Interpenetrating polymer network-based drug delivery systems: emerging applications and recent patents

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Interpenetrating polymer network (IPN) systems use novel polymers that are synthesized by the interlacing of two independent polymers in a cross-linked form. For successful preparation of such IPN systems, at least one of the participating polymers should be synthesized/cross-linked in the immediate presence of the other. The polymers used to fabricate an IPN system are independently cross-linked or cross-linked to each other. They can be prepared by selective combination of the starting polymers to tailor the final product based on the ultimately desired characteristics. The nontoxic nature and biodegradability of natural polymers can thus be combined with the robustness and strength offered by the synthetic polymers by fabricating their IPN systems. The present review aims to summarize the IPN systems in terms of their advantages, disadvantages, and different drug delivery systems based on these polymers and their numerous biomedical applications. This review includes a detailed study of the recent publications and patents describing the use of IPNs in different spheres/formulations.

Keywords:
hydrogel, interpenetrating polymer network, interpenetrating polymer network applications, interpenetrating polymer network patents, microspheres

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Introduction

The recent advancements in polymeric science have led to the development of many novel drug delivery systems [1]. An interpenetrating polymer network (IPN) is a category of such newly developed bioactive materials that are an emerging tool for the pharmaceutical industry [2]. IPNs play an excellent role because of the improved biocompatibility and safety profiles they offer owing to their physical characteristics such as good swelling properties. They can be useful in various domains of drug delivery, such as improving the solubility of hydrophobic drugs, imparting stability to the formulations containing active drugs, drug targeting a specific tissue, improving bioavailability and biodegradability, etc. [3]. The range of applications for IPNs has grown rapidly as they showcase much finer performance over conventional individual polymers. In the pharmaceutical field, mainly in the field of drug delivery systems, IPNs have attracted considerable attention because of their advanced properties as these novel bioactive polymer networks are biocompatible, nontoxic, and biodegradable in nature, thereby lending substantial advantages particularly in controlled and targeted drug delivery. Through various investigations using different drugs it was observed that IPN systems can be harnessed for safe and effective drug delivery [4]. Synergistic effect can be produced using IPN technology by formulating an IPN between a natural and other synthetic polymer, hence gaining the properties of both polymers and consequently avoiding the drawbacks of both. For example, from many studies it can be concluded that, when a natural polymer is interpenetrated with a synthetic polymer, the IPN system thus obtained is expected to have better capability for the controlled release of drugs under physiological conditions. Thus, in recent times, interest has been focused on the advancement of IPN-based drug delivery systems [5,6]. IPN systems can be simply stated to be a combination of two independent polymers [7]. It is also a combination of at least two polymers, where at least one network is synthesized between two or more networks without any covalent bonds or in the presence of other cross-linked polymer networks leading to interlacing between the two at a molecular level and in turn leading to interlacing between the different features and performances of the individual components [1]. In other words, an IPN is a combination of at least two polymers, exhibiting varied characteristics [7], in which at least one network is synthesized and/or cross-linked in the presence of the other polymer network without any covalent bonds between them or in the presence of two or more networks [3]. When the polymer chains of the second system are cross-linked with or penetrated in the network formed by the first polymer, a physically cross-linked network is formed. Each network retains its individual properties so that synergistic improvements in properties like strength or toughness can be seen [8].

Three types of noncovalent physical cross-linking mechanisms are considered to be involved in the formation of IPN polymers:

(1) Block copolymers based on:
    (a) Glassy blocks.
    (b) Crystalline blocks.
    (c) Hydrogen bonded blocks.
(2) Ionomeric sites.
(3) Entrapment of crystalline regions in semi crystalline homopolymers [9].

IPN systems are also termed as 'Hungary Network'. These intelligent polymers are a focus of considerable current scientific research because of their potential technological applications in various fields such as medicine, industry, biology, and environmental cleanup. Some of the important biomedical applications of IPNs are in artificial implants, dialysis membranes, drug delivery systems, burn dressing, etc. [10].

Basis of selection of polymers for formulating a successful interpenetrating polymer network system

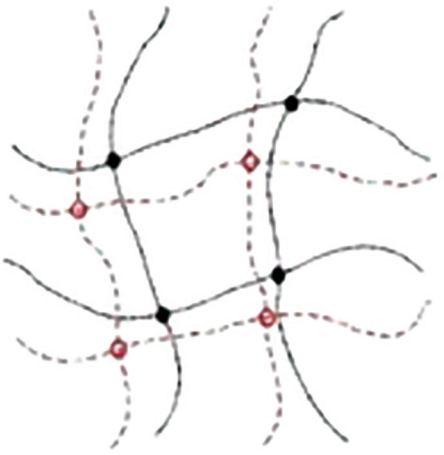
(1) The kinetic profiles of the two polymers should be similar.
(2) One polymer is cross-linked and/or synthesized in the presence of the other polymer.
(3) The two polymers are not markedly phase separated.

IPNs that have only one cross-linked polymer (when the polymers are synthesized separately) or have polymers with vastly different kinetics are still considered IPNs.

IPNs in which the polymers have a vast difference in their kinetics or one polymer is cross-linked or both polymers are synthesized separately are also considered to be IPNs [11].

A pictorial representation of the basic structure of IPNs is given in Fig. 1.

Figure 1



Structure of an interpenetrating polymer network (IPN).

Advantages of interpenetrating polymer network

IPN technology is gaining huge popularity because of its following inherent merits [12]:

(1) An IPN can combine the synergistic properties of both polymers such that when one natural polymer is interpenetrated/cross-linked with the other synthetic polymer the resultant IPN can be better used for the controlled release of the drug [9,13,14] and the drug can be expected to be immobilized [11].
(2) Whenever an IPN hydrogel is formed from two polymers at a given temperature, the possibility of physical phase separation between the component polymers is almost negligible because of the infinite zero viscosity of the gel.
(3) The phase stability of the final product is greatly enhanced and it has greater biological acceptability.
(4) Mechanical properties of the final product are profoundly enhanced [15] because of the combination of both natural and synthetic polymers.
(5) The separated phases remain together as when they are subjected to stress [16].

Disadvantages of interpenetrating polymer network

A disadvantage associated with the use of the IPN is that sometimes the polymers are interpenetrated to such an extent that it becomes difficult to release the active drug from the polymer matrix [1]. Moreover, the quality of the final polymer obtained is highly susceptible to various in-process parameters like the reaction mechanism, reactor-type, and reactor operating conditions [17]. One of the problems encountered may be the lack of effective interface stemming from various factors including the surface energy phenomenon and lack of molecular interaction between phases [18].

Figure 2 shows the process of formation of an IPN system between chitosan, a natural polymer obtained from shrimp and other crustacean shells, and the synthetic polymer polyacrylamide often used as a thickener and suspending agent in pharmaceutical applications.

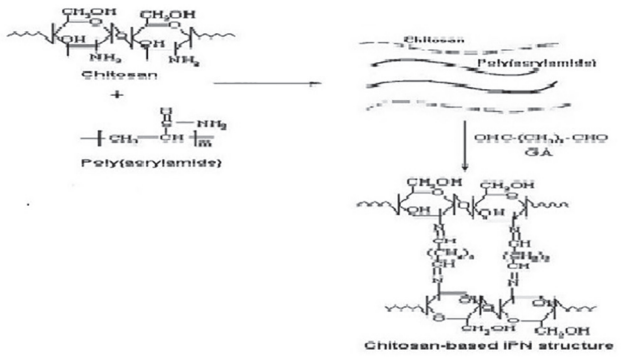
Interpenetrating polymer network-based drug delivery systems

IPN-based systems are mainly used for the controlled release of drugs. Various drug delivery systems have been developed that use IPNs.

Microspheres

Using the novel IPN technique, mucoadhesive microspheres of locust bean gum (LBG) and polyvinyl alcohol (PVA) were prepared by means of the water-in-oil (w/o) emulsion cross-linking method. These mucoadhesive microspheres were cross-linked with glutaraldehyde (GA) to deliver a model oral hypoglycemic drug for prolongation of gastric residence time. These microspheres were then evaluated through Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM), and the mean particle size of the microspheres was measured by optical microscopy. Percentage mucoadhesion of the microspheres showed a dependence on the LBG: PVA ratio and extent of cross-linking. *In-vitro* release studies were performed in 0.1 N HCl buffer solution at pH 1.2 to investigate the controlled release nature of the microspheres. The release of metformin HCl was sustained for up to 8 h [19].

Figure 2



Schematic representation of the formation of an interpenetrating polymer network (IPN) structure.

Buflomedil hydrochloride, a vasodilator drug having high water solubility, has also been administered as a microsphere drug delivery agent by using IPN microspheres based on LBG and PVA fabricated by means of the emulsion cross-linking technique and GA as the cross-linker for oral controlled release. The effects of the gum–polymer ratio, concentration of cross-linker, and internal phase viscosity were then evaluated on the basis of various characteristics like the drug entrapment efficiency, particle size distribution, swelling property, and *in-vitro* characteristics, along with kinetic modeling of microspheres. The microspheres were also characterized by SEM, FTIR, solid-state ^{13}C-NMR, X-ray diffraction study, and differential scanning colorimetry (DSC). The prepared microspheres showed controlled release property without any incompatibility in the IPN device. Hence, IPN microspheres of LBG and PVA can be used successfully as a potential carrier for controlled oral delivery of highly water-soluble drugs [20].

IPN-based microspherical drug delivery systems have also been used for the delivery of antineoplastic drugs such as capecitabine to prolong the delivery of the drug by formation of a chitosan–polyethylene oxide-g-acrylamide intermolecular rigid network [21]. Table 1

Table 1 Interpenetrating polymer network-based polymers for formulation of microspheres

Drugs	Polymer	Cross-linker	Novel carrier	Therapeutic application	Reference
Capecitabine	Poly (ethylene oxide)-g-acrylamide + chitosan	Glutaraldehyde	Hydrogel microsphere	Anticancer	[21]
Diclofenac sodium	Sodium alginate + PVA	Glutaraldehyde	Microsphere	Anti-inflammatory	[22]
Chlorothiazide	Chitosan + hydroxy propyl cellulose	Glutaraldehyde	Hydrogel microsphere	Diuretic	[23]
Amoxicillin	Chitosan+polyvinyl pyrrolidone	Glutaraldehyde	Microsphere	Antibiotic	[24]
Isoniazid	Hydroxy ethyl cellulose + chitosan	Glutaraldehyde	Microsphere	Antitubercular	[25]
Propranolol HCl	Chitosan+gelatin	Glutaraldehyde	Mucoadhesi-ve microsphere	Antihypertensive	[26]
Buflomedil hydrochloride (BH)	Locust bean gum + PVA	Glutaraldehyde	Microspheres	Vasodilator	[20]
Theophylline	Chitosan+methyl cellulose	Glutaraldehyde	Microsphere	Antiasthmatic	[27]
Metformin HCl	Locust bean gum (LBG) + poly vinyl alcohol (PVA)	Glutaraldehyde	Mucoadhesive microspheres	Antihyperglycemic	[19]
Simvastatin	*Lepidium sativum* (LS) + poly (vinyl alcohol) (PVA)	Glutaraldehyde	Microsphere	Hypolipidemic	[28]
Ciprofloxacin	Acrylamide-grafted-guar gum+chitosan	Glutaraldehyde	Hydrogel microsphere	Anti-inflammatory	[29]
Triprolidine hydrochloride	Acrylamide + carboxymethyl cellulose + sodium alginate	Glutaraldehyde	Microsphere	Antihistaminic	[30]

summarizes the microsphere formulations developed using IPN systems.

Transdermal membranes or patches

IPN hydrogel membranes of sodium alginate and PVA embedding an antihypertensive drug, prazosin hydrochloride, were prepared by means of the solvent casting method for transdermal drug delivery. The prepared membranes were thin, flexible, and smooth. X-ray diffraction studies showed amorphous dispersion of drug in the membranes. DSC analysis was used to confirm the IPN formation. An interesting observation was recorded in that, on increasing the concentration of GA, membrane stiffness also increased. The membrane's permeability to water vapor was found to be dependent on the extent of cross-linking. *In-vitro* designing of hydrogels for site-specific oral delivery in the stomach and upper intestine is possible [31].

Semi-interpenetrating polymer network (SIPN) membranes were prepared for an antiasthmatic drug (salbutamol sulfate) using PVA, chitosan, and sodium alginate and GA as a cross-linker. Mechanical properties such as tensile strength and elongation of the membranes were determined, along with permeability properties and drug entrapment efficiency. Using Keshary-Chien diffusion cells, the *in-vitro* drug release profile was determined. In the PVA membranes (pure), the rate of swelling and water vapor transmission were high compared with their IPNs. The result indicated that blending of PVA with other polymers and cross-linking with GA led to higher entrapment efficiency. The drug release profiles showed that the drug permeated through the membranes for up to 20 h [32]. Various examples of hydrogel membranes formulated using IPNs are given in Table 2.

Hydrogels

In studies examining the effect of polyethylene oxide (PEO) on the swelling behavior and enzyme-induced degradation in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) at 37°C of SIPN-based hydrogels, it was found that the surface degradation of the hydrogel decreases the diffusional path length of the drug for faster release as the gel degrades. By varying the PEO molecular weight and amount in gelatine-PEO SIPN, designing of hydrogels for site-specific oral delivery in the stomach and upper intestine is possible [34].

SIPNs of PVA and polymethacrylic acid were prepared by free radical polymerization of methacrylic acid in the presence of PVA using *N*,*N*-methylene-bis-acrylamide as the cross-linking agent. The effect of cross-linking agent and methacrylic acid concentrations on the swelling and release characteristics was evaluated. Insulin was incorporated by the active loading technique in the SIPN hydrogels. The formulations showed decreased insulin release in pH 2.0 buffer, whereas complete release was seen in pH 7.4 buffer. From the studies it can be concluded that SIPNs of PVA/PMMA can be explored for protein delivery, which can protect the protein against the harsh environment of acidic pH but releases the drug in the distal part of the intestine where the enzymatic activity is comparatively low [35].

IPN-based hydrogel was prepared using soy protein and polysodium acrylate and was characterized by FTIR, SEM, DSC, and thermogravimetric analysis (TGA) and investigated for swelling and deswelling behavior. The swelling behavior, water retention, pore size, and pore wall thickness of the hydrogel were controlled by changing the content of soy protein or cross-linker. The swelling ratio was low at pH 1.2 and the fastest to reach equilibrium, whereas when the swelling ratio increased to above pH 4.0 it showed non-Fickian diffusion and below pH 4.0 it showed Fickian diffusion. Thus, the results reveal that novel IPN hydrogels can be of interest in IPN-based drug delivery systems [36].

Certain examples of hydrogels formulated using IPN polymers are summed up in Table 3.

Microgels

By using the IPN system, alginate–gelatin microgels were prepared containing tramadol as an active drug by the chemical cross-linking technique with GA as the cross-linking agent. Microgels were then evaluated for various parameters using FTIR, DSC, etc. The mucoadhesive properties of microgels were evaluated in aqueous solutions by measuring the mucin adsorbed on microgels. The dependence of drug release on the extent of cross-linking and the amount of gelatin used in preparing IPNs were determined by the *in-vitro* release studies. The release rates were then fit to Higuchi's model to compute the various drug transport parameters, which suggest that the release may vary from Fickian to quasi-Fickian depending

Table 2 Hydrogels membrane synthesized using interpenetrating polymer networks

Drug	Polymers	Cross-linker	Novel carrier	Therapeutic application	Reference
Prazosin hydrochloride	Sodium alginate + PVA	Glutaraldehyde	Hydrogel membrane	Antihypertensive	[33]
Salbutamol sulfate	PVA + chitosan + sodium alginate	Glutaraldehyde	Hydrogel membrane	Antiasthmatic	[32]

upon variation in the formulation composition [44] as summarized in Table 4.

Nanogels

Novel IPN-based nanogels composed of polyacrylic acid (PAA) and gelatin were synthesized using the inverse miniemulsion technique. This concept was based on nanoreactors and cross-checked with the template polymerization technique. The gelatin macromolecules were stabilized by acrylic acid monomer in which each droplet was polymerized using ammonium persulfate and tetramethyl ethylene diamine in 1: 5 ratio and SIPN nanogels were formed when cross-linked with *N*, *N*-methylene bisacrylamide and when cross-linked sequentially with GA (Glu) to form IPNs. For the formation of homopolymer, SIPN and an FDA-approved surfactant were used to produce an IPN nanogel, acrylic acid stable gelatine. The droplets were observed in 2% surfactant concentration. Spherical IPN nanogels thus prepared were studied using dynamic light scattering and SEM to rule out any interactions and changes in crystal structure of the polymers. Similarly, SIPNs prepared by the same method, but in great shape, formed nanogels. The presence of interpenetrated polymer component on the surface of the nanogels can be detected by using methods like XPS measurement, infrared spectroscopy (FTIR) and zeta potential measurement etc. Thus, these nanogels were used in cancer targeting [46].

Capsules

With the use of micron-sized colloidosomes of polymethyl methacryalate-*co*-divinylbenzene microgels as reaction vessels, we can prepare supracolloidal IPN-reinforced capsules. By using the technique of radical polymerization of the interior phase, an IPN as scaffold is generated, to produce hollow supracolloidal structures with a raspberry core-shell morphology [47].

Sponges

Sponges prepared by SIPNs of the polymers. Poloxamer and chitosan (CS) are being increasingly used for wound dressing. Possible interactions between the CS and poloxamer in SIPNs and changes in crystalline structures of both polymers were evaluated by FTIR and X-ray diffraction, respectively. Formation of SIPNs with poloxamer remarkably increased the water content of CS because of the hydrophilicity of CS and the poloxamer. These studies suggest that CS/poloxamer sponges can be prepared by the SIPN method and may have potential in wound dressing application owing to the rapid water adsorption, high mechanical strength, and interconnected cross-sectional morphology of SIPNs [48].

In experimental studies it was found that SIPNs composed of silk fibroin (SF) and polyethylene glycol (PEG) can be prepared by photopolymerization of a PEG macromer in the presence of SF to improve the mechanical properties of the SF sponge, which can be used in wound dressing. The morphological structure of the SF/PEG SIPNs was observed to be composed of an interconnected microporous surface and a cross-sectional area. SF/PEG SIPNs showed noncytotoxicity evaluated by a cell proliferation method using L929 fibroblasts. Wound contraction treated with SF/PEG SIPN sponges was faster than that treated with vaseline gauze as a control. Histological observation confirmed that the deposition of collagen in the dermis

Table 3 Hydrogels formulated using interpenetrating polymer network systems

Drugs	Polymer	Cross-linker	Novel carrier	Therapeutic application	Reference
Clarithromycin	Chitosan + PVP	Glutaraldehyde	Hydrogel	Antibiotic	[37]
Curcumin	Poly (ethylene glycol) (PEG) diacrylate cross-linked acrylic polymer	Polyethylene glycol (PEG)	Hydrogel	Anticancer	[38]
Insulin	Poly(acrylic acid)-co-acrylamide + chitosan	*N,N'*-methylene bisacrylamide	Hydrogel	Oral hypoglycemic	[39]
Clarithromycin	Chitosan + poly (vinylpyrrolidone) + poly (acrylic acid)	Glutaraldehyde + *N,N'*-methylene bisacrylamide	Hydrogel	Antibiotic (*H. pylori* infections)	[40]
Insulin	Poly (vinyl alcohol) +poly (methacrylic acid)	*N,N*-methylene bisacrylamide	Hydrogel	Oral hypoglycemic	[41]
	Gelatin + PVA	Gelatin + transglutaminase enzyme	Hydrogel	Tissue engineering	[42]
	PEG/NaOH + acrylic acid	*N,N'*-methylene bisacrylamide	Hydrogel	Wound healing	[43]

Table 4 Microgels formulated using interpenetrated polymer networks

Drugs	Polymer	Cross-linker	Novel carrier	Therapeutic application	Reference
Tramadol	Alginate + gelatin	Glutaraldehyde	Microgels	Analgesic	[44]
Cefadroxil	Acryl amide-g-poly (vinyl alcohol) +chitosan	Ceric ammonium nitrate + glutaraldehyde	Microgels	Antibiotic	[45]

was organized by covering the wound area with SF/PEG SIPNs. The above results showed that SF/PEG SIPNs could be used in wound dressing [49].

Cross-linked sponges have been prepared by freeze-drying amorphous alginate-oxidized nanocellulose in the presence of ionic Ca^{2+} as a cross-linker. On the surface of nanocellulose a new carboxyl group was introduced by chemical oxidization, which played a role in the formation of an alginate-based sponge structure, providing the structural and mechanical stability of sponges. Further, mechanical strength was induced by oxidized cellulose nanocrystals. The improved compression strength of cross-linked sponges as a result of ultrahigh porosity, promising water absorption and retention, can extend the use of this soft material in various practical applications [50].

Nanoparticles

Using the technique of temperature-responsive IPN formation, thermally active metal nanoshells are produced in which therapeutic drugs are dispersed and released upon radiation-induced heating of the metal nanosphere. IPN devices that swell in response to increase in temperature can be successfully used to safely localize and release therapeutic levels of potent drugs. However, to be effective *in vivo* the heating source has to meet several requirements such as being small in size (300 nm in diameter) so as to fit within therapeutic agents and being able to heat through a safe noninvasive external trigger so that it is capable of reaching the nanoshell at high penetration depths *in vivo*. The first and outermost layer of composite nanoparticles is the PEG or surface PEG layer. This process is commonly referred to as PEGylation, and involves either the adsorbing or the grafting of PEG chains to a material's surface. PEGylation allows materials in the form of polymeric nanoparticles that filter out of the blood immediately after injection to remain in circulation for hours and even days. The more these nanoparticles remain in circulation, the more chances they have to interact with tissues and desirable components in the body. These nanoparticles can be used in the field of cancer treatment [51].

Nanoparticles are a recent focus of interest among scientists because of the innumerable benefits they offer over conventional dosage forms. Formulating IPN-based nanoparticles to combine the best of both worlds is a recent trend. A summary of such nanoparticle formulations is given in Table 5.

Films

Synthesized and characterized IPN-based natural polymer curcumin films for accelerating the rate of wound healing were prepared using natural polymers like chitosan, hypromellose, citric acid, and genipin. This helped in developing an effective, biodegradable, and biocompatible film and the physicochemical, biological and mechanical properties of the same SIPN film were evaluated by employing FTIR, DSC and Young's modulus studies. Further *in-vitro* and ex-vivo studies were also performed. Results showed that, when in contact with the dissolution medium, the release of drug occurred at the rate of 1.1 mg during the first hour because of burst release, followed by the release of 2.23 mg of the drug due to bioactive permeation through the skin. Thus, the lipophilic nature of the skin had a great impact on the release rate. Properties of the film were greatly influenced with the degree of cross-linking and concentration of polymeric material [53].

Full-IPN films of PAA/PVA were developed by radical solution polymerization and sequential IPN technology. The film was investigated for various physical and chemical properties. New hydrogen bonds between PVA and PAA were formed, which were shown by FTIR spectrum analysis. The swelling property of the film in distilled water and different pH buffer solution was studied and showed increased swelling ratio on increasing PAA content of the IPN film in all media; the swelling ratio decreased with increasing PVA cross-linking. The constitution of IPN and the swelling ratio of IPNs formed the basis of the tensile strength and elongation at break. The mechanical property of GA (0.5%) for PVA was better. The DSC of the IPN film depicted a single glass transition temperature (Tg) for each sample, and Tg data showed a linear relationship with the network composition. PAA and PVA showed good compatibility and miscibility. The potentiality of IPN films in controlled drug delivery was examined using crystal violet as a model drug. The increase in

Table 5 Nanoparticles formulated using interpenetrated polymer network systems

Drugs	Polymer	Cross-linker	Novel carrier	Therapeutic application	Reference
	Sodium carboxymethylcellulose+poly (acrylamide-co-2-acrylamido-2-methylpropane sulfonic acid)	Poly (acrylamide-co-2-acrylamido-2-methylpropane sulfonic acid)	Nanocomposite hydrogels	Antibacterial	[52]
Gold sulfide	Polyacrylic acid+polyacrylamide	Polyacrylamide-co-poly (acrylic acid)	Nanoparticles or nanoshells	Cancer therapy	[51]

drug release rate was higher at 37°C than at 25°C for all IPNs and slightly increased with decreasing PAA [54].

Films designed for various therapeutic purposes based on the use of the novel interlacing polymer systems are given in tabular form in Table 6.

Tablets

Sustained release cross-linked SIPN xerogel matrix tablets were developed by chemical cross-linking of PEO and gellan gum and epichlorohydrin as cross-linker. To confirm the ideal combination of native polymer and cross-linking agent, a Box–Behnken design was used for the statistical optimization of the matrix system. Formulated matrix tablets showed zero-order release kinetics for 24 h. Swelling and surface erosion were the primary mechanisms for the drug release. A comparison was made of the cross-linked SIPN xerogel matrix tablet with the non-cross-linked polymer. Results showed that the physicochemical properties of the PEO and GG were modified for controlled release of sulpiride with 100% drug release at 24 h in a sustained manner compared with non-cross-linked formulations. Surface morphology of the cross-linked system revealed a porous structure formed by an IPN, which allowed a greater degree of controlled penetration into the system, ascertaining its ability to sustain the drug release. Therefore, from the study it was concluded that the release of sulpiride was sustained from the hydrophilic SIPN xerogel matrix system using PEO-GG as the cross-linker [58].

The IPN technique was used with xanthan gum, which was derivatized to carboxymethyl xanthan gum, which was then further cross-linked *in situ* with Ca^{2+} ions during wet massing for preparing tablets of prednisolone. The study showed no drug–polymer interactions. *In-vitro* release depicted that increasing the amount of Ca^{2+} ion decreased the drug release but that beyond a certain amount the drug release was increased; in contrast, increasing the exposure time in acid solution of pH 1.2 increased the overall release of the drug, which followed the non-Fickian mechanism of drug release. Therefore, it can be concluded that fluctuation in the amount of Ca^{2+} ion modulates the drug release from carboxymethyl xanthan gum matrix tablets [59].

Novel biomedical applications of the interpenetrating polymer network-based drug delivery system

Repair and regeneration of living organs: Scientists have recently developed several novel systems based on the principle of double network (DN) hydrogels [60]. Some tough hydrogels fabricated by DN techniques also exhibit good biocompatibility and low friction resistance with promise in industrial and pharmaceutical sectors, especially for load-bearing artificial soft tissues such as artificial cartilage [61]. Specifically, cellulose-based DN gel and liquid crystalline DN gel exhibit anisotropic mechanical property, which is highly important for anisotropic functioning in the living organism [62]. Poly (N,N0-dimethylacrylamide)[PDMAAm], when implanted in a living body (rabbit), was found to hardly degrade [63], and induced negligible inflammation [64] and spontaneously generated an excellent articular/hyaline cartilage repair without the use of exogenous cells and without fulfilling the osteochondral defect. Recent studies showed that DN gels have good biocompatibility and are a good scaffold for cells cultured on the surface. However, a tough scaffold for three-dimensional cell culture development is also required as it can mimic some cell growth in typical environments such as the chondrocyte in biological cartilage. Further, it would be beneficial to implant the artificial tissues cultured with cells in the body to help the repair and regeneration of living organs [60].

Protein delivery and tissue engineering: A novel class of hydrogels based on the interpenetration of two polysaccharide networks can be utilized for protein delivery. It is shown that SIPNs and IPNs-based Alg-Ca and hydroxyethyl-methacrylate-derivatized dextran (dex-HEMA) can be suitable for in-situ hydrogel-forming applications. IPN beads seeded with equine chondrocytes showed good cell survival and differentiation. They facilitate chondrogenic differentiation. IPNs based on Alg-Ca and dex-HEMA can be potentially applied in regenerative medicine and can be further optimized to enhance specific tissue formation by embedded cells. Thus, IPNs can be promising systems as injectables *in situ* forming hydrogels for protein delivery and tissue engineering [65].

Table 6 Films formed by using interpenetrated polymer networks

Drugs	Polymer	Cross-linker	Novel carrier	Therapeutic application	Reference
	Chitosan + poly (dimethylsiloxane) + polyethylene glycol	Hexamethylene-1,6 di (aminocarboxysulfonate)	Film	Bioadhesive	[55]
	Polyurethane + acrylamide	AB cross-linked	Film	Biomedical	[56]
Poly (dimethyl siloxane)	2-Hydroxyethylmethacrylate + poly (2-hydroxyethyl methacrylate)	Ethylene glycol dimethacrylate	Film	Soft tissue substitute	[57]

Infectious diseases: The localized treatment of infections can be scientifically improved by site-specific antibiotic drug delivery systems, as due to the failure of conventional treatment pH-sensitive polymers have been frequently used to develop the controlled release formulations using the IPN technique. IPN hydrogels prepared by the cross-linking process showed greater swelling, mucoadhesion, and drug release at lower pH values and maintained antibiotic concentration for prolonged periods of time. Thus, hydrogels formed by using the IPN technique can be used as a drug delivery system for treatment of infections [66].

Wound healing management: In a study with the use of natural polymer cellulose pulp, a SIPN hydrogel cell/PEG/poly (sodium alginate) was formed by free radical polymerization when the cellulose pulp dissolved in PEG/NAOH solvent system was polymerized in the presence of monomer acrylic acid with *N*,*N*′-methylene bisacrylamide added as a cross-linker. Water uptake studies for the prepared hydrogels using a buffer of pH 7.4 at 37°C showed that the swelling property of hydrogels was governed by various parameters. The presence of salt in the swelling medium also affects the equilibrium percentage swelling of hydrogel. Thus, the hydrogel system has new possibilities in drug delivery and healing management [67].

Tissue scaffolds: PVA/GE hydrogels based on the IPN structure and prepared by the enzymatic and cyclic freeze–thawing method have shown promise as tissue scaffolds. The size and arrangement of the pores are the result of the number of freeze–thaw cycles and the presence of cross-linking agents. The IPN PVA/GE hydrogels showed excellent physical and mechanical properties, which met ideal medical applications. Because of the swelling property of hydrogels, they exhibited high capability in absorbing fluids and thus can be used for exudative wounds. Appropriate morphology and good proliferation is displayed when fibroblasts are grown over cells treated with extract solutions. Thus, the gels with a cross-linked network structure were stable enough, suggesting that developer scaffolds might be used in tissue engineering [68].

Medical implant: Researchers have focused attention on the development of methods for repairing an orthopedic joint, including replacing natural cartilage with water-swellable IPN or SIPN having a hydrophobic thermoset or thermoplastic polymer and an ionic polymer and engaging the IPN or SIPN with a bone surface defining the joint. The method may also include the step of inserting bone a stem portion into the bone surface. Thus, the shape of an IPN or SIPN was selected from a group consisting of a hat, a cup, a plug, a mushroom, a stem, and a patch, and it could be customized to fit a condyle, tibial plateau, meniscus, labrum, or glenoid [69].

Ophthalmic application: An IPN-based PEG/PAA hydrogel sufficiently permeable to glucose is used in ophthalmic applications — for example, in implant material such as keratoprostheses and intracorneal lens for corneal transplants. Thus, IPN-based hydrogels allow the passage of glucose from the aqueous humor to the epithelium *in vivo*. The results indicated that permeable substrates for ophthalmic and other biomedical purposes created using the PEG/PAA IPN system can be a promising candidate for ophthalmic applications [70].

Cancer therapy: IPN nanoparticles as a novel temperature-responsive agent can be used in formulating an intelligent therapeutic system capable of loading and releasing the therapeutic agent in response to controlled temperature fluctuations. More, specifically PEGylation is advantageous for the polymeric material in the case of treatment of neoplasms due to the inherent nature cancerous tissues to have leaky vasculature. 'Stealth' nanoparticles or long circulating PEGylated nanoparticles accumulate in tumors because of their preferential extravasations through this leaky vasculature. Thus, surface PEG chains could be functional with antibodies, peptides, or other ligands to achieve active targeting of integrins, growth factors, and receptors that are upregulated in tumors. Thus, IPN-based nanoshells can be used for the leaky vasculature of cancer [51].

Control of obesity: Obesity could be controlled by an IPN-based phase-transition gel of PAA by absorption of fat from the intestinal tract. As they enter the gastrointestinal tract, they can absorb cholesterol from the digested food. Because of the high level of cholesterol, the interaction of cholesterol and the phase-transition gel results in expansion of the gel and

Table 7 Miscellaneous applications of interpenetrating polymer network systems

Drugs	Polymer	Cross-linker	Novel carriers	Therapeutic application	Reference
Chlorpheniramine	Chitosan + glutamic acid + glycine	Glutaraldehyde	Beads	Antihistamine	[72]
Chlorpheniramine	Chitosan + glycine	Glutaraldehyde	Bead	Antihistamine	[73]
Cefadroxil	Alginate + chitosan	Glutaraldehyde	Beads	Infection	[74]
Ibuprofen	Sodium carboxymethyl xanthan + sodium alginate	Aluminium chloride	Beads	Antibiotic	[75]

Table 8 Recent patents on interpenetrating polymer network

Patent no.	Work done	Reference
US 20140120177 A1 (2014)	The invention pertains to production of a water-swellable interpenetrating polymer network or a semi-interpenetrating polymer network derived from hydrophobic thermoset or thermoplastic polymer. The ionizable monomer solution is kept in contact with a solid hydrophobic thermoset or thermoplastic polymer leading to diffusion of the ionizable monomer solution into the hydrophobic thermoset or thermoplastic polymer, followed by polymerization forming an ionic polymer inside the hydrophobic thermoset or thermoplastic polymer. Thereby, IPN or semi-IPN is formed. This invention takes advantage of the high mechanical strength of hydrophobic starting materials and combines those materials with certain ionic polymers to achieve the goal of high mechanical strength in addition to other desirable properties. This invention takes strong materials and makes them more water-swellable to fabricate cartilage substitutes, orthopedic joint replacement and resurfacing devices or components thereof, intervertebral disks, stents, vascular or urinary catheters, condoms, heart valves, vascular grafts, and both short-term and long-term implants for different areas of the body. Also these IPNs can be used as a component of various surgical tools and instruments. In all of these applications drugs can be incorporated into the material for localized drug delivery.	[76]
EP 2585541 A1 (2013)	This research describes semi-interpenetrating polymer networks of at least two polymers having different compositions in which at least one polymer is cross-linked and other is not cross-linked and are closely associated with each other to form semi-IPNs that can function as ion-exchange resins. In this invention an inverse suspension polymerization is used to form the semi-interpenetrating polymer network	[77]
US 20120142069 A1 (2012)	The present invention pertains to the matrices of IPNs comprising fibrin and alginate for the culture and maturation of a variety of cell types. Thus, the combination of alginate and fibrin maintains the 3D architecture of follicles and provides an environment supporting follicle growth	[78]
US 8298657 B2 (2012)	In this research, interpenetrating polymer network (IPN) interconnected pore structure to form a predesigned fiber (PSF), dispersible fiber network (DFN) and porogenic dissolve a part of the fabric support is modified by dispersing. The resultant porous, supported, second polymer network has convective flow, diffusive flow, and high capacity, and may include functional capture to provide an adsorptive medium for chromatography and filtration of various compounds including biomolecules	[79]
CA 2290743 A1 (2009)	The research deals with compositions for use in tissue engineering and drug delivery that are based on the formation of a semi-interpenetrating or interpenetrating polymer network by exposure to active species of a solution of two or more polymers, following injection at a site in the patient. Until the release or tissue formation occurs, the resulting viscous solutions retain the biologically active moieties or cells at the site of injection. Studies demonstrated that the active species, which are typically light, can penetrate easily through skin, body fluids (such as synovial fluid), and membranes and thus polymerize polymer solutions	[80]
EP 2459620 A1 (2012)	The invention is related to a combination of semi-interpenetrating polymer network and an emissive material interlaced in the polymer network forming an emissive semi-interpenetrating polymer network (E-semi-IPN). The E-semi-IPN can be used as an E-semi-IPN layer in organic light-emitting devices	[81]
US 20120052305 A1 (2012)	The invention is related to interpenetrating polymer network (IPN) adhesives, which comprise an acrylated polymer system that is curable by radiation, after which a flexible epoxy system is thermally curable. Thus, the IPN adhesive can be used in fabrication of composite and hybrid structures involving both polymer resins and metals, which substantially reduces the residual stress in the structure caused by differential thermal expansion of the composite materials. This provides an effective way to reinforce metal parts while reducing tooling costs and process flow times	[82]
US7909867 B2 (2011)	The invention is based on the designing of a corneal prosthesis based on the interpenetrating polymer network (IPN) hydrogels that are coated with biomolecules, which include two interpenetrating polymer networks: the first hydrophilic polymer network is a telechelic macromonomer such as PEG-diacrylate or PEG-dimethacrylate and the second polymer network is a hydrophilic acrylic-based monomer. In the presence of the first polymer network, the hydrophilic monomer is polymerized and cross-linked to form the second polymer network. IPN hydrogels may be linked to any biomolecule that supports the growth of cornea-derived cells	[83]
CA 2396218 C (2009)	The invention is based on the design of novel wound dressings that can serve a unique dual-purpose role by incorporating two distinct layers, each providing useful features. One surface of the dressing comprises a polyurethane foam (20) and the other surface comprises a nonadherent thin film (30) of polydimethylsiloxane and polytetrafluoroethylene interpenetrating polymer networks (IPN). With the IPN side of the dressing against the wound, which has wound healing properties, the dressing provides nonadherent covering for fragile and sensitive wounds	[84]

(*Continued*)

Table 8 (Continued)

Patent no.	Work done	Reference
US 20090088846 A1 (2009)	The invention relates to the use of IPN systems in the fabrication of arthroplasty devices. The interpenetrating polymer network hydrogel is strain-hardened by swelling and is adapted to be held in place in a mammalian joint by conforming to a naturally or artificially prepared geometry of the bone. The IPN is prepared by a first network, wherein the said first network is a nonsilicone network of preformed hydrophilic nonionic telechelic macromonomers chemically cross-linked by polymerization of its end-groups and the second network is a nonsilicone polymer network of ionizable monomers; the second network has been polymerized and cross-linked in the presence of the first network and has formed physical entanglements with the first network, forming an interpenetrating polymer network hydrogel	[85]
US 20080317818 A1 (2007)	This invention relates to a hydrogel material comprising an interpenetrating polymeric network of two or more polymer networks, wherein at least one of the polymer networks is based on a biopolymer consisting of bioactive agents, which may be a growth factor, retinoid, enzyme, cell adhesion factor, extracellular matrix glycoprotein, hormone, osteogenic factor, cytokine or motifs derived from biologically active protein etc. The hydrogel material can be further utilized in various devices like implants (e.g. corneal implants or therapeutic lens)	[86]
US 20080138430 A1 (2008)	The invention is directed to a novel device/system and extracorporeally controlled method of drug delivery in which devices are prepared using nanoparticles comprising a core of gold sulfide and a temperature-sensitive interpenetrating network polymer shell in which therapeutic drugs are dispersed and operable for release to create a temperature-sensitive drug delivery device that can respond to extracorporeal triggering mechanisms by swelling in response to increases in temperature and releasing its therapeutic content	[51]
US 7087135 B2 (2006)	Novel method of producing sheets composed of an interpenetrating polymer network sheet of polydimethylsiloxane (PDMS) and polytetrafluoroethylene (PTFE) bonded to a backing material for use as wound dressings and scar management products. The new process represents several improvements over previous techniques, such as (a) it is a single-pass process, (b) it requires no second coating of liquid polymer to act as glue, (c) the carrier substrate, (d) no solvents or other processing aids are required, etc.	[87]
US 6943204 B2 (2005)	The invention is related to a process that forms a surface interpenetrating polymer network on polymers. This process involves modification in the properties of the polymer at its surface. By the use of this process the ability of surface modification agents such as heparin is increased, to adhere to the surface of the polymer. Further, the surface interpenetrating network is either entangled in the form of a chain network or through the caternary connections to the polymer substrate, which is quite stable	[88]
US 20040001892 A1 (2004)	The invention is based on the design of a semi-IPN system using a linear polymer molecule that is modified by functionalization with a bioactive moiety. The linear polymer is physically entangled within a matrix based on a thermoresponsive polymer. The bioactive moiety enhances the interaction of a cell with the polymer network. The SIPN polymers thus prepared are flowable at room temperature and turn solid or semisolid at elevated temperatures (e.g. body temperature) and can be used as a drug delivery vehicle and as matrices for tissue engineering	[89]

thereby the gel absorbs the cholesterol and inhibits absorption through the gut wall. By incorporation of bile salts, cholesterol and dietary fat can be removed from the system [71]. Some of the other interesting applications of IPN systems are summarized in Table 7.

A study was conducted on the recent patents based on application of IPN systems for biomedical and therapeutic purposes. A detailed description of the recent patents based on application of IPN systems is given in Table 8.

Conclusion

In this review article efforts were made to summarize different IPN-based drug delivery systems as they have been employed in the development of various dosage forms such as tablets, capsules, microspheres, transdermal films, wound dressings, hydrogels, etc. The review also focuses on the multidimensional applications of interpenetrating systems in diverse fields like tissue scaffolds, protein delivery to controlling hypercholesterolemia, and regeneration of living organs. The basic benefit of IPN systems is that there is freedom to engineer the desired qualities by selecting the polymers carefully by the IPN approach. The use of these systems in chemotherapy, protein delivery, and tissue regeneration requires further research and may prove to be of strategic importance in the future. Moreover, it can be concluded that IPN systems can be used as a carrier system providing better treatment options, eradicating various pathological diseases, and can serve as a better candidate for the treatment of various diseases.

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Conflicts of interest

There are no conflicts of interest.

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