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REVIEW

Injectable controlled-release systems for the prevention and treatment of infectious diseases

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Abstract

Pharmaceutical drugs, including vaccines, pre- and post-exposure prophylactics, and chronic drug therapies, are crucial tools in the prevention and treatment of infectious diseases. These drugs have the ability to increase survival and improve patient quality of life; however, infectious diseases still accounted for more than 10.2 million deaths in 2019 before the COVID-19 pandemic. High mortality can be, in part, attributed to challenges in the availability of adequate drugs and vaccines, limited accessibility, poor drug bioavailability, the high cost of some treatments, and low patient adherence. A majority of these factors are logistical rather than technical challenges, providing an opportunity for existing drugs and vaccines to be improved through formulation. Injectable controlled-release drug delivery systems are one class of formulations that have the potential to overcome many of these limitations by releasing their contents in a sustained manner to reduce the need for frequent re-administration and improve clinical outcomes. This review provides an overview of injectable controlled drug delivery platforms, including microparticles, nanoparticles, and injectable gels, detailing recent developments using these systems for single-injection vaccination, long-acting prophylaxis, and sustained-release treatments for infectious disease.

KEYWORDS
controlled-release, disease prevention, disease treatment, drug delivery, infectious disease

1 | INTRODUCTION

Pharmaceutical drugs such as vaccines, antibiotics, antivirals, and other drugs have been developed to prevent and treat a number of infectious diseases, improving patients' quality of life and survival.[1] The impact of these drugs can be felt in the decline in infectious disease deaths from 2000 to 2019, before the COVID-19 pandemic. Nevertheless, communicable diseases still accounted for more than 10.2 million deaths in 2019, or approximately 18% of all deaths that year.[2] Reducing mortality further will require a coordinated effort that includes new pharmaceutical drugs, improved education about infectious diseases, and enhanced utilization of existing drugs and vaccines. There are many points at which drugs can reduce the infectious disease burden, beginning with vaccination long before a pathogen is encountered, pre-exposure prophylaxis shortly before exposure, post-exposure prophylaxis immediately after exposure, and treatment after infection. However, these methods of prevention and treatment can be limited by factors such as patient adherence, accessibility, cost of treatment, inconvenient dosing schedules or administration routes, associated stigmas, and perceived lack of urgency.

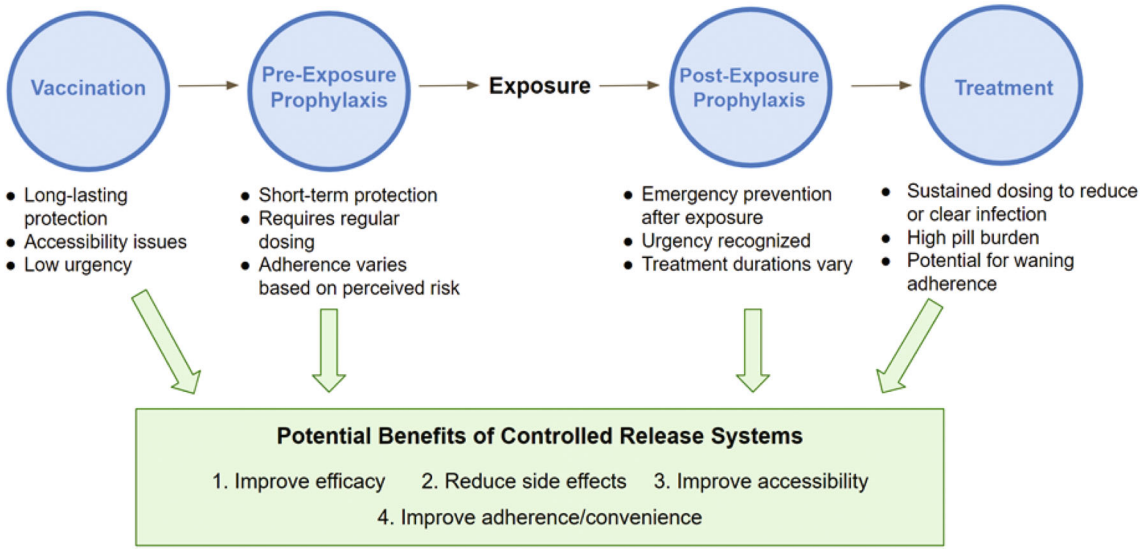
Though vaccines typically offer long-lasting protection against a disease, their clinical impact can be severely limited by underutilization. There are numerous reasons why a patient may not be fully vaccinated, ranging from inaccessibility to a low perceived risk of infection and (real or perceived) side effects of vaccination. However, the key driving factor in low- and middle-income countries is widely considered poor vaccine distribution leading to a vast majority of the 1.5 million vaccine-preventable deaths that occur worldwide each

year.[3] If no vaccination is received (or if it is unnecessary to vaccinate against a disease of low prevalence in the area of residence) and there is an increased risk of exposure, such as international travel, pre-exposure prophylaxis and post-exposure prophylaxis can be used to prevent transmission and contraction of a disease. However, the utility of prophylactic treatments is directly related to their proper administration, which can be undermined by factors such as patient adherence, stigma, and low perceived urgency (in the case of pre-exposure prophylaxis). If the disease is contracted, drug therapies can eradicate the disease, or at least mitigate the symptoms, but limitations can arise due to the cost of treatment, a reduced perception of benefit as well as stigma associated with some diseases, and patient fatigue due to high pill burdens. In all of these situations, a controlled-release platform could help overcome these challenges by improving efficacy, accessibility, and adherence while also possibly reducing the side effects of the drug (Scheme 1).

Many current infectious disease treatments are administered orally since oral delivery is convenient for the patient and non-invasive; however, the duration over which oral drugs can act is limited by their residence time in the GI tract (which can be reduced in malnourished populations),[4] low bioavailability, and low patient adherence due to the need for frequent dosing. One example of low adherence due to a high pill burden is the treatment of tuberculosis (TB), which requires a prolonged and complex oral dosing regimen, resulting in poor patient adherence, treatment failure, and the potential emergence of drug-resistant TB.[5] Low adherence rates are a significant public health problem, with as many as 50% of the 3.8 billion prescriptions written each year taken improperly.[6] The lack of tight adherence to a prescribed dosing schedule poses a significant threat to the therapeutic efficacy of chronic infectious disease treatment.[7] The factors underlying poor adherence to these treatments are very similar to challenges facing pre- and post-exposure prophylaxis, including forgetting to take a drug, skipping doses due to low perceived risk, stigma, cost, side effects, inaccessibility to adequate healthcare, and a false notion of feeling healthy even though treatment is not complete. Intensive adherence counseling for human immunodeficiency virus (HIV) antiretroviral therapy has been implemented in some cases in an attempt to promote the completion of the full course of treatment, which has been observed to be as low as 51%,[8] but it may not be possible to efficiently scale this approach—particularly in low-resource settings—and data assessing the benefit of this strategy is extremely limited.[7]

Another limitation of oral administration is the low bioavailability of some drugs. After being absorbed in the stomach and small intestine and undergoing first-pass metabolism, the quantity of active drug in circulation is significantly lower than other, more direct delivery methods, increasing cost.[9,10] Extended-release formulations have been developed to extend the circulation time of drugs after oral administration, yet these remain subject to first-pass metabolism and therefore have limited residence time while still requiring multiple doses.[11] One potential alternative to the oral dosing of drugs is the development of injectable formulations. Injectable controlled-release systems are of particular interest when drug distribution, cost, and patient adherence are otherwise challenging. Their ability to sequester a drug, prevent it from being metabolized, and then release it at a later time enables these systems to act as a substitute for multiple doses administered over an extended period of time while also avoiding first-pass metabolism.

Additionally, these systems have the potential to finely tune circulating drug levels, which may be important for drugs with small therapeutic windows, the range over which the drug is both safe and effective.[12] This is not uncommon for drugs that treat infectious diseases. For example, some drugs used to treat malaria offer only a small range within which the drug level is between the relatively high



SCHEME 1 Sequential prevention and treatment options for infectious diseases, along with the associated limitations and potential benefits that controlled-release systems could provide.

level needed to kill the parasites and the concentration toxic to the patient.[13] By engineering drug delivery systems that release drug at or near the rate that it is metabolized and eliminated, these systems can maintain safety and efficacy for a much longer period of time than oral drug formulations that lead to drug peaks and troughs without the need for re-dosing.

Despite the proven effects and benefits of vaccines and other pharmaceutical drugs, patient nonadherence to frequent dosing schedules and/or multiple injections is extremely detrimental to both global health and associated healthcare costs.[14] A controlled-release vaccination platform could reduce the number of injections necessary, which could improve patient adherence and accessibility while alleviating the burden on the healthcare system compared to multiple injections.

Two prevalent classes of drug delivery systems used to improve the prevention and treatment of infectious diseases are injectable micro- and nanoparticles, and injectable in situ-forming implants. Particulate carriers are used for their size tunability based on the application, their improved bioavailability, controlled-release profile, and adjuvancy.[15,16] Injectable implants have been developed with the goal of addressing common issues associated with traditional implants, such as invasive insertion and removal procedures and controlling the release profile.[17,18] These gels are able to act as a liquid during injection, and then experience a phase transition in response to selected stimuli, such as temperature, solvent composition, pH, or light.[19] This review will integrate studies looking at the use of the two classes across various infectious disease applications, including vaccines, pre- and post-exposure prophylaxis, and chronic disease treatments.

2 | VACCINE DELIVERY

Immunization remains one of the most successful disease-fighting methods currently in existence. Clinically-approved vaccines offer protection from more than 20 life-threatening diseases and prevent between 3.5 and 5 million deaths annually.[20] Despite this proven success, there are still 1.5 million vaccine-preventable deaths annually.[21] Most traditional vaccination schedules consist of a prime-boost or prime-boost-boost regimen with a waiting period between injections. Childhood immunization dropout (i.e., not completing an entire immunization schedule) in low- and middle-income countries (LMICs) is a challenge that could be addressed if single-injection vaccines, which confer immunity after a single administration, were available.

According to the World Health Organization, in 2021, 18.2 million infants did not receive any doses of the diphtheria-tetanus-pertussis vaccine—a combination vaccine considered among the most basic—and an additional 6.8 million infants were only partially vaccinated; importantly, more than 60% of these 25 million children reside in just 10 LMICs.[22] Though there are many factors contributing to dropout, poor vaccine accessibility in low-resource settings due to logistical constraints is among the most impactful. A single-injection vaccine that eliminates the need for a follow-up visit and simultaneously improves accessibility could significantly reduce the burden of vaccine-preventable diseases in LMICs and worldwide. In addition to directly converting the 6.8 million infants who currently receive one dose to full vaccination status, the vaccination campaigns used to distribute vaccines in many areas could reduce costs by as much as a factor of three since each infant now only requires one visit to complete immunization. The cost savings associated with this change could then be reallocated to expanding vaccination campaigns to areas that currently have poor coverage or be assigned to another high-value purpose.

Microneedle patches have recently gained renown for their ability to elicit a strong immune response while having a user-friendly application process. However, these delivery systems have yet to be implemented at scale and they still require multiple doses, which will necessitate storage stability. Other factors, including patient adherence to proper application schedules and cost, will also need to be considered as the technology matures.[23] The development of controlled-release, single-injection vaccines could provide a way to mitigate the challenges associated with the current vaccination regimens or even elicit a more robust immune response for poorly immunogenic vaccines, leading to greater levels of seroconversion (i.e., protection) or longer-lasting immunity.

2.1 | Micro- and nanoparticles

Microparticles and nanoparticles have been widely used in preclinical models as carriers for drugs and vaccines. The size of the particle used largely depends on the application and desired target tissue, as nanoparticles are able to pass through capillaries into the bloodstream after injection, whereas microparticles will typically remain near the injection site.[24] Encapsulating a drug within a particle that releases it over an extended duration has many benefits, including enabling precise dosing, overcoming solubility challenges, and enhancing bioavailability relative to oral administration.[15,24] Additionally, aside from altering antigen exposure kinetics, recent studies have shown that many biomaterials can themselves function as adjuvants, eliciting a more robust immune response.[1] Although biomaterial adjuvants that act exclusively as immune enhancers represent a rapidly growing area of research, this review is not focused on materials that only serve as immune enhancers. Readers are referred to a recent article by our group that explores emerging biomaterial adjuvants.[25]

One material widely used in drug delivery systems that has demonstrated both the ability to release protein and peptide antigens over time and serve as an adjuvant is poly(lactic-co-glycolic acid) (PLGA), and is attractive as a vaccine carrier for a variety of reasons. It is found in many FDA-approved devices across a broad spectrum of applications ranging from implants and surgical sutures to drug delivery systems,[26,27] it is hydrolytically degraded into biocompatible products that are rapidly cleared from the body,[28,29] it is commercially available at a variety of molecular weights,[30] its release rate can be modified by altering the ratio of lactic acid to glycolic acid, molecular weight, or end group,[31-33] and it is relatively easy to use in micro- and nanoparticle formulation methods, which enables its use as a minimally invasive, injectable system.[34,35] For prophylactic vaccines, it is

especially critical that the materials used have an excellent safety profile. Fortunately, seminal work by Dr. James M. Anderson—a pioneer in the area of cell-material interactions—showed that PLGA and its degradation products are highly biocompatible, eliciting only mild inflammation and a muted foreign body reaction in rats.[29]

Another single-injection vaccine uses a layer-by-layer coating process to produce microparticles that release antigens after a predetermined delay.[36] The fabrication process involves coating ovalbumin (OVA)-loaded calcium carbonate ($CaCO_3$) microparticles with alternating layers of tannic acid (TA) and polyethylene glycol (PEG), which interact via hydrogen bonding (Figure 1A). The authors of this work hypothesized that by varying the number of layers of coating, they could obtain release at multiple time points with a lag time before OVA release that is proportional to the coating thickness. Particles were coated with 0, 20, or 30 bilayers and combined into a single injection, along with uncoated particles, to achieve release on days 0, 14, and 21 (Figure 1B, C), mimicking a traditional prime/boost/boost vaccination regimen, albeit somewhat accelerated. When injected into mice, the desired release profile was observed. The single-injection vaccine also resulted in OVA-specific antibody titers that were significantly higher than those in the control groups, and similar to the group that received three injections of uncoated OVA-loaded particles (dosing schedule shown in Figure 1D), which was used to account for both the adjuvancy of the materials and antigen release timing (Figure 1E). On day 36, mouse splenocytes were harvested and re-stimulated with OVA in order to observe the cellular immune response. The single-injection vaccine group produced the highest proliferation indexes in splenocytes when restimulated with OVA, demonstrating that it induced strong humoral and cellular immune responses (Figure 1F).

Another notable example of using particles to create a controlled-release vaccine is the work by Watkins and colleagues, who developed a single-injection vaccine against influenza. The authors demonstrated the release of recombinant outer membrane vesicles (rOMVs) fused to an influenza antigen from PLGA particles.[37] Their data show that *Escherichia coli*-derived rOMVs physically coupled to an adjuvant with an antigen can improve the immune response to an influenza vaccine. The authors conducted both in vitro and in vivo studies with PLGA particles containing the matrix 2 protein ectodomain of influenza (M2e4xHet)—an antigen known to protect against different influenza A subtypes in mice—fused to rOMV to determine the protection conferred by this vaccination method. In vivo, 4 weeks after vaccination, mice that received an injection of PLGA particles loaded with M2e4xHet-rOMV had a 30-fold increase of geometric mean titer levels compared to the mice that received soluble M2e4xHet-rOMVs (prior to the boost dose). Further, there was no statistically significant difference between the mean titer achieved in this single-injection controlled-release group and the mean titer resulting from two injections of soluble M2e4xHet-rOMVs administered at 0 and 4 weeks when serum was analyzed at 6 weeks. To evaluate the protection efficiency of the rOMV-loaded PLGA particles, mice were exposed to a lethal dose of influenza virus A/Puerto Rico/8/1934 (PR8). The group vaccinated with two injections of soluble M2e4xHet-rOMVs, as well as the group vaccinated with M2e4xHet-rOMV-loaded PLGA particles, had a 100% survival rate following the challenge and exhibited no significant weight loss difference. In contrast, mice who received only phosphate-buffered saline (PBS) all lost more than 30% of their body weight, necessitating humane euthanasia, and underscoring the effectiveness of the single-injection vaccine. Other groups have also used bacterial proteins as adjuvants that enhance the immune response to vaccination from controlled-release formulations;[38] for example, Liu et al. entrapped extracellular cytolytic protein produced by *Streptococcus agalactiae* (CAMP factor) in PLGA microspheres to create a single-injection vaccine and found that they produced a sustained increase of antibody titers in vivo compared to the control group which received a single injection of either PBS or CAMP factor in solution.[39]

Though OVA is an excellent model vaccine, it is not a clinically relevant antigen as a non-pathogenic protein without a specific epitope target that can be used to determine the protection conferred by a controlled-release vaccine. Because the stability of vaccines encapsulated in particles can pose a significant challenge depending on the nature of the antigen and release system, testing with clinically relevant vaccines is an essential step in single-injection vaccine development. One study encapsulated bivalent H1 (fused Ag85B and ESAT6 proteins) in PLGA nanoparticles with the goal of creating a single-injection vaccine against *Mycobacterium tuberculosis* (*Mtb*).[40] The authors hypothesized that this method would eliminate the need for adjuvants, decrease the number of required doses, and improve antigen stability and sustained release. After studying in vitro release, they determined that encapsulated H1 experiences a burst release of around 19% over the first 2 h, and after 12 h approximately 42% of the protein had been released. However, following this burst release over the first 1–2 days, the release rate was much slower and continued through day 32, by which time approximately 92% of the H1 protein had been released. The authors used this information to design an in vivo study, in which the burst release would serve as the priming dose, and the subsequent sustained release would act as the boost dose. Interestingly, they found that the single-dose vaccine produced IgG antibody titers in mice on day 28 that were approximately 6.4-fold higher than the group that was vaccinated with a single injection of antigen alone, and around 7.9-fold higher on day 42 post-injection. Additionally, after lethal challenge, mice that were vaccinated with the single-injection vaccine had a mean survival of 177 days, compared to mice that were vaccinated with a single injection of soluble H1, who had a mean survival length of 80 days.

Earlier controlled vaccine delivery platforms based on biodegradable microparticles were created by the O'Hagan group, who produced single-injection vaccine formulations that released diphtheria toxoid (DT) from PLGA microspheres. Their top formulations produced antibody levels in rats comparable to that of three immunizations with DT absorbed to alum from week 32 onwards.[41] The group also used the platform to release tetanus toxoid (TT) in a single-injection vaccine format.[42] Similar to their findings with the DT single-injection vaccine, the authors found that a single injection of TT encapsulated in PLGA produced antibody levels comparable to three

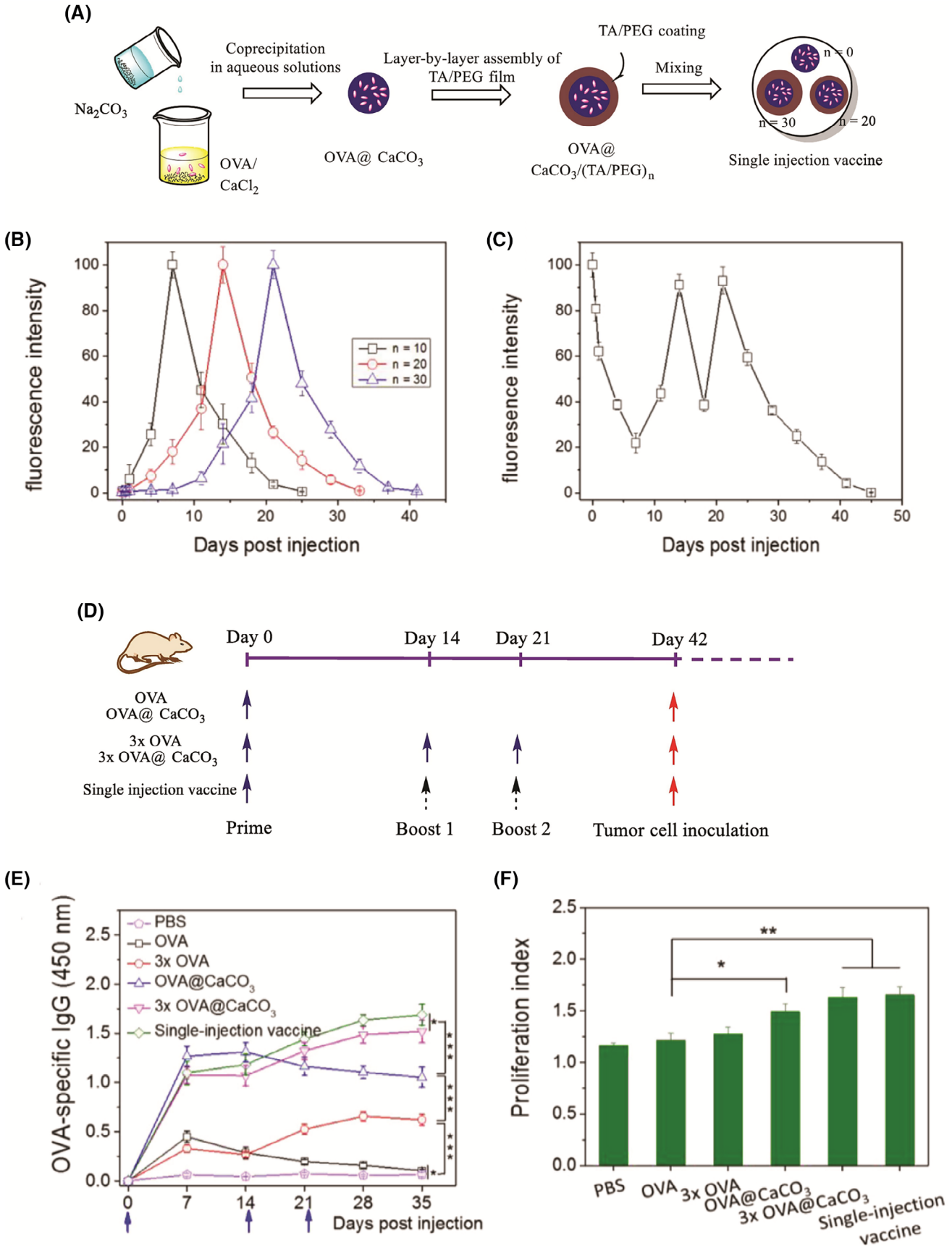


FIGURE 1 Legend on next page.

injections of alum-absorbed TT from week 32 and beyond. However, the authors note that the antibody response from microparticles containing both antigens (DT and TT) was lower than the response induced by the single antigens encapsulated in PLGA microparticles, which they hypothesized is likely due to antigenic competition between DT and TT, leading to lower antigen presentation. Interestingly, in both cases, the best immune response came from a single injection of alum-absorbed antigen (either DT or TT) encapsulated in PLGA microparticles, which the authors believe was due to the alum/PLGA combination priming the immune system better than either alum or PLGA alone. Another notable delivery technology in this space is the more recent development of microfabricated particles with a PLGA shell surrounding a vaccine-filled core. By combining these microparticles with different PLGA properties, the authors created a single-injection vaccine that exhibited multiple pulsatile release events to simulate a traditional vaccine regimen and produced anti-OVA antibody titers higher than two bolus injections.[43] Another platform from the same group was then modified to release inactivated poliovirus vaccine (IPV) stabilized with cationic polymers to counteract acidification inside the degrading PLGA microspheres. The microparticles released biologically active IPV in vitro at two time points, 1 month apart, and created an immune response comparable to or better than traditional bolus injections for multiple types of IPV.[44] These examples serve as demonstrations of the potential benefits of particle encapsulation in the area of controlled-release vaccination; however, additional translational challenges remain.[45,46]

2.2 | Injectable in situ-forming depots

In situ-forming depots are another common platform to create single-injection vaccines. These gels are injected in liquid form before experiencing a phase transition in situ in response to a stimulus such as temperature, solvent diffusion (e.g., a water-miscible organic solvent diffusing into water after injection), pH, light, a chemical reaction, or the removal of shear stress.[47] Foundational work with thermosensitive hydrogels was done by Kim and colleagues, demonstrating the benefits of biodegradable biocompatible poly(ethylene oxide (PEO) and poly(L-lactic acid) (PLLA) to deliver therapeutics.[48] Furthermore, PEO has since been used to formulate poloxamer 407, a triblock copolymer made up of PEO and poly (propylene oxide) (PPO) that is present in multiple FDA-approved products, including some intravenously injectable systems.[49] Though poloxamer 407 has been used in multiple drug delivery applications, it can have poor thermodynamic and kinetic stability, since it has a relatively low critical micelle concentration,[47] limiting its utility in sustained-release applications.[50,51] However, Chung et al. showed that poloxamer 407-grafted chitosan polymers had improved aqueous stability and biocompatibility, due to the poloxamer 407 segment.[52] Bobbala et al. used this advancement to create a poloxamer 407-chitosan (CP) polymer-based thermosensitive single-injection vaccine delivery platform that released OVA as a model vaccine with a sustained release profile.[53] These CP gels are soluble at physiological pH and undergo a phase transition between 30 and 35°C. Using a double emulsion method, PLGA nanoparticles were synthesized and served as nanocarriers for OVA within the gel. They found that in vitro, the particle-loaded CP gels had completely released OVA by day 18, whereas the CP gels containing soluble OVA (i.e., without particles) had completely released their OVA by day 14. Additionally, T cell expansion in the lymph nodes of single-injection immunized mice was significantly greater on day 49 than the control groups (particles only and alum) and comparable to the soluble OVA-loaded CPs. Similarly, OVA-specific IgG serum levels of mice who received NP-loaded gels or gels containing free OVA were approximately 20-fold higher than the group that received only OVA-loaded particles without the CP hydrogel, indicating the ability of the hydrogel to promote a robust immune response.

Wang et al. also observed promising results using a PLGA-PEG-PLGA thermosensitive hydrogel to achieve sustained OVA release.[54] In their study, three injections 10 days apart of either thermosensitive gel, soluble OVA, or Freund's Adjuvant mixed with OVA were administered to mice. The signal from fluorescently labeled OVA persisted for 7 days at the injection site, compared to mice receiving soluble OVA, in which the signal was undetectable after 2 days (Figure 2A, B). Additionally, anti-OVA IgG titers in mice treated with the controlled-release system were significantly higher than in the group receiving soluble OVA 7 days after administration. However, the titer levels were still approximately 3.5-fold lower than the positive control (Freund's Adjuvant mixed with OVA) (Figure 2C). All groups dosed with aqueous concentrations of PLGA-PEG-PLGA showed significantly higher proliferation indices of harvested splenocytes compared to mice receiving a soluble dose, and mice receiving the highest dose of aqueous PLGA-PEG-PLGA displayed splenocyte proliferation rates that were statistically similar to cells isolated from mice receiving OVA with Freund's Adjuvant (Figure 2D).

Reducing the regimen burden associated with vaccinations could greatly improve full immunization numbers worldwide. Work using injectable microparticles and nanoparticles, as well as injectable in situ-forming implants show promising results towards the development of controlled-release vaccines that could realize that goal. These platforms, along with others, could improve accessibility, and thereby patient adherence, by reducing the number of doses required to receive the full protective benefits of a vaccine.

FIGURE 1 Layer-by-layer encapsulation of ovalbumin (OVA), a model antigen, into layer-by-layer particles and the resulting immune response. (A) Schematic illustrating the layer-by-layer microparticle fabrication process and components of the single-injection vaccine. (B) In vivo release profiles when using various numbers of bilayers. (C) In vivo release of the single-injection vaccine with peaks at day 0, 14, and 21. (D) Timeline of in vivo injections. (E) OVA-specific antibody titers for experimental and control groups. (F) Proliferation index of harvested splenocytes after re-stimulation with OVA. This article was published in *Biomaterials Advances*, Volume 137, Wang H., Cui L., Luo Y., Zhou X., Liu R., Chen Q., Guan Y., Zhang Y., Construction of single-injection vaccine using new time-controlled release system, 212,812, Copyright Elsevier (2022).

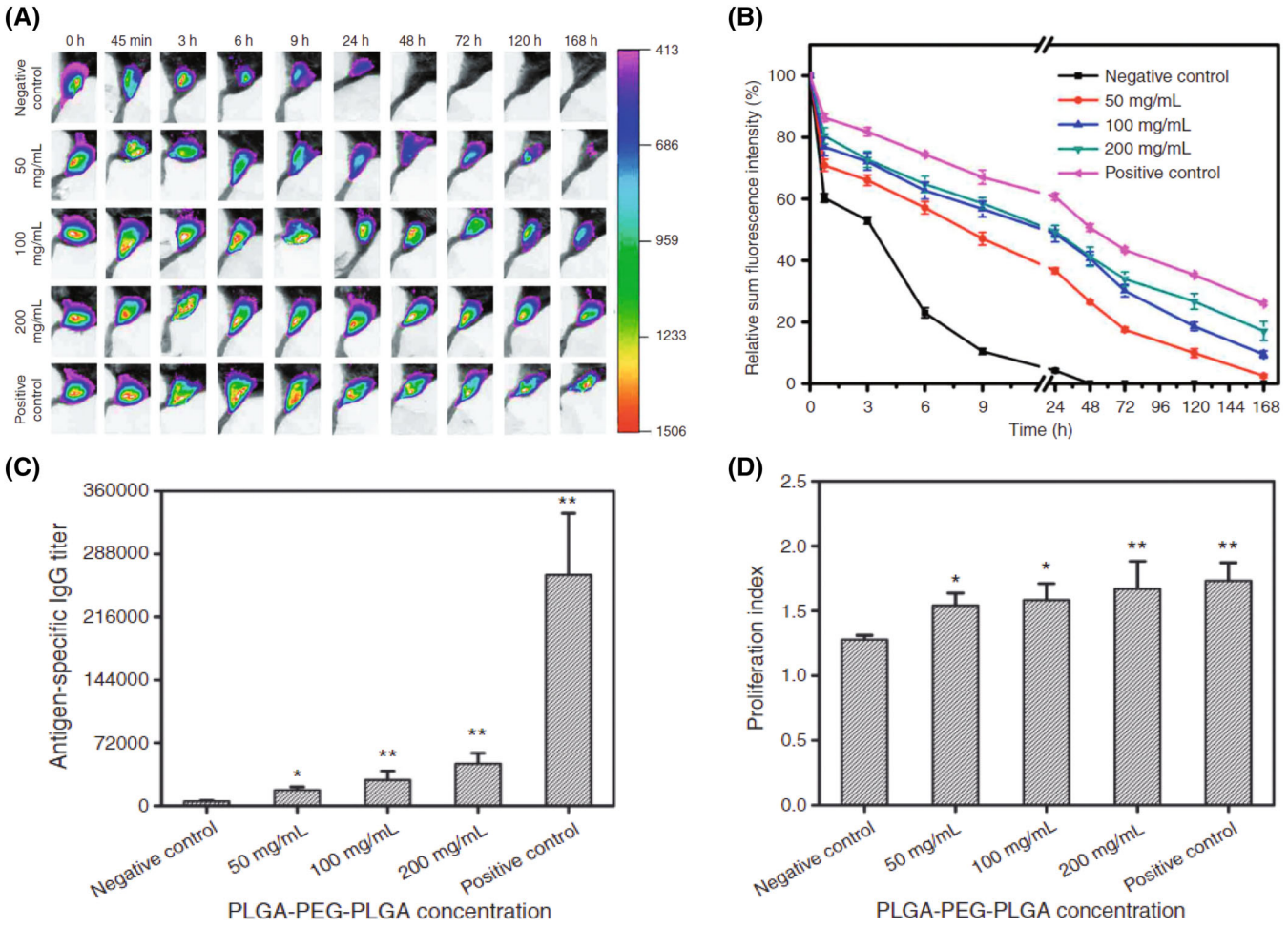


FIGURE 2 Controlled-release vaccine using PLGA-PEG-PLGA hydrogels to deliver ovalbumin, a model antigen. (A) In vivo fluorescence intensity images of mice in each experimental group showing antigen persistence. (B) Quantification of in vivo fluorescence intensity in each experimental group. (C) Antigen-specific antibody titers resulting from controlled OVA release. (D) Proliferation index of splenocytes following restimulation with OVA. Wang X., Zhang Y, Xue W., Wang H., Qiu X., Liu Z., *Journal of Biomaterials* Applications: Vol. 31, issue 6, pp. 923–932, copyright © 2016 The Author(s), reprinted by permission of SAGE Publications.

3 | PRE- AND POST-EXPOSURE PROPHYLACTIC SYSTEMS

Pre- and post-exposure prophylaxis are strategies used to prevent the transmission of infectious diseases like HIV to at-risk individuals.[55] Pre-exposure prophylaxis is useful for populations that are at elevated risk for contracting a disease while post-exposure prophylaxis is useful to stop the pathogen from taking root or to prevent transmission to other individuals, often by blocking pathogen replication or survival.[56] Many drugs can be taken for pre-exposure prophylaxis as well as post-exposure prophylaxis, making the potential benefits of developing a controlled-release system for those drugs even greater. Unlike vaccinations, which produce immunological memory and provide lasting protection, prophylactic therapeutics are generally small-molecule drugs that are effective while in circulation but lose their effect shortly after treatment is stopped or taken improperly.[57] In addition to HIV, prophylactic treatments have also had success with diseases such as TB[58] and malaria.[59] However, in many cases, adherence can be low due to a high pill burden that presents a significant challenge to sustained efficacy, providing ample motivation for developing long-acting drug formulations.

3.1 | Micro- and nanoparticles

Microparticles and nanoparticles have been extensively explored for extending the duration of prophylactic drug activity. One such example is tenofovir alafenamide (TAF) and emtricitabine (FTC) for HIV. Current clinically approved coformulations of TAF and FTC are limited by factors such as administration site reaction and low drug concentration at the injection site compared to plasma. By encapsulating these drugs in PLGA particles via the double emulsion technique, Mandal and colleagues showed the ability to increase in vitro cell viability from approximately 66% when exposed to soluble TAF + FTC in the culture media to approximately 88% when exposed to nanoparticles containing TAF + FTC.[60] The authors also found that

encapsulating those drugs in PLGA prolonged tissue residence times for TAF and FTC, with half-lives that were effectively 6.5- and 9.3-fold longer, respectively. Additionally, it was reported that drug accumulation at the site of infection (vaginal and rectal tissues) was greater than in circulating plasma following subcutaneous injection. Mice treated with TAF + FTC NPs demonstrated 80% protection when challenged 4 days after administration, and 60% protection when challenged 7 or 14 days after administration. In contrast, the control group receiving one injection of TAF + FTC in solution was 100% infected when challenged 4, 7, or 14 days after administration. In an attempt to mitigate suboptimal adherence and viral rebound, Tatham and colleagues loaded maraviroc, a CCR5 antagonist used to treat HIV, into a nanodispersion formulated with polyvinyl alcohol (PVA) and sodium 1,4-bis(2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate by emulsion-templated freeze-drying.[61] The authors observed a 3.4-fold increase in the drug's area under the curve (maximum concentration versus time) in serum using a rat model. They also observed a 2.6-fold increase in half-life, from 53.23 h for the soluble drug to 140.69 h. For the sake of comparison, the oral drug has a half-life of 17 h. The minimum effective concentration (adjusted from humans to rats) was also maintained for up to 10 days.

One study found that monthly injections of the nanocrystal formulation of an HIV-1 integrase inhibitor, cabotegravir (CAB-LA), showed comparable results to standard oral therapy, with 92.5% of participants having less than 50 copies/mL of HIV1-RNA present at week 48 compared to 95.5% of participants who received standard oral therapy.[62] Though monthly injection results were comparable to traditional therapy and have the potential to greatly improve adherence in real-world usage scenarios, there can be substantial donor site reactions, and patient preference between once-daily oral administration and a monthly injection may vary. Kulkarni et al. developed a poloxamer-coated hydrophobic and lipophilic cabotegravir (CAB) prodrug with controlled hydrolysis and tissue penetration properties in hopes of mitigating some of the issues associated with CAB, while extending the duration of treatment efficacy to 1 year per injection, in order to minimize the need for physician oversight.[63] The formulated fatty acid ester CAB prodrug encased in poloxamer 407 (NM2CAB) achieved plasma concentration above the effective viral inhibition concentration for up to 365 days after a single intramuscular injection in mice. Similarly, using the device in non-human primates resulted in detectable levels of the drug in plasma for nearly a year. However, in both non-human primates and mice, the plasma levels were higher for monthly injections of CAB compared to the single injection of NM2CAB, which could outweigh the benefit of a one-yearly injection depending on factors such as the patient's risk level, adherence level, accessibility, and financial limitations. These examples demonstrate the utility of microparticles, nanoparticles, and coatings in improving current methods of pre- and post-exposure prophylaxis.

3.2 | Injectable in situ-forming depots

Another application in which injectable in situ-forming implants could be particularly beneficial is the long-term delivery of prophylactic drugs to prevent the transmission or development of HIV. Benhabbour and colleagues have developed an ultra-long-acting biodegradable system composed of N-Methylpyrrolidone (NMP) and PLGA that can deliver HIV prophylactics for up to 1 year.[64] This injectable depot, which forms by solvent exchange, has the ability to incorporate multiple drugs (e.g., MK-2048 and dolutegravir (DTG), darunavir (DRV), ritonavir (RTV), atazanavir (ATV), or combinations thereof) in a single injection, which could relieve the burden of drug resistance. After optimizing NMP:PLGA ratios to extend the release of both MK-2048 and DTG in vitro (Figure 3A), the authors determined plasma concentrations and release rates for MK-2048, DTG, DRV, RTV, ATV, and drug combinations in vivo. The longest observed release was from the MK-2048-ISIF formulation, which was dosed at 550 mg/kg and showed sustained plasma concentrations above clinically relevant values for up to 1 year in mice. Figure 3B shows the plasma concentration of the selected drug versus time after administration in days, for the MK-2048-ISIF group, in which the dotted line represents the protein-adjusted inhibitory concentration required for 90% viral inhibition (PA-IC90).

Notably, this implant also demonstrated its capacity to be removed in the case of an allergic reaction or other adverse event. After removal, blood serum concentrations returned to pre-treatment levels within 1 week.

Traditional vaccination methods stimulate the immune system to produce neutralizing antibodies; however, passive immunization—in which antibodies, rather than antigens, are administered—is another method of preventative protection. This strategy has been most widely used in immunocompromised individuals who may not be able to mount a sufficient immune response to produce their own antigen-specific neutralizing antibodies but has also been investigated for pre-exposure and post-exposure prophylaxis.[65] Passive immunization confers protection immediately, as it does not require a host immune response, which can traditionally take weeks to months to achieve maximum protection.[66] However, passive immunization is limited by short antibody circulation time, which is typically on the order of weeks, and the need to be administered intravenously which can cause poor patient adherence and accessibility issues.[67] Using polymeric gels could extend the circulation time of the antibody, allowing the platform to work over a longer period of time (relative to the antibody's half-life) to meaningfully prolong protection. Kasse et al. used this approach to develop a subcutaneous supramolecular hydrogel that facilitates passive immunization against SARS-CoV-2 for prophylactic applications.[68] The hydrogel was able to restrict antibody diffusivity by approximately 60-fold in vitro. Additionally, in vitro stability testing of Centi-C10, a high-affinity monoclonal antibody that binds to the wild-type SARS-CoV-2 receptor binding domain (RBD), revealed that encapsulating the antibody in the hydrogel allowed it to retain approximately 40% of its initial binding activity after 3 weeks of constant agitation at 37 °C compared to a retention of <10% of its initial binding activity when incubated in PBS. Though this in vitro data is promising, additional optimization with in vivo testing is still needed to make this a viable clinical option for pre- or post- exposure prophylaxis.

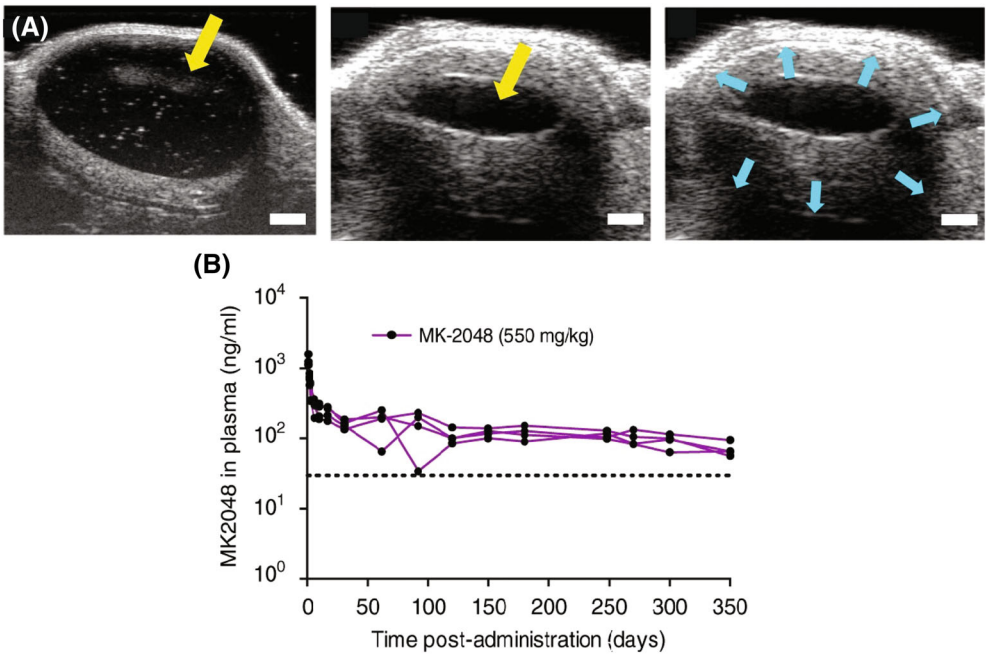


FIGURE 3 Prophylactic drug release from NMP-PLGA depots. (A) In vivo ultrasound images of in situ-forming implant after subcutaneous injection on (A1) day 0 and (A2) day 2. Dark center (yellow arrow) indicates the portion of the implant remaining in the liquid state. (A3) Day image of implant, blue/green arrows represent the outer boundary of the implant. (B) In vivo plasma levels of MK-2048 loaded at 33 ng/mL in which the dotted line represents the PA-IC90 value. Reprinted with permission from *Nature Communications*, Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery, Benhabbour S.R., Kovarova M., Jones C., Copeland D.J., Shrivastava R., Swanson M.D., Sykes C., Ho P.T., Cottrell M.L., Sridharan A., Fix S.M., Thayer O., Long J.M., Hazuda D.J., Dayton P.A., Mumper R.J., Kashuba A.D.M., Garcia J.V., http://creativecommons.org/licenses/by/4.0/.

Many groups are currently working to develop in situ-forming prophylactic depots. For example, some groups have capitalized on the in situ-forming gel properties of diblock polymeric products, which release the drug upon hydrolytic degradation. This type of system has been used for the delivery of HIV prophylactic drugs—specifically TAF and its metabolite, tenofovir—and demonstrated sustained release with clinically relevant concentrations for up to 60 days *in vivo*[69] and 180 days in vitro.[70] Another group created an injectable thermoresponsive PLGA hydrogel that releases long-acting rifabutin and provides protection from *Mtb* infection in a challenge model, continuing to achieve therapeutically relevant plasma concentrations for 16 weeks.[71] Additionally, bacterial burden 4 weeks after exposure (6 weeks post-injection) in the drug-loaded gel group was more than 1000-fold lower compared to the placebo group. The placebo group also experienced a significant bacterial burden in the liver and spleen, whereas the treatment group had no detectable bacterial burden or pathology associated with *Mtb* infection. This device will be discussed in detail in a later section, as it was used for both prophylactic therapy and the treatment of TB.

The use of particles and injectable implants for pre- and post-exposure prophylaxis for the prevention of infectious diseases has produced promising results, as detailed above. Pre- and post-exposure prophylaxis treatments typically offer short-lived protection and are therefore sensitive to patient adherence, which makes the development of controlled-release drug delivery systems targeting these applications clinically and commercially compelling. Ultimately, these systems seek to improve the real-world efficacy of current drugs, which are known to be effective at certain levels to decrease disease transmission and prolong survival.

4 | INFECTIOUS DISEASES TREATMENTS

Despite advances in both the prevention and treatment of infectious diseases like hepatitis B, malaria, and TB, they are, at present, both prevalent and unavoidable given the current healthcare ecosystem. However, they are major contributors to morbidity and mortality worldwide and should be seen as high-value targets for decreasing global suffering. Treating these diseases typically takes anywhere from 6 months to the remaining lifetime of the patient, depending on the pathogenesis of the diseases.[72-75] Some patients may prefer frequent oral administration to less frequent injections, but effective clearance of the infection is heavily dependent on high patient adherence.[76] Reducing the pill burden on the patient is one way to promote greater adherence and thereby real-world treatment outcomes in treating infectious diseases. Adefovir, a commonly prescribed antiviral for the treatment of hepatitis B, is taken orally each day for several years, or even the patient's lifetime.[77,78] An injectable, sustained-release platform delivering Adefovir could prevent disease progression, liver cirrhosis, liver failure, and carcinoma by extending the

duration over which a dose is effective.[79,80] Long-acting drug delivery platforms that pass through the gastrointestinal system are sparse, but Verma et al. demonstrated the multi-week release profile of a gastric-resident drug depot composed of a spray-coated polymer matrix to release TB antibiotics (tested with isoniazid and rifampicin, among others), albeit with potential administration challenges.[81] With a similar goal, Liang et al. have developed injectable PLGA nanoparticles that release rifapentine over 12 days with minimal off-target toxicity.[82] Table 1 describes current work with controlled-release systems for the use of infectious disease treatment. Some studies included in the table only include in vitro data, and while it is promising, follow-up in vivo studies will be necessary to garner additional excitement for clinical infectious disease treatment.

4.1 | Micro- and nanoparticles

Like the other drug classes discussed in this article, microparticles and nanoparticles have been widely explored for infectious disease treatment. For example, Antonov et al. developed controlled-release PLGA carriers of Levofloxacin (LFX) as a TB treatment.[97] They demonstrated the release kinetics and bactericidal effects of their bioresorbable LFX-loaded PLGA microparticles and scaffolds, which were produced using a particles from gas saturated solution (PGSS) technique. In vitro release studies showed that the PGSS fabrication method with trifluoromethane(scCHF$_3$) produced particles that released 100% of the LFX by day 35 with a significantly lower initial burst release than other fabrication methods tested, such as cryomilling of bioactive PLGA/LFX scaffolds fabricated using a supercritical fluid (SCF) plasticization and swelling method. The in vivo experiments to determine the anti-TB activity of the controlled-release system were conducted in mice infected with *Mtb* H37Rv by inhalation. To quantify the bactericidal effect of the systems, the lungs of mice from each group were harvested on day 7, 14, 21, and 28, and the number of colony-forming units (CFU) of *Mtb* in each lung was recorded. The experimental groups all experienced an initial delay in decreasing CFU compared to the oral administration control group (which was administered 5 days per week for the entirety of the four-week study). However, although the oral administration group elicited a steadier decrease in CFU than the experimental group, by the end of 4 weeks, the *Mtb* CFUs in the lungs of the LFX oral administration and LFX-PLGA microparticles were not statistically different ($p = .1$), demonstrating the anti-TB potential of LFX-loaded PLGA microparticles.

Polymeric particle encapsulation is also being explored as a method of extending the therapeutic duration of artemether, a drug used to treat chloroquine-resistant strains of *Plasmodium falciparum* (i.e., malaria), which has a half-life of only a few hours.[98,99] Mangrio and colleagues demonstrated that encapsulating artemether in the core of particles surrounded by a PLGA shell using coaxial electrospraying enhances not only encapsulation efficiency but also produces a sustained release profile with minimal toxicity to Caco-2 cells.[100] Additionally, by measuring the plasma concentrations of artemether in rats, they found that the AUC for the PLGA-encapsulated drug was approximately six times higher than the free drug. Bhide and Jindal have fabricated artemether-loaded PLGA nanorods in order to evaluate the effect of shape and aspect ratio on nanocarriers.[101] They embedded artemether-loaded PLGA nanospheres in a PVA/glycerol film and stretched the film to different extents in order to form different shapes. The in vitro release profile showed that particles stretched into nanorods showed a significantly slower release until the 24-h time mark than both the free drug and nanospheres (mitigating the burst release seen with the free drug and nanospheres alone), however, in vivo studies have yet to be reported.

In order to relieve the pill burden and toxicity of current treatment methods for hepatitis B, PLGA microspheres were developed by Ayoub et al. to release adefovir in a controlled manner for days to weeks.[102] Adefovir-loaded PLGA microspheres were prepared by single emulsion/solvent evaporation, and the effective half-lives of the drug alone and drug released from microspheres were determined to be 62.16 h and 359.10 days, respectively. Additionally, plasma concentration in rats of free drug peaked after the first hour (7.45 μg/mL) and remained constant for 8 h before being effectively reduced to zero after 24 h while the group receiving drug-loaded PLGA microspheres achieved a peak plasma concentration (7.4 μg/mL) after 6 h and then remained relatively steady near 6.5 μg/mL for 15 days.

These examples, along with similar work by other groups,[103–106] demonstrate the potential that microparticles and nanoparticles hold in fabricating controlled-release platforms for the treatment of multiple infectious diseases, such as TB, malaria, and hepatitis B.

4.2 | Injectable in situ-forming depots

Injectable in situ-forming hydrogels also show potential as controlled-release systems for the treatment of infectious diseases with the potential to reduce the pill burden associated with current drug formulations. For example, rifabutin (RFB), a drug used orally to treat pulmonary TB, is commonly prescribed to be taken twice a day for 3–6 months.[107] One injectable system that aims to lighten the RFB dosing schedule encapsulated and subsequently released RFB from an in situ-forming implant whose phase transition occurs by solvent exchange and PLGA precipitation upon injection.[71] Mice were challenged with an *Mtb* aerosol and LA-RFB was injected 7 days later. Mice were then monitored for up to 28 days to assess treatment efficacy (Figure 4A). A single injection of the drug-loaded depot decreased *Mtb* CFU counts to $8.8 \times 10^5 \pm 1.4 \times 10^4$ CFU/g in the lung 1 week after exposure and achieved no detectable burden in the liver or spleen (Figure 4B). *Mtb* was then undetectable 3 weeks after injection, and no pathological tissue changes were noticed whereas CFU values for the placebo group were higher in all organs tested, with $1.7 \times 10^6 \pm 3.2 \times 10^5$ CFU/g in the lung, $1.5 \times 10^4 \pm 9.7 \times 10^3$ CFU/g in the liver, and $2.6 \times 10^5 \pm 7.2 \times 10^4$ CFU/g in the spleen (Figure 4C), effectively demonstrating the depot's single-injection ability to reduce bacterial burden in the lung and prevent bacteria from spreading to distal organs in mice, reinforced by the histology staining comparing tissue conditions between the experimental and control groups in Figure 4D.

TABLE 1 Recent notable controlled-release systems for the treatment of infectious diseases not discussed in detail elsewhere in this review.

Disease	Method used	Motivation	Results & potential clinical impact	References
Malaria	Release of artemisone from an injectable poly(sebacic acid-ricinoleic acid) hydrogel	Reduce toxicity associated with the necessary high dose of treatment and maintain therapeutic concentrations over a longer period of time	In mice, early treatment (2 days post-infection) completely suppressed parasitemia, and late treatment (5 days post-infection) with a higher drug dose completely reduced parasitemia with no signs of side effects (in both cases, control mice died from cerebral malaria)	83
	Starch-lipid depot (starch with glycerol monostearate) releasing artesunate or artemether	Avoid potential microacidity associated with PLGA to protect antimalarial agents while improving the half-life of artesunate and artemether	Released clinically relevant doses of artesunate and artemether for 6 days in vitro	84
	Ivermectin released from poly-D, L-lactide and poly-E-caprolactone	Reduce toxicity and dramatic changes in blood concentration of drug	Released sufficient amounts of ivermectin for 6 months in vitro	85
	Intramuscular drug depot of lipid-based deconquinate for long-term chemoprophylaxis of malaria	Controlled release of treatment for liver-stage malaria infection to reduce dosing frequency and toxic effects of oral deconquinate delivery	Intramuscular administration of the depot maintained effective therapeutic levels in mice for 4–6 months, as well as offered protection from infection in mice for 120 days	86
Tuberculosis (TB)	Oil-in-water emulsion method to make PLGA microspheres releasing rifapentine for osteoarticular TB	Avoid side effects caused by oral and intravenous antibiotics and improve adherence	Agarose detection test and minimum inhibitory concentration results higher than that of free RIF and above reported necessary concentration in vitro	87
	Injectable rifampicin-loaded chitosan/hydroxyapatite bone cement that releases drugs and serves as a scaffold for bone regeneration in osteoarticular TB	Injected onto remaining bone after debridement surgery to avoid long-term anti-TB chemotherapy	Concentrations above minimum inhibitory concentration after 31 days with minimal cytotoxicity in vitro	88
	Rifampicin-loaded nanostructured lipid carriers (NLS) to selectively deliver drugs to macrophages (where the etiological agent of TB is predominantly located)	Reduce the side effects of long-term chemotherapy and improve adherence	Drug-loaded NLS improved bone marrow-derived macrophage uptake and significantly decreased the intracellular bacterial growth in vitro	89
	Mesoporous silica nanoparticles—either coated with PEI (releasing rifampin) or having a cyclodextrin-based pH-operated valve that opens only at acidic pH (to release isoniazid into MTB macrophages)	Target specificity to increase efficacy and therapeutic effect while decreasing toxicity	Acidic elute from pH-gated NP-INH reduced intracellular CFU by 1.5 logs compared to free INH, and 3 logs more compared to the neutral eluate from an equivalent amount of pH-gated NP-INH in vitro PEI-coated MSNP reduced intracellular CFU by 1.6 logs compared to free RIF and uncoated NP-RIF in human macrophages in vitro	90
Hepatitis B	PLGA microspheres loaded with entecavir formulated using in situ crystallization solid-in-oil-in-water double emulsion (S/O/W), traditional S/O/W, and spray drying in oil	Maintain benefits of entecavir while avoiding side effects associated with daily oral delivery on an empty stomach	A single injection of S/O/W formulated microspheres in rats maintained adequate plasma drug levels until day 42	91

(Continues)

TABLE 1 (Continued)

Disease	Method used	Motivation	Results & potential clinical impact	References
Cryptococcal meningitis	Injectable PLGA-PEG-PLGA thermogel to release amphotericin B to treat cryptococcal meningitis	Reduce the number of lumbar punctures needed to treat the infection, therefore lowering neurotoxicity and other adverse effects	A single injection reduced bacterial load in rats by almost 14-fold compared to soluble drug injections, and by 24-fold compared to the blank gel group. Additionally, it reduced the number of lumbar punctures and improved survival from 27.8% to 94.4%	92
	Propolis-loaded poly(n-butyl cyanoactylate) nanoparticles functionalized with polysorbate 80 to cross the blood-brain barrier and reduce cryptococcal infection	High concentrations of drugs needed to be present in CSF fluid (due to the inability of the drug to cross the blood-brain barrier) can cause off-target toxicity	Effectively lowered fungal burden in the brains, lungs, and kidneys of mice, showing the ability of a single injection to treat cryptococcal meningitis and cross the blood-brain barrier	93
HIV	Nanocrystallization of rilpivirine in nanosuspensions with different surfactants	Improve viral suppression by extending therapeutic duration and improving adherence	A single injection was able to maintain plasma concentrations for 3 months in beagle dogs	94
	PLGA nanoformulations containing two antiretrovirals	Improve adherence to long-term antiretroviral therapy by reducing dosing frequency	NPs sustained serum levels of both drugs in mice for at least 49 days and yielded a 3-log reduction of viral load compared to the mock-treated group	95
	HIV protease inhibitor released from biphasic PLGA/PVP matrix formulated using different methods (spray drying, oil-in-water emulsion, media milling)	Enable the formulation of poorly water-soluble drugs	A single intramuscular injection of different formulations, showed sustained release profile for up to 28 days after an initial burst in beagle dogs, with one of the spray dried formulations achieving the highest average plasma drug concentration	96

In the case of antimalarials, in situ-forming hydrogels that form from lyotropic liquid crystalline preconcentrates (LLCPr) to release artemether and lumefantrine artemisinin-based combination therapy have been developed by Dawre and coworkers. These systems can release their payloads over days[47] with 90% of artemether and lumefantrine released by hour 51.8 and 98.49 for the depot groups, respectively, and 10.9 and 25.53 for the free drugs, respectively, in an ex vivo model. Other notable work developing in situ-forming hydrogels includes polymeric micro- or nanospheres mixed with in situ-forming gels[108,109] and thermoresponsive hydrogels[110,111] with the ability to deliver drugs with extended release profiles, showing promise for treating infectious diseases such as TB and malaria.

5 | TRANSLATING TECHNOLOGIES TO THE CLINIC

Though the results from drug and vaccine delivery systems presented in this review are very promising, their clinical impact has yet to be felt. These technologies face challenges—both technical and practical—that must be overcome prior to widespread adoption. The technical challenges relate to the ability of these devices to function as desired. This means that drugs or vaccines are released in a bioactive form at a rate necessary to achieve an effective, yet safe, concentration of drug at the target site. Maintaining bioactivity may be particularly difficult for proteins, which can degrade via a number of mechanisms during device preparation and release that are not relevant for small molecules.[112] The practical challenges are also not unsubstantial as technologies that are most useful in LMICs face the prospect of limited profitability and limited infrastructure to support their use, despite their potential for an outsized positive impact on global health.

From a technical perspective, there are several strategies that can be employed to enhance the likelihood of translation. First, some drugs are inherently more stable than others and could be prioritized. As suggested by the large number of controlled-release systems that release small-molecule drugs and the dearth of those that release proteins, it is typically easier to maintain stability when the drug is a small molecule. Second, the size of the therapeutic window varies between drugs; therefore, drugs with larger therapeutic windows could be prioritized to increase the likelihood of long-duration release and translational success. Third, it is important that controlled-release systems are developed and optimized using the clinically relevant drug or vaccine since device performance can vary greatly between drugs in the same model. This is particularly problematic in the vaccination arena, where OVA is often used as a model antigen. In itself, the use

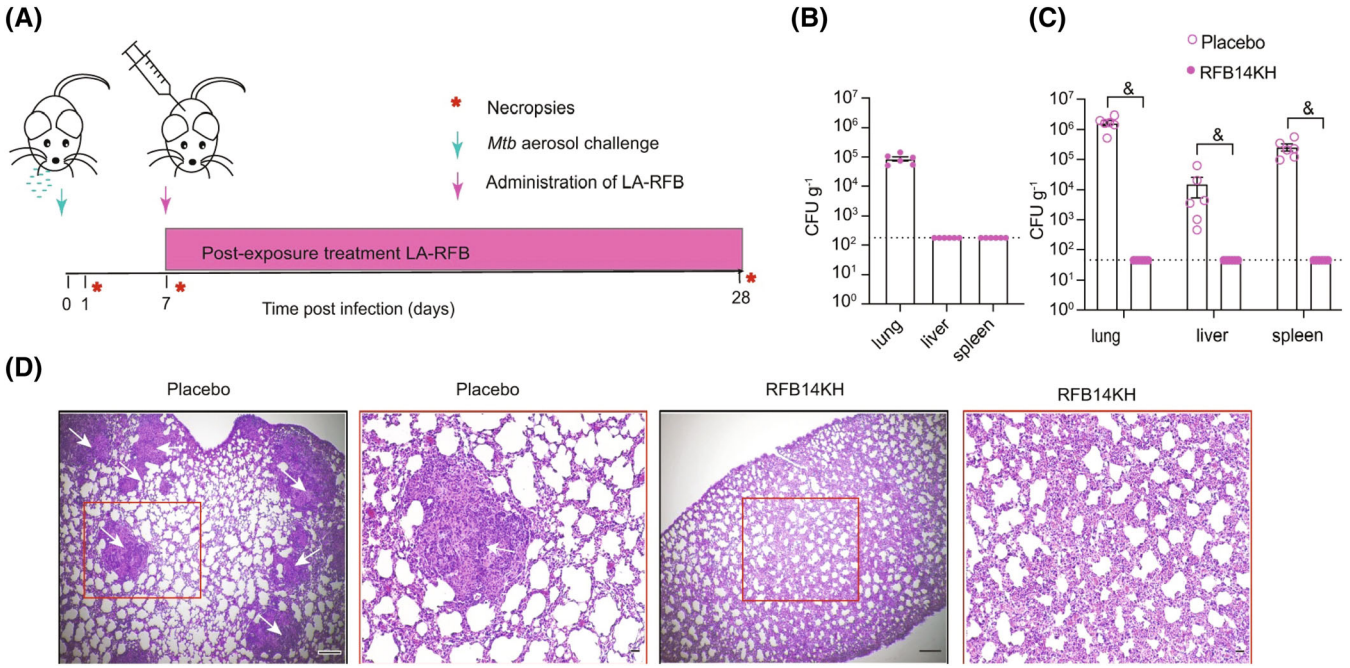


FIGURE 4 *Mycobacterium tuberculosis* (*Mtb*) clearance by controlled-release rifabutin (RFB). (A) Experimental schematic of the in vivo infection and treatment timeline used. (B) Bacterial burden in mice lungs, livers, and spleens, 1 week post-exposure and (C) 3 weeks after drug dosing for the placebo and treatment groups. (D) H&E staining of lung sections showing pathological changes in mice treated with placebo but not in mice treated with in situ-forming depot. Reprinted with permission from *Nature Communications*, A long-acting formulation of rifabutin is effective for prevention and treatment of *Mycobacterium tuberculosis*, Manse Kim, Claire E. Johnson, Alan A. Schmalstig, Ayano Annis, Sarah E. Wessel, Brian Van Horn, Amanda Schauer, Agata A. Exner, Jason E. Stout, Angela Wahl, Miriam Braunstein, J. Victor Garcia, Martina Kovarova, http://creativecommons.org/licenses/by/4.0/.

of OVA is well-justified as there are good tools to study the immune response to OVA (e.g., tetramers); however, studies should then progress to using clinically relevant (i.e., vaccine) antigens. Since OVA alone is not infective, there are no key epitopes that must be bound by antibodies to have a neutralizing effect. As a result, reports of OVA responses are unable to identify potential antigen stability issues, which are pervasive among biodegradable drug delivery systems. Significant loss of antigen can occur during encapsulation and release from polymers such as PLGA, for reasons such as its degradation products altering the environment inside the system and exposure to solvents during fabrication.[113,114] Though stabilization strategies have been reported, such as the use of basic excipients to control pH,[115] stabilization still remains a large challenge to overcome with many such systems.

From a practical perspective, the translation of injectable controlled-release systems for infectious diseases to the clinic has been stymied by their primary environmental use in LMICs. Infectious diseases are far more prevalent in LMICs than in high-income countries, which factors in heavily when for-profit entities assess the market opportunity. As the gross national income per capita is less than $4255 in LMICs,[116] individuals and governmental health ministries may simply lack the ability to pay much more, despite their technical advantages. As a result, controlled-release systems that offer both improved efficacy/availability *and* are the same cost—or better yet, less expensive—are those that will be most readily adopted in LMICs.[117] There are several ways this issue could be addressed. First, the increase in cost could be marginal, but the global demand large enough such that companies can more than recoup their initial investments in technology development and clinical trials. Second, comparatively rare use in high-income countries could yield a substantial profit while usage in LMICs is provided at or near the cost of producing and distributing it. Third, despite the added cost of producing controlled-release formulations, there could be opportunities to reduce net cost by, for example, reducing the number of personnel required for vaccination campaigns, achieving dose-sparing of a costly drug, or reducing the number of disposables (e.g., syringes and needles) required.[118]

In concert with marginal cost minimization, the minimization of up-front costs for technology development and clinical trials would also be helpful. Employing materials with precedence in clinically approved products, such as PLGA, could make the regulatory pathway smoother. Additionally, some trials may require more follow-up than others. In particular, prophylactics and therapeutics directly affecting the immune system may require more involved (and expensive) clinical trials than those that do not since the effects are not limited to the duration over which the drug or vaccine can be detected in the body. A potential consequence of this is that the FDA approves immune-modulating drugs less frequently than over-the-counter and small-molecule drugs whose effects subside after the drug is eliminated. The mean annual number of total new drug approvals between 2010 and 2018 was 41, while the annual mean number of vaccine

approvals in the same timeframe was 1.8.[119] Therefore, infectious disease drugs that do not rely on or trigger an immune response may be more readily translated due to lower risk and clinical trial cost.

6 | CONCLUSIONS

As evidenced by the numerous examples described above, injectable controlled-release systems have the potential to reduce burdens to infectious disease treatment and prevention, yet substantial technical and practical challenges remain before this potential can be realized. The factors contributing to suboptimal drug efficacy are numerous and vary depending on the application; however, two of the most common factors are poor patient adherence due to taxing dosing schedules and a lack of healthcare access, common in regions where infectious diseases are most prevalent. Microparticles, nanoparticles, hydrogels, and other in situ-forming depots are promising tools that may be able to improve the real-world activity of prophylactics and treatments. Nevertheless, there has been limited success to date. In particular, retaining the bioactivity of biologics during delivery system formulation and in vivo release remains a substantial challenge that must be overcome before the benefits of these systems can be fully realized in the clinic.

The development of single-injection vaccines has been an active area of research, as it holds the potential to significantly decrease the annual number of vaccine-preventable deaths due to infectious diseases. These formulations would greatly reduce the burden of vaccine transportation and administration, which can be logistically challenging in many areas, by truncating dosing schedules to improve vaccination coverage. Additionally, with the need for only one injection, there would also be a secondary effect of lowering immunization cost via a reduced scope of vaccination campaigns. Furthermore, these platforms might be capable of enhancing the immune response to vaccines, resulting in higher seroconversion rates and/or longer-lasting immunity. One challenge, however, is delivering clinically relevant antigens in an immunity-conferring conformations. To date, a large fraction of studies with promising in vivo data use ovalbumin as a model vaccine because there are well-established methods for evaluating the resulting immune response. Unfortunately, it is not possible to assess the retention of ovalbumin structure in the same way as a vaccine since, as a non-pathogenic protein, there are no epitopes important for eliciting a specific immune response (e.g., neutralizing antibody production for humoral immunity). For this reason, it is important that emerging delivery platforms demonstrate the ability to release clinically relevant antigens and be evaluated with assays that test the functionality of the immune response generated, such as cell-based antibody neutralization, T cell activation studies, and challenge models.

In some instances, vaccines may not be the most cost-effective disease-prevention strategies or a potent vaccine for the specific infectious disease of interest may not exist. For example, when a United States resident travels to a region where malaria is endemic, a pre-exposure prophylactic course may be preferred. Similarly, pre- and post-exposure prophylactics are commonly prescribed to people who have a high risk of contracting HIV. Regardless of the scenario, pre-exposure prophylaxis is maximally effective only if it is taken on a stringent schedule, which places a high burden on the patient. Though oral delivery systems are convenient for the patient and less invasive than injections, current oral formulations lack the ability to sustain release over an extended period of time due to the finite passage time through the gastrointestinal tract. Therefore, injectables are currently the best method to prolong the duration of drug activity over days, weeks, or months and the benefits of a long-acting sustained-release prophylactic therapy may outweigh the increase in invasiveness while also improving the drug's effectiveness at preventing disease transmission. Many systems in preclinical development have demonstrated strong potential as controlled-release platforms in vitro, yet these studies are not always indicative of how the system will perform in the body. Therefore, conducting in vivo studies is a crucial component of long-acting formulation development since it provides a better understanding of not only how the system will release, but also how the body and immune system will respond to be on the path to clinical translation. Fortunately, the effective circulating drug concentration necessary to provide protection is often known, enabling a pharmacokinetic study to act as a proxy in determining the duration of protection conferred by a long-acting injectable formulation.

If a patient has already been exposed to a pathogen, it is too late for traditional vaccination or pre-exposure prophylaxis, leaving post-exposure prophylaxis or treatment as the remaining options. Treatment can sometimes last a lifetime and can entail complicated dosing schedules and/or a high pill burden. These long-term therapies have also been correlated to severe adverse effects, such as liver cirrhosis, liver failure, and carcinoma.[36,37] Long-acting injectable drug formulations that reduce the cumulative amount of drug required by avoiding first-pass metabolism and/or avoiding the peaks and troughs associated with oral dosing could reduce the cytotoxic effects of metabolizing organs, such as the liver.[29] Like pre-exposure prophylaxis, the extension of activity and significant reduction in administration frequency are among the most important factors motivating the development of controlled-release prophylaxis and treatment. For instance, a six-month treatment for pulmonary TB consists of daily oral administration of four first-line drugs in different combinations over the course of treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol).[120] If an injectable controlled-release system had the ability to release these drugs at the appropriate time, a single injection could replace up to 470 pills in patients undergoing TB treatment, thus significantly alleviating the treatment burden and mitigating adherence problems, which could outweigh the one-time increase of invasiveness compared to an oral system. Again, pharmacokinetic studies can be used as a more accessible assay for determining PEP and treatment efficacy, though disease models typically serve as the gold standard.

As a leading cause of death and morbidity worldwide, there is a clear clinical need for improved management of infectious disease. Drugs and vaccines have greatly reduced this burden, but existing formulations are limited by challenging real-world use conditions. Reducing the number of injections required or transitioning from oral administration to parenteral injections holds promise to overcome technical and logistical challenges that currently undermine the impact of existing drugs. Though yet to experience clinical success for

infectious disease, the lessons learned from clinically approved controlled-release systems used for other applications and careful consideration of the practical constraints imposed by their primary use in LMICs should accelerate their translation to the clinic.

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CONFLICT OF INTEREST STATEMENT

Kevin J. McHugh is an inventor on multiple patents granted and pending that are related to controlled drug delivery, including the technology discussed in References 42,43. Kevin J. McHugh is also a consultant for Nanocan Therapeutics.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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