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Cross-Linking Interpenetrating Polymer Network Hydrogels – A Novel Approach for Controlled Drug Delivery System

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R. NAGARAJU, N. RAMYA KRISHNA*

Department of Pharmaceutics, Marri Laxman Reddy College of Pharmacy, Dundigal, Hyderabad-500 043, Telangana, India.

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ABSTRACT

The ever-increasing developments in pharmaceutical formulations have led to the widespread use of biodegradable polymers in various forms and configurations. In particular, interpenetrating polymer network (IPN) and semi-IPN polymer structures are regarded as the most useful novel biomaterial containing two polymers, each in network form. These are capable of releasing drugs in a controlled manner have gained wider importance in recent years. The excellent biocompatibility and safety due to its physical characteristics such as impart stability of the drug in the formulations, improve the solubility of hydrophobic drugs, excellent swelling capacity and its biological characteristics like biodegradability, bioavailability, drug targeting in a specific tissue. The drug release from these systems depends on the pH of the media and temperature in addition to the nature of the system. These networks can be prepared as smart hydrogels following chemical or physical crosslinking methods to show remarkable drug release patterns compared to single polymer systems. This article is focused on the features, types of IPN, preparation methods of IPN and crosslinking methods. Semi-IPN has also been investigated to satisfy the specific needs of the biomedical field. Hence, the evaluation of swelling, mechanical and biocompatible properties consider more attention before the IPN's hydrogels are applied.

INTRODUCTION:

In the area of drug delivery, polymers have been widely used as valuable excipients in making tablet and capsule-based formulations[1]. Among the various polymers employed, hydrophilic biopolymers are quite suitable in oral applications due to their inherent advantages over synthetic polymers [2]. To overcome the poor biological performance and to improve the mechanical strength properties, IPN's have been introduced that are prepared from the blending of natural or synthetic polymers alone or in combination [3]. The ability of these crosslinked three-dimensional network hydrogels to swell in water or biological fluids made them as a potential candidate to deliver bioactive molecules, particularly in controlled release applications [4-6].

An IPN can be distinguished from the regular polymeric blends in a way that the IPN swells, but doesn't dissolve in solvents and offers improved properties, depending on the composition and degree of crosslinking[7]. The network structures were first reported by Aylsworth in 1914[8] and later termed as IPN'S in 1960 by Miller[9]. Due to their advantageous physicochemical properties compared to the conventional polymers, research efforts on IPN and semi-IPN polymer networks have progressed rapidly in a controlled release area[10, 11]. In recent years, researchers have shown much interest in these systems to develop formulations in the form of tablets, microparticles, nanoparticles, hydrogels and so on[12].

In general, when a hydrophilic polymer is interpenetrated into a relatively hydrophobic polymer core, the resulting IPN hydrogel exhibits improved capability of immobilizing a drug and this has opened up new avenues for designing novel CR systems for a variety of drugs[13,14]. A combination of judicially selected natural and synthetic polymers has been found to be useful in enhancing the release of short half-lived drugs under physiological conditions. To achieve this, the properties of natural and synthetic polymers have been modified by grafting or polymerization, blending and other means. Grafting of vinyl monomers on to natural polymers such as cellulose has been widely accepted[15-17].

Definition of IPN:

IPN's are conventionally defined as an intimate combination of two polymers, at least one of which is synthesized or crosslinked in the immediate presence of the other. The two or more networks can be a vision to been tangled in such a way that they are concatenated and cannot

be pulled apart, but not bonded to each other by any chemical bond[18]. The conditions of eligibility as an IPN are as follows:

1. The two polymers are synthesized and/ or crosslinked in the presence of the other.

2. The two polymers have similar kinetics.

3. The two polymers are not dramatically phase separated.

The IPN's that have only one polymer crosslinked (where the polymers are synthesized separately) or where the polymers have vastly different kinetics are still considered to be the IPN's[19].

Advantages of IPN[20]:

1. The IPN hydrogel is formed from two polymers at a given temperature, the physical separation between the component polymers would be impossible because of the infinite zero-viscosity of the gel.

2. IPN produces synergistic properties from the component polymers.

3. IPN systems are known to increase the phase stability of the final product.

4. IPN increases the mechanical properties of the final product.

5. As long as the reacting ingredients are blended thoroughly during the synthesis, thermodynamic incompatibility can be made to overcome due to the permanent interlocking of the network segments.

6. IPN provides more efficient drug loading compared to conventional hydrogels.

Features of IPN[20]:

The ideal characteristics of an IPN are as follows:

1. An ideal IPN can suppress creep and flow.

2. IPN can swells in solvents without dissolving.

3. IPN is distinguishable from blends, block copolymers, and graft polymers.

4. To keep the separate phases together when the blends are subjected to stress.

5. These systems differ mainly because of the number and types of cross-links that exist in the system.

6. Materials formed from IPN share the properties that are characteristic of each network. A composite or an ideal IPN of two or more different polymers would be a better choice.

7. A polymer comprising two or more polymer networks which are at least partially interlaced on a molecular scale but not covalently bonded to each other and cannot be separated unless chemical bonds are broken.

8. Most ideal IPN are heterogeneous systems comprised of one rubbery phase and one glassy phase which produce a synergistic effect yielding either high impact strength or reinforcement, both of which are dependent on phase continuity.

9. Hence, IPN based systems have gained the good potential to develop the controlled release delivery of drugs.

Classification of IPN'S:

IPN's are classified based on chemical bonding and on arrangement pattern. The IPN consists of at least one of the constituent polymers that are crosslinked in the immediate vicinity of other polymers such that the network cannot be separated unless the chemical bonds are disrupted. If only one polymer of the IPN's is crosslinked, whereas the others have a linear structure, then the semi-IPN is formed. If all the member polymers are crosslinked the full-IPN is formed[21].

Based on chemical bonding[22]:

1. Covalent semi-IPN: It consists of two separate polymer systems that are crosslinked to form a single polymer network.

2. Noncovalent semi-IPN: In this type, only one of the polymer systems is crosslinked.

3. Noncovalent Full-IPN: In this type of IPN two separate polymers are independently cross-linked.

Based on the arrangement pattern:

Novel IPN: Polymer comprising two or more polymer networks which are at least partially interlocked on a molecular scale but not covalently bonded to each other and cannot be separated unless the chemical bonds are broken.

1. **Sequential IPN:** The second polymeric component network is polymerized following the completion of polymerization of the first component network.

2. **Simultaneous IPN:** Both component networks are polymerized concurrently, then the IPN may be referred to simultaneous IPN.

3. **Semi-IPN:** If only one component of the assembly is cross-linking leaving the other in a linear form, then the system is termed as semi-IPN.

4. **UV-induced IPN formation:** Formation of IPN structured hybrid was induced by the irradiation of UV light from 175 watts Xenon lamp filtered with a Toshiba UV-D33S glass filter. E.g. UV-induced IPN structure of polyurethane acrylate or silica hybrids[23].

5. **Magnetically active IPN formation:** Initially ferric oxide nanoparticles are formed by a free radical polymerization reaction and then the other polymer is added into the reaction with the crosslinker and the reaction is allowed to form a gel[24].

6. **Sunlight-induced IPN formation:** This technology is suitable in the fast-drying protective coating and adhesives. It is cost effective and easy to implement[25].

7. **Bio-erodible IPN:** These are prepared by using bio-erodible polymers. They are desirable for long term delivery of peptide. IPN can be useful to increase compatibility[26].

8. **IPN electrolytes:** A new type of solid polymer electrolyte (SPE) was prepared by the sequential interpenetration of crosslinked methoxyoligo (oxyethylene) methacrylate (MOEnM) and poly (Methyl Methacrylate) (PMMA). When the IPN'S were swollen with liquid electrolyte solutions, they showed structure that was between the chemically crosslinked gels SPE's and the porous SPE. They could swell or hold much more electrolyte solution than the porous SPE[27].

9. Latex IPNs: These IPNs are prepared in the form of latex which has a core and shell structure. The polymers are synthesized by emulsion polymerization of monomer 2 together

with the cross-linker and activator in the original seed latex of cross-linked polymer 1. The morphology of the IPN depends upon how the IPN components are polymerized[28].

10. Gradient IPNs: In this case, a film can be made with polymer network 1 predominantly on one surface and polymer network 2 on the other surface, with a composition gradient existing throughout the interior[29].

11. Thermoplastic IPNs: These materials contain physical cross-links rather than chemical cross-links (like ionic and hydrogen bond). As such they are hybrids between polymer blends and IPNs. Such cross-links may utilize block copolymers, ionomers, and/or semi-crystalline polymers. Being thermoplastic, they flow at elevated temperatures[29].

Characteristics of IPN'S[30]

- Forms insoluble network
- Biocompatible IPNs formed with biocompatible polymers.
- Forms non-separable network
- Shows adhesive property
- High tensile strength
- IPNs are distinguishable from blends, block copolymers and graft copolymers in two ways. Firstly an IPN swells but does not dissolve in solvents and secondly creep and flow is suppressed.

Properties of IPN

Hydrogels are called hydrophilic gels having considerable attention for their use in the field of pharmaceutical and biomedical engineering. This can be used as a carrier for drug and another therapeutic biomolecule if it is biodegradable, biocompatible and non-toxic *in situ.*

1) Swelling properties

All polymer chains in hydrogels are crosslinked to each other physically or chemically and thus, considered as one molecule irrespective of its size. So, there is no concept of molecular weight of hydrogels sometimes called infinitely large molecules or supermolecules. A small

change in environmental condition may trigger fast and reversible changes in the hydrogel. The alteration in environmental parameters like pH, temperature, electrical signal, presence of enzyme or other ionic species may lead to a change in the physical structure of the hydrogel. These changes may occur at the macroscopic level as precipitate formation, changes in size and water content of hydrogels. The difference in concentration of mobile ions in the hydrogel interior relative to the external solution, changes in solvent pH, drives the volume change. Hydrogels with acidic or basic functional groups respond to the fluctuations in the external environmental pH. Degree of ionization of the functional groups explains its swelling profile and hence the volume change. Polyacrylic acid is such type of pH-sensitive hydrogel where swelling ratio changes due to the ionization of carboxyl groups on the polymer chain[31].

2) Mechanical properties

The evaluation of a mechanical property is essential in biomedical applications viz. ligament and tendon repair, wound dressing material, the matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. Changing the degree of crosslinking the desired mechanical property of the hydrogel could be achieved. Increasing the degree of crosslinking a stronger hydrogel could be achieved through the higher degree of crosslinking decreases the percent elongation of the hydrogels creates a more brittle structure. Hence there is an optimum degree of crosslinking to achieve a strong and elastic hydrogel. Copolymerization with co-monomer may result in hydrogen bonding with the hydrogel which has also been utilized by the researchers to achieve desired mechanical properties[32].

3) Biocompatible properties

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility consists basically of two elements: a) bio-safety i.e. appropriate host response not only systemic but also local (the surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis and (b) bio-functionality i.e. the ability of a material to perform the specific task for which it is intended. This is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact

with the body through the healing and cellular regeneration process as well as scaffold degradation[33].

Preparation of IPN

1. **Casting Evaporation:** This method has been used widely to form a cross-linked polymer network. In this method each polymer constituent is heated until it is dissolved and then added to cross-linker solution[34]. In the case of the sequential process, solution of polymer I am added to the cross-linker solution followed by the addition of polymer II solution. In both cases, the solution is heated and mixed and then cast and dried. IPN gels can be prepared by this technique.

2. **Emulsification Cross-Linking:** This method is based on phase separation. Generally, the single emulsion cross-linking technique is based on w/o emulsion but recently w/w emulsion method has also been developed to form IPN[35]. The main advantage of w/w emulsion method is that there is no use of organic solvents which might leave a toxic residue that is incompatible with IPN biomaterials. In w/o emulsification method the water-soluble materials are dissolved in the aqueous phase at a specific temperature to form homogenous solution by stirring. This aqueous phase is added to oil phase to prepare w/o emulsion[36] but in w/w emulsion technique an aqueous solution of water-soluble polymers are emulsified as a dispersed phase in an aqueous solution of another polymer that acts as the co35inuous phase. Then the dispersed polymer phase is cross-linked to form the IPN network[35].

3. **Miniemulsion/Inverse Miniemulsion Technique:** This technique allows one to create small stable droplets in a continuous phase by the application of high shear stress[37]. The idea of miniemulsion polymerization is to initiate the polymer in each of the small stabilized droplets. To prevent the degradation of miniemulsion through coalescence, a surfactant and a co-stabilizer are added that are soluble in dispersed phase but insoluble in a continuous phase. This process of IPN formation can be divided into three steps. In the first step, constituent polymers are obtained by sonication using specific initiator. In the second step, one of the constituent polymers is polymerized and cross-linked using a cross-linking agent. As a result, a semi-IPN is formed until the second stage. In the third step, a full IPN is formed polymerizing and cross-linking the second constituent polymer by the addition of second cross-linker.

In the case of inverse mini-emulsion (water-in-oil), hydrophilic monomers can be easily polymerized. In this case, the monomer solution is mini-emulsified in a continuous hydrophobic phase. The polymerization process can be initiated either from the continuous phase or from the droplet. Koul et al. synthesized novel IPN nanogels composed of poly (acrylic acid) and gelatin by inverse miniemulsion technique. Acrylic acid monomer stabilized around the gelatin macromolecules in each droplet was polymerized using ammonium persulfate and tetra-methyl ethylene diamine and cross-linked with N, N-methylene bis-acrylamide (BIS) to form semi-IPN nanogels, which were sequentially cross-linked using glutaraldehyde to form IPNs[38].

Synthesis of IPN's:

The IPN's can be synthesized by innumerable methods.

A) *In-situ* synthesis of IPN's and semi-IPN's:

1. It involves the mixing of reactants before triggering polymerization reaction or crosslinking. Thus, the synthesis of two networks may or may not be initiated at the same time, leading either to the simultaneous or sequential formation of networks. In these *in-situ* synthesis, the morphology of the polymer can be modulated almost at will and can be made highly different by altering the proportions of two pattern polymers, the order and/ or relative rates of the formation of two networks [10,12].

2. IPN and semi-IPN's can also be prepared by one-pot inverse mini-emulsion[39] involving three steps. The first step involves the initiation by ammonium persulfate for a radical generation. The second step involves the accelerator, tetramethylethylenediamine (TEMED) and crosslinker, N, N-methylene bisacrylamide (MBA) which are used to polymerize and crosslink the monomer to form the semi-IPN. In the third step, Glutaraldehyde is used as a crosslinker to form full-IPN.

3. They can also be produced by crosslinking with gamma radiation[40,41].

B) Synthesis of sequential IPN: In this preparation, the first polymer network is synthesized and subsequently swollen with all the precursors necessary for the formation of the second network, which is then carried out within the first network. In this process, the first network determines the morphology of the final polymer. In this, sense, pore-filling electrolyte

membranes can be considered as IPN's or semi-IPN's, depending on whether or not the polymer substrate is crosslinked. Pores of the polymer substrate are filled with polyelectrolyte precursors and linear or network polyelectrolyte is synthesized within the porous structure. This pathway is referred to as ' impregnation synthesis'[42].

IPN – Based Drug Delivery Systems:

IPN based drug delivery systems are designed to deliver drugs at a particular rate with minimum fluctuation for a desired period of time. Several approaches are being pursued improved delivery of therapeutic products like sheets, films, hydrogel, calcifiable matrix, sponges, tablets, capsules, transdermal patches, microspheres, etc, [43].

Sheet:

A novel method of producing an IPN based drug delivery system is sheeting. Polymeric material comprising an interpenetrating network of a polyol (allyl carbonate) e.g., Nouryset®200 and epoxy resin is prepared by polymerizing 70 to 95 parts by weight of the polyol (allyl carbonate) by radical initiation and polymerizing partially or entirely simultaneously an epoxy resin-forming mixture by acid catalysis. The epoxy resin-forming mixture comprises 10-90 % wt of aliphatic or cycloaliphatic polyepoxide and 90-10% wt of a poly/anhydride adduct. Sheets can be used in various types of wound dressings and scar management products[44]. IPN films can be used as a piezodialysis membrane. These membranes are not mosaic membranes. It was found that some of these membranes did show piezodialysis effects. One of the successful applications of IPN based delivery systems is the alkyd/ poly (glycidyl methacrylate) based film which shows good mechanical as well as tensile strength. Biodegradable collagen films or matrices have served as scaffolds for survival of transfected fibroblasts. While these methods seem to allow adequate cell survival, the concerns about long-term biocompatibility of non-degradable materials should be taken into account. In several models, long-term expression of a foreign gene after implantation of transfected cells has not been achieved[45].

IPN Film As A Calcifiable Matrix System:

One of the problems with implantable biomaterials is their calcification, which is influenced by the structure of the implantable system, and determines it's *in-vivo* therapeutic efficiency and clinical fate[46]. Calcification of tissue or systems depends on the chemical factor that

operates at the cellular level around various tissues or biomaterials. Both collagen and elastin are major components of connective tissues, which possess a structure that comprises collagen fibers intimately associated with a remarkably stable elastin network. The suitability of collagen and elastin in many potential medical applications in reconstructive and plastic surgery including controlled delivery of bone morphogenetic protein has been reported. IPN matrix films composed of various combinations of collagen and elastin were developed and evaluated for their suitability as drug delivery systems. Biomaterials should possess mechanical properties capable of withstanding the forces and motions experienced by the normal tissues and have sufficient fatigue strength to ensure a long life of the implant *in-vivo*[47].

Tablets:

IPN prepared from chitosan/ carbopol inter-polymer complex can be used as extended-release matrix tablet. The solid nature of IPN based tablets seems *in-vivo* to have a great potential for anti-hypertensive action by blending with hydrophilic interpolymer complexes and a hydrophobic waxy polymer[48].

Capsules:

Supracolloidal IPN reinforced capsules using micron-sized colloidosomes of poly(methyl methacrylate-co-divinyl benzene) microgel were used as scaffold via radical polymerization of the interior phase to produce hollow supracolloidal structures with a raspberry core-shell morphology[49].

Hydrogel:

Hydrogels have been widely used as a drug carrier due to its ease in manufacturing and self-application. The production of a large and constant surface area is one of the major merits for them to be widely used for clinical and fundamental applications. Various combinations of polymers were made into hydrogel formulations to investigate their potential as a drug delivery system. The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. An attempt of combining collagen and hyaluronic acid into IPN hydrogels was made to develop delivery systems to enhance the mechanical strength of natural polymers and to overcome the drawbacks of synthetic polymers. The hydrogels were found stable and

resilient. Antibiotics- loaded interpenetrating network hydrogel based on poly (acrylic acid) and gelatin for treatment of experimental osteomyelitis[50].

Microspheres:

One of the successful applications of the interpenetrating network is for the controlled release of drugs. A micro-spherical formulation of poly (vinyl alcohol) and guar gum hydrogel microspheres for the controlled delivery of Nifedipine by emulsion cross-linking method was developed for treatment in severe hypertension[51]. Another approach was developed by the IPN formation of a graft copolymer of guar gum with modified poly (acrylamide) to form hydrogel microspheres. The microspheres were loaded with two antihypertensive drugs, Verapamil hydrochloride (water-soluble) and Nifedipine (water-insoluble) to investigate their controlled release characteristics[52]. IPN based microspherical formulation was also used for the prolonged delivery of anti-cancer drugs such as Capecitabine by the formation of chitosan-poly (ethylene oxide-g-acrylamide) inter-molecular rigid network and 5-Fluorouracil hydrogel microspheres of chitosan and pluronic F-127 for controlled release of drugs[53].

Therapeutic Applications Of IPN Based Systems:

The physical and biological characteristics such as enhanced solubility of hydrophilic drugs, excellent swelling capacity and imparting drug stability during formulation, in addition to their biodegradability, biocompatibility, weak antigenicity and targeting of a drug in a specific tissue make hydrogels of IPN's suitable for controlled release of drugs. Majority of IPN's and semi-IPN's developed to deliver anticancer, antibiotic, anti-inflammatory, antituberculosis and antihypertensive drugs to treat the infectious diseases, chronic pain and for immunotherapy. Considering the vast amount of literature on such systems, we present here typically the well-known systems that include the extent of encapsulation and time of release in addition to preparation method and carrier system used[54].

CONCLUSION:

The study of IPN for drug delivery systems may lead to a better understanding of critical diseases. The concepts of high swelling capacity, specificity, and sensitivity play an important role in targeting delivery of drugs by understanding the nature of drug delivery systems and their durability in the body, which can interact with the systems, can be

identified. IPN and semi-IPN's were introduced in pharmaceutical and biomedical fields. Since then, several CR formulations have been developed and tested to investigate *the in-vitro* release of therapeutics to extend their short half-life. This review summarizes published results on the CR of therapeutics through formulations containing hydrogels. Even though many potential applications of these systems are envisioned, considerable challenges and issues are yet to be resolved, such as heterogeneity which remains a major problem, and it is hard to precisely control the functionality of these systems. The importance of biocompatible and biodegradable hydrophilic polymers have wide applications in drug delivery, because of their propensity to combine with other polymers to form crosslinked three-dimensional IPN network hydrogel that tends to swell in water/ biological fluids.

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