A comprehensive review on the COVID-19 vaccine and drug delivery applications of interpenetrating polymer networks

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Abstract

An interpenetrating polymer network (IPNs) is a concoction of two or more polymers (natural, synthetic, and/or a combination of both) in which at least one polymer is synthesized or crosslinked in the intimate presence of the other. These three-dimensional networked systems have gained prominence in a series of biomedical applications, especially in the last two decades. The last decades witnessed a surge in the meaningful applications of interpenetrating polymer networks, especially in drug delivery as simple IPN systems advanced and resulted in the formation of highly efficient microspheres, nanoparticles, nanogels, and hydrogels, intelligent enough to sense and respond to changes in external stimuli such as temperature, pH, and ionic strength. The structure of the polymers, crosslinking agents, crosslinking density, and polymerization method play an integral role in determining the properties and application of IPNs in drug delivery. This review article is a modest effort to highlight the importance and applications of different types of interpenetrating polymer networks for the sustained, site-specific drug delivery of various therapeutic formulations, as witnessed in scientific research literature over the past 22 years (2000–2022). A special section of the manuscript is devoted to studying the efficacy of network polymers in vaccine delivery and highlighting the future scope (if any) of incorporating the IPN system in COVID-related vaccine/drug delivery.

Keywords Interpenetrating polymer networks (IPNs) · Drug delivery · Crosslinked structure · Controlled release · COVID

Abbreviations

APC Antigen-presenting cell
AuP Gold porphyrin
BIS N, N’-methylene bis acrylamide
CAN Ceric ammonium nitrate
CAP Capecitabine
CIPRO Ciproflaxin
COVID Coronavirus disease
CTG Carboxymethyl tamarind gum
DL Diltiazem
DMA Differential mechanical analysis
DNA Deoxyribonucleic acid
Dox Doxorubin
DSC Differential scanning colorimetry
FTIR Fourier transform infra-red
FU Fluoro uracil
GG Gum ghatti
HepG2 Hepatoma G2
HIV Human immunodeficiency virus
IPN Interpenetrating polymer network
mRNA Messenger RNA
NEMA N-ethylmaleamic acid
NMR Nuclear magnetic resonance
PAA Poly acrylic acid
PAAm Polyacrylamide
PEG Poly ethylene glycol
PTX Paclitaxel
PVA Polyvinyl alcohol
PVP Polyvinyl pyrrolidone

Highlights

• The three-dimensional network of IPN systems is particularly valuable for drug encapsulation and a site-specific, targeted drug delivery.
• The structure-property relationships of these polymeric systems can be utilized for novel biomedical applications.
• A novel application is the targeted delivery of protein-based and mRNA-based vaccines such as a COVID-19 vaccine proposed as a novel approach in this perspective.
• Network polymers can ensure a sustained vaccine delivery at a specific site for a prolonged time period.
• It can maximize the availability and efficacy of the vaccine while reducing the need for multiple booster shots.
Interpenetrating polymer networks (IPNs) are a term used to define such a polymeric network. One polymer chain permeates another cross-linked polymeric chain/s without forming any covalent bonds between the two. The polymeric chains are so strongly interlaced in an IPN that it is not theoretically possible to separate them without detaching some chemical bonds [3]. IPNs garnered significant scientific interest and appreciation in the last two decades owing to their unique characteristic of combining the valuable properties of two or more individual polymers into a single polymeric network. As a result of this combination, in some cases, an interpenetrating polymer network is reported to possess entirely new properties previously not found in any of its single constituent polymers. It is analogous to synthesizing a new chemical compound with entirely new and more valuable characteristics than its constituent atomic elements. However, in this particular case, no covalent bonds are involved.

Interpenetrating polymer networks are viable for controlled and targeted drug delivery as their three-dimensional networked structure allows easy encapsulation of the drugs. A single polymer itself cannot regulate the complex parameters associated with drug delivery applications; crosslinking two or more polymer networks is a better approach. Natural polymers can deliver drugs at a controlled rate for extended periods with greater bioavailability. On the other hand, synthetic polymers can offer high mechanical strength. IPNs offer a means to preserve and combine these meaningful features of each polymer type to form an interlocked structure with improved stability for sustained/controlled drug release. The shortcomings witnessed in the literature about therapeutic dose administration by conventional routes can be overcome by using IPNs. A drug passing through the body without any external encapsulation can undergo biodegradation in the body via a series of chemical and enzymatic reactions. This may result in reduced therapeutic efficiency of the drug when it reaches its site of action. Drug entrapment in three-dimensional polymeric networks can prevent this, ensuring a specific amount of drug is released at a specific site for a controlled period. The “IPNs in drug delivery applications” section contains a detailed discussion of the application and efficacy of a wide range of IPN systems in drug delivery operations.

Other than drug delivery, the scientific community has also reported widespread applications of interpenetrating polymer networks as wound dressing formulations [4–6], for tissue engineering to design artificial scaffolds [7, 8] and injectable supports [9] and bone graft substitutes [10], etc. Incorporating natural and/or biopolymers even of synthetic origin is believed to offer a sustainable approach to IPN synthesis owing to the low toxicity profiles of such polymer subunits. Polymers like chitosan, alginate, and natural gums [11, 12] are biocompatible and biodegradable, making them good candidates for synthesizing IPN systems that could be utilized in future drug delivery and tissue engineering applications.

Stimuli-sensitive IPNs such as pH-sensitive and thermosensitive IPN systems are emerging as excellent options for controlled and targeted therapeutic delivery. Such IPNs are also called “smart” polymeric multicomponent systems as they can intelligently respond to an exogenous and/or an internal stimulus like variations in pH, temperature, and pressure. These intelligent polymers are sensitive and can be modified easily in terms of shape and volume to respond to the selected stimuli and to perform their drug delivery tasks at specific sites in the body in a controlled manner. These specific stimuli responsiveness characteristics also offer additive protection to the encapsulated drug from the surrounding biological environment. IPN hydrogels and nanogels fall under the intelligent IPNs category.

Effective drug delivery in therapeutic and preventive vaccines is another primary concern of the scientific research community, especially since the onset of the coronavirus pandemic in the world. The literature cites evidence of the use of interpenetrating polymer networks in the safe and efficient delivery of vaccines as well. Polymeric nanomaterials such as hydrogels and nanogels have been used for the safe encapsulation of different types of vaccines aimed at the fine-tuned modulation of the immune system against a variety of viral infections. A thorough discussion on this aspect of polymeric drug delivery and its potential extension to COVID-related drugs and vaccines using interpenetrating polymer networks is another primary goal and a novelty of this comprehensive review article discussed in the “IPNs for vaccine delivery” section.

A previously published document by Raina et al. [3] is an excellent review regarding the efficacy of interpenetrating polymer networks as an enterprising drug delivery system. This perspective, although not exhaustive, is developed by going through an extensive literature survey on the subject matter and thus can be consulted as a comprehensive source of information on the drug delivery applications of IPNs. Most of the existing literature has discussed mainly the synthesis, preparation, and applications of drug delivery system of IPNs. This study has discussed synthesis, preparation,
applications, disadvantages, limitations, and large-scale production of IPNs comprehensively. The main novelty of this article is that it has focused on a COVID-related vaccine delivery system mainly which is lacking in existing literature.

A brief historical perspective

The preparation of the first interpenetrating polymer network dates back to 1914 [13]. Aylsworth developed this network polymer based on phenol and formaldehyde, vulcanizing it with rubber and sulfur to provide the polymer with extra mechanical strength and thickness [13, 14]. Another such high-impact polymer network was then synthesized in 1974 by Amos. It was developed by graft copolymerization of styrene-butadiene rubber with polystyrene. The research in this domain further led to an ion exchange resin synthesis, the name interpenetrating polymer network. IPNs were employed for the first time by John Miller around 1960 when he prepared a homo IPN via a styrene suspension polymerization reaction [3, 15]. Afterward, there was no looking back. A series of IPNs were developed by polymer chemists worldwide, ranging from simple IPN systems to innovative and stimuli intelligent IPNs nanomaterials that are being utilized for many applications today.

IPN synthesis and characterization

The structural fabric of an interpenetrating polymer network consists of two or more polymers firmly entwined to form a three-dimensional network wherein one polymer must be either crosslinked or be synthesized in the intimate presence of the other. Its synthesis is quite different from any other polymer blend, graft, and/or block. It is sometimes known as a polymeric alloy. In IPN synthesis, polymers are blended to create a polymer mixture with reduced phase separation ability. Interpenetration then improves the compatibility of the polymers present in this blend as crosslinking creates a permanent entanglement between the polymer subunits. IPNs can be synthesized the same way as other types of polymers: from synthetic, semi-synthetic, natural, or a mix of synthetic and natural monomers. The most commonly employed polymers in an interpenetrating polymer network are as shown in Fig. 1. IPN synthesis generally includes three main steps:

1. Three chemical immiscible phase formations
2. Coating agent deposition
3. Rigidization of coating agent

Based on these three steps, an interpenetrating polymer network can be fabricated using any of the following synthetic techniques.

(I) Casting evaporation: This method is based on the heating of the polymers followed by casting to produce an intercalated polymeric structure [16]. It is a widely utilized technique for creating cross-linked polymer networks. This procedure incorporates heating the whole polymer until it is completely dissolved, then mixing it with the cross-linker solution. The cross-linker solution receives polymer-I addition as part of the sequential procedure. In both instances, the solution was heated, mixed, cast, and dried. The creation of IPNs gels is accomplished via the casting evaporation process [17].

(II) Emulsification crosslinking: The emulsion cross-linking method, which is mostly a single emulsion cross-linking method, is based on w/o emulsion. However, w/w emulsion method is also used to make IPN today [18]. It is a phase separation technique; emulsions such as water-in-oil (w/o) emulsion or an oil-in-water (o/w) emulsion are crosslinked to produce an interpenetrating polymer network. The w/o emulsion can be prepared by dispersing water-soluble polymers in aqueous media, followed by the addition of the oil phase. The o/w emulsion, on the other hand, is prepared by the reverse of the previous method. Both emulsification methods follow a final crosslinking step to yield an IPN system as the final product.

(III) Mini-emulsion/inverse mini emulsion: In this method, an o/w emulsion is prepared by dispersing hydrophobic monomeric droplets in an aqueous medium. The hydrophobic monomeric droplets are initially prepared by applying shear stress and sonicating the polymers with the required initiators [19]. Crosslinkers are then added to crosslink the polymer and produce the IPNs. The inverse mini emulsion method is the exact opposite of the mini emulsion, where hydrophilic monomeric droplets are dispersed in a hydrophobic phase, i.e., forming a w/o emulsion followed by crosslinking [3].

(IV) Coacervation phase separation: The method involves a partial desolvation of the polymer by adding solvents and/or thermodynamic changes. Two or more oppositely charged polymers can then react to form a complex IPN system.

(V) Radiation polymerization: This method is based on polymer processing by irradiating with gamma rays. One advantage of the method is that it usually does not require any chemical initiators and/or crosslinking agents; it is a single-step process all the way from preparation to sterilization [20].

Other techniques such as those incorporating centrifugal force, shear stress, enzymatic-induced crosslinking, ionic-induced crosslinking [21], pan coating, spray drying, and air suspension coating have also been reported as effective strategies for the IPN synthesis. Sterilization is a post-polymer synthesis requirement whenever an interpenetrating polymer network
Fig. 1  Popularly employed natural and synthetic polymers in preparing interpenetrating polymer networks
is prepared for biomedical applications and the transport of sensitive agents such as pharmaceutical drugs. A series of sterilization techniques can be employed for the said purpose, including chemical treatment such as treatment with ethylene oxide, decontamination by irradiation, autoclaving at high temperature (121 °C), and using moisture or dry heat, etc. [3]. Irradiation with high-energy gamma (gamma) and beta (beta) rays is recommended for polymer networks because it increases the mechanical stability of the polymers [10].

Characterization is another crucial parameter after the synthesis and preparation of IPNs like all other polymers. The word characterization is a cumulative term encompassing morphological, spectroscopic, and thermal characterization. The morphology of an interpenetrating polymer network can be studied using microscopic techniques such as scanning electron microscopy (SEM) [22] and transmission electron microscopy (TEM) [23]. Factors such as shape, intensity, the extent of crosslinking, mixing, and phase distribution are essential in investigating an IPN architecture. The thermodynamic stability of the polymeric network is evaluated via thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Infra-red spectroscopy (FTIR) and NMR provide information about the microstructure and miscibility of IPNs [24, 25]. The mechanical properties of the IPNs like hardness, tensile strength, and elongation at breaking are tested by a compression test, esthesiometry and tearing tests, etc. Differential mechanical analysis (DMA) can also be employed by applying a strain or stress onto a polymer sample at controlled frequencies and recording the phase angle and deformation data response. Having detailed information on the structural characteristics of the IPNs is essential to understanding the conditions necessary for its formation and inspecting the effect of any possible chemical variations on the interpenetrated polymers [3].

**IPN structure-property relationship**

The chemical compatibility between constituent polymers in an interpenetrating polymer network significantly affects its morphology, which can have a pronounced effect on IPN properties. Other factors such as the synthesis/polymerization method, crosslinking density, and interfacial tension between component units can also influence the properties of a network polymer. IPNs are considered superior to simple polymer mixtures owing to their valuable properties, such as a higher mechanical and thermodynamic stability and no toxicity. Also, biodegradability in natural IPNs is specifically beneficial for applications in the biomedical field [26]. Thermodynamic incompatibility obtained from small entropy gain during the mixing of simple polymer mixtures results in their multiphase morphology, thus poor stability [27]. In the case of the union of a natural polymer with a synthetic polymer in the IPNs, eminently enlarged phase stability is expected in the end product. The biological acceptability and the mechanical strength of different polymers intercalated into a single networked system take its chemistry and applications to an improved level.

**IPN classification**

Interpenetrating polymer networks can be classified based on the types of chemical bonding and/or the method of synthesis.

**IPN classification based on synthesis method**

Interpenetrating polymer networks can be classified into the following eight main types based on the synthesis method.

1. **Sequential IPNs:** Sequential IPNs are based on the synthesis of a polymer network A by the reaction of the monomer with the initiator and the crosslinking agent. This polymer network A is then allowed to swell in the presence of a monomer B containing the initiator and the crosslinking agent to form a polymer network B. Crosslinking density governs the structural morphology of a sequential IPN.

2. **Simultaneous IPNs:** In simultaneous IPNs, both polymer networks A and B are synthesized simultaneously by independent and/or non-interfering chemical ways. The monomers, catalysts, and crosslinkers for both A and B are mixed simultaneously to execute the individual polymerization reactions. Simultaneous IPN offers the highest entanglement with minimal phase separation in the final polymer network [28].

3. **Full IPNs:** A full interpenetrating polymer network synthesis method is based on an individual crosslinking of IPN components without any induced crosslinking between individual polymers A and B.

4. **Semi-IPNs:** One polymer (A or B) is present as a crosslinked network in a semi-interpenetrating polymer network. In contrast, the other polymer (B or A) either exists in a linear or a branched form.

5. **Gradient IPNs:** A gradient IPN synthesis is based on the partial swelling of polymer network A by a monomer B followed by a quick polymerization reaction until a diffusional equilibrium develops. This method provides enhanced structural solidarity to the interpenetrating polymer network.

6. **Graft/joined IPNs:** This type of IPN synthesis involves the grafting of polymer A on polymer B without any homopolymer crosslinking. This slight grafting of polymers allows improved interfacial bonding in the polymeric network.

7. **Thermoplastic IPNs:** Thermoplastic interpenetrating polymers combine IPNs with polymer blends in the presence of physical crosslinking agents such as ionomers. These physical crosslinkers join poly-
meric chains such that at low temperatures, these IPNs behave as thermosets (maintaining their shape and size). At the same time, they are free to flow, i.e., to break their physical crosslinks and behave as thermoplastics.

(VIII) Functional silicone fluids with thermoplastic resin IPNs: This IPN type is a subclass of thermoplastic IPNs prepared by blending molten thermoplastic resins with functional silicone fluids.

Other IPNs related materials include latex interpenetrating elastomeric networks: linear polymers coagulated with subsequent crosslinking by different reactions; conterminously grafted copolymers: grafted polymeric network formed by attaching two ends of polymer B with individual polymer A molecules; non-bonded crosslinked IPNs: a polymerized large ringed structure consisting of a double bond; and latex IPNs: a network structure consisting of a micro-IPNs enclosed in each particle.

IPN classification based on chemical bonding

Interpenetrating polymer networks can be classified based on chemical bonding into two main types [16].

I Non-covalent IPNs: This type is based on incorporating inorganic material into the organic network of IPNs. Two distinct phases in a non-covalent IPNs lead to restricted molecular interactions, thus lowering the stability of the networked structure. However, this phase interaction can be improved by hydrogen bond formation between suitable entities such as organic polycrylates and silicon alkoxides.

II Covalent IPNs: Covalent IPNs are formed by incorporating silicon alkoxides along the polymeric backbone through free radical polymerization. It allows better interfacial tension and molecular interaction between constituent polymeric units.

IPN microspheres

Microspheres are microscopic particles varying from 1 to 1000 μm [15]. It is reported that IPN microspheres can be used to deliver proteins and nucleic acids to the targeted biological sites. When these microspheres are used as biomaterials, the fact that they are round and porous makes it easier to load them with drugs. Several research groups have reported preparing and applying interpenetrating polymer network microspheres and microbeads for targeted oral drug delivery [29]. A stable IPN microsphere was prepared by emulsion crosslinking of acrylamide grafted locust bean gum (a high molecular weight branched polysaccharide composed of galactose and mannose) polyvinyl alcohol using glutaraldehyde as the crosslinking agent. Buflomedil hydrochloride was encapsulated into the IPN microspheres. A high drug entrapment efficiency (51–73%) was reported [30]. A controlled drug release was witnessed for a prolonged time without collapsing the polymeric matrix. The authors reported crosslinker amount, polymeric blend ratio, and the amount of loaded drug as essential factors in controlling the drug release profile. These IPN microspheres were regarded as promising drug-carrying vehicles, especially for highly water soluble, short half-life drugs. A microporous interpenetrating polymer network based on carrageenan and guar gum was also reported for drug delivery applications [31]. Carrageenan is a high molecular weight polysaccharide with a helical structure of D-galactose and 3,6-anhydrogalactose subunits. The sulfate groups extended outwards from a spiral chain of carrageenan, allowing adequate crosslinking in the polymeric network. Guar gum, a non-ionic polysaccharide composed of D-mannopyranosyl linear chain units having α-D-galactopyranose at the branch points, enabled topical entanglement and helix-helix aggregation in the IPNs. Microwave irradiation was employed for crosslinking purposes. Metronidazole (an antiprotozoal) was encapsulated as the model drug in the IPN microspheres. A 72% drug release profile was recorded for 12 h. Analytical characterization techniques showed that the IPNs, which has a honeycomb-like structure, have high mechanical and thermal stability.

IPN nanomaterials

IPN nanoparticles offer numerous advantages in drug delivery applications, including better in vivo stability due to a lower chance of interaction with the biological surroundings, thus adequate drug protection, easy application and/or removal without invasive procedures, direct administration to the targeted tissue, a predominantly higher surface for drug absorption, and lastly, a highly reproducible method of preparation. Polymeric nanoparticles’ chemical formulation and physical properties can be invariably modified following their applications. This feature adds to the value of IPNs nanomaterials as drug carriers as they can easily overcome biological barriers, such as clearance through kidney glomeruli and prevent the risk of nonspecific accumulation in different body organs [32], otherwise a major concern and cause of cell toxicity in the incorporation of polymers in drug delivery applications.

Polymeric nanomaterials can be shaped as hydrogels, nanoparticles, nanotubes, nanocages, etc. IPN hydrogels can form aqueous solutions with high colloidal stability, entrapping natural macromolecules [33]. This property offers an additive benefit for controlled drug delivery applications. The natural polymers that have been explored for IPN hydrogel development include protein, peptide chains, and polysaccharides, such as salecan, cellulose, dextrose, chitosan, alginate, and xylloglucan [34, 35]. A gel composition based on interpenetrating polymer networks at the
nanoscale offers increased elasticity and enhanced mechanical strength. Different types of polymeric networks entwined in a single system offer a synergistic effect incorporating more than one phase at a time. For instance, a rubbery phase and a glass phase in the IPN hydrogel exhibit properties of both but remain separated even when subjected to shear stress. Diversity in IPNs may also exist by varying the number of crosslinks present in the network [36]. A polymeric solution can be converted into a gel via chemical crosslinking or photopolymerization. The hydrophilic functional moieties of the polymer chains offer the hydrogels the ability to retain water and swell in an aqueous media, facilitating the drug unloading process [37]. Hydrogels can also be synthesized with stimuli-responsive polymers to respond to environmental stimuli, including temperature, pH, or the ionic strength of the media, disintegrating and releasing the drug at the targeted site [38–40].

Nanogels and/or hydrogel nanoparticles are a sub-class of hydrogels which are nanometer in size (ranging from 1 to 1000 nm) and can also be employed as efficient drug delivery systems. Nanogels are swollen networks made up of amphiphilic and/or hydrophilic polyionics polymers that can be natural or synthetic [28]. The preparation of IPNs dendrimers is also a major advancement in IPN nanomaterials. Dendrimers are nanosized hyperbranched, globular structures having a precise molecular weight and multivalent surface functionalities. These are highly ordered structures with an inner core and an outer shell. The internal cavities present in an IPN dendrimer can be used to encapsulate different therapeutic agents, including drugs, proteins, nucleic acids, and antibodies [41]. Literature evidence also infers the possibility of engineering IPN nanomaterials for upgradation and/or downregulation of the immune system, i.e., stimulating an immune response against infectious diseases and allergies while suppressing it in the case of an autoimmune disorder [42], thus, widening the scope of applying interpenetrating polymer networks in clinical applications.

“Smart” polymeric multicomponent systems

Smart polymeric multicomponent systems means that a small change in an outside stimulation of any polymeric solvent can cause a big change in a system’s function, structure, or stability [43]. Because these systems are smart and can respond quickly, they are used to make advanced functional drugs. The application of the smart polymers is increasing continuously with the development of new drugs. As scientists work to create ever-more-potent pharmaceuticals, they are paying more and more attention to the methods of administration now in usage. Traditional methods of medication administration cause an initial increase in blood drug levels, followed by a peak and subsequent decrease. Commercially available controlled release devices have been shown to be effective in either maintaining drug levels within the therapeutic range with a single dosage or targeting medication to a specific location while reducing systemic drug levels [44]. The delivery of insulin to patients with diabetes mellitus, anti-arrhythmics to patients with heart rhythm disorders, gastric acid inhibitors for ulcer control, and nitrates to patients with angina pectoris are just a few clinical scenarios where the approach of a constant drug delivery rate is insufficient. Another clinical scenario where a responsive delivery system of anti-inflammatory medications might be helpful is the beginning of infection on medical device or biomaterial surfaces. Furthermore, research in the field of chronopharmacology suggests that the timing of the start of several illnesses is strongly influenced by the circadian rhythm. As a result, time-dependent drug delivery is necessary for medications like blockers, birth control, general hormone replacement, vaccination, and cancer treatment. The abovementioned treatment problems have been optimized by developing drugs with smart and responsive materials [45]. A stimulus-sensitive “smart” IPN hydrogel was prepared by radical polymerization using a temperature-sensitive poly(N-isopropylacrylamide) and a pH-sensitive hyaluronic acid. The hydrogel loaded with luteolin was tested for transdermal drug delivery against hyperproliferation of keratinocytes in the epidermal layer of the skin [22]. Luteolin is a potent therapeutic agent, often used to alleviate skin conditions such as psoriasis. A drug incorporation efficiency of 42.8% was reported using the particular hydrogel, and the highest drug release was observed at 25 °C, at pH 5.5. Another novel UV-triggered IPN drug delivery system was reported [46]. The interpenetrating polymer network was prepared using silicone as the host polymer and a spiropyran functionalized guest polymer. The authors reported that the hydrophobic spiropyran moieties transformed to hydrophilic merocyanine upon photoirradiation, releasing the drug without degrading the drug delivery system. A stimulus-responsive drug release of dopamine, L-dopa, and prednisone was reported to be up to 90–95% with the IPNs prepared in this study.

IPNs in drug delivery applications

Drug delivery refers to a method or a process of administering a pharmaceutical compound to achieve specific therapeutic benefits in animals and humans [47]. A successful drug delivery operation can be divided into two distinct steps: spatial placement and temporal delivery. Spatial placement refers to targeting the drug to specific organs, tissues, and/or specific sub-cellular compartments. In contrast, on the other hand, temporal delivery refers to controlling the rate at which the drug is released to these targeted sites [48].

Various obstacles can hinder a successful drug delivery operation, including low drug solubility in physiological fluids, environmental or enzymatic degradation of the drug and non-specific toxicity, and inability to cross biological membrane...
barriers, resulting in low bioavailability overall. Polymeric structures such as interpenetrating polymer networks can be promising drug delivery carriers. Their three-dimensional crosslinked morphology supports compact drug encapsulation, safe intracellular transport, and sustained release at the targeted site [49]. Interpenetrating polymer networks can be used as effective delivery vehicles to transport active constituents of a drug in the form of a tablet, capsule, microsphere, hydrogel film, sponges, and/or transdermal patches. Transdermal IPN drug delivery facilitates the delivery of drugs in lower doses for a more extended time, avoiding the need to first pass through any metabolic route. This section explores the specific application of IPNs in delivering different types of drugs.

Researchers highlight one possible limitation of using the IPNs for drug delivery over its numerous advantages. Strong interpenetration of different polymers as present in the IPNs can make it difficult for drugs to escape [3]. This difficulty can be handled by manipulating the design and chemistry of the interpenetrating polymer networks at the synthesis and drug encapsulation stages. Stimuli-responsive nanosized IPNs, as discussed earlier, are at a lower risk of facing this issue because of increased sensitivity to external stimuli and their increased surface area. The drug loading/encapsulation efficiency of an IPN can be determined by using the relative formula given in Eq. (1). The actual drug content can be measured via UV-Vis spectrophotometry [29]. The drug release profile of an IPN system is also noted as a percent drug release [50].

$$\% \text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100\%$$

(1)

**Delivery of anticancer drugs**

Researchers have reported successful interpenetrating polymer networks for encapsulation and delivery of chemotherapeutic drugs for many different types of cancers, including metastatic breast cancer, colorectal cancer, and gastric cancer. Agnihotri et al. [51] studied and reported a controlled, in vitro gastrointestinal release of a drug encapsulated in a semi-IPN matrix. The polymeric network was synthesized by a free radical polymerization reaction of chitosan with polyethylene oxide and polyacrylamide. Ceric ammonium nitrate was used as the initiator in this case. Similarly, Rohkade et al. [52] synthesized a chitosan-based IPN hydrogel microsphere using the emulsification crosslinking method. Glutaraldehyde was employed as a crosslinker, and the IPNs obtained were loaded with 5-fluorouracil, an antimetabolite helpful drug for cancer treatment. A sustained drug release was witnessed over 24 h of encapsulation in the IPN microsphere.

Another stimulus-responsive semi-IPN hydrogel was prepared using a thermo sensitive N-isopropylacrylamide and a pH-sensitive N-ethylmaleamic acid (NEMA) [2]. Free radical polymerization was carried out in the presence of N,N’-methylenebisacrylamide as the crosslinking agent. Doxorubicin hydrochloride was encapsulated as the model drug, and the in vitro drug profile was tested in a stimulating tumor environment (phosphate buffer pH 6.5 and 37 °C temperature, comparable to human physiological conditions). The authors deduced that incorporating pH-sensitive monomers into a thermosensitive polymer network usually weakens the latter’s thermostensitivity in copolymerized hydrogels as the incoming monomers interrupt the continuous sequence of the pendant groups in the parent polymer chain.

NEMA was proposed as an alternative choice, claiming that N-ethylmaleamic acid consists of both an amide (-CONH) functional group and a weakly acidic carboxylic (-COOH) group; thus, it introduced pH sensitivity without disturbing the continuity of amide hanging groups in the N-isopropylacrylamide hydrogel network. A rapid drug release profile was recorded without leakage on its way to their targeted site, establishing the research protocol successful. A recent study [53] prepared an interpenetrating polymer network hydrogel based on polyethylene glycol-diacylate and modified gelatin. The IPN hydrogel was loaded with gold (III) porphyrin (AuP), a lipophilic metal compound considered useful for anticancer applications. The authors claimed a sustained AuP release from the IPN hydrogel following first-order kinetics in an in vitro experimental protocol performed on mice lung cancer cells. AuP visibly inhibited tumor growth by up to 60% and reduced angiogenesis. No cytotoxic signs were observed in any of the treatment groups, thus rendering the polymeric hydrogel biocompatible.

Similarly, a semi-IPN nanoparticle hydrogel was prepared and tested for drug delivery of a widely popular chemotherapeutic drug, paclitaxel (PTX) [54]. The semi-interpenetrating polymer network was developed by irradiation polymerization using poly (ethylene glycol) diacylate and hyaluronic acid. The researchers reported a sustained drug release for up to 13 days in mice used as model animals. The tumor growth was effectively inhibited without causing any harmful effects. The IPN hydrogel thus exhibited good biocompatibility and biodegradability at the same time.

The IPN nanogel composed of natural gelatin and poly (acrylamidoglyclic acid) was synthesized by simple free radical emulsion polymerization [55]. The nanogel was tested for anticancer drug delivery by loading a hydrophobic curcumin drug. A 42–48% encapsulation efficiency was exhibited by the nanogel, facilitating targeted drug release in a phosphate buffer solution. Curcumin encapsulated nanogel also exhibited pH-sensitive properties and released the drug to the targeted colorectal cancer cell line in a sustained manner. Full IPN and semi-IPN systems have also been explored as sustained drug delivery systems for drugs that treat non-melanoma-type skin cancer [56]. A better dose control minimized side effects, and high cell specificity by
using IPNs for drug delivery is reported primarily to treat skin-related ailments.

**Delivery of antibiotics**

Antibiotic drugs can be entrapped for delivery in interpenetrating microgels. IPN microgels are intermolecularly crosslinked polymeric gel particles homogeneously distributed in a solvent system. Complete dissolution of an antibiotic drug can be retarded up to and above 10 h when caged in an IPN microgel matrix. Based on their colloidal size, IPN microgel particles can also exhibit conformational changes in response to variations in environmental parameters [57, 58].

A pH-sensitive interpenetrating microgel system was developed based on chitosan, acrylamide grafted polyvinyl alcohol (PVA), and a hydrolyzed version of this acrylamide grafted PVA [58]. The microgel was tested for the controlled release of cefadroxil, an antibiotic drug commonly used against bacterial infections of the skin and throat. Analytical characterization techniques ensured a uniform drug distribution inside the polymeric matrix. Hydrophilic interactions between chitosan and polyacrylamide modified PVA assisted the formation of a uniform microgel blend. The incorporation of PVA lends elastic properties to the microgel beads. The IPN matrix exhibited promising characteristics for controlled drug release, a prolonged drug release witnessed for more than 10 h.

In another study, interpenetrating hydrogel microspheres prepared by a water-in-oil (w/o) emulsion crosslinking method for sustained release of ciprofloxacin hydrochloride, a quinolone antibiotic that is used to treat bacterial fevers such as pneumonia, typhoid, and diarrhea, were reported [59]. A xanthan gum-based superabsorbent polymer and polyvinyl alcohol were used to prepare these IPN microspheres. Hydrophilic interaction again played an integral role in the hydrogel preparation. The in vitro drug release profile was tested in both an acidic (pH 1.2) and an alkaline (pH 7.4) medium. The researchers reported an inverse relationship between the polymeric network density and drug release rate. The denser the networked structure by adding a higher amount of crosslinker, the more sustained the drug release.

The drug release profile of a penicillin-based antibiotic, amoxicillin, was also tested in an earlier study using a semi-IPN [60]. The semi-interpenetrating polymer network was prepared by crosslinking chitosan with polyvinylpyrrolidone (PVP). Both porous freeze-dried hydrogels (pore diameter: \(39.20 \pm 2.66\mu m\)) and non-porous air-dried hydrogels were prepared, exhibiting a pH-dependent swelling behavior. However, the porous semi-IPN hydrogels displayed a superior swelling, and drug release potential than the non-porous ones. Seventy-three percent amoxicillin was released in 3 h at pH 1 from freeze-dried polymeric networks and 33% drug release reported from air-dried polymeric hydrogels.

**Delivery of antihypertensive drugs**

Different types of interpenetrating polymer networks have also been incorporated into the safe delivery of hypertensive drugs. IPN microspheres based on gel gum and polyvinyl alcohol were used to encapsulate and deliver an antihypertensive drug called carvedilol [61]. Carvedilol is a non-cardio selective \(\beta\)-blocker that is frequently used in conditions such as angina pectoris. The microspheres were prepared by an emulsion crosslinking method. The researchers reported a strong effect of the size and morphology of IPN microspheres on drug encapsulation efficiency and its liberation. PVA is an easy to process pH and thermostable polymer, while gel gum is a natural polysaccharide. The incorporation of both polymers in an interpenetrating polymer network provides the IPN structure with high mechanical strength as well as biocompatible and non-toxic properties. A crystalline dispersion of the drug was witnessed in the polymeric matrix with a drug encapsulation efficiency of up to 87%. A prolonged drug release profile was recorded up to 12 h in vitro in the simulated gastric fluid and the intestinal fluid.

In another study [62], the IPN hydrogel composed of sodium alginate and polyacrylic acid was reported for the transdermal delivery of prazoosin hydrochloride, an antihypertensive drug specifically used to treat abrupt blood pressure fluctuations. The hydrogel exhibited a reversible swelling behavior, sensing physiological and environmental pH changes leading to an oscillatory drug release pattern. Semi-IPN microspheres prepared by w/o emulsification crosslinking of chitosan and N, N’-dimethylacrylamide were used to deliver chlorothiazide, a diuretic drug formulation [62]. Uniform molecular dispersion of the drug in the polymeric matrix followed by a sustained release for up to 12 h was reported rendering the IPN drug delivery protocol successful.

In an earlier study [63], a unique IPN hydrogel synthesis was reported and tested for antihypertensive drug delivery applications. The IPN hydrogel was prepared by networking polyvinyl alcohol with polyacrylic acid but without the addition of any crosslinker. The fabricated hydrogel’s swelling behavior and drug delivery were tested in vitro in a stimulated intestinal fluid by encapsulating diltiazem hydrochloride. Seventy-nine percent drug entrapment efficiency and a controlled drug release up to 24 h were reported in rats as model animals. Reduction in blood pressure recorded up to 40.1%. The clinical study claimed a superior drug carrying potential of IPN hydrogels compared to standard hydrogels. Thacharodi et al. [64] explored the potential of a collagen-chitosan-based IPN hydrogel patch for delivering propranolol hydrochloride transdermally. Five milligrams of drug was released from the patch in 24 h, establishing the possibility of utilizing an interpenetrating polymer network as transdermal patches for drug delivery.
Delivery of anti-inflammatory drugs

Anti-inflammatory drugs hold immense therapeutic significance in relieving pain, bringing down the high temperature by reducing other short-term and long-term inflammatory symptoms, including sprains, strains, and arthritis. These drugs can be packaged in interpenetrating polymer networks for effective delivery at specific pain points. A targeted drug delivery of ketoprofen, a gastroprotective anti-inflammatory drug, was reported in IPN microbeads [65]. The polymeric microbeads were prepared by graft copolymerization of polyacrylamide (PAAm) and gum ghatti (GG) in the presence of sodium alginate. The IPN microbeads demonstrated excellent pH sensitivity, a significant drug release profile reported under gastrointestinal/alkaline (pH 7.4) conditions compared to the amount of drug release witnessed under acidic (pH 1.2) conditions in the stomach in vivo clinical trials performed using Wistar rats as model animals. An alkaline pH leads to the alkaline hydrolysis of -CONH2- group to -COO- in PAAm-grafted-GG, releasing the entrapped drug. This example demonstrates the significant impact of an IPN structural morphology on its properties.

IPN microstructures based on gelatin and carboxymethyl tamarind gum (CTG) were explored to deliver acyclovir, a non-steroidal, anti-inflammatory drug often used to treat arthritic conditions [27]. A high drug encapsulation efficiency of IPN microbeads was recorded as high as 96%. A slow drug release rate (less than 10% in 2 h) was reported in an HCl solution (pH 1.2), while an extended-release (up to 60%) was observed in phosphate buffer (pH 6.8). The researchers observed a prominent influence of the functional groups present in the IPNs on polymeric chain swelling and relaxation, controlling its drug release profile. Negatively charged carboxyl functional groups present on gelatin undergo electrostatic forces of repulsion at high pH levels, causing extended swelling of the networked structure, thus a faster drug release. Physical crosslinking/blending of gelatin with a natural polymer like CTG enhanced its mechanical strength and formed a solid IPN-drug biocomposite. The anti-inflammatory activity of the released drug lasted for 7 h in albino rats, marking the success of the in vivo clinical study.

Delivery of antiviral drugs

Temperature and pH-sensitive drug delivery systems are specifically beneficial for the site-specific transport of antiviral drugs [66]. Polymer chemists reported the preparation of dual responsive interpenetrating polymer network hydrogel microbeads [67] by functionally modifying guar gum by co-polymerization using N-vinylcaprolactum and sodium alginate. These IPN hydrogel microbeads were then used for a colon-specific drug delivery. The hydrogel was used to encapsulate an anti-HIV drug called zidovudine in it. Poly (N-vinyl caprolactam) grafting on guar gum appreciably improved its intrinsic viscosity. A maximum of 68% drug entrapment was reported, and a high drug release rate was recorded at pH 7.4 at 37 °C. Encapsulation in IPN microbeads enhanced the drug release time up to 34 h. Similarly, IPN-based anti-HIV drug delivery was reported using semi-IPN microspheres [68] prepared by w/o emulsification crosslinking using PVA and dextran-grafted-acrylamide. Abacavir sulfate was the model drug encapsulated in the IPN microspheres; the in vitro drug release studies reported a pH-dependent drug release from the polymeric network.

Even after considering all these efficient drug delivery sources for antiviral drugs, we cannot neglect the fact that viral infections can be dealt with better with a prophylactic approach, i.e., disease prevention rather than treatment after falling sick and what could be a better prophylactic approach than vaccination and immunization regimens. Interpenetrating polymer networks can serve as potential vaccine carriers if designed intelligently. The proceeding section discusses the promising application of network polymers in vaccine delivery and its associated pros and cons.

Other than those discussed in the “IPNs in drug delivery applications” section, interpenetrating polymer network-based drug delivery systems have also been applied, particularly for transporting anti-malarial [69], anti-diabetic [70], anti-asthmatic [71], and anticonvulsant [72] drugs. In another relevant study [73], researchers reported the targeted delivery of insulin in an interpenetrating polymer network hydrogel. The IPN hydrogel was prepared using polyacrylic acid co-acrylamide and carboxymethyl chitosan. Insulin was entrapped in it and orally delivered to rats used as model animals. The authors observed a pH-sensitive insulin release, an enhanced rate recorded on increasing the pH from 1 to 6.2. The carboxylic acid functional group in polymeric chains is protonated under acidic conditions, leading to the shrinkage of the hydrogel. The formation of hydrogen bonds between insulin and the polymeric chains restricted insulin release under acidic conditions.

On the other hand, an elevated pH led to ionization and swelling of the polymeric chains, thus easing the insulin release. A 60–99% drug release profile was reported within 2 h. This example again highlights the importance of the structural variations present in an IPN on its properties and potential applicability in drug delivery. Kurakula et al. [74] highlighted the future application of povidone-iodine (PVP-I) as an antiviral agent against COVID-19. They left a question mark on whether this drug-loaded polymer can be used as a medical aid in these pandemic-affected times. This initiative can be supported further by interpenetrating PVP, a synthetic polymer with natural polymers, to prepare biocompatible, least toxic IPNs as a defensive action against the deadly virus.

IPNs for vaccine delivery

Vaccination is a cost-effective mechanism to prevent and fight against diseases. It could either be prophylactic or therapeutic. Vaccination against viral infections involves a preventative...
strategy, while vaccination against cancer falls under the therapeutic category. A fundamental principle of prophylactic subunit vaccination is the induction of an antigen-specific immune response. Antigens (weakened particles mimicking intracellular pathogens) are enclosed in vaccines as the active pharmaceutical ingredients. When these antigens are released into the body cells through vaccines, antigen-presenting cells (APCs) recognize, carry, and present these antigens to the T-cells; the white blood cells are integral for immunogenicity. APCs release co-stimulatory factors called cytokines and activate the T-cells. T-cell differentiation occurs to induce antigen-specific cytotoxicity. The exact immunization mechanism is followed in case of a pathogenic attack where the T-cells are activated in the presence of APCs triggered by ligands characteristic of the invading pathogens. Immunity acquired through vaccines can help fight the body against any actual pathogenic attack.

Polymeric entities can be employed as vehicles to ensure the effective transport of these vaccines to targeted sites. Incorporating interpenetrating polymer networks in vaccine delivery is a relatively new idea that can improve vaccine performance and potency. Unlike conventional vaccine administration, sustained drug release from IPNs can ensure solid and long-lasting antibody responses. This may alleviate the need for multiple and frequent vaccine doses and boosters instead of a conventional vaccination regimen. Polymeric nanogels have proved the most fruitful in this regard so far. Polymeric nanogels can act as “integrated adjuvants,” combining the immunomodulatory properties with targeted antigen delivery functions [75, 76]. An adjuvant is a term used in immunological studies to define any substance that can accelerate, prolong, or enhance an antigen-specific immune response [77]. The biodegradable, biocompatible, and mucoadhesive properties of IPNs nanogels can make them promising adjuvants to enhance the efficiency of subunit vaccines [77].

APCs prefer particulate antigen uptake over soluble antigen uptake. Antigen-loaded IPN nanoparticles can act as antigen depots, slowly releasing antigen for prolonged bioavailability and better immune response quality. In vitro clinical trials have revealed that as vaccine delivery systems, polymeric nanoparticles work by activating dendritic cells followed by co-stimulation of cytokines. Activated dendritic cells migrate to the regional lymph nodes, presenting antigens to the T-cells, turning on a humoral immune response in the body [78]. The intrinsic properties of the polymeric nanogels, including their chemical composition, shape, and size; any charge present on their surface; and/or their interaction with water and other solvents (hydrophilicity and hydrophobicity), however, play determining roles in their incorporation in vaccine delivery operations and in shaping the induced immune response as a result. Polymer research studies claim that the encapsulation of a vaccine in polymeric networks prevents the in vivo degradation of its constituent antigens. Enclosure in polymeric systems can also increase a vaccine’s active targeting specificity [32].

Nonetheless, very few examples of vaccine delivery applications and efficacy of interpenetrating polymer networks are available in the scientific literature; thus, this end is always open to research. This particular review article is a little effort to open a new windowpane in this area by relating the research studies conducted on vaccine delivery using different polymer systems in general and how those can be extended to incorporating IPNs in vaccine delivery operations.

**Protein-based vaccines**

The weakened and/or inactive foreign particles that make up the chemical composition of most vaccines available against viral infections are called antigens. These antigens are essentially proteins; thus, all the antigen vaccines fall under the protein-based vaccine category [79]. Continuous antigen delivery for long periods is considered effective in inducing immunity. Encapsulation of vaccine components in three-dimensional polymer networks like IPNs can fulfill the said task. Prolonged antigen exposure allows enough time for affinity maturation and antibody isotype switching to generate a robust immune memory [80]. Polymeric nanogels are specifically helpful for delivering protein-based vaccines. They offer an active surface for protein absorption; antigens from IPN nanogels can form surface conjugated complexes with antibody molecules, thus making them faster and more effective immunomodulatory mechanisms expected.

Factors such as molecular weight and chemical composition, including the types of co-polymers, crosslinkers, and crosslinking density, control vaccines’ targeting release mechanism. For instance, a polymer network with a higher molecular weight results in slower drug release. Similarly, the functional groups present at the surface of a polymer network say a nanogel can be modified with targeting moieties to achieve site-specific vaccine delivery. Stimuli-responsive IPN nanogels such as those sensitive to acid hydrolysis (acetal or hydrazide bonds) or those containing functional groups susceptible to reduction can serve as vaccine carriers even better. The timely release of antigens in response to slight variations in pH and temperature also increases the residence time of the antigen at the specific site, eliminating the need for multiple vaccinations [81]. These functional group moieties can additionally aid in strengthening the immune system by activating a complementary system, i.e., triggering a series of proteins and enzymes capable of promoting inflammatory and phagocytotic reactions [76]. Sustained antigen presentation to the T cells from a few hours to a few days is worthwhile. It improves T cell expansion and differentiation leading to an enhanced immune response. On the other hand, excessive antigen presentation for weeks and/or months
may lead to T cell death. Instead, thus, polymer design and drug encapsulation strategy are two critical preliminary considerations when developing polymeric networks for vaccine delivery.

Two different techniques can reportedly encapsulate subunit vaccines in polymers: physical entrapment and chemical conjugation. Physical entrapment of antigens involves loading the components into the core and/or onto the surface of the polymer via polymerization, emulsification, self-assembly, or complexation method. In order to achieve a sustained protein release from an IPN matrix, the diffusion of the protein through the pores of the polymeric network is suggested while keeping the matrix intact [82]. Natural polymers such as alginate and chitosan are recommended for designing porous polymer networks. A supercritical enhanced atomization spray drying technique was used to develop a polymeric vaccine [83]. Aqueous solutions containing inactive infectious particles and chitosan were prepared and converted into nanospheres by employing intense shear stresses generated by depressurization of liquid-gas (supercritical CO2-N2) mixtures to break up the liquid phase into sub-micron droplets. The immunization efficiency of the developed vaccine was tested against Strangles infection using a mice model. Chemical conjugation for preparing vaccine-loaded polymeric systems involves covalent binding of the antigen/protein into the polymeric particles using conjugation techniques such as ligation and metal-catalyzed cycloaddition click reaction.

Other than chitosan, polyacrylates such as poly (methyl methacrylate) and poly (tert-butyl acrylate), hyaluronic acid, alginate [84], and cyclodextrin [85] have also been explored for designing polymeric adjuvants for vaccine delivery. Poly(lactide-co-glycolide)-based micro- and nanoparticles have also been explored for vaccine delivery applications [86].

DNA vaccines

Vaccines can also be developed using hereditary materials such as nucleic acids: DNA and RNA. Compared to conventional vaccines, DNA vaccines hold a higher disease-preventing potential as they can induce both an antibody and a cell-mediated immune response [87]. However, choosing a suitable vector for carrying DNA and RNA-based vaccines is more challenging than designing a delivery system for protein-based vaccines. A perfect drug delivery vector for vaccines based on nucleic acids must fulfill four conditions: (i) interact effectively with DNA, (ii) be stable in body fluids, (iii) target specific cells, and (iv) be able to cross membranes in order to release the drug. Network polymers satisfy all the necessary conditions. DNA can be encapsulated in polymeric networks in either condensed or non-condensed form [88]. Cationic polymers are usually employed as DNA condensing agents through electrostatic forces of attraction. The integrity of the DNA-polymer depends on many factors, including complex size, stability, toxicity, and protection against DNase degradation during intracellular trafficking. Adsorption of nucleic acid onto cationic nanoparticles can facilitate the immediate release of DNA at the targeted site. Researchers have reported the application of chitosan-based nanoparticles encapsulating a cocktail of DNA encoding nine immunogenic antigens of a respiratory virus using a mice model. High levels of cytotoxic T cells with antiviral action were observed post vaccine administration in the pulmonary cells of the animal [89]. Oral delivery of another chitosan-DNA-based vaccine encoding a mite dust allergen with improved proinflammatory immune response was reported [90].

RNA vaccines

Messenger RNA (mRNA) can also be incorporated as a principal component in formulating effective vaccines. mRNA-based vaccines offer a higher safety profile and more precise and reproducible immune response, and most importantly, they are cost-effective and offer an added incentive of faster production [91]. The first report of injecting an mRNA into animals for vaccination purposes was received in the 1990s, encoding an influenza virus nucleoprotein [92]. mRNA vaccines are packaged with single-stranded genetic sequences that instruct the host cells to produce proteins, yielding an immune response against suspected pathogens. Despite their numerous advantages over conventional antigen and DNA-based vaccines, RNA-based vaccines have a few shortcomings.

mRNA molecules have a large molecular size and are negatively charged, hydrophilic, and fragile, making the passage of a naked mRNA molecule through the lipophilic cell membranes quite complex. Network polymers can facilitate intracellular transport of these mRNA molecules by encapsulation and/or complexation. Cationic polymers can efficiently complex anionic mRNA through electrostatic forces of attraction to form a polyplex or a micelleplex. Polymer-based vectors have been shown to be more stable than traditional lipid-based vectors in RNA-based vaccine delivery. Polymeric networks have the potential to act as cytoplasmic delivery vehicles, crossing various extracellular barriers for carrying the vaccine components to their target sites, i.e., to ribosomes inside the cells. Most vaccines designed for combating the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are also mRNA-based vaccines.

The prospective application of an IPN in COVID vaccines

Coronavirus is a spherically shaped virus with spiked-shaped immunogenic proteins present on its surface. The virus has an
RNA genome and a lipid bilayer surrounding it. It attacks the lung cells by disintegrating its outer envelope and inserting this RNA genome into the target cells. mRNA-based vaccines trigger an immune response in the body by mimicking the RNA genome of the virus itself. The characteristics studied for developing polymeric networks like IPNs to deliver RNA vaccines can be applied as an extension to prepare a COVID vaccine.

There will always be a need to consider a series of factors when designing interpenetrating polymer networks for carrying COVID vaccines, including the molecular weight, shape, and size of the polymeric carriers. These factors, in turn, control the rate of glomerular filtration, governing effective removal and clearance of the polymeric carriers from the body by excretion. The size preferable for interaction with APCs and transportation to lymph nodes may not be suitable for efficient renal clearance [93]. IPNs composed of slowly degrading and/or non-biodegradable polymeric subunits may pose a risk of bodily accumulation, resulting in toxicity; designing biodegradable IPNs primarily from natural polymers is thus a more viable option.

The onset of disease conditions such as infections or inflammation causes changes in the pH of the human organs. pH-sensitive polymers can be manipulated to respond to these changes and specifically release the enclosed vaccine at the targeted sites. Ionizable polymers with pKa values ranging from 3 to 10 can be used to design effective IPN systems. Polyacids containing acidic functional groups such as carboxylic acid, polybases based on basic entities such as amines, and natural polymers such as dextran, hyaluronic acid, and chitosan (containing NH2 and OH groups) can be used for this purpose [94]. Usually, an inflammatory action leads to acidosis, i.e., a reduced pH. The primary amines of IPNs-friendly polymers such as chitosan become positively charged by accepting protons. This idea can be further investigated for designing IPN systems for COVID vaccine delivery.

The messenger RNA is a negatively charged molecule. The hydrophilic and polar nature of polymers present in an interpenetrating polymer network can also prove beneficial for developing strong interactions with and enclosing the mRNA molecules of the vaccine. Natural polymers can be derivatized, such as the derivatization of chitosan to carboxymethyl chitosan to introduce an additional -COO group to interact with the vaccine better. The review written by Mallakpour et al. [84] is an exciting lead in using natural polymers as adjuvants in vaccine delivery systems. A comprehensive review on incorporating nanoparticles in COVID-related therapeutics is provided by Sharma et al. [95]. It can be read as an additional reference to take the initiative of designing IPN nanomaterials for vaccine delivery further.

Disadvantages and limitations of Interpenetrating Polymer Networks (IPNs)

There are some disadvantages and limitations to IPNs in clinical adoption. It is a very important factor of a drug delivery system to deliver the active drug within the correct site and speed. Sometimes, it may be very difficult to extract the active drug due to excessive penetration among the polymers [16]. In addition, several factors during production can affect the final polymer’s quality, including the reactor type, reaction mechanism, and operating circumstances [16]. There is another problem associated with IPNs which is the lack of effective interface. The surface energy phenomena and the insufficient chemical engagement between phases may contribute to the problem of ineffective interfaces [36]. The lack of an efficient interface is problematic for the non-covalent system, and it also threatens the covalent system. The mechanical property of IPNs is an important parameter in context of pharmaceutical applications which can be hampered at the time of crosslinking. The proper integrity of the drug delivery system means the polymers must be maintained to work properly in the pharmaceutical applications and throughout their whole lifetime. The therapeutic agent must be protected by the drug delivery system until it is discharged from the system, and the drug delivery system must be able to preserve its integrity until then. Though increasing the degree of cross-linking may improve the mechanical properties of IPNs, high degree of cross-linking can make the brittle structure of IPNs [96].

Another major issue of IPNs is large-scale production of drug delivery systems. The manufacture of IPNs on a wide scale is the biggest obstacle to drug delivery research and development. For ultimate commercialization, laboratory or pilot technology must always be scaled up. Though it is easy to improve the performance of IPNs in laboratory on a small scale, it is a very hard and complex procedure to maintaining the better performance at a large and global scale. It might be difficult to maintain the concentration and composition of polymers on a big scale. Even though IPN drug delivery technologies have received several patents and research grants, commercialization is still in its early stages. This is largely because academic scholars conduct the majority of the research investigations. However, more work has to be done to transition IPN-based drug delivery devices from the experimental stage to pilot scale manufacturing and expand their useful applications. This can be done by taking a number of things into account, such as increasing selectivity without sacrificing biocompatibility and stability, optimizing polymer modification techniques, using the right engineering configurations, understanding how transport works, and using materials and methods that do not cost too much. After analyzing the whole information about IPN, this study has summarized the brief description of IPN in a single graphical image. Figure 2 represents a brief graphical summary of IPN.
Challenges and future outlook

Successful vaccination of diseases such as polio and smallpox has dramatically improved the health sector worldwide. However, traditional immunization approaches somehow lag in treating ailments such as malaria, tuberculosis, and HIV. The encapsulation of vaccines in three-dimensional polymeric networks, such as interpenetrating polymer networks, may provide an auspicious opportunity to combat these threats while also instilling new hope in improving the efficacy of the COVID vaccination protocol. New IPNs can be designed to encapsulate and deliver coronavirus vaccines for sustained, site-specific release of its components, reducing the need for subsequent booster shots. However, this idea is still at its juvenile stages and requires extensive research and contemplation in the upcoming years. The World Health Organization (WHO) reports frequent mutations of the SARS-CoV-2 virus [87].

These ever-new variants make the synthesis and application of any IPN design for vaccine delivery a very challenging task. Hit and trial experiments with different polymers, crosslinking agents, and synthesis techniques can be employed to propose a single IPN formulation capable of performing the drug delivery task for the mRNA vaccine components against the coronavirus disease.

Further development is also required in the analytical characterization of drug-loaded IPN carriers to study chemistry and possible interactions between a proposed polymeric network and different vaccine components. Modifying the structural morphology to synthesize novel IPNs is relatively more straightforward at the lab scale, but maintaining a uniform chemical composition and concentration simultaneously is still a considerable challenge in the large-scale production of such designs. Commercialization of biocompatible IPNs is at an early stage and requires further development.

Concluding remarks

To summarize, incorporating an interpenetrating polymer network as a drug delivery vehicle is a promising approach for site-specific, controlled drug release. Proper placement of any drug at the targeted site maximizes drug availability.
### Table 1  Literature review of some representative examples of interpenetrating polymer networks in different drug delivery applications since the last decade

| SL no. | Network type          | Monomers and polymers                                          | Initiator                | Crosslinker                           | Method of preparation                           | Encapsulated drug                     | Ref |
|--------|-----------------------|----------------------------------------------------------------|--------------------------|----------------------------------------|-----------------------------------------------|---------------------------------------|-----|
| 01     | Dual responsive semi-IPN hydrogel | N-iso propylacrylamideethylmaleic acid and sodium alginate | Potassium per sulfate (K2S2O8) | N, N'-methylenebis (acrylamide) (BIS) | Free radical polymerization                  | Doxorubicin hydrochloride (Dox)       | [2] |
| 02     | IPN microspheres      | Sodium alginate and locust bean gum                            | -                        | Calcium chloride (CaCl2)               | Ionotropic gelation                           | Capecitabine (CAP)                    | [90]|
| 03     | Semi-IPN hydrogel     | Salecan and poly (methacrylic acid)                           | Ammonium persulfate      | N, N'-methylenebis (acrylamide) (BIS)  | Free radical polymerization                  | Doxorubicin (Dox)                     | [91]|
| 04     | Semi-IPN microspheres | Acrylamide, polyvinyl alcohol, and sodium alginate             | Benzoepheneone           | Ferric chloride (FeCl3)                | Graft copolymerization in the presence of UV irradiation | 5-urao-uracil (5-FU) | [92]|
| 05     | IPN hydrogel microspheres | Xanthan gum, polyacrylic acid, polyvinyl alcohol               | -                        | Glutaraldehyde                         | Water-in-oil (w/o) emulsification polymerization | Ciproflaxin hydrochloride (CIPRO)    | [52]|
| 06     | IPN microgel          | Chitosan, acrylamide graft polyvinyl alcohol and hydrolyzed acrylamide grafted polyvinyl | Ceric ammonium nitrate (CAN) | Glutaraldehyde                         | Graft copolymerization                      | Cefadroxil                            | [51]|
| 07     | IPN hydrogel          | Alginate, gelatin and hydroxyapatite                           | -                        | Glutaraldehyde                         | Composite polymerization                     | Ciproflaxin hydrochloride (CIPRO)    | [93]|
| 08     | IPN microspheres      | Gellan gum and polyvinyl alcohol (PVA)                        | -                        | Glutaraldehyde                         | Water-in-oil (w/o) emulsication               | Carvedilol                            | [54]|
| 09     | Semi-IPN microspheres | Chitosan and N, N' dimethylacrylamide                         | Potassium persulfate (K2S2O8) | Glutaraldehyde                         | Water-in-oil (w/o) emulsification             | Chlorothiazide                        | [55]|
| 10     | IPN hydrogel          | Polyvinyl alcohol (PVA) and polyacrylic acid (PAA)            | Benzoyl peroxide         | -                                      | Modified emulsion method without crosslinker | Diltiazem hydrochloride (DL)         | [56]|
| 11     | IPN microbeads        | Polyacrylamide (PAAm), gum ghatti, and sodium alginate        | Ceric ammonium nitrate   | Ca2+ ions and glutaraldehyde         | Graft copolymerization in the presence of microwave irradiation followed by dual crosslinking | Ketoprofen                            | [58]|
| 12     | IPN microstructures   | Gelatin and carboxymethyl tamarind gum (CTG)                  | -                        | Glutaraldehyde                         | Bio-composite formation by physical crosslinking | Aceclofenac                          | [24]|
| 13     | IPN hydrogel microbeads | Guargum, poly (N-vinyl caprolactam), and sodium alginate   | -                        | Glutaraldehyde                         | Graft copolymerization                      | Zidovudine                           | [60]|

**Drug delivery application type: anticancer**

**Drug delivery application type: antibiotic**

**Drug delivery application type: antihypertensive**

**Drug delivery application type: anti-inflammatory**

**Drug delivery application type: anti-viral**
and therapeutic efficiency and minimizes any associated side effects. Designing new IPNs with biodegradable and biocompatible polymers can improve drug delivery characteristics. Considering the previous relevant points, effective IPN systems can be developed for vaccine delivery, specifically mRNA vaccine delivery. Multiple sustained doses for extended periods can also alleviate the possible side effects of a vaccine expected from a single, prompt heavy dose. Nevertheless, this area inevitably requires rigorous research and scientific effort to acquire any desirable outcome soon. Table 1 represents examples of IPNs in different drug delivery applications since the last 12 years.

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References

1. Silverstein MS. Interpenetrating polymer networks: so happy together? Polymer. 2020;207:122929. Available from: https://www.sciencedirect.com/science/article/pii/S0032386120307540.
2. Dadfar SMR, Pourmahdian S, Tehranchi MM, Dadfar SM. Novel dual-responsive semi-interpenetrating polymer network hydrogels for controlled release of anticancer drugs. J Biomed Mater Res, Part A. 2019;107(10):2327–39.
3. Raina N, Rani R, Khan A, Nagpal K, Gupta M. Interpenetrating polymer network as a pioneer drug delivery system: a review. Polym Bull. 2020;77(9):5027–50.
4. Pulat M, Kahraman AS, Gümüşderelioğlu M. Sequential antibiotic and growth factor releasing chitosan-PAAm semi-IPN hydrogel as a novel wound dressing. J Biomater Sci Polym Ed. 2013;24(7):807–19.
5. Huang Y, Zhao X, Zhang Z, Liang Y, Yin Z, Chen B, et al. Degradable gelatin-based IPN cryogel hemostat for rapidly stopping deep noncompressible hemorrhage and simultaneously improving wound healing. Chem Mater. 2020;32(15):6595–610.
6. Yang C, Xue R, Zhang Q, Yang S, Liu P, Chen L, et al. Nanoclay cross-linked semi-IPN silk sericin/poly(NIPAm/LMSH) nanocomposite hydrogel: an outstanding antibacterial wound dressing. Mater Sci Eng C Mater Biol Appl. 2017;81:303–13.
7. Crosby CO, Stern B, Kalkunte N, Pedahzur S, Ramesh S, Zoldan J. Interpenetrating polymer network hydrogels as bioactive scaffolds for tissue engineering. Rev Chem Eng. 2022;38(3):347–361. Available from: https://doi.org/10.1515/recce-2020-0039 [cited 2022-05-08].
8. Fares MM, Shirzaei Sani E, Portillo Lara R, Oliveira RB, Khademhosseini A, Annabi N. Interpenetrating network gelatin methacryloyl (GelMA) and pectin-g-PCL hydrogels with tunable properties for tissue engineering. Biomater Sci. 2018;6:2938–2950. Available from: http://dx.doi.org/10.1039/C8BM00474A.

9. Shojarazavi N, Mashayekhan S, Pazooki H, Mohsenfard S, Banisadasi H. Alginate/cartilage extracellular matrix-based injectable interpenetrating polymer network hydrogel for cartilage tissue engineering. J Biomater Appl. 2021;36(5):803–17.

10. Avadhanam V, Inagavle G, Zheng Y, Kumar S, Liu C, Sandeman S. Biomimetic bone-like composites as osteo-odonto-keratoprosthesist kit substitutes. J Biomater Appl. 2021;35(8):1043–60.

11. Kaity S, Ghosh A. Carboxymethylation of locust bean gum: application in interpenetrating polymer network microspheres for controlled drug delivery. Ind Eng Chem Res. 2013;52(30):10033–45.

12. Hajikhani M, Khanghahi MM, Shahrousvand M, Mohammadi-Rovshandeh J, Babaei A, Khademi SMH. Intelligent superabsorbents based on a xanthan gum/poly (acrylic acid) semi-interpenetrating polymer network for application in drug delivery systems. Int J Biol Macromol. 2019;139:509–520. Available from: https://www.sciencedirect.com/science/article/pii/S014181301936542.

13. Aylsworth J. Best invention ever; US Patent 1111284, 1914.

14. Aylsworth A, Jiang SX, Desbois A, Hou ST. Characterization of the mechanism and food applications. Trends Food Sci Technol. 2021;116:342–358. pii/S0924224221000139.

15. Koul V, Mohamed R, Kuckling D, Adler HP, Choudhary V. Interpenetrating polymer network (IPN) nanogels based on gelatin and poly (acrylic acid) by inverse miniumulsion technique: synthesis and characterization. Colloids Surf B. 2011;83(2):204–13.

16. Elbarbary AM, Ghobashy MM. Phosphorylation of chitosan/HEMA interpenetrating polymer network prepared by γ-radiation for metal ions removal from aqueous solutions. Carbohydr Polym. 2017;162:16–27.

17. Swain S, Bai T. Carrageenan-guar gum microwaved irradiated microporous interpenetrating polymer network: a system for drug delivery. Int J Polym Mater Polym Biomater. 2019;68(5):256–265. Available from: https://doi.org/10.1080/00914037.2018.1449391.

18. Lei Y, Jia X, et al. A pH-sensitive semi-interpenetrating polymer network hydrogels constructed by konjac glucomannan and poly (γ-glutamic acid): synthesis, characterization and swelling behavior. Int J Biol Macromol. 2020;157:229–239. Available from: https://www.sciencedirect.com/science/article/pii/S0141813021012411.

19. Park JC, Hwang YS, Lee JE, Park KD, Matsumura K, Hyon SH, et al. Type I atelocollagen grafting onto ozone-treated polyurethane films: cell attachment, proliferation, and collagen synthesis. J Biomater Res. 2000;52(4):669–77.

20. Zhao J, Zhao X, Guo B, Ma PX. Multifunctional interpenetrating polymer network hydrogels based on methacrylated alginate for the delivery of small molecule drugs and sustained release of protein. Biomacromolecules. 2014;15(9):3246–52.

21. Gachuz EJ, Castillo-Santillán M, Juarez-Moreno K, Maya-Cornejo J, Martinez-Richa A, Andrio A, et al. Electrical conductivity of an all-natural and biocompatible semi-interpenetrating polymer network containing a deep eutectic solvent. Green Chem. 2020;22:5785–5797.

22. Hsu HJ, Bugno J, Lee SR, Hong S. Dendrimer-based nanocarriers: a versatile platform for drug delivery. Wiley interdisciplinary reviews Nanomedicine and nanobiotechnology. 2017 Jan;9(1).
42. Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomaterials. Nat Nanotechnol. 2007;2(8):469–78.

43. Mukherji D, Marques CM, Kremer K. Smart responsive polymers: fundamentals and design principles. Annual Review of Condensed Matter Physics. 2020;11:271–99.

44. Langer R, Tirrell DA. Designing materials for biology and medicine. Nature. 2004;428(6982):487–492.

45. Schmaljohann D. Thermo-and pH-responsive polymers in drug delivery. Adv Drug Deliv Rev. 2006;58(15):1655–70.

46. Ghani M, Heiskanen A, Kajtez J, Rezaei B, Larsen NB, Thomsen P, et al. On-demand reversible UV-triggered interpenetrating polymer network-based drug delivery system using the spiropyran-merocyanine hydrobicity switch. ACS Appl Mater Interfaces. 2021;13(3):3591–604.

47. Ward MA, Georgiou TK. Thermoresponsive polymers for biomedical applications. Polymers. 2011;3(3):1215–1242. Available from: https://www.mdpi.com/2073-4360/3/3/1215.

48. Kaity S, Ghosh A. Facile preparation of acrylamide grafted locust bean gum-poly(vinyl alcohol) interpenetrating polymer network microspheres for controlled oral drug delivery. J Drug Delivery Sci Technol. 2016;33:1–12.

49. Smith GN, Brok E, Schmiele M, Mortensen K, Bouwman WG, Duif CP, et al. The microscopic distribution of hydrophilic polymers in interpenetrating polymer networks (IPNs) of medical grade silicone. Polymer. 2021;224:123671. Available from: https://www.sciencedirect.com/science/article/pii/S0032386121002949.

50. Rehmani S, Ahmad M, Minhas MU, Anwar H, Zangi MH, Sohail M. Development of natural and synthetic polymer-based semi-interpenetrating polymer network for controlled drug delivery: optimization and in vitro evaluation studies. Polym Bull. 2017;74(3):737–761.

51. Agnihotri SA, Aminabhavi TM. Novel interpenetrating network chitosan-poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capricetamine. Int J Pharm. 2006;324(2):103–15.

52. Rokhade AP, Shelke NB, Patil SA, Aminabhavi TM. Novel hydrogel microspheres of chitosan and pluronic F-127 for controlled release of 5-fluorouracil. J Microencapsul. 2007;24(3):274–88.

53. Lee P, Lok CN, Che CM, Kao WJ. A Multifunctional hydrogel delivers gold compound and inhibits human lung cancer xenograft. Pharm Res. 2019;36(4):61.

54. Wang Y, Li Q, Zhou JE, Tan J, Li M, Xu N, et al. A photopolymerized semi-interpenetrating polymer networks-based hydrogel incorporated with nanoparticles for local chemotherapy of tumors. Pharm Res. 2021;38(4):669–80.

55. Madhusudana Rao K, Krishna Rao KSV, Ramanjaneyulu G, Ha CS. Curcumin encapsulated pH sensitive gelatin based interpenetrating polymeric network nanogels for anti cancer drug delivery. Int J Pharm. 2015;Jan;478(2):788–95.

56. Jimenez-Rosas A, Flores-Merino MV. A brief review of the pathophysiology of non-melanoma skin cancer and applications of interpenetrating and semi-interpenetrating polymer networks in its treatment. Regenerative Engineering and Translational Medicine. 2018;4(4):187–205.

57. Thorne JB, Vine GJ, Snowden MJ. Microgel applications and commercial considerations. Colloid Polym Sci. 2011;289(1):625.

58. Krishna Rao KSV, Vijaya Kumar Naidu B, Subha MCS, Sairam M, Aminabhavi TM. Novel chitosan-based pH-sensitive interpenetrating network microgels for the controlled release of cefadroxil. Carbohydr Polym. 2006;66(3):333–344. Available from: https://www.sciencedirect.com/science/article/pii/S014486170001561.

59. Bhattacharya SS, Mazahir F, Banerjee S, Verma A, Ghosh A. Preparation and in vitro evaluation of xanthan gum facilitated superabsorbent polymeric microspheres. Carbohydr Polym. 2013;98(1):64–72.

60. Risbad MV, Hardikar AA, Bhat SV, Bhonde RR. pH-sensitive freeze-dried chitosan–polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. J Control Release. 2000;68(1):23–30. Available from: https://www.sciencedirect.com/science/article/pii/S016836590000208X.

61. Agnihotri SA, Aminabhavi TM. Development of novel interpenetrating network gelatin gum-poly(vinyl alcohol) hydrogel microspheres for the controlled release of carvedilol. Drug Dev Ind Pharm. 2005;31(6):491–503.

62. Hosseinzadeh H. Interpenetrating network polymer hydrogels of sodium alginate and poly(acrylic acid) for controlled release of prazosin hydrochloride. Orient J Chem. 2012;03(28):349–52.

63. Ray D, Gils P, Mohanta G, Sahoo P. Comparative delivery of diltiazem hydrochloride through synthesized polymer: hydrogel and hydrogel microspheres. J Appl Polym Sci. 2009;11(6):959–68.

64. Thachandri D, Panduranga Rao K. Collagen-chitosan composite membranes controlled transdermal delivery of nifedipine and propranolol hydrochloride. Int J Pharm. 1996;134(1):239–241. Available from: https://www.sciencedirect.com/science/article/pii/0378517396044535.

65. Boppana R, Krishna Mohan G, Nayak U, Mutalik S, Sa B, Kulkarni NV. Novel pH-sensitive IPNs of polycrylamide-g-gum ghatti and sodium alginate for gastro-proective drug delivery. Int J Biol Macromol. 2015;75:133–43.

66. Rani P, Sen G, Mishra S, Jha U. Microwave assisted synthesis of polycrylamide grafted gum ghatti and its application as flocculant. Carbohydr Polym. 2012;89(1):275–281. Available from: https://www.sciencedirect.com/science/article/pii/S014661712002202.

67. Essawarma S, Rao KSVK. Synthesis of dual responsive carbohydrate polymer based IPN microbeads for controlled release of anti-HIV drug. Carbohydr Polym. 2017;156:125–134. Available from: https://www.sciencedirect.com/science/article/pii/S0146617116310773.

68. Sullad AG, Manjeshwar LS, Aminabhavi TM. Novel semi-interpenetrating microspheres of dextran-grafted-acrylamide and poly(vinyl alcohol) for controlled release of abacavir sulfate. Ind Eng Chem Res. 2011;50(21):11778–84.

69. Krishna Rao KSV, Espenti C, Kummmara MR, Essawarma S, Raju R. Development of gelatin-lignosulfonic acid blend microspheres for controlled release of an anti-malarial drug (pyronaridinone). Indian Journal of Advances in Chemical Science. 2015;01(3):25–32.

70. Kulkarni RV, Patel FS, Nanajapahai HM, Naikawadi AA. In vitro and in vivo evaluation of novel interpenetrated polymer network microparticles containing repaglinide. Int J Biol Macromol. 2014;69:514–22.

71. Rokhade AP, Shelke NB, Patil SA, Aminabhavi TM. Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline. Carbohydr Polym. 2007;69(4):678–687. Available from: https://www.sciencedirect.com/science/article/pii/S0144861707001154.

72. Prajapati VD, Gandhi AK, Patel KK, Patel BN, Chaudhari AM, Jani GK. Development and optimization of modified release IPN macromolecules of oxcarbazepine using natural polymers. Int J Biol Macromol. 2015;73:160–9.

73. Yin L, Ding J, Fei L, He M, Cui F, Tang C, et al. Beneficial properties for insulin absorption using superporous hydrogel containing interpenetrating polymer network as oral delivery vehicles. Int J Pharm. 2008;350(1–2):220–9.

74. Kurakula M, Rao GSNK. Pharmaceutical assessment of polyvinylpyrrolidone (PVP): as excipient from conventional to controlled delivery systems with a spotlight on COVID-19 inhibition. J Drug Delivery Sci Technol.. 2020;60.

75. De Temmerman ML, Rejman J, Demeester J, Irvine DJ, Gander B, et al. Polymeric particles in vaccine delivery. Curr Opin Microbiol. 2010;62(4–5):378–93.

76. Jani GK. Development and optimization of modified release IPN macromolecules of oxcarbazepine using natural polymers. Int J Biol Macromol. 2015;73:160–9.

77. Rice-Ficht AC, Arenas-Gamboa AM, Kahl-McDonagh MM, Ficht TA. Polymeric particles in vaccine delivery. Curr Opin Microbiol. 2010;13(1):106–12.
78. Broos S, Lundberg K, Akagi T, Kadowaki K, Akashi M, Greiff L, et al. Immunomodulatory nanoparticles as adjuvants and allergen-delivery system to human dendritic cells: implications for specific immunotherapy. Vaccine. 2010;28(31):5075–85.
79. Skwarczynski M, Toth I. Peptide-based synthetic vaccines. Chem Sci. 2016;7(2):842–54.
80. Lofthouse S. Immunological aspects of controlled antigen delivery. Adv Drug Deliv Rev. 2002;54(6):863–70.
81. Schijns VEJC, Lavelle EC. Trends in vaccine adjuvants. Expert Rev Vaccines. 2011;10(4):539–50.
82. George M, Abraham TE. Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan-a review. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2006;114(1):1–14.
83. Rodrigues MA, Figueiredo L, Padrela L, Cadete A, Tiago J, Matos HA, et al. Development of a novel mucosal vaccine against strangles by supercritical enhanced atomization spray-drying of Streptococcus equi extracts and evaluation in a mouse model. Eur J Pharm Biopharm. 2012;82(2):392–400. Available from: https://www.sciencedirect.com/science/article/pii/S0939641112002305.
84. Mallakpour S, Azadi E, Hussain CM. Chitosan, alginate, hyaluronic acid, gums, and β-glucan as potent adjuvants and vaccine delivery systems for viral threats including SARS-CoV-2: A review. Int J Biol Macromol. 2021;182:1931–40.
85. Petitjean M, García-Zubiri IX, Isasi JR. History of cyclodextrin-based polymers in food and pharmacy: a review. Environ Chem Lett. 2021;19(4):3465–76.
86. Shae D, Postma A, Wilson JT. Vaccine delivery: where polymer chemistry meets immunology. Ther Deliv. 2016;7(4):193–196.
87. Zhang M, Hong Y, Chen W, Wang C. Polymers for DNA vaccine delivery. ACS Biomater Sci Eng. 2017;3(2):108–25.
88. Bolhassani A, Javanzad S, Saleh T, Hashemi M, Aghasadeghi MR, Sadat SM. Polymeric nanoparticles: potent vectors for vaccine delivery targeting cancer and infectious diseases. Hum Vacc Immunother. 2014;10(2):321–32.
89. Kumar M, Behera AK, Lockey RF, Zhang J, Bhullar G, De La Cruz CP, et al. Intranasal gene transfer by chitosan-DNA nanospheres protects BALB/c mice against acute respiratory syncytial virus infection. Hum Gene Ther. 2002;13(12):1415–25.
90. Li GP, Liu ZG, Liao B, Zhong NS. Induction of Th1-type immune response by chitosan nanoparticles containing plasmid DNA encoding house dust mite allergen Der p 2 for oral vaccination in mice. Cell Mol Immunol. 2009;6(1):45–50.
91. Wu Z, Li T. Nanoparticle-mediated cytoplasmic delivery of messenger RNA vaccines: challenges and future perspectives. Pharm Res. 2021;38(3):473–8.
92. Pardi N, Hogan MJ, Weissman D. Recent advances in mRNA vaccine technology. Curr Opin Immunol. 2020;65:14–20.
93. Nevagi RJ, Skwarczynski M, Toth I. Polymers for subunit vaccine delivery. Eur Polym J. 2019;114:397–410. Available from: https://www.sciencedirect.com/science/article/pii/S0014305718320676.
94. Carreira AS, Gonçalves FAMM, Mendonça PV, Gil MH, Coelho JFJ. Temperature and pH responsive polymers based on chitosan: applications and new draft copolymerization strategies based on living radical polymerization. Carbohydr Polym. 2010;80(3):618–630. Available from: https://www.sciencedirect.com/science/article/pii/S0144861710000093.
95. Sharma A, Kontodimas K, Bosmann M. Nanomedicine: a diagnostic and therapeutic approach to COVID-19. Front Med. 2021;8. Available from: https://www.frontiersin.org/article/10.3389/fmed.2021.648005.
96. Pal K, Banthia A, Majumdar DK. Polymeric hydrogels: characterization and biomedical applications. Des Monomers Polym. 2009;12(3):197–220.

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