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Shidhaye.S*, Surve. C, Dhone. A, Budhkar. T

Department of Pharmaceutics, Vivekanand Education Society's College of Pharmacy, Mumbai-400074

Emailid-supriya.shidhaye@ves.org

INTERPENETRATING POLYMER NETWORK-AN OVERVIEW

ABSTRACT

Interpenetrating polymer network (IPN) is one of the valuable novel biomaterials. IPN based drug delivery system is designed to deliver drugs at a predetermined rate for a designed period of time with minimum fluctuation. Due to its physical and biological characteristics such as enhanced solubility of hydrophobic drugs, imparting drug stability in the formulation, good swelling capacity, biodegradability, biocompatibility and targeting of drug in a specific tissue makes it suitable for drug delivery as well as biomedical applications. IPN based drug delivery is used for controlled release of drugs. These systems are also used for tissue engineering such as cartilage scaffolds, bone substitutes etc. The invention of IPN has far reaching and profound long-term implications for the pharmaceutical industry and indeed medicine as a whole. This article gives a brief review of the entire features of IPN in both as a drug delivery matrix system and a system for tissue engineering as well its potential therapeutic applications.

KEYWORDS: Interpenetrating polymer network, Controlled release, Pharmaceutical applications, biomedical applications.

INTRODUCTION

It has been proven over a past few decades that polymeric blends showed superior performances over the conventional individual polymers and hence has wide range of applications. Hydrophilic biopolymers are quite suitable in oral applications due to their inherent advantages over the synthetic polymers. The importance of biocompatible and biodegradable polymers is widely increasing in pharmaceutical applications because of their ability to form cross linkedthree-dimensional network hydrogels that tend to swell in water or biological fluids. These systems thus can be used as a potential candidate to deliver bioactive molecules in controlled release system. The blends obtained from natural and synthetic polymers alone are not always able to meet the complex demand of Biomaterials. Natural polymers have the advantage of non-toxicity, low cost, biodegradability, biocompatibility and safety. But their mechanical properties are vey poor. In contrast Synthetic polymers have broad range of mechanical properties.IPN can produce synergistic effect by sharing the properties of both natural as well as synthetic polymers. An Interpenetrating polymer network (IPN) [1] is a polymer comprising of two or more networks which are at least partially interlaced on a polymer scale but not covalently bonded to each other. The two or more networks can be envisioned to be entangled in such a way that they are concatenated and cannot be pulled apart, but not bonded to each other by any chemical bond. IPNs do not interpenetrate on a molecular scale; they may, however, form finely divided phases of only tens of nanometers in size. Many IPNs exhibit dual phase continuity, which means that two or more polymers in the system form phases that are continuous on a macroscopic scale.

1. ADVANTAGES OF IPN[1, 2, 3]

1. IPNcanproduce synergistic effect(s) from the component polymers such as when locust bean gum as a natural polymer is interpenetrated with polyvinyl alcohol as a synthetic polymer, the resultant IPN can be used to have control release of drugs. [4, 5, 6]
2. Permanent interlocking of the network segment occurs. Due to which thermodynamic incompatibility is overcome as the reacting ingredients are blended thoroughly at the time of synthesis.
3. IPN enhance mechanical strength, phase stability and biological acceptability of the entire product.
4. Due to the infinite zero-viscosity of the gel, phase separation between the component polymers is almost impossible.

The only disadvantage found with IPN is that, sometimes the polymers get interpenetrated to such an extent; the drug release from the matrix becomes difficult.

2. FEATURES OF IPN [7]

The ideal characteristics of an IPN are as follows:

1. An ideal IPN can suppress creep and flow.
2. IPN can swell in solvents without dissolving.
3. IPN is distinguishable from blends, block copolymers, and graft copolymers.
4. 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.
5. Hence, IPN based systems have gained good potential to develop the controlled release delivery of drugs.

3. TYPES OF IPNs [7]

IPNs can be made in many different ways as follows:

1. **Sequential IPN-**Polymer network I is made. Monomer II plus cross-linker and activator are swollen into network I and polymerized in situ.
2. **Simultaneous interpenetrating network (SIN)-**The monomers plus cross-linkers and activators of both networks are mixed. The reactions are carried out simultaneously, but by noninterfering reactions. An example involves chain and step polymerization reactions.
3. **Latex IPN-**The IPNs are made in the form of latexes, frequently with a core and shell structure.
4. **Gradient IPN.** Gradient IPNs are materials in which the overall composition or cross-link density of the material varies from location to location on the macroscopic level. For example, a film can be made with network I predominantly on one surface, network II on the other surface and a gradient in composition throughout the interior.
5. **Thermoplastic IPN-**Thermoplastic IPN materials are hybrids between polymer blends and IPNs that involve physical crosslinks rather than chemical cross-links. Thus, these materials flow at elevated temperatures, similar to the thermoplastic elastomers, and at use temperature, they are cross-linked and behave like IPNs.
6. **Semi-IPN-**Compositions in which one or more polymers are cross-linked and one or more polymers are linear or branched are semi-IPN (SIPN).

4. INTERPENETRATING POLYMER NETWORK VERSUS POLYMER BLEND

1. Chemical structure [7]

Simply by mixing two or more polymers (polymer blend) do not create an interpenetrating polymer network.IPNs, in many ways, are related most closely to block copolymers. In the block copolymer systems, the length of the block determines the size of the domains. In the same way, the level of cross linking plays a major role in determining the domain size of IPNs. Short blocks or short chain segments between cross-links both are responsible for small domains. However, there are some important differences. Short block lengths are important because they increase miscibility between component polymers. For the case of IPNs, there is growing evidence that cross-links decrease the miscibility of the system relative to the corresponding blend, for systems in which the linear component polymers are miscible.

Miscibility

Earlier it was been discovered that if two immiscible polymers were formed into an IPN, the glass-transition temperatures of the two polymers were shifted inward [8-9]. This shift wasinterpreted as an increase in the miscibility of the two polymers caused by the presence of cross-links.[10] At that time theory held that the cross-links in IPNs played a role similar to junction points in block copolymers in increasing the miscibility [11].Also, the size of the phase domains of IPNs was discovered to be smaller than expected for the corresponding blends; often on the order of 20-80 nm.The development of rather broad interphases between the two phases wasnoted and led to the observation that the two components were mixing over a 5-10-nm range. Thus, the shifts in the glass-transition temperature might have been caused by the interphase mixing rather than by thermodynamic changes.

Whether an IPN forms a lower or an upper critical solutiontemperature phase diagram is unknown because no complete phase diagram for an IPN has ever been reported. Thus, the effect of temperature on IPN miscibility is unknown. This factor is important because, like many other polymer systems, polymerization is carried out at elevated temperatures and properties are measured at lower temperatures. Thus, if an IPN were more miscible at higher temperature, its nonequilibrium properties might be measured at some lower temperature and yield the

apparent effect of increased miscibility. In general all of the compositions that exhibit inward glass-transition temperature shifts were immiscible in both the blend and IPN states. The Only conclusion that can be drawn under these circumstances was that a better dispersion was achieved in the IPN than in the blend.
The thermodynamic requirements for polymer-polymer miscibility were understood better much later and a number of miscible polymer pairs had been investigated. A comparison between a Blend miscibility and IPN miscibility was hence necessary. [12]

5.INTERPENETRATING POLYMER NETWORK BASED COLLOIDAL CARRIERS VERSUS NORMAL COLLOIDAL CARRIERS

1.IPN based colloidal carrier system may give a more controlled release than the normal carriers because the polymers are more closely interlinked with each other.

2. The possible degradation of the drug in the IPN based colloidal carrier may be comparatively less than the normal carriers.

3. IPN have been shown to have better stability in the biological environment, mediate better bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers than the normal colloidal carriers.

4. The cytotoxicity of nanoparticles or their degradation products and biocompatibility is a major problem. IPN based nanoparticles may be superior in these respects.

6. PHARMACEUTICAL APPLICATIONS OF IPN BASED DRUG DELIVERY SYSTEM

a)IPN based microspheres

IPN is primarily used for the controlled release of the drugs. IPN microspheres based on xanthan gum (XG) and polyvinyl alcohol (PVA) were prepared by an emulsion cross-linking method using glutaraldehyde as a cross-linker to deliver an anti-inflammatory drug, Diclofenac sodium (DS)[13] to the intestine. FTIR spectroscopy was done to confirm the formation of IPN and the chemical stability of DS inside the microspheres. *In-vitro* release studies were carried out at pH 1.2 and 6.8 dissolution media.*In-vivo* pharmacokinetic evaluation performed in rabbits indicated that micro particles showed slow as well as prolonged drug release when compared with a DS solution. Thus it was concluded that these IPN micro spheres offer a potential candidate for oral controlled release of water-soluble DS.

IPN based micro spherical formulation was also used for the prolong delivery of anti-cancer drug such as capecitabine by formation of chitosan-poly(ethylene oxide-g-acrylamide) inter-molecular rigid network[14].

Semi-IPN hydrogel microspheres composed of chitosan and hydroxypropyl cellulose (HPC) were prepared by emulsion crosslinking method for controlled release of Chlorthiazide[15]. Several formulations were prepared by varying the ratio of polymers, amount of glutaraldehyde and % drug loading. *In-vitro* release studies showed the dependence of release rate on the drug loading, extent of cross-linking and the amount of HPC used to prepare the micro spheres and the slow release was extended up to 12 hours [15].Semi-IPN micro spheres consisting of chitosan-(dextran-g-acrylamide) were prepared by emulsion crosslinking method using glutaraldehyde as across 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 [16].

b) IPN based tablets

Interpenetrating network (IPN) matrix tablets composed of polyacrylamide grafted-sodium alginate (PAam-g-SAL) copolymer and sodium alginate (SAL) were prepared by wet granulation method for the sustained release of Diltiazem HCl (DTZ)[17]. Ca^{+2} ions in the form of calcium gluconate were used as cross linking agent. The confirmation of formation of IPN was done by FTIR spectroscopy. The drug release was primarily controlled by viscosity of the gel formed and the relative magnitude of swelling capacity of IPN matrix followed by dissolution of the polymers. The formation of calcium alginate gel structure governed the swelling capacity of the matrix and the co-polymer was used to impart the rigidity. The study concluded that IPN matrix tablets of PAam-g-SAL and SAL can be used for sustained release of DTZ.

c) IPN based capsules

Interpenetrating polymer networks (IPNs) hydrogel capsules consisting of polyacrylamide and polyvinyl alcohol for sustained drug release [18].Supracolloidal IPN reinforced capsules using micron-sized colloidosomes of poly(methyl methacrylate-co-divinylbenzene) microgels were used as scaffold via radical polymerization of the interior phase to produce hollow supracolloidal structures with a raspberry core–shell morphology[19].

d)IPN based transdermal membranes[13]

IPN hydrogel membranes consisting of sodium alginate and polyvinyl alcohol were prepared by solvent casting method for the transdermal delivery of Prazosin hydrochloride, an antihypertensive drug through skin. Glutaraldehyde was used as a crosslinking agent. Differential scanning calorimetric (DSC) analysis was done to confirm the formation of IPN and showed that the stiffness of the membrane can be increased by increasing the concentration of glutaraldehyde. The *in-vitro* drug release study was demonstrated through excised rat abdominal skin and indicated that drug release depends upon the amount of glutaraldehyde in membranes. The slow drug release was extended up to 24hr, whereas sodium alginate and polyvinyl alcohol membranes frequently discharged the drug. The developed IPN membranes were safe and less irritant as showed by primary skin irritation and skin histopathology study.

e)IPN based nanoparticles

Development of nanoparticles has proved to be a revolutionary technique. A thermally responsive polymer-metal Nano composite system which consist of a solid gold nanoparticle core and thermally responsive IPN shell was prepared, which was than PEGylated. The aim of this study was to prepare Gold nanoparticles (GNPs) ,which were then incorporated inside a polyacrylamide (PAAm)/poly(acrylic acid) (PAA) [20] IPN shell by an in-situ inverse emulsion polymerization. The surface of the nanocomposite system was then PEGylated by means of covalent grafting of a linear methoxy-PEG-N-hydroxysuccinimide to the primary amine groups of the PAAm network. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were performed to confirm the synthesis and incorporation of gold nanoparticles within the IPN shell. The temperature swelling response of the IPN particles was demonstrated by dynamic light scattering. The successful PEGylation of the nanocomposite system was confirmed by zeta-potential analysis. Novel quasi-interpenetrating network/gold nanoparticles composite matrices were studied on DNA sequencing performances by capillary electrophoresis technique[21]

f) IPN based hydrogels

Several combinations of polymers were prepared into hydrogel formulations to determine their potential as a drug delivery system. The efficacy of antibiotics loaded IPNs hydrogel composed of poly(acrylic acid) and gelatin[22]was studied for treatment of experimental osteomyelitis. N, N'-methylene bisacrylamide and glutaraldehyde were used as a crosslinking agent. An *in-vivo* study was performed on rabbits. After the treatment macroscopic evaluation was done which indicated that depending upon the drug loading of implants redness, swelling, local warmth and drainage decreased. Collagen and polyhydroxyethylmethacrylate[23] into hydrogels was made to develop a delivery system for anticancer drugs.The main aim of the study was the incorporation of three potent anticancer agents i.e. 5-Fluorouracil (%FU),BleomycinA2(BLM) and Mitomycin C (MMC) into hydrogel matrices. It was observed that the drug entrapment efficiency was varied in the order of MMC>5-FU>BLM. *In-vitro* drug release studies were performed in phosphate buffer(pH 7.4) at 37°C. The study concluded that release profiles followed zero-order kinetics and release rate was independent of time. Hybrid copolymers ofcollagen with polyethylene glycol-6000 and polyvinyl pyrrolidonewere prepared for the controlled delivery of contraceptive steroids [24].

g) IPN based sheet

The most promising method of developing IPN based drug delivery system is sheeting. An IPN composed of polymeric material like polyol(allyl carbonate) [25] 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 an epoxy resin forming mixture composed of 10-90 weight % of aliphatic or cycloaliphatic epoxide and 90-10 weight % of polyol/anhydride adduct.

h)IPN based sponges

IPN based sponges are mainly used in wound dressings and hemostyptics. The main advantages of collagen include 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 as well as its protection against mechanical harm and secondary bacterial infection. Collagen promotes growth and cellular mobility and hence, inflammatory cells can actively penetrate the porous scaffold. Because of this a highly vascularized granulation bed is formed which encourages the creation of new granulation tissue and epithelium on the wound. Therefore collagen sponges can be considered as active dressings which help in the process of healing. Collagen in combination with glycosaminoglycan (GAG) polymers is capable of controlling differentiation and proliferation of cells. Chitosan sponge/poloxamer[26] sponges prepared by SIPNs method have good possibility for wound dressing application due to rapid water absorption, high mechanical strength and interconnected cross-sectional morphology of SIPNs.

i)IPN based films

IPN films can be used as a piezodialysis membrane. One of the successful applications of IPN based delivery systems is the uralkyd/poly(glycidyl methacrylate) based film which shows good mechanical as well as tensile strength[27]. The graft copolymerisaion of type I atelocollagen onto the surface of polyurethane (PU)[28] films, treated with ozone, was performed. It was observed that they could enhance the

attachment and proliferation of fibroblasts and growth of cells. Films composed of collagen and polyvinyl alcohol mixtures cross linked with glutaraldehyde vapor have been investigated as depot formulation for recombinant human growth hormone. [29]

j) IPN film as calcifiable matrix system [13]

Calcification is one of the problems encountered with implantable biomaterials which is influenced by the structure of the implantable system and determines its *in-vivo* therapeutic efficiency and clinical fate. Calcification of tissue or system mainly depends upon chemical factors that can operate at the cellular level around different tissues or biomaterials. Elastin and collagen both are chief components of connective tissues that possess a structure which compromises collagen fibers closely associated with a remarkably stable elastin network. IPN based matrix films composed of various combinations of collagen and elastin were developed and evaluated for their suitability as drug delivery systems as well as in tissue calcification. Biomaterials should possess good mechanical properties which are able to withstand the forces and motions experienced by the normal tissues and have adequate fatigue strength to ensure a long life of the implant *in-vivo.*

8. BIOMEDICAL APPLICATIONS OF IPN BASED DRUG DELIVERY SYSTEM

a) IPN as a bioengineered tissue

Tissue engineering has now become a promising field which provides functional replacement of impaired tissues or organs to patients. It requires mechanically stable, biocompatible and biodegradable scaffolds to allow adherence of cells and its proliferation. Various biodegradable polymers such as PGA, PLGA, PLA and collagen based porous three-dimensional scaffolds have been extensively used in the tissue engineering of bone, cartilage, skin etc. Collagen gel[30] as human skin substitutes has been used in tissue engineering and led to the development of bioengineered tissues such as heart valves, blood vessels and ligaments. Collagen also shows hemostatic properties that can promote blood coagulation and play an important role in tissue repair process. Highly porous scaffolds based on collagen and hydroxyapatite composite were prepared by solid-lipid phase separation method for bone tissue engineering. *In-vitro* examination of cell proliferation and attachment on the scaffolds were performed. The study concluded that collagen-hydroxyapatite composite showed good biocompatibility and hydroxyapatite did not affect the histocompatibility of the scaffold materials. Thus, the porous collagen-hydroxyapatite composite is suitable as scaffold for bone tissue engineering.

b) IPN as bone substitutes

Bone has the unique ability for regeneration among various tissues in the human body. Grafted demineralized bone collagen in combination with hydroxyapatite [31] was found to be an excellent osteoinductive material and could be used as a carrier of bone morphogenetic protein (BMP) for expression of biological activity *in-vivo* and also used as bone substitute. Enzymatically degradable IPN (edIPN) composed of poly(AAm-co-EG/AAc) was developed which was amenable to present the cell signaling domain Arg-Gly-Asp (RGD). The relative effects of implant surface chemistry and topography on osseointegration inside the rat femoral ablation implant model was studied. The result showed that moderate enhancement of peri-implant bone formation was observed after 28 days using the enzymatically degradable IPN (edIPN) devoid of peptide modification.[32]

c) IPN as cartilage scaffolds

A biodegradable polymer scaffold composed of collagen and chitosan was tried in the form of interpenetrating polymeric network(IPN) for *in-vitro* culture of human epidermoid carcinoma cells (HEp-2) using glutaraldehyde as a cross linking agent. *In-vitro* culture studies were performed using HEp-2 cells, over the selected scaffold and its growth morphology was examined through optical photographs taken at different magnifications at various days of culture. The results indicated that the scaffolds prepared from collagen and chitosan can be used as a substrate to culture HEp-2 cells and also as an *in-vitro* model to test anticancerous drugs.In another study, alginate and alginate: chitosan semi IPN scaffolds were prepared by freeze-drying process. These structural and cellular outcomes demonstrate potential utility of chitosan semi IPNs in alginate scaffolds. Comparative results found in relation to alginate scaffolds, support the necessity for alginate: chitosan scaffolds for improved cartilage tissue engineering. [33]

9. NEW PATENTED TECHNOLOGY

Fluoropassivation®

This is a novel, patented technology, whereby the surface of each fiber within a macroporous polyester matrix is totally covered by fluoropolymer molecules. The process ensures that the fluoropolymer molecules bond with the polyester giving an interpenetrating molecular network at the interface between the two polymers. The thinness of the covering (less than 10 nanometers) does not allow it to be seen using mainstream technology - this can however be achieved by using Secondary Ion Mass Spectroscopy (SIMS). The output from the SIMS instrument visualizes the presence of fluorine atoms over the total surface, providing evidence of a completely fluoropassivated structure. The result is the formation of a new biomaterial. *In vitro*, *in vivo and ex vivo* studies on platelet deposition confirm that the Fluoropassiv™ biomaterial exhibits significantly reduced thrombogenicity [34] compared to polyester and ePTFE. Improved healing is evidenced in animal models by more complete pseudo intimal development and vasa vasorumformation.Fluoropassivation is used in the production of Thin Wall peripheral grafts and carotid patches.[35] No clinical data is available which evaluates the long-term impact of the fluoropassivated surface modification treatment. Fluoropassivated carotid patches received FDA clearance in April 1998. It is available in USA from 1st April 1999.[36-37]

10. CONCLUSION

IPN are polymers comprising of two or more polymers which are not covalently bonded to each other but partially interlaced. Its major advantages include its high mechanical strength, phase stability and biological acceptability.It can be used to provide prolonged drug delivery to eradicate critical diseases like AIDS, cancer and cardiac diseases as well as inflammatory diseases like rheumatoid arthritis and osteoarthritis. IPN is mainly designed to deliver drugs to a specific site of action with minimum fluctuation at a predetermined rate for maximizing drug availability and minimizing the dose related side effects and thus the effects of pharmacotherapy can be optimized. It can be concluded from its utilization as a drug delivery matrix system (*in-vitro*) as well as in tissue engineering that these systems may lead to better understanding of numerous pathological diseases and can serve as a potential candidate for various therapeutic applications in future.

11. OUTLOOK

The outlook for IPNs is exceedingly bright. These new materials have the following advantages:

1. IPNs form a series of tough plastics, broad-temperature damping materials, and reinforced elastomers that can be used wherever thermosets are required.

2. The presence of cross-links in a multiphase material gives an added mode of control over the morphology, especially in the development of finely divided domains or dual phase continuity.
3. The thermoplastic IPNs and the gradient IPNs provide a series of physical and mechanical properties that may be difficult to match with other polymers or combinations of polymers.However, Development of IPN system faces major challenges both technologically and economically.

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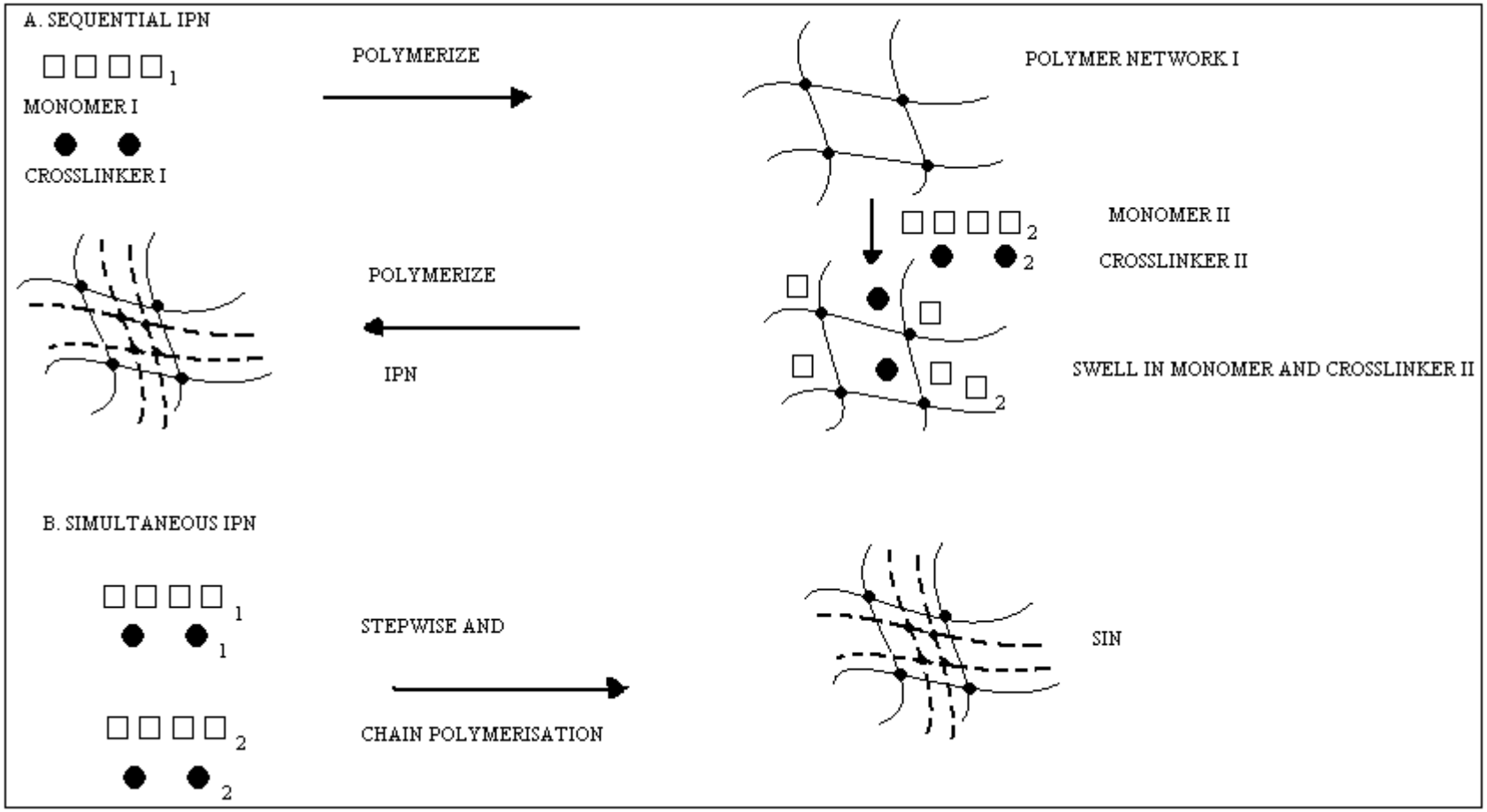
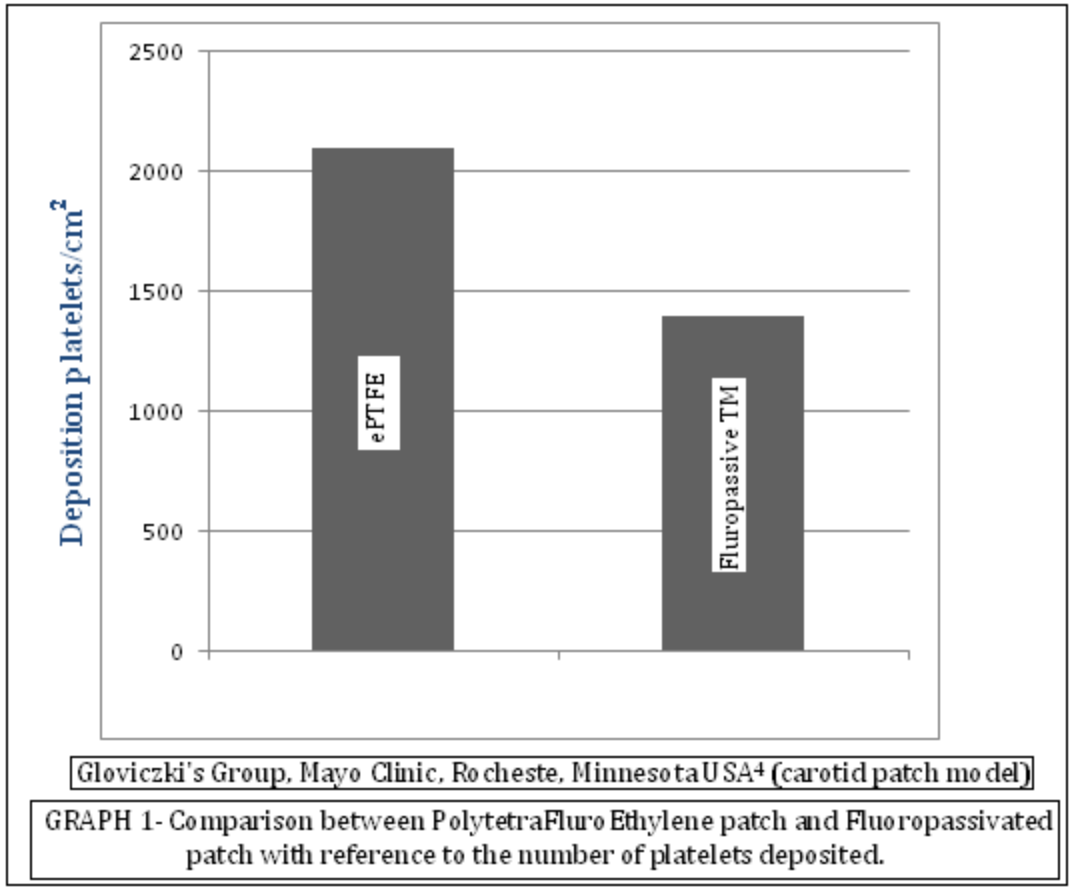


FIGURE 1- Methods of Preparation of Interpenetrating polymer network. (A) Method of preparation of Sequential IPN. (B) Method of preparation of Simultaneous IPN.

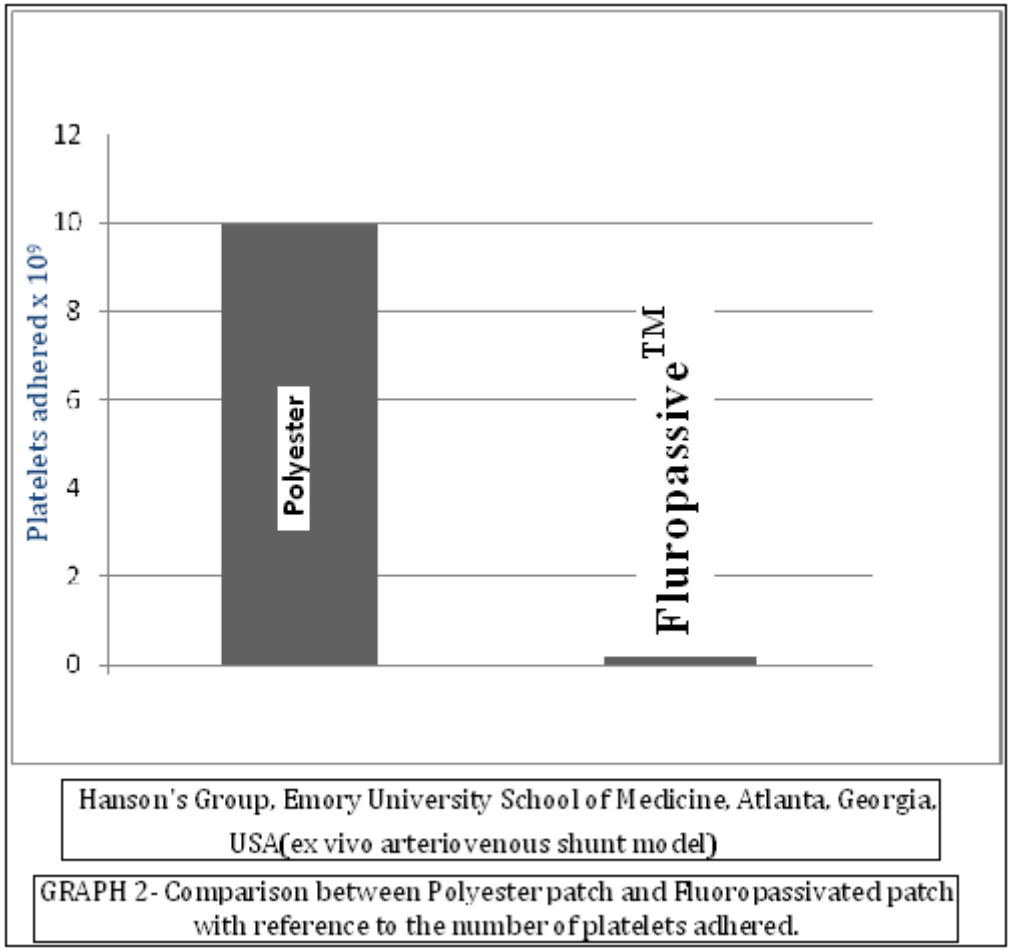
	System	Method of measurement	Blend miscibility	IPN miscibility	Comments
1	Linear PSH-cross-PSD semi II	SANS	Miscible to 8 X 105 g/mol	Miscible to 3 X 105-4 X104 or 4 X104-1 X 104 g/mol	Semi-II IPN somewhat less miscible.
2	Phenolic-EVA copolymer	FTIR	Single phase	Cross-linking phenolic leads to phase separation	IPN less miscible.
3	PSD-PVME cross-linked and grafted by γ radiation	SANS	Single phase	Spinodal temperature increases from 140 to 430°	IPN-graft more miscible.
4	PPO-PS blends, SIPNs, and IPNs	DSC, DMS and TEM	Single phase	Single phase	All compositions miscible.

TABLE 1- Comparison between Blend Miscibility and IPN Miscibility

PSH- Polystyrene H, PSD-Polystyrene D, EVA- Ethylene vinyl acetate, PVME-poly(vinyl methyl ether), SANS-Small angle neutron scattering, FTIR-Fourier transform IR spectroscopy, DCS-Differential scanning Calorimetry, DMS-Dynamic mechanical spectroscopy, TEM-Transmission electron microscopy.



GRAPH 1- Comparison between PolytetraFluro Ethylene patch and Fluoropassivated patch with reference to the number of platelets deposited.



GRAPH 2- Comparison between Polyester patch and Fluoropassivated patch with reference to the number of platelets adhered.