjuvants like alum remain crucial for achieving responses equivalent to standard vaccines. PLGA itself may also act as an adjuvant by mimicking pathogen characteristics, potentially benefiting populations with poor vaccine responses. Most HBV-SAVs studied so far utilize continuous release, raising concerns about immune tolerance from prolonged antigen exposure, although recent studies have not confirmed such effects. Regulatory perspectives currently favor pulsatile release systems that mimic conventional dosing intervals, supporting better memory B cell maturation and secondary responses. Hence, further research is needed to align release kinetics with optimal immune outcomes for successful SAV development [40-41].

Table 1. Animal studies of hepatitis B single administration vaccines (SAVs).

SAV Formulation	Immune Response
HBsAg(7.5 µg) PLGA 50/50-COOH microspheres	Immune response Inferior results after the sixth week
HBsAg(7.5 µg) PLGA 50/50 microspheres	Comparable serum antibody titres to control
HBsAg(30 µg)	Antibody response comparable to control

PLG505, PLG858 (10 μm) microspheres	
HBsAg(20 μg) PLGA 50/50 with trehalose	Immune response comparable to the control
HBsAg(20 μg) PLGA 50/50 with Mg(OH) 2	Significantly lower immune response than the control
HBsAg(1 μg) loaded PLA microspheres with alum	Comparable antibody titres to the control

3.3 Preclinical Insights into Vaccine-Induced Granulomas and Reactogenicity

Vaccines are administered to healthy individuals, so a favorable benefit-risk balance is crucial. Reactogenicity refers to the side effects following vaccination, and an optimal vaccine should exhibit high immunogenicity with minimal reactogenicity. Side effects vary based on the vaccine and recipient, and are typically classified as local (e.g., pain, redness, swelling) or systemic (e.g., fever, fatigue, headache). These reactions result from the body's innate immune response to the vaccine. Maintaining a balance between inducing a strong immune response and minimizing side effects is key in vaccine development, with reactogenicity being evaluated throughout preclinical and post-market stages.

For single-administration vaccines (SAVs), reactogenicity is influenced by both the vaccine components and the adjuvants or excipients used. In animal studies of inactivated polio vaccine (IPV) delivered via SAVs, no adverse effects were observed, which aligns with the known safety of IPV and PLGA-based delivery systems. PLGA/PLA microspheres are well-established as biocompatible and biodegradable, and are FDA-approved for injectable use. Hepatitis B vaccines, being subunit-based, naturally have low reactogenicity, although this can limit their immune-stimulating power. Adjuvants like alum are used to compensate, but most SAV versions of these vaccines exclude alum. Among these, only one study reported adverse effects—a mouse trial by Zheng et al. showed transient lumps at the injection site, likely caused by microsphere deposits, not granulomas. These lumps resolved within six weeks.
Subcutaneous administration is known to increase the risk of granuloma formation—itchy skin nodules with local changes such as redness and discoloration. Aluminum-based adjuvants have been associated with such granulomas and may even contribute to chronic inflammatory conditions like macrophagic myofasciitis. Newer adjuvant technologies may raise the risk of both local and systemic reactions. However, research by Boopathy et al. showed that sustained vaccine release can enhance immunity by promoting stronger and longer-lasting B cell responses. This suggests that using SAVs for adjuvant delivery might reduce the required adjuvant dose, lowering side effects and improving vaccine compliance and coverage [44-47].

4. The Road to Implementation: Overcoming Formulation Hurdles

Developing a new process that alters an existing vaccine formulation, such as adapting it into a single-administration vaccine (SAV), involves establishing scalable manufacturing, ensuring formulation stability, validating analytical methods, and possibly conducting additional clinical studies. This transition—often referred to as the "valley of death"—is critical in determining commercial viability. Regulatory guidelines (e.g., ICH) require evaluation of quality attributes to confirm no negative impact on safety or efficacy. Clinical requirements vary by product and disease, and changes to formulation may lead to it being considered a new candidate. Bridging studies can compare original and modified versions. However, meeting cGMP standards for early-phase trials can be costly and complex, particularly for academic labs or small companies [48].

5. Single-dose vaccines for the Coronavirus pandemic

The rapid expansion of the COVID-19 pandemic made developing a SARS-CoV-2 vaccine a top global health and economic priority. To quickly immunize large populations and generate rapid protection, a single-dose vaccine became a key goal. Numerous vaccines entered preclinical and clinical testing, with some demonstrating safety and the ability to induce functional antibody responses after just one dose. These candidates typically target the virus's spike (S) protein and use RNA or viral vector platforms. One RNA vaccine progressed to phase III trials, with phase I data showing it safely induced seroconversion in all participants and functional antibodies in some—highlighting the RNA platform's potential in pandemic settings. Similarly, adenoviral vectors have shown strong single-dose performance. A chimpanzee adenovirus-based vaccine (ChAdOx1 nCoV-19) produced neutralizing antibodies in 90–100% of recipients in a phase I/II trial. Another trial using a non-replicating adenovirus type-5 (Ad5) vector also reported significant antibody responses after one dose. Additionally, a study by Mercado et al. found that a single dose of an Ad26-based vaccine generated protective neutralizing antibodies in non-human primates. These findings underscore how various technologies have been rapidly leveraged to create effective single-dose COVID-19 vaccines [49].

Conclusion

Over the past few decades, significant progress has been made in the development of single-administration vaccines (SAVs). Researchers have investigated various microencapsulation techniques and excipients, providing key insights into overcoming formulation challenges. Promising outcomes from animal studies suggest that SAVs may induce strong and durable immune responses in humans. The focus has now shifted toward commercialization, emphasizing scalable production, reliable excipient sourcing, and targeting appropriate multi-dose vaccines for conversion to SAVs.As vaccines gain increasing societal relevance, there are expanding funding and marketing opportunities for SAVs. Capitalizing on these, along with leveraging expiring patents for long-acting injectables, may accelerate the commercialization process. Reducing production costs will be essential for SAVs to gain market traction and significantly impact global health.

Although SAV technology was conceptualized decades ago, its commercial advancement has been slow. Traditional approaches like multivalent vaccines and mandatory immunization programs have overshadowed SAV development. However, the rapid technological advancements spurred by the COVID-19 pandemic offer new momentum for SAV innovation. SAVs could play a transformative role in managing future infectious disease outbreaks. Given the proven success of PLGA-based long-acting injectables in the pharmaceutical market, similar approaches could be applied to vaccine formulations.

Key priorities include controlling production costs and improving the antigen loading capacity of delivery systems. Focusing initial efforts on higher-priced vaccines used in developed countries may offer viable early markets, though sourcing such vaccines for early R&D could be difficult. A practical strategy might involve first generating proof-of-concept data using model or low-cost vaccines before progressing to more expensive ones. A critical goal is to achieve controlled (pulsatile or sustained) antigen release that can outperform traditional multi-dose schedules. Advances in technologies like microfluidics and spray drying have improved control over release profiles and encapsulation efficiency. Stabilizing antigens within microspheres remains a vital challenge, as solving this could lower manufacturing and logistical costs.SAVs are gaining traction and are expected to see renewed interest in the coming years. These technologies offer added value over conventional vaccines by enabling controlled release that could enhance immune responses. Future SAV development will benefit from integration with advanced vaccine types such as nucleic acids, potentially improving stability, efficacy, and immunogenicity. Though SAVs have come far since the 1980s, challenges remain. The technology may not suit all vaccines due to variations in stability

and processing tolerance. However, advancing SAVs with more stable platforms—such as toxoid and subunit vaccines—can pave the way for broader applications, including complex formats like RNA-based vaccines delivered via lipid nanoparticles or enhanced with tailored adjuvants to elicit specific immune responses.

Conflict of Interest
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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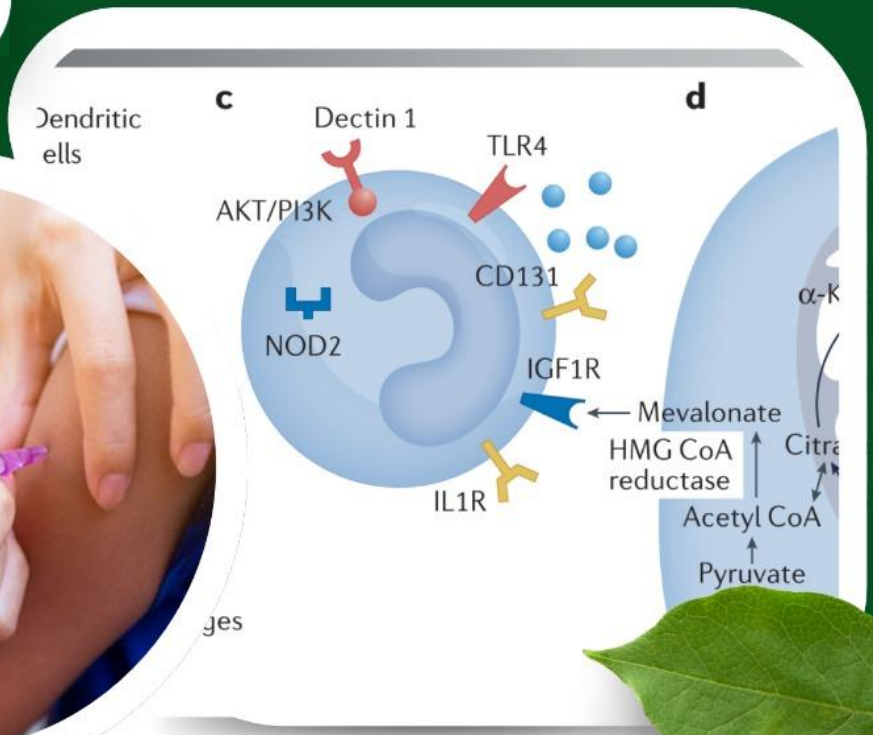

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