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Review Article

INTERPENETRATING POLYMER NETWORK IN DRUG DELIVERY FORMULATIONS: REVISITED

SUBHASISH PRAMANIK*, PRITHVIRAJ CHAKRABORTY

Department of Pharmaceutics, Himalayan Pharmacy Institute, Majhitar, Sikkim, India. Email: subhasish.pharma@gmail.com

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ABSTRACT

Interpenetrating polymer network has gained a lot of interest in drug delivery system due to its ease of modification during its synthesis and development state, which evolved novel physicochemical and mechanical properties within the formulation. In this work, a detailed revision was done which includes its methods of preparations, factors that influence their properties, basic characterization parameters, and use in drug delivery systems along with patented formulations.

Keywords: Interpenetrating polymer network, Characterization, Semi-interpenetrating polymer network.

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INTRODUCTION

In the modern science of drug discovery, the polymer is widely used and valuable excipients in the different pharmaceutical formulation. It also has a high performance in the parenteral area, controlled drug release, and drug targeting to specific organs. Now in recent years, polymer mixture or blending is used to improve the polymer properties to subside the poor biological properties or progress in mechanical strength of the polymer [1].

An interpenetrating polymer network (IPN) is defined as a combination of binary or additional polymers in network form with at least one is synthesized and/or cross-linked in the presence of another [2]. When single water-loving polymer chain permeates a different network of polymer in the absence of any chemical bonds between them, then semi-IPN was formed. In semi-IPN, a single cross-linked network constructs while in IPN, more than on cross-linked network construct, permeating among them [3]. IPN hydrogels are distinctively promising for biomedical administration. Especially to create a stage of biomimetic for tissue engineering, which provides collaborate benefit of a synthetic polymer with the bioactivity of naturally obtained biomaterials [4]. An IPN can be characterized from polymer blend or grafts in two ways: one in which IPN swells without dissolving in solvents and another one is where sneak and flow are suppressed. Individual polymer retains its individual properties, so synergic action such as strength or toughness is retained. There is also altered in polymer complexation, and graft copolymer implicate either chemical bond and/or cross-linking (Fig. 1) [5]. The properties of natural and synthetic polymers are improved by graft copolymerization and give them a novel property [6]. The individual polymer is linked together by cross-linking but not chemically linked [7].

In polymer science, polymers play an important role to develop several innovative drug delivery system. IPN has influenced the use of conventional individual polymers and also diversify the applications which have grown rapidly. In the pharmaceutical field, primarily in the area of drug delivery, the advanced property of IPNs pays great attention. Biodegradable, biocompatible, and nontoxic polymer earns a special place, principally in controlled and targeted drug delivery applications. Biopolymers are used to form IPN beads which are used for test masking of bitter drugs in drug delivery system [8]. Recently, IPNs have found worldwide applications in medical science. Gradient homo-IPN used as a permanent joint between the elements of the new type of artificial cornea in which peripheral skirt is made by polymers [9]. By appropriate choice of polymers and selecting a suitable crosslinking agent, the IPN properties can be enhanced which precisely include porosity, elasticity, and degree of swelling and responsive behavior [10].

KINDS OF IPN

IPN can be ordered in many different ways (Fig. 2).

Based on chemical bonding

Irretrievable chemical links are formed by the chemical bond which, in turn, helps in absorption of water and/or bioactive compounds without dissolution, and drug release permits through the diffusion process [11].

Covalent semi-IPN

When two separate polymer network forms, a single polymer network by cross-linking is called covalent semi-IPN.

Non-covalent semi-IPN

When only one polymer organization is cross-linked, it is called as non-covalent semi IPN.

Non-covalent full IPN

When the binary individual polymer is independently cross-linked; it is called as non-covalent full IPN.

Based on the arrangement pattern

There are different types of method for synthesis of IPNs.

Simultaneous IPN

The two different polymer, crosslinker and the initiator/activator both components are mixed in one single step. The process of concurrent IPN preparation can be done by simultaneous polymerization through noninterfering reaction [12].

Sequential IPN

Sequential IPN can be simply blended. The monomer of the subsequent polymer is responsible for swelling of the first cross-linked polymer. Crosslinker and the activator help to form the network between two polymers [13].

Latex IPN

The major problem in IPN is difficulty in molding when they are formed because they are thermosets. To overcome this problem,

latex IPN is used. Each micro IPN is a particle which is prepared in the form of latex. In this type of IPN networks of the single latex particle, the second monomer comes together and binds with the first cross-linking monomer of the original seed of latex with crosslinking agent and initiator by polymerization technique. It is also termed as an interpenetrating elastomeric network [14].

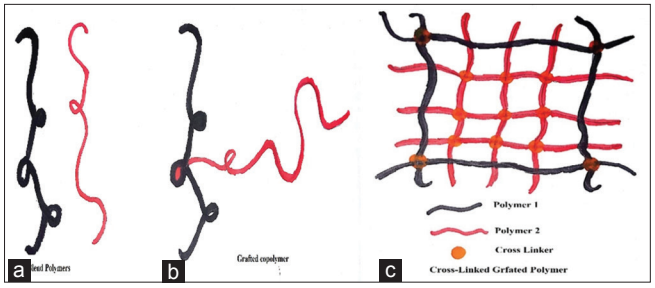

Fig. 1: (a) Blend polymer, (b) grafted polymer and (c) cross-linked grafted polymer

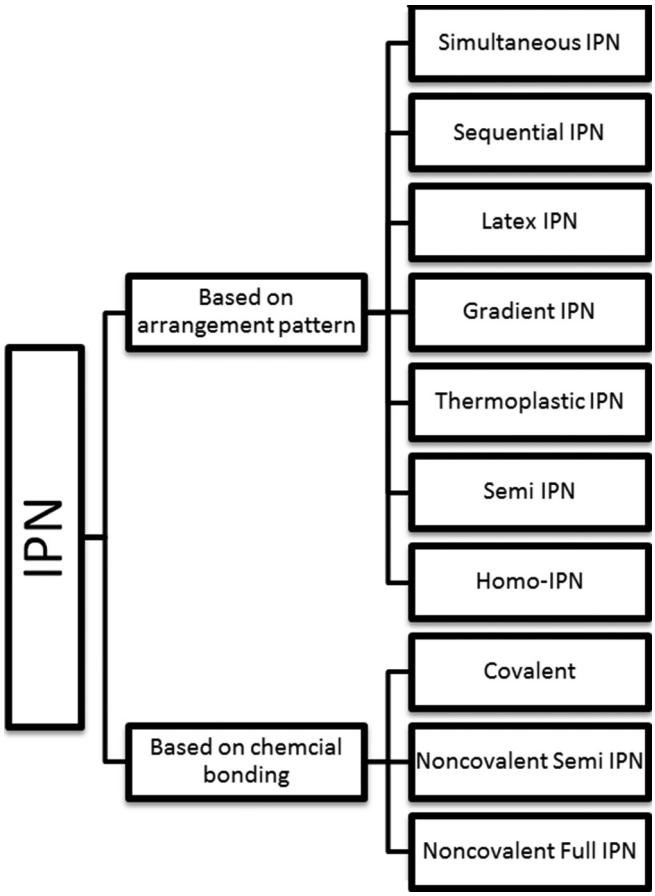

Fig. 2: Different forms of interpenetrating polymer network

Gradient IPN

In this type of IPN composition/cross-link, density varies as a function of position in a sample. Here, the first cross-linked polymer is partially swollen by the monomer of a second cross-linked polymer, followed by rapid polymerization technique before reaching to diffusional equilibrium [15].

Thermoplastic IPN

These type of IPN replaces the design of chemical cross-linkers by the use of physical cross linkers such as thermoplastic elastomers. The thermoplastic IPN entail two physically cross-linked polymers which arise from an ionic group, glassy domains, and crystallinity. In this type of IPN, the materials flow at elevated temperature, behave like a conventional thermoset IPN where one element is a block copolymer, and the other one is the semi-crystalline or a glassy polymer [16,17].

Semi-IPN

One or more polymers are cross-linked and form this type of IPN. These type IPNs have a linear structure as an alternative to a network structure. The IPNs properties can be changed by the linear component. These type of IPNs are prepared by either sequential or simultaneous process [18-21].

Homo-IPN

In this type of IPN, both polymers have formed a network which has the same structure. In theoretical work, homo-IPN are used as model materials [22,23].

HISTORY OF IPN

Survey on patent literature reveals (Table 1) the information that the IPNs were investigated over and over again, at the beginning of the 19th century. The first known person, J. W. Aylsworth who invented IPNs in 1914, combined the new phenol-formaldehyde compositions with natural rubber and sulfur at the time when he was the chief chemist of Thomas A. Edition working in West Orange, NJ laboratory [24].

Aylsworth also made the world's first rubber-toughened by adding natural rubber and sulfur, decades before rubber-toughened styrenics were commercialized.

In those times, Edition had switched to the platter type from the cylinder-type phonograph records with new phenol formaldehyde material developed by Leo Baekeland. However, since the plates were extremely brittle, the plates were made thick by Aylsworth's solution mixed in natural rubber and sulfur which develops a network structure while heat in gas the phenol formaldehyde composition is deeply cross-linked and form an interpenetrating network [25].

METHODS OF PREPARATIONS

Ionotropic gelation method

This technique is based on the interaction of an ionic polymer with opposite charge polymer. Sodium alginate and the polymer were dispersed and mixed thoroughly in distilled water and stirred for complete solubility. Then, the solution was poured dropwise with the

Table 1: Early IPN patents

Sl. No.	Inventor	Pat. No.	Polymer 1	Polymer 2	Application
1	J. W. Aylsworth	U. S. Pat.,1,111,284; 1914	Phenol- formaldehyde	Natural rubber	Toughen phonograph records
2	H. Hopff	Ger. Pat., 623,351; 1935	PVC	Natural rubber	Plastic materials
3	J. J. P. Staudiner& H. M. Hutchinson	U. S. Pat., 2,539,377; 1951	Poly (methyl methacrylate)	Poly (methyl methacrylate)	Smooth- Surfaced plastics
4	G. S. Solt	Br. Pat. 728,508; 1955	Positively charged network	Negatively charged network	Ion-exchange resin

IPN: Interpenetrating polymer network, PVC: Polyvinyl chloride

help of 23 gauze syringe needle to another aqueous media of another ionic polymer (Al+3, Ca+2, etc.) with continued stirring [26-29].

Emulsification cross-linking

This method is based on phase separation. This method is used widely to form a cross-linked polymer network. Usually, the cross-linked is prepared by water-in-oil (w/o) emulsion. In w/o emulsification aqueous polymeric solution was prepared by adding the water-soluble polymer form homogeneous solution by stirring. After that, this aqueous phase was added to the oil phase [30,31]. Recently, water-in-water (w/w) emulsion has been developed to form IPN. The toxicity effect of w/w emulsion is less compare to w/o emulsion as there is no use of an organic solvent as w/w emulsification technique is completely dependent on the aqueous environment [32,33].

Free radical polymerization

Free radical polymerization is mainly used for polymer synthesis. It is a technique of polymerization where a polymer is formed by consecutive addition of free radicals. First, the free radical site is created on the backbone polymer, and then the chemical compound gets attached through the chain extension process [34]. The effect of adventitious impurities is much less compared to other ionic chain-growth reaction.

First, in a round-bottom flask, the polymer was dissolved in distilled water. Then, it is permitted to hydrate for 4 h by continuous passing the nitrogen gas by heating at 80°C. Another polymer was added into this mixture with an initiator. This process is continued for 1 h with continuous application of nitrogen gas. After 1 h, the grafted copolymer was cooled at room temperature [35-38].

Wet granulation method

Wet granulation is a technique of mixing of dry powder with granulating fluid which can be removed by drying. The liquid solution which is used for granulation can be either aqueous based or solvent based.

The required amount of polymer is blended manually for 15 min. Then, the required amount of blending agent is added to prepare cohesive mass and the wet mass pass through # 22/24 mesh screen. The resulting are dried at 40°–60° C for 12 h. After completion of the drying stage, the dry granules were passed through #22 mesh screen. Then, magnesium stearate mixed with the granules and compressed into a tablet [39-42].

A detailed portrayal of IPN based drug delivery is systems listed in Table 2.

PHARMACEUTICAL FACTORS INFLUENCING IPN

Mechanical strength

In the field of pharmaceutical application, the mechanical property of IPN is an essential factor. During the life span of application, the integrity of the drug delivery system needs to be maintained unless that is designed as a biodegradable polymer. A drug delivery system is designed to protect sensitive therapeutic agent until it is released out of the system and hence the system needs to maintain its integrity. To achieve the desired mechanical property of the IPN, the degree of cross-linking is to be modified accordingly. An increase in the degree of cross-linking of the system results in a strong polymer network, but this can increase the brittleness in the structure of the system. Hence, an optimum degree should be achieved and maintained to get a comparatively strong IPN-based drug delivery system and also not allowing to be brittle. Another method to achieve the desired mechanical properties of IPN is copolymerization [62].

Large scale production

Large scale production is a challengeable task for IPNs drug delivery. IPNs are usually investigated for laboratory scale for improved performance rather than large scale. The difficulty in large scale is to maintain the concentration and composition of polymers. Hence, it is an ongoing process to scale up IPNs production process. There are quite a lot of factors such as improving the selectivity and non-compromising biocompatibility, stability, use of proper engineering configurations, optimizing polymer modification techniques and using cost-effective materials and methods which can affect the scale-up technique.

Sterilization

In the past decade, intensive research on the field of IPNs for drug delivery applications has been done [63]. For uses in drug delivery and medical application, sterilization capability is needed. IPNs based devices (such as drug delivery vehicles, and implants) are prepared, are sterilized, and disinfected (depending upon necessity) before medical use as per good manufacturing practice condition. The sterilization method should not effect on cross-linking or any structural variations or lead to chain scission or alteration in mechanical properties of IPNs.

Dry or moist heat, chemicals (ethylene oxide), or radiation are used as a traditional method for sterilization [64]. The most widely employed method is steam sterilization by autoclaving at 121°C., but it has limitation for its use in most of the polymeric materials, as it has a possibility of inducing melting and/or hydrolysis of the polymer matrix. For its effective treatment at ambient temperature, chemical sterilization with ethylene oxide gas is used for hydrolytically unstable polymers. The biocompatibility of the biopolymer is retained as chemical additives are not used in the radiation cross-linking.

CHARACTERIZATION OF IPN

Different characterization procedures were cited in pieces of literature for evaluation of IPN microbeads as well as microsphere formulations. Some of them are:

Particle size analysis

By the help of a digital microscope or optical microscope, the particles size can be determined. In an optical microscope, the eyepiece micrometer is calibrated using the stage micrometer. This process is tedious and mainly used during laboratory scale up [65].

Fourier-transform infrared analysis

It is an analytical technique, which is used to identify the functional group in structure and intermolecular interaction of organic, polymeric and in some cases inorganic materials. The samples were crushing with potassium bromide. Then under hydraulic pressure of 600 kg, the samples were converted into pellets and they were scanned in the range of 500 and 4000 cm^{-1} [10].

Drug entrapment efficiency

The quantity of drug absorbed into IPN particles is estimated by drug entrapment efficiency. The required amount of IPN particles was pasted in mortar and pestle and dissolved in 50 ml solution of phosphate buffer (pH 6.8). At 50°C, the solution was heated for producing desired drug extraction. The drug extracted is calculated by suitable analytical spectroscopy method [66,67].

Percentage of yield

It is calculated by the ratio of the total amount of the prepared microspheres and the initial weight of polymer and drug which is taken as the theoretical value [68].

$$\text{Percentage of yield} = \left[\frac{\text{The total amount of microspheres}}{\text{Intial amount of polymer and Drug.}}\right] \times 100$$

X-ray diffraction analysis

Many forms of polymers are there such as crystalline, semi-crystalline, amorphous, or crystalline. XRD is performed to evaluate the sample of different polymer which provides solid state of structural information such as degree of crystallinity. Moreover, scanning is also performed up to 2θ range of 0–50°C using CuKα radiation source [69,70].

Table 2: IPN-based drug delivery

Sl. no.	Polymers	Drug	Therapeutic use	Carrier system	Application	Ref.
1	Locust bean gum, sodium alginate	Capecitabine	Anticancer drug	Microbeads	Extended-release drug delivery	[28]
2	Sodium carboxymethyl cellulose, sodium carboxymethyl xanthan	Diclofenac sodium	Anti-inflammatory drug	Hydrogel	Controlled release	[32]
3	Polyacrylamide, xanthan, sodium carboxymethyl cellulose	Ketoprofen	Anti-inflammatory drug	Hydrogel beads	Gastroprotective drug delivery system	[36]
4	Tamarind seed polysaccharide, sodium alginate	Propranolol HCl	Antihypertensive drug	Hydrogel tablet	Controlled release	[39]
5	Polyacrylamide, sodium alginate	Diltiazem- HCl	Anti-arrhythmias	Matrix tablet	Sustained release	[40]
6	Polyacrylamide, gum ghatti, sodium alginate	Ketoprofen	Anti-inflammatory drug	Microbeads	Gastroprotective drug delivery system	[43]
7	Polyvinyl alcohol, poly[2-(dimethylamino) ethyl methacrylate]	Riboflavin	Riboflavin deficiency	Hydrogel	Controlled drug release	[44]
8	Sodium alginate, tamarind seed	Diltiazem hydrochloride	Anti-arithmetic drug	Microbeads	Controlled drug delivery	[45]
9	Polyacrylamide, sodium alginate	Ketoprofen	Anti-inflammatory drug	Hydrogel beads	Gastroprotective drug delivery system	[46]
10	Polyvinyl alcohol, pullulan	Pirfenidone	Idiopathic pulmonary fibrosis	Microspheres	Controlled release	[47]
11	Polyacrylamide-g-Guar gum, chitosan	Ciprofloxacin	Antibiotic drug	Hydrogel microspheres	Extended-release	[48]
12	Sodium carboxymethyl of locust bean gum, polyvinyl alcohol	Buflomedil hydrochloride	Peripheral arterial disease	Microspheres	Controlled drug delivery	[49]
13	Locust bean gum, sodium carboxymethyl cellulose	Diclofenac sodium	Anti-inflammatory drug	Microbeads	Enhance drug release	[50]
14	Glutamic acid, chitosan	Chlorpheniramine maleate	Anti-Histaminic	Microsphere	Controlled release	[51]
15	Sodium carboxymethyl cellulose, egg albumin	Simvastatin	Lipid-Lowering agent	Hydrogel	Controlled release	[52]
16	Chitosan, polyacrylic acid, polyvinyl pyrrolidine, and N, N'-methylenebisacrylamide	Clarithromycin	Antibiotic	Hydrogel	Stomach-specific drug delivery	[53]
17	Chitosan, acrylamide, and polyvinyl alcohol	Cefadroxil	Antibiotic	Microgels	Controlled release	[54]
18	Sodium alginate, polyvinyl alcohol	Prazosin hydrochloride	Anti-hypertension drug	Hydrogel	Controlled release	[55]
19	Sodium alginate, polyvinyl alcohol	Diclofenac sodium	Anti-inflammatory drug	Hydrogel	Controlled release	[56]
20	Polyacrylamide, carrageenan, and sodium alginate	Ketoprofen	Anti-inflammatory drug	Microbeads	Targeting drug delivery	[57]
21	Carboxymethyl xanthan and sodium alginate	Ibuprofen	Anti-inflammatory drug	Hydrogel	Sustained release	[58]
22	Chitosan, guar gum, acrylamide	5- Fluorouracil	Anti-metabolic drug	Microspheres	Controlled release	[59]
23	Gum tragacanth, polyacrylic acid, acrylamide and methyl methacrylate	Pantoprazole sodium	Anti-ulcerative drug	Hydrogel	Controlled release	[60]
24	Locust bean gum and Sodium alginate	Nimesulide	Anti-inflammatory drug	Hydrogel beads	Controlled release	[61]

List of some IPN application in drug delivery system. IPN: Interpenetrating polymer network

Swelling index

pH-sensitive response of IPN microbeads is proven by swelling index. Weighed required amount of microbeads was allowable to swell in 25 ml buffer solution of pH 1.2, pH 7.4 at 37°C. The pH of the encompassing solution is customized between 1.2 and 7.4 pH. In a predetermined time, microbeads are isolated from buffer solution, and adhered solution on the surface of the microbeads is removed lightly. The comparison in weight is measured before and after swelling [71].

$$\text{Swelling Index} = \frac{\text{Weight of wet microbeads} - \text{Weight of dry microbeads}}{\text{Weight of dry microbeads}}$$

Thermo gravimetric analysis (TGA) analysis

TGA is used to measure the mass of the microbeads over time as temperature changes. TGA of IPN microbeads is performed with TGA instrument. The study is carried out in an inert atmosphere (Nitrogen) and a heating rate of 10°C/min from 25°C to 600°C [72,73].

Differential Scanning Calorimetry (DSC) analysis

DSC is a very powerful thermal analysis technique which is used to evaluate polymer material properties such as thermal stability, melting point, purity, crystallization, specific heat capacity, and oxidation behavior. This study is performed in the presence of a nitrogen atmosphere and heating rate 10°C/min from 25°C to 400°C [74,75].

Scanning electron microscope (SEM) analysis

The use of an electron microscope, which produces a picture of a sample by scanning the surface with targeted beams of electrons, is done using a SEM. The sample is coated with platinum using sputter coater and focused under a microscope at room temperature and detect the photograph at voltage 10–40 kV [76,77].

Atomic force microscope (AFM) analysis

AFM is also known as scanning force microscope. It is composed of scanning probe microscopy with the resolution on order of a fraction of micro millimeter which gives high resolution compared to optical diffraction. The frequency resonance of the probe is 250 kHz [78].

Texture analysis

Texture analysis or tensile analysis is performed to measure the responsive behavior such as bio adhesiveness within the developed IPNs as viscosity, hydrogen bonding capacity, and concentration of polymer as well as different other environmental factors have a notable effect on the adhesion force required for an IPN to be responsive as a bioadhesive [79,80].

CONCLUSION

In multicomponent polymer literature, the prospect of IPN is one of the oldest as well as the newest and fast-growing field. In polymer science, IPN and semi-IPN technologies have been studied for more than 60 years. IPN has not solely used as a biomaterial in tissue engineering and drug delivery, however, conjointly used in different fields of science such as fuel cells, star cells, and food packaging and also used for development of an industrial application for new materials and consumer products. With the help of IPN concept, we can prepare a very small domain size of materials with dual phase formulation. IPN has many merits such as swelling capacity, mechanical strength, specificity, oxygen permeability, nutrient, and durability in the body. This can be a result of the presence of cross-links in each polymer that reduces creep and flow, permitting comparatively of stable materials with a vast area of the module to be prepared.

AUTHOR'S CONTRIBUTIONS

All the authors contributed equally.

CONFLICTS OF INTEREST

None.

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