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Review article

# Engineered drug delivery devices to address Global Health challenges

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Dedicated to the memory of Sung Wan Kim. A remarkable scientist and a great human being.

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ABSTRACT

There is a dire need for innovative solutions to address global health needs. Polymeric systems have been shown to provide substantial benefit to all sectors of healthcare, especially for their ability to extend and control drug delivery. Herein, we review polymeric drug delivery devices for vaccines, tuberculosis, and contraception.

## 1. Introduction

The advent of the recent global pandemic with COVID-19 has not only highlighted the difficulties in dealing with such an international disease, but it has also given credence for international institutions to promote the development of novel and efficient drug delivery systems [1]. The application of innovative platform technologies coupled with advances in materials science provide a glimmer of hope for solving the most prevalent global health challenges (Fig. 1). In this review, we explore some of the most promising polymeric systems capable of addressing these challenges.

## 2. Material science in vaccine delivery

Although there has been much progress in the fight against diseases, such as polio and diphtheria, global vaccination has stalled at approximately 86% [2]. Enhanced worldwide coverage will require sustainable innovative vaccine platforms. Here, we highlight new advances in polymer science that aim to address the limitations of current vaccine delivery systems for the benefit of global health.

### 2.1. Single injection vaccines for improved compliance

Developing single-injection immunizations that show equivalence, if not enhancement, may negate the poor compliance that plagues global vaccine programs [3]. Single-injection immunizations are placed as one of the top priorities in grand health challenges globally [4]. Initially, Preis and Langer were the first to demonstrate the potential of single injection vaccine delivery systems through the continuous release of antigens from an implanted ethylene vinyl acetate (EVA) copolymer pellet in mice [5]. Prolonged exposure of antigens elicited a strong and persistent antibody response; this was comparable to the secondary

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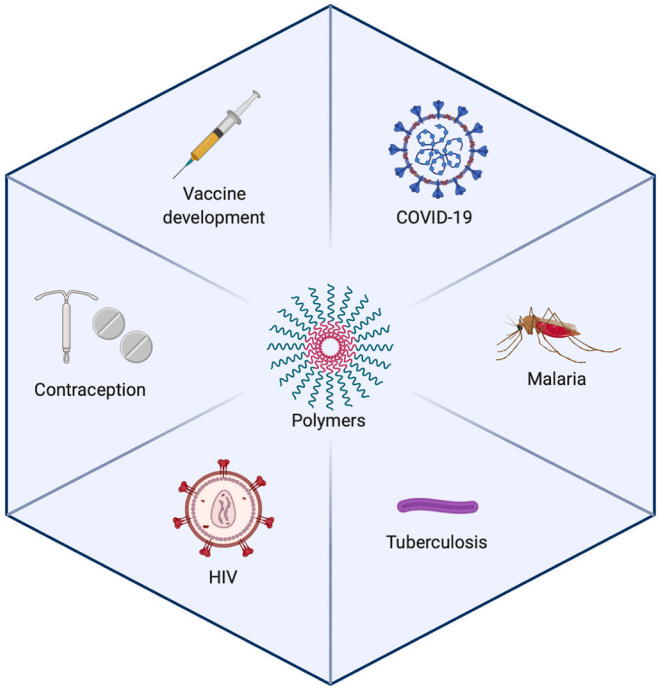


**Fig. 1.** Application of materials sciences in global health challenges; created with BioRender.

response induced after two injections of similar dosage of antigen emulsified in complete Freund's adjuvant7 weeks apart. This system caused no adverse inflammatory reaction at the site of implantation, prompting the World Health Organization (WHO) to instigate the "Program for Vaccine Development" focusing on the development of an effective single-dose vaccine.

Although the first example of single-dose immunizations was based on sustained release of an antigen, pulsatile release more closely replicates the conventional vaccine schedule. Poly(lactide-*co*-glycolic acid) (PLGA) microparticles (MPs) are primary examples of pulsatile antigen delivery systems (Fig. 2) [3]. PLGA is found in FDA approved devices and is biocompatible, biodegradable, and one of the most widely studied synthetic polymers in drug delivery and diagnostics. Antigen-encapsulated PLGA MPs with varying sizes and compositions were

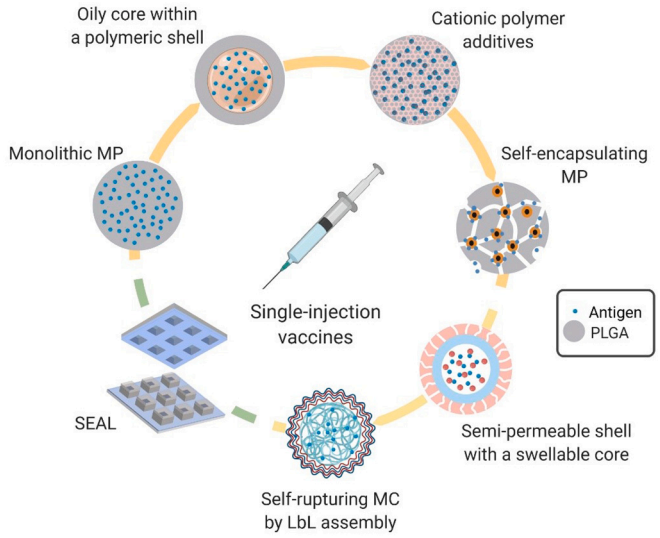


**Fig. 2.** Polymeric platforms for single-injection vaccine delivery; created with BioRender.

designed to modulate the release and achieve booster doses (*i.e.*, small MPs <10 μm for priming and larger, slow-releasing MPs for self-boosting).

### 2.2. Polymer degradation mechanisms and antigen release profiles

#### 2.2.1. Bulk-eroding polymers

Polymer degradation mechanisms have a direct influence on antigen stability and release profiles. Bulk-eroding polymers are those wherein water readily permeates into the polymer matrix and allows for degradation to occur throughout the matrix. This is often accompanied by the burst release of an encapsulated antigen. PLGA, which undergoes degradation by hydrolysis of an ester linkage, is an example of a bulk-eroding polymer system. Antigen release from PLGA MPs follows a triphasic mechanism: (1) an initial burst of antigen located at or near the surface, which acts as a priming dose for the intended vaccine, (2) a lag phase with minimal release, and (3) a second burst of antigen release as water penetrates through the matrix and hydrolyzes the matrix polymer creating a network of pores that cause the MPs to fall apart. This acts as the vaccine self-boost at a time concordant with the intended vaccination schedule. The delayed release is often defined by the polymer characteristics, including molecular weight (MW), composition, and crystallinity.

Following the WHO's report on PLGA as a potential vaccine carrier, various antigens including tetanus toxoid (TT) [6], diphtheria toxin (DT) [7], hepatitis B [8,9], human immunodeficiency virus (HIV) [10], rotavirus [11] and malaria [12] have been encapsulated in PLGA MPs for single-injection immunizations. The antigen-specific antibody responses have been comparable to that of conventional multi-dose vaccines. Other multivalent vaccine carriers have also been created with the ultimate goal of achieving a "one-shot vaccination" for infants. For example, tetravalent PLGA MPs containing *Haemophilus influenzae* B and DT were shown to be highly immunogenic against all four antigens, as determined by antibody titers in guinea pig sera [13]. Unfortunately, antigen stability remains the Achilles heel for PLGA MPs and limits their practical application. Significant loss of antigen occurs as a result of exposure to organic solvents, high shear stress of double-emulsion fabrication process, aggregation from water permeation inside the MP matrix, as well as antigen sensitivity to the acidic microenvironment within the MP matrix [14,15]. Several methodologies have been attempted to negate the reduction in antigen bioavailability including the addition of small molecule stabilizing agents (*i.e.*, excipients) [16,17], liposome co-encapsulation/entrapment [18] and antigen or polymer modifications through the addition of hydrophilic polyethylene glycol (PEG) block(s) [19]. Although such methods enhance the antigen stability under certain conditions, developing a multifaceted approach to minimize the adverse effects of all the sources of damage has proved to be challenging.

To protect the antigen from aggregation and denaturation, strategies such as encapsulation of antigen in a protective oil layer prior to entrapping in PLGA MPs (Fig. 2) have been pursued [20]. The oil reservoir of an antigen minimizes the water-mediated inactivation process. In particular, mineral oil can enhance the immunogenicity of the encapsulated antigen due to its adjuvant properties. TT-loaded oil core MPs showed a pulsatile release profile *in vitro* with a second burst occurring within ~20 or 60 days from the initial burst, depending on polymer properties [20]. Compared to monolithic systems, the core-shell morphology provided antigen release in a relatively pulsatile fashion with an initial burst effect as low as 8% of the loaded antigen. In another study, a hydrophilic hydroxypropyl cellulose core within a PLGA shell was examined for protection of the antigen upon exposure to organic solvents during microencapsulation [21]. In this approach, hepatitis B surface antigen (HBsAg) was encapsulated and was found to have improved stability. The MPs elicited strong antigen-specific antibody response upon single injection in mice that was similar to two injections of alum adjuvant vaccines that were 15 days apart. Compared

to conventional PLGA MPs, *in vitro* release studies showed that the inclusion of a hydrophilic core led to an even larger initial burst release followed by a smaller pulse at day 15.

An alternative to the aforementioned strategies is the electrostatic complexation of antigens with basic cationic polymer additives (Fig. 2). Complexation with a polymer can prevent antigen aggregation and denaturation. Cationic polymers can buffer acidic microenvironments during hydrolysis of the matrix. Compared with small molecule excipients that can quickly diffuse out of the polymer matrix, polymers remain in the MP matrix for prolonged periods of time and release out simultaneously with encapsulated antigen upon degradation of the matrix. For example, poly(L-lysine) (PLL) and Eudragit E PO are examples of polymers that can form stable complexes with the negatively charged inactivated polio vaccine (IPV) [22]. PLGA MPs formulated with small amounts of Eudragit E PO additive demonstrated improved stability of the highly pH-sensitive IPV. MPs experienced 2 burst releases about 25 days apart *in vitro*, which follows a clinically relevant vaccination schedule. Upon single administration of the MPs, a non-inferior neutralizing immune response was observed in rats for IPV serotypes 1 and 2, but not type 3. In addition, an alternative formulation that incorporated a branched polyethylenimine (PEI) in the organic phase as a pH-modulator and PLL in the aqueous phase as a complexation agent with IPV, led to stabilization of IPV type 3 (but less so for type 1 and 2) and induction of a comparable IgG titer to two bolus injections. Although these results are promising, there is more work required for the clinical translation of these strategies to improve IPV stability within the particle.

Another strategy to protect the antigen involves a "self-encapsulating" MPs (Fig. 2) that is designed to avoid antigen exposure to organic solvents and high shear stress during preparation [23]. In this method, porous PLGA MPs are made using the traditional double emulsion method but with added leachable trehalose as a porogen and calcium/aluminum based adjuvant gel ($CaHPO_4/Al(OH)_3$) as an antigen trapping agent. Porous MPs are then loaded by incubating them in an aqueous antigen solution that allows diffusion and binding of the antigen to the trapping agent. Subsequent heating of the MPs above the hydrated glass transition temperature ($T_g$) of PLGA closes the pores and entraps antigen within the MP matrix. OVA-loaded self-encapsulating MPs released the OVA antigen over ~42 days *in vitro* (achieving 67% of total antigen release) with a burst of about 28% on day 1. A single-dose administration of the MPs in mice elicited an anti-OVA serum IgG antibody response, significantly higher than the conventional prime-boost vaccination regimen of soluble antigen admixed with $CaHPO_4$ adjuvant. Additionally, MP administration enhanced antigen specific $CD8\alpha^+$ T cell response compared to soluble OVA admixed with $CaHPO_4$ adjuvant system [24]. One challenge for this system is that trehalose, a common excipient to enhance vaccine stability, can interfere with loading of the antigen [25]. Moreover, the incubation period to achieve enough antigen loading (1 day at room temperature and 1 day at 4 °C) followed by an additional incubation at elevated temperature (2 days) can adversely affect the viability of thermo-labile antigens, as shown for HBsAg with an *in vitro* release of only 10% of total loaded amount [25].

Compared to PLGA, various other biodegradable polymers have also been explored for the controlled release of an antigen. For example, poly(ε-caprolactone) (PCL) is a semi-crystalline and hydrophobic polyester that has been investigated for vaccine development. Although it is a bulk-eroding polymer, its crystallinity leads to more resistance against water diffusion within the particle compared to PLGA and hence provides a more stable pH microenvironment than PLGA. PCL MPs have been reported for single-injection vaccine platform against brucellosis. The *in vitro* release profile of subcellular Brucella antigenic extract from PCL MPs displayed a pulsatile release profile with pulses about 15 days apart, while retaining a neutral pH during degradation [26]. However, the very low $T_g$ of PCL (−60 °C) can limit its application due to instability of particles especially during storage or at body temperature.

#### 2.2.2. Surface-eroding polymers

Surface-eroding polymers are a class of biodegradable polymers that are more resistant to water penetration. Degradation occurs at the polymer/water interface through hydrolysis, and antigen is released at the MP surface as the polymer breaks down. The surface erosion mechanism offers a less acidic microenvironment within the particle which results in higher antigen stability. Polyanhydrides (PAnhs) are one of the most widely studied polymers of this class and have found many uses in the medical devices and pharmaceutical sectors. Copolymers composed of 1,6-bis(p-carboxyphenoxy)hexane and sebacic acid (P(CPH-*b*-SA)) are examples of commonly used PAnhs. The molecular weight (MW) and block ratios determine the rate of degradation of these polymers. *In vitro* release studies of TT-loaded MPs using P(CPH-*b*-SA) at 20:80 block ratio depicted an initial antigen release of approximately 80% within 5 days; this was followed by continuous release of the remaining antigen up to day 10 [27]. Single injection of these MPs in mice induced a high overall TT-specific IgG response, which was comparable to two bolus injections (5 days apart) [27]. A limitation of this polymer system is the low glass transition temperature ($T_g < 25$ °C) of the copolymer that can compromise MP integrity. Poly(ortho) esters (POEs) are another class of surface-eroding polymers that have been explored for vaccine delivery. The degradation of POEs are affected by the polymer MW and the alkyl substituents on the polymer. MPs containing lysosome, a model protein, encapsulated in a biodegradable microporous membrane showed pulsatile antigen release with the timing of the pulses dependent on the alkyl substituents [28].

The inherent nature of surface-eroding polymers generally makes them more suitable for sustained delivery (*e.g.*, zero-order kinetic). Other strategies have been investigated to achieve burst release, including a multi-laminated structured system with interspersed antigen-filled and antigen-free polymer layers. An example of this used a composite cylindrical device (4.5 mm) comprised of a 4-layered structure that included the drug-loaded fast-eroding (poly(1,3-bis[p-carboxyphenoxy]propane-*co*-sebacic acid) (P(CPP-*co*-SA)) layer coated with a drug-free P(CPP-*co*-SA) layer, a drug-free slow-eroding poly(D,L-lactic acid) (PLA), and finally a drug loaded P(CPP-*co*-SA) layer [29]. The *in vitro* release of carboxyfluorescein, a model small molecule, demonstrated two rather continuous release phases over the course of a week.

## 3. Osmotic rupture for antigen release

Instead of relying on polymer degradation for antigen release, MPs may also be fabricated with a swelling core surrounded by a semi-permeable membrane (Fig. 2). This can result in the pulsatile release of cargo through increased osmotic pressure within the core. An example of such system is the Explotab®, a sodium starch glycolate (a strong osmotic agent), coated with a Eudragit S film (water soluble above pH 7) plasticized with dibutylphthalate, and finally an outer layer of Eudragit NE (water insoluble) containing a small amount of hydroxypropylmethyl cellulose (HPMC) additive as a porogen. Upon contact with an aqueous environment, the water soluble HPMC dissolves away from the matrix, creating a semi-permeable membrane upon which water penetrates and swells the core. Swelling continues until rupture of the middle layer resulting in the release of the payload. When these MPs were loaded with hemoglobin-, a pulsatile release pattern was observed. The release time can be controlled (from 3 days to 26 days) by increasing the porogen concentration [30].

Alternatively, "self-rupturing" MPs have also been made using a layer-by-layer (LbL) deposition (Fig. 2). This system involves a dextran-based cationic core made of dextran-hydroxyethyl methacrylate dex-HEMA *co*-polymerized with cationic dimethylaminoethyl methacrylate (DMAEMA) for subsequent bio-polyelectrolyte deposition. The core was surrounded by a multilayer coat of bio-polyelectrolytes. The penetration of water through the semi-permeable membrane swelled the encapsulated hydrogel and hydrolyzed the carbonate ester linkage within the backbone. This led to degradation of the gel, leaving the surrounding

membrane impermeable to the gel's degradation products and the biomolecule cargo, causing sudden rupture of the membrane. The degradation kinetics can in turn be tuned by altering microgel properties such as crosslink density [31].

A common problem with LbL assembled MPs, especially those containing weak polyelectrolytes, is their instability upon a small change in pH or ionic strength of the media. Within physiological conditions, this may lead to early release [32]. Nevertheless, the allows encapsulation of small MPs (<3 μm) within a large MP (~150 μm). Upon rupture of the large microcarrier, small MPs are released and can be efficiently phagocytosed by antigen presenting cells (APCs). To achieve this, a large microcarrier is designed with bio-polyelectrolyte (sulfate/poly-$_L$-arginine bilayers) multilayer coating on a dex-HEMA-DMAEMA microgel that comprises of small MPs made by dextran sulfate/poly-$_L$-arginine bilayers on $CaCO_3$ sacrificial template [33]. There is extensive *in vitro* work supporting this system; however, the *in vivo* efficacy has been limited due to stability, unknown clearance of the polyelectrolytes from the body, and especially cellular infiltration and degradation of the polyelectrolyte shell by recruited inflammatory cells [34].

Among all the platforms mentioned, PLGA MPs are by far the most extensively studied for single-injection immunizations. Despite holding significant promise, there are still several challenges for their clinical translation. One primary challenge is that emulsion particles have a significant initial burst followed by a second smaller "pulse" after a delay; this contrasts with the clinical vaccination regimen that usually requires the same dose for the prime dose and booster. The booster from the MPs is typically a broad continuous release rather than a true pulse [35]. Despite differing views and reports as to what type of release kinetics is more effective in inducing protective immunity, pulsatile antigen release kinetics is still preferred for regulatory approval [36,37]. Furthermore, there is a lack of synchrony between the release of the antigen and adjuvant used. Co-administration of an adjuvant with antigen is usually required for inducing immunity. Significantly different physicochemical differences between antigen and adjuvant (*i.e.*, much smaller adjuvants size compared with protein antigens) results in a more rapid release of the adjuvant.

The next generation of vaccines attempt to circumvent the problems associated with current techniques. A notable platform that overcomes many challenges associated with emulsion-based particles is based on microfabrication techniques (Fig. 2) [38]. This bottom-up approach called StampEd Assembly of polymer Layers (SEAL) has enabled fabrication of 3D PLGA MPs with a built-in antigen reservoir. The 3D core-shell micro-cubes are first filled with an antigen and adjuvant and sealed by aligning the polymer lids with the bases upon brief heating (~3–5 min) to above the PLGA $T_g$. The antigen thermal stress is minimal during this short heating time. This approach demonstrated a much sharper pulsatile release profile, mimicking that of a bolus injection. A single injection of OVA-filled MPs admixed with a soluble dose showed superior anti-OVA IgG in mice sera compared to two bolus injections at a similar dose due to the particle adjuvant effect. Such reservoir containing particles with burst release offer a new approach to vaccines. Although further research remains in this area for successful clinical translation, this technology appears promising for efficient single dose immunization.

## 4. Polymer science in the development of efficient particles as carriers

Developing innovative antigen delivery systems are critical to advancing vaccine development. Polymer science provides a strong tool to tailor physicochemical properties required for an effective vaccine. As such, polymeric carriers, if rationally designed, can enhance the adjuvant properties or even replace the conventional adjuvants due to their self-adjuvant properties. Leveraging advances in polymer chemistry, particles with desired size, charge, hydrophobicity and morphology can be designed to promote the stimulation of the immune response [39]. Such flexibility in design enables fabrication of vaccine delivery carriers where classical vaccines have failed. Here, we highlight various synthetic polymeric particles that address the limitations of current vaccine delivery systems.

The high virulence of certain pathogens (*e.g.* Hepatitis B virus, Hepatitis C virus, and HIV) has shifted the field of vaccines toward development of safer vaccines compared to traditional ones (*i.e.*, live attenuated or inactivated pathogens) to avoid the risk of pathogen reversion. Subunit vaccines represent a new generation of vaccines that are highly purified and much safer than traditional vaccines. They are usually specific proteins or synthetic peptide components of the disease pathogens. Lack of pathogen associated molecular patterns required for antigen recognition makes them safe but not very immunogenic. Hence, the induced immune response by subunit vaccines is usually short-lived or incomplete, requiring periodic boosting. Adjuvants, defined as components that enhance intrinsic immunogenicity of antigens, are often necessary to trigger immune response against these poorly immunogenic antigens. Aluminum hydroxide (alum) is one such example; it is one of the first vaccine adjuvants approved for human-use and remains the most common one [40]. The adsorption of vaccine antigens onto alum is the conventional approach for enhancing immunogenicity through the formation of a depot at the injection site and enhancing antigen presentation. Unfortunately, patients may experience allergic reactions to alum, and vaccines that use alum may also require multiple doses at timed intervals to achieve long-lasting immune responses. More importantly, alum's inability to induce a potent cellular immune response makes it ineffective against intracellular pathogens and warrants the development of safer and more effective approaches to inducing immunogenicity.

Polymeric MPs/nanoparticles (NPs) have emerged as effective antigen carriers to enhance antigen immunogenicity and to minimize inflammatory responses associated with existing adjuvants. In addition to the ability of these carriers to protect the encapsulated antigens, their particulate nature and small size (0.1–10 μm, similar to the dimension of viruses and bacteria), allows them to be readily recognized and phagocytosed by APCs. Depending on their size, polymeric particles either rapidly travel to the lymph nodes (LNs) (20–50 nm) or be retained in the interstitial space (0.5–10 μm) and require APCs such as dendritic cells (DCs) to transport them to the LNs. This depot formation at the injection site provides sustained release of antigen/adjuvant, whilst also reducing the spread of antigen systemically. More importantly, particle systems can promote antigen cross-presentation and induce cellular responses, which is in stark contrast to soluble antigens released from alum. As a result, these particles may enable the use of less potent antigens and offer a potential dose-sparing strategy. Another remarkable advantage of particle delivery systems are their ability for simultaneous delivery of antigen and adjuvant to the same APCs, which is an important feature for stimulating a robust immune response. In general, particle carriers can augment the immune response either by enhancing antigen presentation and subsequently antigen uptake by DCs (passive targeting) or directly targeting DC-specific receptors by surface coupling an antibody or a ligand [41]. Toll-like receptor agonists (TLRa) are among the most potent adjuvants that can stimulate DCs to express antigen and co-stimulatory molecules for production of selective cytokines inducing T cell responses.

A variety of polymeric particles have been developed as vaccine carriers with antigens and adjuvants encapsulated inside or conjugated onto the particle surface. The synergistic effect of antigen-loaded PLGA MPs/NPs along with alum gel is also reported to enhance antibody titer for TT [42]. The immune-potentiating effect of alum, even at a very low dose, is attributed to depot formation for release of antigens from MPs and its ability to attract immunocompetent cells [17,42–44]. PLGA particles have also been reported for their self-adjuvant effect. PLGA NPs with encapsulated or conjugated antigens are extensively explored to prolong antigen presentation and proved to be efficient in inducing higher antigen-specific antibody titers [45,46]. Alternative to

adsorption of antigen on alum, antigen-adsorbed on the surface of PLGA and PLA particles also showed adjuvant effects, as reported in immunization of mice against influenza virus [47]. PAnhs have also been reported for their inherent adjuvant effect and immune activation properties. For example, amphiphilic polyanhydride NPs made of P(CPH-*co*-SA) and P(CPTEG-*co*-CPH) formed an antigenic depot upon administration in mice that persisted for as long as 12 weeks depending on the copolymers' ratio. PAnh-based NPs also showed lower systemic inflammatory response and tissue damage at the injection site compared to alum or Freund's incomplete adjuvant [48].

Self-assembled amphiphilic copolymers also serve as nanoscale delivery systems for subunit vaccines. One such example is a graft copolymer composed of N-(2-hydroxypropyl) methacrylamide (HPMAm) and methacrylamide (MAm) segments with PEG side chains conjugated to TLRa that self-assembled into immunogenic NPs (700 nm) at high TLRa density. The particles promoted retention of adjuvant for up to 20 day in draining LNs [49]. This localization enhanced APCs uptake, whereas systemic distribution was observed for free agonist. Subcutaneous co-administration of NPs with soluble OVA on day 0 and 14 in mice enhanced $CD8^+$ T cell response and OVA-specific IgG titers skewed toward a Th1 phenotype. Mice immunized with either OVA, or to a lesser extent, SIV Gag protein admixed with NPs, showed increased antigen specific $CD8^+$ T cells response and significant protection against a post-vaccination challenge, indicating the effectiveness of targeting TLR receptor in antigen cross-presentation and induction of a cellular response [50]. Additionally, other polymers may be explored for their unique drug delivery properties [51–54].

### 4.1. Intracellular delivery

Inducing a robust $CD8^+$ cytotoxic T lymphocyte (CTL) response is the ultimate goal for subunit vaccines, which requires antigen presentation on the major histocompatibility complex (MHC) class I molecules. Antigens taken up from the extracellular environment and transported into endosomes within DCs generally enter the MHC class II antigen processing pathway; the MHC class I antigen loading pathway uses cytosolic peptides for presentation. A strategy to enhance the antigen presentation on MHC class I involves antigen delivery to the cytosol of DCs. Such intracellular delivery carriers are especially critical for DNA and RNA vaccine delivery. Hence, designing MPs capable of escaping *endo*-lysosomal barriers and releasing their payload directly into the cytosol is critical for efficient cross-presentation and induction of CTL response. This is especially important for developing vaccine delivery systems against intracellular pathogens, such as hepatitis C, HIV, and malaria.

pH-sensitive polymers that degrade within acidic pH environment of endo/lysosome may be well-suited for cytosolic delivery of antigens. Such pH-dependent release was conferred to PLGA NPs by addition of ammonium bicarbonate (Fig. 3A) [55]. Ammonium bicarbonate regulated the antigen release within endosomes and lysosomes (pH ~ 6.5 and 5.0, respectively) by reacting with acidic protons producing $CO_2$ and ammonia. OVA-loaded PLGA NPs with ammonium bicarbonate were efficiently captured by DCs *in vitro*, escaped the lysosome into cytoplasm, and enhanced antigen cross presentation. Additionally, the NPs also induced upregulation of co-stimulatory markers and inflammatory cytokines. Immunization of mice with these NPs led to more OVA-specific $CD8^+$ T cells, a stronger cytotoxic capacity, and an enhanced serum IgG response with higher IgG2a/IgG1 ratio. Furthermore, polymers bearing hydrazide or acetal groups are known to undergo acid hydrolysis. MPs based on these polymers can increase osmotic pressure within the phagosome and disrupt the phagosomal membrane [56,57].

Reducing environments, especially those within the lysosome containing a high concentration of reducing agents such as glutathione, can also be leveraged to trigger release. Polymers containing disulfide bonds are known for their susceptibility to reduction and cleavage of the disulfide bond and release of antigen. Using LbL deposition, an antigen was encapsulated in a single component, polycation-free, thiolated poly (methacrylic acid) ($PMAA_{SH}$) hydrogel MPs with disulfide linkages between layers, Fig. 3B [58]. Mice vaccinated with OVA-loaded $PMAA_{SH}$ MPs induced markedly higher T cell stimulation and proliferation of both $CD4^+$ T and $CD8^+$ T cells compared to soluble OVA [59]. Interestingly, MPs increased $CD4^+$ T cell proliferation by up to 70-fold, while $CD8^+$ T cells were increased by only factor of 6. This may be due to phagocytosis of the MPs; phagosomes have a less reducing environment than the cytosol or the nucleus and may result in inefficient disulfide reduction [60].

Another platform for cytosolic delivery is amine-containing polymer-based particle systems. These particles have a "proton-sponge" effect that can disrupt the phagosomal membrane and deliver their payload directly to the cytosol. This means that the buffering effect of the basic polymers in the phagosomal acidic environment leads to an influx of protons for further acidification, and subsequently induces a high osmotic pressure that leads to rupture. Various multifunctional copolymers with pH-sensitive "endosomolytic segments" have been designed for cytosolic delivery [61]. An example of such a system for enhanced cross-presentation is micellar NPs based on an amphiphilic block copolymer (BCP) for co-delivery of antigen and adjuvant [62]. The BCP is composed of multiple functional segments that includes a core forming segment made of triblock terpolymer containing poly(butyl methacrylate) (PBMA) to drive the self-assembly, poly(dimethylaminoethyl methacrylate),PDMAEMA, as an endosomal-releasing segment, and a pH-responsive block of poly(propylacrylic acid), Fig. 3C [62]. The cationic corona is formed by a block copolymer comprised of a poly (pyridyl disulfide ethyl methacrylate) block for the reversible conjugation of antigen, and a PDMAEMA block for electrostatic complexation with adjuvant. This micellar NP enhanced the intracellular delivery of OVA and CpG and class I antigen presentation compared to soluble OVA in an *in vitro* T cell activation assay. Mice immunized with these OVA-conjugated NPs showed enhanced $CD8^+$ and $CD4^+$ T cell response and a greater humoral response with balanced IgG1/IgG2 antibody titer indicating the accessibility of the antigen to both MHC class I and MHC class II processing pathways.

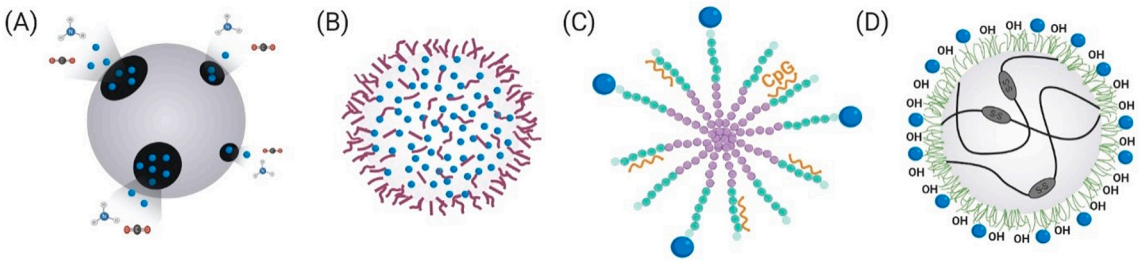


**Fig. 3.** Polymeric particulates for intracellular delivery of antigen shown in blue. (A) PLGA NPs containing ammonium bicarbonate. (B) $PMAA_{SH}$ hydrogel MC formed by LbL assembly. (C) Micellar NP formed by BCP self-assembly. (D) NP with crosslinked PPS core and polyhydroxylated surface; created with BioRender. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

To supplement the current vaccine approach that relies on antigen uptake by peripheral DCs to enhance immune responses, there are efforts to directly target the DCs residing in LNs. Targeting DCs in the LNs where the population of DCs are high may obviate the need for sophisticated cell-specific targeting. Ultra-small NPs with sizes of 25 nm were fabricated to have a hydrophilic corona of Pluronic and a hydrophobic crosslinked polypropylene sulfide core that underwent degradation within the oxidative environment of lysosomes [63]. Upon intradermal injection, the NPs were transported and retained in the draining LNs for up to 120 h. This study also utilized complement cascade activation as opposed to commonly explored TLR activators and inflammatory cytokines. Complement activation has the advantage of being a direct biochemical defense mechanism to kill and opsonize microorganisms, whilst also modulating DC maturation to enhance the immune response. To initiate the complement cascade, NPs were engineered to have hydroxylated surfaces, Fig. 3D. OVA-conjugated NPs administered intradermally in mice induced LN DC maturation, as well as $CD4^+$ and $CD8^+$ T cell proliferation on par with unconjugated OVA co-injected with an endotoxin lipopolysaccharide. This study highlights two alternative strategies for vaccination, including interstitial-to-lymphatic delivery of antigen and adjuvants to LN resident DCs and the *in situ* complement activation to mature these cells. Thus, further exploration of effective vaccine delivery pathways is warranted.

### 4.2. DNA/RNA delivery

DNA vaccines are promising candidates for protection against viral, bacterial or parasitic infections and have the potential for therapeutic treatment of cancer and chronic viral infections. This type of vaccines has the advantage of safely activating both the humoral and cell-mediated immune response. A plasmid DNA (pDNA) that encodes for a protein antigen of interest is the basic component of a DNA vaccine formulation. For a DNA vaccine to be effective, the carrier should preserve the pDNA structure in a transcriptionally active form and efficiently transfect APCs. Cytoplasmic delivery and access to the cell nucleus are required for the synthesis of the encoded protein. Endogenous expression of the encoded antigen by transfected APCs followed by processing and presenting the antigenic peptide fragments through MHC molecules facilitates the generation of an immune response. Polymeric MPs may enable DNA delivery with less adverse effect compared with conventional delivery systems, such as viral vectors and cationic liposomes (*i.e.* lipofectamine) [64].

A large variety of cationic polymers capable of efficiently condensing anionic DNA cargo have been studied for gene delivery [65]. PLGA MPs fabricated using cationic surfactants were extensively studied for DNA delivery. A phase I clinical trial for an HIV vaccine involved a prime dose of cetrimonium bromide-containing cationic PLGA MPs with adsorbed DNA followed by a boost with a recombinant envelope glycoprotein in MF59 adjuvant. This vaccine elicited potent strain-specific neutralizing antibodies in all participants [66]. However, the neutralization breadth, key missing element in development of HIV vaccine, was very limited., broadly cross-neutralizing antibodies.

Damage to the structure of plasmid DNA may occur within the acidic PLGA microenvironment. Therefore, blending cationic polymers to buffer the acidic pH may help to preserve the integrity of the plasmid. The cation-sponge effect of these basic polymers is well-suited for DNA delivery. Poly (β-amino esters) (PBAEs) are reported to provide high loading capacity through electrostatic complexation with DNA and maintain the supercoil structure of pDNA. Blending PLGA with 25% PBAE retained a similar release profile to that of PLGA MPs whilst significantly enhancing the transfection efficiency similar to that of lipofectamine 2000 [67]. Despite several additives having been shown to enhance the transfection efficiency of PLGA MPs (*e.g.* poly(ethylenimine) (PEI) and PBAEs), their use for DNA delivery is still limited due to the low loading efficiency and slow PLGA degradation. PLGA MPs, even at their fastest release, cannot achieve the delivery and expression of DNA encoding antigen within the lifespan of DCs *in vivo* [68].

pH-sensitive polymers that degrade in the phagosomal acidic microenvironment can potentially address some of the hurdles for intracellular delivery of nucleic acids. POEs are a good example of a pH-sensitive polymer systems that also degrades through surface erosion. Upon acidification in the late phagosome, the acid-labile orthoester linkage of POEs rapidly breaks down and releases the cargo [69]. POE MPs with a tertiary amine-containing co-monomer, *N*-methyldiethanolamine (MDEA), were shown to delay the release of electrostatically bound DNA; this system induced a robust immune response *in vivo* [69]. A follow-up study on these polymers showed that blending POE with a small amount (0.04 wt%) of PEI can further modulate the release of DNA and enhance the immune response [70]. PEI-DNA complexes released upon degradation of the MPs were shown to increase the endosomal escape of pDNA through the proton sponge mechanism [71]. PEI within POE MPs were found to be distributed preferentially on the surface, which resulted in the peripheral localization of DNA due to the complex formation with PEI. The surface orientation of the PEI and DNA can enhance the preferential cellular uptake through an interaction with pattern recognition receptors that recognize foreign DNA [72]. This study highlights how simple physical blending can modulate the MP surface properties while also maintaining bulk properties (*e.g.*, pH-sensitivity) [73,74].

Alternatively, pH-responsive amphiphilic BCPs have also been designed to overcome endosomal barriers. Self-assembled BCPs can provide improved mechanical properties and subsequently better retention of their payload compared to phospholipid-based systems. A multifunctional amphiphilic BCP was designed for DNA delivery; this system was comprised of PDMAEMA, poly(diethylaminoethyl methacrylate) (PDEAEMA) block for DNA condensation, and a second segment containing poly(diethylaminoethyl methacrylate), PDEAEMA and PBMA [75,76]. At physiological conditions, the BCP self-assembled into micelles with a hydrophilic PDMAEMA corona, which underwent pH-induced dissociation at acidic pH. The BCP demonstrated high transfection efficiency in two monocyte cell lines [76]. Compared with pDNA, mRNA is a safer strategy due to the inability to integrate within the host genome.

Other materials, including lipid-based systems, also hold significant promise for vaccine development. One such example is the lipid NP-encapsulated mRNA for SARS-CoV-2, which has been utilized for vaccine protection and delivery by several companies including Moderna and Pfizer-BioNTech. Clinical trial conducted by Moderna showed high neutralization responses and Th1-skewed CD4 T cell responses in all participants against SARS-CoV-2 [77]. Both platforms have been approved by FDA for emergency use vaccination, further highlighting the importance of the development of new vaccine delivery platforms,

## 5. Microneedles for drug delivery

Another challenge in global health is development of needle-free vaccine delivery systems [4]. Microneedles (MN) have attracted considerable interest for vaccine applications due to the following reasons: (1) providing painless administration of the active pharmaceutical ingredients and large molecules, (2) avoiding first-pass metabolism, and (3) increasing the immunogenicity of administered antigens allowing for a dose-sparing effect. From an immunological perspective, MNs can increase vaccine effectiveness by delivering antigen intradermally to the epidermis and dermis wherein a significant population of APCs reside. MN delivery systems can be further utilized for delivery of antigen loaded particles [78].

Dissolvable MNs are especially promising for vaccine delivery and are fabricated from water-soluble synthetic polymers, such as poly(vinyl pyrrolidone) (PVP) and poly(vinyl alcohol) (PVA) or natural polymers (*e.g.*, sugars, carbohydrates) with embedded antigen. These MNs rapidly dissolve within the interstitial fluid and deliver the cargo to the skin APCs. They also offer several advantages, including an adjuvant effect

[79], whilst stabilizing vaccine components for an extended period at room temperature through integration into the MN polymer matrix. This obviates the need for "cold chain" requirement, which is necessary for current vaccines [80]. PVP MN array was the first example of soluble MNs, proving their efficiency in generating superior antibody and cellular response as well as complete protection against lethal influenza challenge in mice, compared with conventional routes [79]. NP-loaded MNs have also demonstrated enhanced immune the response. For instance, MNs made of Gantrez ™ AN-139 a copolymer of methyl-vinylether and maleic anhydride (PMVE/MAnh), loaded with antigen encapsulated PLGA NPs, generated an antigen-specific cellular immune response in mice. This provided complete protection against a murine para-influenza model through the activation of antigen-specific cytotoxic $CD8^+$ T cells [81]. Rapidly dissolvable MNs made of PVA, sucrose, and PLGA MPs loaded with either OVA or rHBsAg were created and administered to mice at a prime-boost schedule 21 days apart [25]. It was demonstrated that antigen-specific IgG titers on par with the conventional alhydrogel-adsorbed antigen vaccination regimen.

Natural polymers, such as carboxymethyl cellulose (CMC), can also be used for fabrication of dissolving MNs. Multilayered rapidly dissolvable MNs of CMC were used for the delivery of Fluvax® 2008, a commercial influenza vaccine, with added Quil A as an adjuvant, and showed superiority compared to IM injection [82]. Recently, CMC MN arrays have been reported for delivery of recombinant protein subunit vaccines against Middle East Respiratory Syndrome (MERS) and COVID-19 [83]. Several MERS vaccine variants (with or without integrated immunostimulatory TLR ligands) were tested. Among those, only one variant, monophosphoryl lipid A (TLR-4 agonist) adjuvanted vacci-neshowed antibody response when delivered subcutaneously, while all of the MERS vaccine variants when delivered by MN induced significantly higher level of antigen-specific IgG and neutralizing antibodies, exceeding that of subcutaneous administration. The MN array also induced significantly high antigen-specific antibody response for all SARS-CoV-2 subunit vaccines as early as 2-weeks post immunization.

While MNs have been mainly explored for rapid release of vaccines (*i.e.*, prime/boost dose), PLGA MNs have been recently reported for single administration of vaccine with programmed delayed burst at a clinically relevant vaccination schedule. Building off of the SEAL technology, these core-shell MNs were fabricated using similar 3D-manufacturing approach. MNs containing a clinical vaccine (Prevnar-13) provided complete protection in rats against lethal dose of *S. pneumoniae* upon single administration [84].

Overall, minimally invasive MN-mediated vaccine delivery holds great promise for promoting vaccine accessibility worldwide, as well as vaccine efficiency. There are a variety of novel polymer materials that can be considered for transdermal delivery [85–88]. Continued progress has led to a plethora of designs (*i.e.*, multilayered MNs, multi-length arrays for targeted delivery to different skin layers) for a range of antigens (inactivated virus such as IPV or live-attenuated measles vaccine stability [89,90]). Recent clinical trial data seem to show promise for MN vaccine delivery [91,92]. However, there is only a handful of companies capable of MN mass production (*e.g.*, 3 M, Corium international, *etc.*). Thus, accessibility still needs to be optimized. Furthermore, concerns regarding immunological issues need to be addressed including further investigation on the potential implications of polymer dissolution in the skin, the possibility of microbial penetration, and the bioavailability of differing antigens following administration. Despite these concerns, the valuable impact of these delivery devices, particularly in the developing world, as well as globally remains an exciting prospect.

## 6. Improving delivery for global chronic infectious diseases

An example of the application of polymers in the fight of chronic infectious diseases is that of tuberculosis (TB) which continues to thrive globally with a prevalence of 10 million in 2017 [93]. Due to poor drug adherence, this has led to drug resistance and severe morbidity and mortality. One major reason for this poor compliance is the multitude of drugs that tuberculosis patients are required to take over a protracted period [94]. Therefore, methodologies to enhance and improve compliance of medication are needed to bolster treatment and reduce multi-drug resistance.

### 6.1. Inhaled antibiotics

Pulmonary delivery of TB drugs may be ideal given that the primary site for the TB infection are the lungs [95–97]. In particular, lower doses of TB drugs can be delivered through inhalation and still result in effective treatments, thus reducing the chance of toxicity and enhancing localized drug concentrations [95].

There have been a multitude of studies evaluating the efficacy of inhaled anti-TB drugs [98–110]. Natural polymers, including trehalose and leucine, and synthetic polymers of PLGA have all been used as excipients for inhaled drug formulations. Inhaled colistin, capreomycin, amikacin/kanamycin/gentamycin, streptomycin, and isoniazid have all been administered in patients [98–104]. A number of these clinical studies have been performed in extensively drug resistant patients where treatment options were severely limited [98–103]. Recently, inhaled capreomycin was evaluated in a phase I study where healthy adult participants were administered a single inhaled dry powder dose of capreomycin. The highest dose of capreomycin exceeded the minimum serum inhibitor concentration for *M. tuberculosis* [104]. Furthermore, inhaled pyrazinoic acid esters, spectinamide, rifampicin, clofazimine, isoniazid, and pretomanid have been tested *in vivo* with positive results in relevant animal models [105–110].

With inhalers costing the same as syringes and needles to manufacture, there may be significant economic benefit for pulmonary delivery, especially in drug resistant patients. With proper use instruction, disposable single use inhalers would enable safe effective dosing in patients [95].

### 6.2. Long-dwelling drug depots

There are several long-dwelling drug depots that aim to improve compliance. One potential form of depot is a long residence gastric device that releases drug at a steady rate (Fig. 4). Our lab has demonstrated a multi-gram gastric device for continued release of medication [111,112]. Drug was suspended in a silicone matrix coated with PEG. This system demonstrated extended release for up to 30 days and longer. The drug-polymer matrix was then inserted onto a coiled nitinol wire for extended gastric residence. For pharmacokinetic (PK) studies in a swine model, the device was placed and removed through a nasogastric tube. The PK of doxycycline from the gastric resident system loaded up to 10 g of drug demonstrated extended release for 30 days in pigs [112]. There was no evidence of damage to the gastric mucosa, gastric obstruction, or weight loss. As a part of the study, the team surveyed patients in a TB clinic in India and found patient acceptability would be high for such a device [111].

Furthermore, long-dwelling polymeric and ceramic composite implants have been developed for extended release of TB drugs for the treatment of osteoarticular TB [113,114]. Osteoarticular TB manifests in 10–35% of patients with extra pulmonary tuberculosis [113–115]. These implants have been designed to be placed during debridement of infected bones and facilitate bone regeneration. The material selection for implantation is critical as it needs to account for mechanical strength and bone regeneration. Polymers and ceramic composites such as hydroxyapatite, tricalcium phosphate, and PVA facilitate the required bioactivity and porosity. Utilizing a multilayer strategy of drug-PVA with hydroxyapatite, scaffolds were created with increased compressive strength (2.9 MPa) compared to hydroxyapatite alone (0.9 MPa). These scaffolds were later implanted into the femurs of animals, which revealed that the implants provided extended release of drug for up to

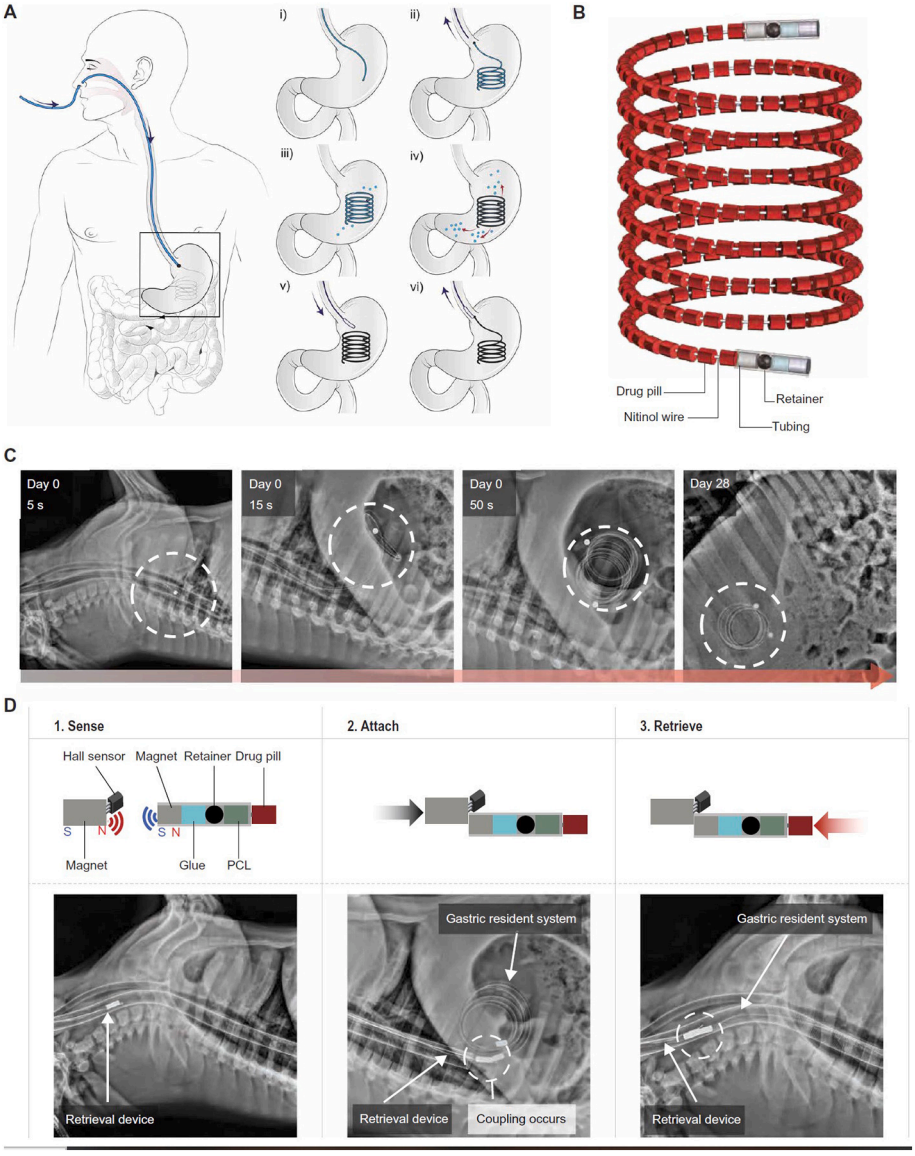


**Fig. 4.** Gastric residential device for delivering anti-tuberculosis medications. (A) Placement of the device through a nasogastric tube. (B) Cartoon representation of the assembled device. (C) Radiographic evaluation of the device in the stomach over 28 days. (D) Method of sensing and retrieving the device from the stomach using a Hall effect sensor. Used with permission from reference [112].

12 weeks post-implantation achieving concentrations above the minimum effective concentration. Further, the implant achieved histologic confirmation of bone regeneration at 12 weeks post-implantation [113].

### 6.3. Nanotechnology-based approaches

Nanomedicines have been evaluated for the treatment of tuberculosis, which others have reviewed in great detail [116,117]. Despite much promise on this front, clinical translation remains elusive.

Apart from inhaled systems, notable nanotechnologies for TB include oral and subcutaneous systems. Pyrazinamide has been encapsulated in niosomes, non-ionic surfactant polymeric vesicles, and evaluated in a guinea pig model infected with *M. tuberculosis* [118]. After three weeks of twice weekly subcutaneous administration, it was reported that the pyrazamide-loaded niosomes achieved significantly lower root specific lung weights and fewer colony forming units compared to free drug doses at twice weekly and 6 days weekly [118]. Orally administered PLGA particles encapsulating streptomycin, isoniazid, and pyrazinamide were found to have significantly greater biological activity against *M. tuberculosis* compared to standard intramuscular streptomycin and oral isoniazid and pyrazinamide [119].

### 6.4. 3D printed compartmental dosage forms for TB

Additive manufacturing is a powerful tool for generating devices of defined sizes and shapes with high integrity. Groups have evaluated drug delivery using additive manufacturing processes, including mouth guards and tissue reconstruction scaffolds [120]. For TB, the generation of both oral compartmental dosage forms and hierarchical scaffolds have been created for local delivery of agents to combat TB [121,122].

One strategy to reduce the total number of tablets is to combine drugs for tuberculosis. However, combining certain anti-tuberculosis agents together may be challenging due to their differing stabilities. To overcome this, 3D printed oral dosage forms of isoniazid and rifampicin have been developed to delay release of the rifampicin [122]. Isoniazid and rifampicin were individually combined with polyethylene oxide and then hot-melt extruded to create filaments. The shell of the dosage form was 3D printed out of PLA, manually filled with the drug

filament and then capped on one end to enable delayed drug release. Through sealing the compartment, they found a difference in drug release *in vitro* but not *in vivo* in rats [122]. Such a system offers significant protection for unstable drugs, as well as reducing drug burden on the patient.

Others have evaluated the use of 3D printing for developing drug scaffolds specifically in osteoarticular tuberculosis. Isoniazid and rifampicin were combined with carboxylated mesoporous bioactive glasses and methyl-functionalized mesoporous silica NPs to increase drug loading. After combining the ceramic particles with poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate), the full paste was 3D printed into a scaffold. These systems were tested in rabbits demonstrating prolonged drug release with no hepatotoxicity or renal toxicity. In addition, implantation in the rabbit femur revealed bone regeneration at the site of the implant. These systems offer the opportunity to incorporate drug release within orthopedic applications [121].

There have been numerous strides from a preclinical front to advance technologies that would benefit tuberculosis patients. Unfortunately, due to the challenges of treating TB including prolonged latency, drug penetration, and drug resistance, few technologies have been translated [111]. Inhaled anti-TB drugs have been clinically tested and are among the most promising for immediate translation given the ease of administration and acceptance of inhaler use [95]. However, a major challenge that remains for the inhaled route is whether sufficient drug can be delivered.

## 7. Contraception: Providing simple and cheap drug delivery solutions

Contraception is a major public health concern as unintended pregnancies account for approximately 45% of total pregnancies in the United States [123]. Despite the clinically available contraceptive methods of barriers, intrauterine devices (IUDs), implants, oral agents, and patches, there still remains issues with compliance and ease of administration [124]. As such, there are large efforts to improve contraception through newer drug delivery systems. Here, we summarize some of the major clinical and pre-clinical polymeric contraceptive devices.

### 7.1. Implants

Subdermal polymer implants (Nexplanon® and Implanon®) are long-acting reversible forms of contraception that have gained significant traction. These systems are a combination of EVA copolymer and etonogestrel formed into match-stick sized implants. The etonogestrel impedes ovulation and thickens the cervical mucus [125]. The implant is placed in the medial aspect of the arm in the subdermal tissue and provides controlled drug release for up to 3 years.

### 7.2. Intrauterine systems

Intrauterine devices (IUDs) have been well-established as long acting reversible methods of contraception [125]. These devices are T-shaped and are placed directly into the uterus. There are five FDA-approved IUDs currently on the market with the promise for others, including (non-hormonal) Paragard® and (hormonal) Mirena®, Kyleena®, Liletta®, and Skyla®. The polymers used to control drug elution of the hormones are non-degradable silicones, such as polydimethylsiloxane (PDMS) that surround a polyethylene frame [126]. The two different classes of IUDs achieve this using slightly different methods. The non-hormonal IUD involves releasing small copper ions toxic to sperm. The hormonal IUDs inhibits ovulation and increases cervical mucus that blocks sperm. IUDs need to be replaced between 3 and 10 years, depending on the type of IUD.

### 7.3. Microneedles for contraceptives

MN strategies have been investigated for the delivery of levonorgestrel. To improve release of microneedles off their backing layer, an effervescent backing involving sodium bicarbonate and citric acid were included to generate carbon dioxide bubbles. The MNs were found to separate from the patch in less than 12 s using the effervescent backing compared to >50 s for other backings that including PVP and PVA/sucrose. This was further supported through *ex vivo* studies showing release of MNs in porcine skin using the effervescent backing was 96%, compared to release of MNs from PVP or PVA/sucrose backing at <45% and < 35%, respectively [127].

The pharmacokinetic analysis of the MNs in rats demonstrated that the levonorgestrel plasma concentration stayed above the therapeutic threshold of >0.2 ng/mL for more than 30 days. Ultimately, the plasma concentration dropped down to zero by 60 days. There were no signs of skin irritation. To investigate the safety and tolerability of the effervescent MN patch, the patches were applied to the skin of ten women of reproductive age. It was found that 92% of MNs separated from the patch with an application time of <1 min. Although, mild erythema was noted at the application site immediately after administration, this largely resolved within 1 h. A post-administration assessment of the subjects revealed that 90% would prefer a monthly MN patch compared to oral administration [127].

### 7.4. Gastric systems

Oral dosage of contraceptives is highly favorable due to their ability to rapidly discontinue the medication, ease of use, and an ability to self-administer. However, approximately half of women on oral contraceptives have missed one or more dosages over the course of 3 months [128]. To improve patient adherence, a once-a-month contraceptive pill was developed to release levonorgestrel for 3 weeks with a hormone-free period of 1 week. These pills are oral gastric resident dosage forms that open up to six connected polymeric arms that were unable to pass the pylorus due to the size and shape of the device.

To evaluate stability of the drug in acidic conditions, they placed the drug in simulated gastric fluid for 24 h, which showed no significant degradation of the drug. Drug release from two different polymers, including poly(sebacic anhydride) and PDMS, demonstrated the ability to control release rates based upon drug loading and polymer type. As a result, multiple oral gastric resident device forms were created: one with three arms of the poly(sebacic anhydride) and PDMS and another with all six arms of PDMS. Both devices demonstrated near constant-release of drug. For the device with two polymers, there were multiple peak serum concentrations occurring on days 3, 11, and 17. Whereas, for the PDMS only device, the serum concentration of levonorgestrel occurred on day 2 and then slowly reduced over the course of 3 weeks. Lastly, the stability of the device in the stomach of three swine over the course of a month showed that the device largely remained intact. This strategy offers the unique opportunity for prolonged, safe oral delivery of contraceptive agents [129].

### 7.5. Microchips

An implantable microchip has been developed to deliver drugs at defined rates by the user or provider. Hormones and peptides have been proposed to be excellent candidate drugs due to their potency. Clinical testing of this system focused initially on delivery of human parathyroid hormone fragment (hPTH) for the management of osteoporosis. The device was implanted in eight female osteoporotic patients with endpoints including pharmacokinetics, safety, bioactivity of the drug, and reproducibility of drug release. Pulsatile release of hPTH was found to be comparable to subcutaneous injection of hPTH. The study also showed good tolerability among patients with minimal pain [130].

Given their ability to deliver high potency drugs, long functional

time (> 15 years), and programmability, the implantable microchip has been proposed for use as a valuable method for contraception. The microchips would be placed in the arm, buttocks, or upper abdomen and set up to deliver levonorgestrel. Additionally, the dosage could also be adjusted as required [131]. This offers a unique strategy over a much longer time frame than others.

These novel strategies for contraception may enable greater compliance and ease of use compared to current standards. However, there remain challenges in providing global access due to cost or need for aseptic conditions for implantation. Smaller technologies that allow for implantation through a hypodermic needle will no doubt aid access globally.

## 8. Conclusion

The field of materials science continues to enhance our application of drug delivery for the betterment of global health challenges. There remains significant promise in polymeric vaccines and devices for addressing current health challenges. Yet, one of the major drivers for such innovation to continue is the unyielding support from major funding sources, such as foundations and local and federal grant giving agencies. This is pivotal to address the unmet global need for sustainable and scalable solutions in health. This coupled with mechanisms to develop user acceptance requires ongoing public engagement and accessibility dialogues so as to build sustainable community and professional healthcare relationships to enhance user uptake.

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