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Biomedical Applications of Interpenetrating Polymer Network System

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Abstract: Interpenetrating polymer network (IPN) has been regarded as one of the novel technology in recent years showing the superior performances over the conventional techniques. This system is designed for the delivery of drugs at a predetermined rate and thus helps in controlled drug delivery. Due to its enhanced biological and physical characteristics like biodegradability, biocompatibility, solubility, specificity and stability, IPN has emerged out to be one of the excellent technologies in pharmaceutical industries. This article focuses mainly on the biomedical applications of IPN along with its future applicability in pharmaceutical research. It summarizes various aspects of IPN, biomedical applications and also includes the different dosage forms based on IPN.

Keywords: Biomedical, double network, drug delivery, IPN, tissue engineering.

INTRODUCTION

The concept of IPN goes back as far as 1914 and the first interpenetrating polymer network (IPN) was invented by Aylsworth and the term IPN was firstly given by Miller in 1960s in a scientific study about polystyrene network [1]. An Interpenetrating polymer network may be defined as any material which contains two or more polymers in the network form [2]. IPN is obtained when at least one of the polymers is synthesized or cross-linked in the immediate presence of the other polymer without any covalent bond between them [3].

In other words, IPN may also be defined as the combination of two or more polymers in the network form in which one polymer is cross-linked in the presence of other [4]. There are three conditions of polymer which are necessary in the composition of IPN. These conditions are as follows [5]:-

1) At least two polymers must be synthesized and cross-linked in the presence of the other.
2) Both polymers have similar kinetics.
3) Polymers are not dramatically phase separated.

An IPN is differentiating from other polymer combination in two ways [6]:-

1) IPN swells, but does not dissolve in the solvent.
2) Prevents the action of creep and flow.

They are also different from polymer complex and graft co-polymer because they either involve in chemical bond or in low degree of cross-linking. From this point of view only, IPN can be generally named as "polymer alloys" [7]. IPN is not prepared by normally mixing the two or more polymers and also does not produce from co-polymers. IPN based drug delivery system may follow zero order pattern with less fluctuation [8]. IPN is regarded as novel biomaterial. A combination of polymers, i.e. synthetic and natural polymers, is useful in increasing the release of short half-lived drug under physiological condition [9]. If we increase the mechanical properties of IPN, it will be acceptable for preparing microsphere for controlled drug delivery [10]. The chemical and physical combination method as well as properties of multipolymers play as important role in the controlled release of the drug because they help to provide a convenient route for the modification of properties to meet specific needs. Among these methods, IPN based drug delivery system is one of the newly developed method for designing the novel controlled release drug delivery system [11].

Double network gels also obtained from interpenetrating polymer network where the properties of two networks can be done in contrast such as, rigidity, molecular weight, network density etc. They are generally synthesized with the help of two steps:- in first step, they are synthesized by sequential free-radical polymerization process. In this process, the highly relative molecular mass is neutral. In the second step, polymer network is incorporated with in a swollen heterogeneous polyelectrolyte 1st network [12].

IPN formulation is one of the important/successful methods for developing a product with better physico-mechanical properties than the normal polyblends [13]. IPN can be made in different ways. IPN is also found in the form of latex which is known as interpenetrating electrometric network (IEN) [14]. Gradient IPN is one of the other forms which is formed when the film made with a network of one polymer on the one surface and the network of another polymer on the other surface, there is a gradient inside the film. On the other hand, when one polymer is cross linked and another is linear or branched, it is called semi-IPN [15].

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IPNs can be prepared through different techniques as given in the literature but *in-situ* technique proves that it is the most convenient technique. In this technique, all reactants are combined together and reaction can take place with the formation of two networks which can be started at the same time [16]. The procedure for the synthesis of IPNs can be divided in to two categories-

1. Simultaneous synthetic method: In simultaneous synthetic method, both monomers are mixed together to form polymer network simultaneously through different reaction routes.

2. Sequential synthetic method: In sequential synthetic method, different network reactions are controlled sequentially by adding different monomers. Now a days, mostly commercial materials are prepared by sequential IPNs, because of their flexibility and easy to process ability.

When IPNs are used for coating purpose, they cannot be prepared by the sequential or simultaneous interpenetrating polymerization because of the presence of volatile monomer. For this purpose, they can be prepared from preforming prepolymers which contain complementary functional groups that increase their miscibility [17]. In IPNs, cross linking of mutual chain entanglement produce finer dispersion of one polymer in to the other [18].

Advantages of IPN [19, 20]**:** There are the following inherent advantages due to which IPN system gained huge popularity in the modern era of polymers. They are as follows-

1. IPN system helps in increasing the mechanical strength, phase stability and biological acceptability of the final product.
2. IPN is also helpful in producing the synergistic effect from the component polymer.
3. Due to the infinite zero-viscosity of the gel, phase separation between the component polymers is not possible.
4. Due to permanent interlocking of the network segment, thermodynamic incompatibility can be made to overcome as the reacting ingredients are blended thoroughly at the time of synthesis.
5. IPN also potent to develop the controlled release system for delivering the drug.
6. When the blends are subjected to stress they keep the phases separate.

Disadvantages of IPN [21, 22]: The main disadvantage of IPN is that, sometimes the polymers interpenetrate to such an extent and the drug released from the matrix becomes difficult. The problem with the non-covalent system is that it can also be a problem with the covalent system due to the lack of an effective interface.

Features of IPN [2, 23]: There are the following ideal characteristics of IPN which are as follows-

1. In ideal IPN creep and flow is suppressed.
2. IPN can swell but does not dissolve in solvent.
3. IPN has high tensile strength.
4. Most ideal IPNs are heterogeneous systems which contain one rubbery phase and one glassy phase to produce a synergistic effect yielding.
5. When the blends are subjected to stress, they keep the phases separated together.
6. IPN mainly forms insoluble network.
7. IPN systems differ mainly due to the number and types of cross-links.
8. They show adhesive property.
9. Hence, IPN based systems have gained good potential to develop the controlled release delivery of drugs.

IPN based Drug Delivery System: IPN based drug delivery systems are used to deliver the drug at a specific rate for desired period of time with low fluctuation.

Now a days, there are many approaches which are being used for improving the delivery of therapeutic materials like-films, hydrogels, tablets, capsules, microspheres, sheets, sponges, matrix, transdermal patches, nanoparticles etc. some of the important IPN based drug delivery systems are discussed here [24].

Films: IPN based films are used as piezodialysis membrane which are non-mosaic membrane. The important application of IPN delivery system is the uralkyd/poly (glycidylmethacrylate) based film which shows better mechanical and tensile strength [3, 25]. Biodegradable collagen films or matrices have served as scaffolds for the survival of transfected fibroblasts [26].

IPN based films which are prepared by the mixture of collagen and polyvinyl alcohol, cross-linked with glutaraldehyde vapor shows depot formulation for recombinant human growth hormones [27]. In many animal models, after implantation of transfected cells, a long term expression of the foreign gene has not been achieved [28]. Suh *et al*., studied the graft copolymerization of type I atelocollagen onto the surface of polyurethane (PU) films treated with ozone was performed [29]. It has been observed that they could enhance an attachment and proliferation of fibroblasts and growth of cells.

An interesting use of thermo-responsive polymer films was shown by Zakharchenko *et al*., prepared a belayed of PVCL on top of PNIPAAm with encapsulated magnetic nanoparticles [30]. At temperatures greater than the lower critical solution temperature (LCST) the films were flat and allowed for adsorption of nanoparticles, cells or drugs onto the surface, upon cooling the films rolled up entrapping the absorbed particles which could then be released by heating again. This is a novel approach for the encapsulation and release of nanoparticles and cells with the addition of the magnetic particles allowing manipulation of the films by an external field [31]. Some of the IPN based films with their applications are shown in Table **1**.

Hydrogel: To determine potential in a drug delivery system, hydrogel formulations were prepared by the combination of polymers [45]. Hydrogels are the three dimensional polymeric network which are chemically cross-linked [46] and have the capacity to hold the water in its structure due to the presence of hydrophilic functional groups [47].

Table 1. List of the drugs delivered through IPN based films.

S.No.	Name of Polymers	Cross-linker	Drug	Formulation	Reference
1.	Polyurathane+ Polysiloxane	Phenol formaldehyde Resin	_	Polymer Film	[3]
2.	Chitosan + Xanthan Gum	Glutaraldehyde	Amoxicillin	Hydrogel Film	[32]
3.	Sod. Alginate + Gelatin	Calcium	Azure B	IPN Film	[33]
4.	Polyvinyl Alcohol + Polyacrylic Acid	Glutaraldehyde	Crystal violet	IPN film	[34]
5.	Polydimethylacrylamide + hyaluronic acid + glucose oxidase	-	-	Semi-IPN Film	[35]
6.	Prevulcanized Natural Rubber latex + Chitosan	Glutaraldehyde	-	Semi-IPN Film	[36]
7.	Methoxyoligo(oxyethylene)methacrylate + Poly(methylmethacrylate)	1,4 butane-diol-dimethyl amide	-	IPN Film	[3]
8.	Chitosan + hypromellose + citric acid	Genipin	Curcumin	Semi-IPN Film	[37]
9.	Polyaniline + Polyvinyl alcohol	Ammonium persulfate	-	Thin Film	[38]
10.	Polyurethane urea, N - isopropylacrylamide, acrylic acid, and Butylmethacrylate	-	-	Semi-IPN Film	[39]
11.	Aluminum substrate + 1,4-butylene glycol	Trimethylolpropane	-	IPN Thin Film	[40]
12.	Hemicellulose+ Chitosan	Glutaraldehyde	-	Semi-IPN Hydrogel Film	[41]
13.	2-hydroxy-3-methyacryl-oxypropyl trimethylammonium chloride (HMPTAC) + ethylene glycol dimethacrylate (EG-DMA)	-	-	IPN Film	[42]
14.	Poly(dimethylsiloxane) + Polyethylene glycol + Chitosan	Hexamethylene-1,6-di-(aminocarboxysulfonate)	-	Bioadhesive Film	[43]
15.	Chitosan + Poly(aniline)	Glutaraldehyde	-	Biosensor Film	[44]

Development of Smart Drug Delivery System (SDDS) which is also known as Stimuli-sensitive delivery system is one of the major success in drug delivery by IPN Hydrogels. The concept of SDDS is based on the conversion of physic-chemical properties of the polymer system [48]. Hydrogels are widely used in drug carrier because of its self-application and due to its easily manufacturing. IPN Hydrogels were prepared to increase the mechanical strength of the natural polymers. Hydrogels was also found resilient and stable [49]. Environmentally sensitive hydrogels can be produced from hydrophilic, stimuli-responsive polymer networks that can change the volume in response to an external signal such as a change in temperature or chemical environment. These materials are attractive and candidate for various biomedical applications and artificial muscles [50]. *In situ* forming IPN hydrogels of calcium alginate and dextran hydroxyethyl-methacrylate were developed and evaluated for protein release as well as for the behavior of embedded cells. It was observed that after an initial burst release bovine serum albumin was gradually released from the IPN hydrogels for up to 15 days. Encapsulation of expanded chondrocytes in the IPNs revealed that cells remained viable and were able to re-differentiate. IPN was described as a promising system as injectable in situ forming hydrogels for protein delivery and tissue engineering applications [51].

Eltjani-Eltahir Hago *et al.* developed interpenetrating polymer network PVA/GE hydrogels by a combination of enzymatic and physical methods, used freezing-thawing process and *in situ* with synthesis of gelatin/mTG in PVA solution. The morphology and crystalline structures of interpenetrating polymer network PVA/GE were also observed by some experimental analysis techniques, such as scanning electronic microscope (SEM). Moreover, in order to understand the initial behavior of fibroblasts cells, proliferation was assessed *in vitro* using fibroblast like L 929 cell culture [52].

Steffensen *et al.,* developed soft hydrogels interpenetrating silicone, a polymer network for drug-releasing medical devices. IPN materials with PHEMA content in the range of 13%–38% (w/w) were synthesized by using carbon dioxide-based solvent mixtures under high pressure. These IPNs were characterized with regard to microstructure as well as ability of the hydrogel to form a surface-connected hydrophilic carrier network inside the silicone. A critical limit for hydrogel connectivity was found both *via* simulation and by

Table 2. List of the drugs delivered through IPN based hydrogel.

S.No.	Name of Polymers	Cross-linker	Drug	Formulation	Reference
1.	Chitosan + Polyvinyl pyrrolidone	Glutaraldehyde	Clarithromycin	Semi-IPN Hydrogel	[53]
2.	Polydimethylsiloxane / polyethylene glycol + chitosan	Hexamethylene-1,6-di-amino carboxysulfone	-	Semi-IPN Hydrogel	[43]
3.	Gelatin + Methacrylic acid	Glutaraldehyde and Methylene bisacrylamide	Glipizide	IPN Hydrogel	[54]
4.	Chitosan + Polyvinyl pyrrolidone + Polyacrylic acid	Glutaraldehyde and N,N-methylene bisacrylamide	Clarithromycin	IPN Hydrogel	[55]
5.	Methacrylic acid + Polyethylene glycol	Tetra Ethyleneglycoldimethacrylate	Atorvastatin, Theo-phyllin	Hydrogel	[3]
6.	Locust bean gum (Carboxymethyl sulfate derivative)	-	Tramadol HCl	Hydrogel Beads	[56]
7.	Chitosan + Polyanilin	Glutaraldehyde	-	Semi-IPN Hydrogel	[44]
8.	Chitosan and Polyacrylamide	-	-	Semi-IPN Hydrogel	[57]
9.	Sodium Alginate + Poly(lactic acid)	Glutaraldehyde	Penicillamine	IPN Hydrogel	[58]
10.	Poly(Ethylene Oxide) + Poly(Methyl Methacrylate)	-	-	IPN hydrogels	[59]
11.	Konjac glucomannan + Polyacrylic acid	N,N-methylene-bis-acrylamide	-	IPN Hydrogels	[60]
12.	Chitosan + Polyvinyl alcohol	Glyoxal	-	IPN Hydrogels	[61]
13.	Gelatin + Polyvinyl alcohol	Transglutaminase enzyme	-	IPN Hydrogels	[52]
14.	Polyacrylamide-co-solfopropylacrylate potassium + Polyacrylonitrile	N,N-methylene-bis-acrylamide	-	IPN Hydrogel	[62]
15.	Polybutyl acrylate + Polyhydroxylethyl acrylate	Ethylene glycol dimethacrylate	Iron Oxide	Hydrogel	[3]

visualization of water uptake in approximately 25% (w/w) PHEMA, indicating that entrapment of gel occurs at low gel concentrations. The optimized IPN material was loaded with the antibiotic ciprofloxacin, and the resulting drug release was shown to inhibit bacterial growth when placed on agar, thus demonstrating the potential of this IPN material for future applications in drug-releasing medical devices [114]. Some of the IPN based hydrogels with their applications are shown in Table **2**.

Microspheres: Microspheres are one of the classes of newest IPN based drug delivery system. Microspheres are free flowing powder, which are solid usually small spherical particles made up of natural or synthetic polymers and ideally having a particles size range from 1-1000 μm in diameter [63]. Microspheres are the carrier linked delivery system having a core which contains drug and outer layer of polymer as coating material [64]. IPN microspheres are the versatile carrier for controlled release of the drug and also for the targeting application because they encapsulate a wide range of drugs, increased bioavailability, biocompatibility, patient compliance and sustained release characteristics [65]. The hydrogel microspheres were developed from the formulation of polyvinyl alcohol and Guar gum for controlled delivery of Nifedipine by emulsion cross-linking method for livery of Nifedipine by emulsion cross-linking method for the treatment in severe hypertension [66].

Ray *et al*., developed an interpenetrating polymer network based on microspherical formulation from Sodium alginate and Polyvinyl alcohol by the emulsion cross-linking method in which Glutaraldehyde is used as a cross-linker. This IPN based formulation was used for the controlled release of Diclofenac Sodium [67]. Interpenetrating polymer network based microspheres was also used as a carrier for prolonged delivery of anti-cancer drug [3].

The rationale of developing mucoadhesive microspheres are that the formulation will be confined on the biological surface for localized delivery of the drug and the drug will be released close to the site of action with continuous enhancement of bioavailability [68]. IPN microspheres based on Xanthan gum and Polyvinyl alcohol were developed by emulsion cross-linked method to deliver the anti-inflammatory drug. In this formulation Glutaraldehyde is used as cross-linker [8].

Al-Kahtani AA *et al*., prepared semi-interpenetrating polymer network microspheres of chitosan-(dextran-g-acrylamide) by emulsion cross-linking method.

Table 3. List of the drugs delivered through IPN based microspheres.

S.No.	Name of Polymers	Cross-linker	Drug	Formulation	References
1.	Sodium alginate + Polyvinyl alcohol	Glutaraldehyde	Diclofenec Sodium	IPN Microspheres	[70]
2.	Gellan gum + Poly(N-isopropylacrylamide)	-	Atenolol	Semi-IPN Microspheres	[71]
3.	Sodium alginate + Poly (vinyl alcohol)	Glutaraldehyde	Naproxen	IPN Microspheres	[72]
4.	Xanthan gum + Superabsorbent polymers + Poly(vinyl alcohol)	N,N'-methylene bisacrylamide	Ciprofloxacin HCl	IPN hydrogel microspheres	[65]
5.	Chitosan + Hydroxyethyl cellulose	Glutaraldehyde	Isoniazid	IPN blends microspheres	[73]
6.	Hydroxypropyl -methylcellulose + Poly (vinyl alcohol)	Glutaraldehyde	Ciprofloxacin hydrochloride	IPN Microspheres	[74]
7.	Acryl amide grafted Carboxymethylcellulose + Sodium alginate	Glutaraldehyde	Triprolidine hydrochloride Monohydrate	IPN Microspheres	[75]
8.	Sodium carboxymethyl cellulose + poly(vinyl alcohol)	Glutaraldehyde	Diclofenac Sodium	IPN Hydrogel Microspheres	[76]
9.	Chitosan + Methylcellulose	Glutaraldehyde	Theophylline	IPN Microspheres	[11]
10.	Chitosan + Gelatin	Glutaraldehyde	Isoniazid	IPN Microspheres	[77]
11.	Gelatin + Sodium carboxymethyl cellulose	Glutaraldehyde	Ketorolac Tromethamine	Semi-IPN Microspheres	[78]
12.	Acrylamide grafted dextran + Chitosan	-	Acyclovir	Semi-IPN Microspheres	[4]
13.	Lepidium sativum + poly(vinyl alcohol)	Glutaraldehyde	Simvastatin	IPN Microspheres	[10]
14.	Chitosan + guargum-g-acrylamide	Glutaraldehyde	5-Fluorouracil	Semi-IPN Microspheres	[79]
15.	Locust bean gum + Poly vinyl alcohol	Glutaraldehyde	Metformin HCl	IPN Mucoadhesive Microspheres	[80]

Glutaraldehyde was used as a cross-linking agent. Theophylline, an antiasthmatic drug was successfully incorporated into it by varying the ratio of dextran-g-acrylamide and amount of glutaraldehyde. The % encapsulation efficiency in between 50 and 78 was achieved. *In-vitro* release studies of theophylline from these matrices at pH 1.2 and 7.4 dissolution media demonstrated that slow release was extended up to18 hrs at 37°C [69]. Some of the IPN based microspheres with their applications are shown in Table **3**.

Tablets: IPN can also be used for preparing an extended release matrix tablet from Chitosan / Carbapol inter-polymer complex. IPN based tablets are solid in nature and have great potential for anti-hypertensive action by blending with hydrophilic inter-polymer complexes or a hydrophobic waxy polymer [81]. Kulkarni *et al.*, prepared IPN matrix tablets of sodium alginate and carrageenan for controlled release of Propranolol HCl. by wet granulation/covalent cross-linking method and subsequently compressed into tablets. The pure drug showed rapid and complete dissolution within 60 min but IPN based tablets showed slower and prolonged drug release over 18 h. The study concluded that the cross-linking time of granules affected the release of drug from IPN matrix [82]. Some of the IPN based tablets with their applications are shown in Table **4**.

Sheet: Sheeting is one of the new method of producing IPN based drug delivery system [70]. These are mainly used in various types of wound dressings and scar management products [85]. An IPN composed of polymeric material like polyol (allyl carbonate) e.g. nouryset®200 and epoxy resin is developed by 70-95 parts by weight of polyol (allyl carbonate) by means of radical initiation and polymerizing partially or completely concurrently is an epoxy resin forming mixture composed of 10-90 weight % of aliphatic or cycloaliphatic epoxide and 90-10 weight % of polyol/anhydride adduct [86].

Sponges: IPN based sponges are also used as drug delivery system. They were mainly used in wound dressings and hemostyptics and also very helpful in the treatment of severe burns [87]. The advantages of collagen are-

a) Their capacity to easily take up large quantities of tissue exudates and provide smooth adherence to the wet wound bed with preservation of moist climate.

b) Its protection against mechanical harm and secondary bacterial infection.

Collagen also promotes growth and cellular mobility and hence, inflammatory cells can actively penetrate the porous scaffold. Due to this a highly vascularized granulation bed is formed which encourages the creation of new

Table 4. List of the drugs delivered through IPN based tablets.

S.No.	Name of Polymers	Cross-linker	Drug	Formulation	References
1.	Polyacrylamide grafted-sodium alginate + Sodium alginate	Ca2+ ion	Diltiazem HCl	IPN Matrix Tablets	[83]
2.	Sodium alginate + Carrageenan	-	Propranolol HCl	IPN matrix tablets	[82]
3.	Tamarind Seed Polysaccharide + Sodium Alginate	-	Propranolol HCl	IPN hydrogel tablets	[84]

Table 5. List of the drugs delivered through IPN based sponges.

S.No.	Polymers	Cross-linkers	Drug	Formulation	References
1.	Chitosan + Poloxamer	-	-	Semi-IPN Sponges	[25]
2.	Elastin + Collagan	Glutaraldehyde	-	IPN Sponges	[89]
3.	Collagen + Fibronectin	Glutaraldehyde	Hyaluronic acid	IPN Sponges	[90]
4.	Elastin + Collagen	Glutaraldehyde	Glycosaminogycans	IPN Sponges	[91]
5.	Collagen + fibroblast	-	-	IPN Sponges	[92]

Table 6. List of the drugs delivered through IPN based capsules.

S.No.	Name of Polymers	Cross-linker	Drug	Formulation	Reference
1.	Polyacrylamide + polyvinyl alcohol	-	Crystal violet and Bromothymol blue	IPN Capsules	[94]

Table 7. List of biomedical applications.

S.No.	Polymers	Drug	Applications	References
1.	Xanthan gum + Poly vinyl alcohol	Ciprofloxacin hydrochloride	Sustained release application.	[65]
2.	Polypropylene + Collagen gel	-	Abdominal wall repair in dogs	[95]
3.	Gum ghatti + poly vinyl alcohol	Ranitidine HCl	Mucoadhesive microspheres for anti-ulcer drug delivery	[96]
4.	Polyacrylamide-co-ethylene glycol +acrylic acid	-	Modulate bone formation in the peri-implant region in the rat femoral ablation model.	[97]
5.	Chitosan + Poly(acrylic acid-co-acrylamide)	Insulin	Superporous hydrogel for oral delivery	[98]
6.	Alginate + Chitosan	-	Improved cartilage tissue engineering	[99]
7.	Honeycomb + Collagen	-	Dermal tissue engineering	[100]
8.	Gelatin + Chitosan	Propranol HCl	Microsphere for nasal delivery.	[101]
9.	Poly(2-acrylamide-2-metyl-propane sulfonic acid) + Poly(N,N0-dimetylacrylamide)	-	Artificial cartilage	[12]
10.	Chitosan + Alanine	Chlorpheniramine	Oral controlled release of drug	[102]
11.	Collagen + hydrated gel	-	Development of bioengineered tissues such as heart valves, blood vessels and ligaments	[103]

(Table 7) contd….

S.No.	Polymers	Drug	Applications	References
12.	Collagen + Chitosan	-	Cartilage Scaffolds: Test anticancerous drugs and *in-vitro* culture of human epidermoid carcinoma cells (HEp-2)	[104]
13.	Locust Bean Gum + Poly (vinyl alcohol)	Metformin HCl	Mucoadhesive Microspheres for Controlled Release	[80]
14.	Chitosan + Poly(aniline)	-	Biosensor film	[44]
15.	Chitosan + Guargum-g-acrylamide.	5-Fluorouracil	Microspheres for controlled release and improve the bioavailability of drug	[79]
16.	Chitosan + Poloxamer		Sponge for wound dressing	[105]
17.	Chitosan + Poly(vinyl pyrrolidone)	Clarithromycin	*H.pylori* infection and management of peptic ulcer	[55]
18.	Chitosan + Poly(dimethylsiloxane) + Polyethylene glycol	-	Bioadhesive Film	[43]
19.	Hydroxyl ethyl cellulose + Chitosan	Isoniazide	Blend microspheres for oral controlled release	[77]
20.	Hydroxyapatite + Collagen + bone morphogenetic protein	-	Acquired and Congenital Orthopaedic defects	[106]
21.	Polyvinyl pyrrolidone + Chitosan	Amoxicilline	Controlled release system for antibiotics	[107]
22.	Collagen + Hydroxyapatite	-	Bone Tissue engineering	[108]
23.	Polyacrylamide + Poly(ethylene glycol)	-	Controlled inflammatory response	[109]
24.	Chitosan + Acryl amide-g-poly (vinyl alcohol)	Cefadroxil	Micro gel for oral controlled release of drug	[110]
25.	Acrylic acid + Chitosan	-	Corneal epithelial wound healing	[111]
26.	Chitosan + Poly vinyl alcohol	Clarithromycin	Controlled released hydrogel microsphere	[112]
27.	Dextran-g-acryl amide + Chitosn	Theophylline	IPN Microsphers for Oral controlled release	[69]
28.	Chitosan + Hydroxypropyl cellulose	Valganociclovir hydrochloride	Controlled Release of an Anti HIV Drug	[113]

granulation tissue and epithelium on the wound [25]. Collagen-based materials can be produced into a three-dimensional sponge for use as a wound dressing and as a support for cell cultured skin components [88]. Some of the IPN based sponges with their applications are shown in Table **5**.

Capsules: IPN based capsules are one of the important approach for delivery of drug. IPN capsules are also used as drug delivery systems for sustain release of drug. Interpenetrating polymer networks (IPNs) hydrogel capsules consists of polyacrylamide and polyvinyl alcohol for sustained drug release. Supracolloidal IPN reinforced capsules using micron-sized colloidosomes of poly(methyl methacrylate-co-divinyl benzene) micro gels were used as scaffold via radical polymerization of the interior phase to produce hollow supracolloidal structures with a raspberry core-shell morphology [93]. Some of the IPN based capsules with their applications are shown in Table **6**.

Biomedical Applications of IPN Based Drug Delivery System: Some of the biomedical applications of IPN based drug delivery systems with their applications are shown in Table **7**.

CONCLUSION

It can be concluded from the whole literature survey that IPN based systems have wide applications in pharmaceuticals and medical sciences. IPN based polymeric materials can significantly change the release behavior of drug, protein/peptide, hormones and medicinal active agents. The study of IPN for drug delivery system may be helpful in understanding of critical diseases like acquired immune deficiency syndrome (AIDS), cancer and cardiac diseases as well as inflammatory diseases like rheumatoid arthritis, osteoarthritis and meningitis etc. IPN is mainly used as a carrier system for delivery of short biological half-life drugs. IPN has various advantages like excellent swelling capacity, specificity, and mechanical strength which play an important role in controlled and targeted drug delivery. Current study supports the theory that IPN can provide the resources to deliver the drugs at a prolonged controlled release for specific targets. IPN based biomaterials can serve as a potential candidate for tissue engineering and drug delivery system and are expected to become a useful matrix substance for various biomedical and therapeutic applications in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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