IPN Systems for Cancer Therapy

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Abstract

Interpenetrating polymer network (IPN) is the innovative biomaterial that forms a breakthrough in the polymeric science. It is an intelligent polymeric multicomponent system which is biocompatible and biodegradable as well known for its specific drug-releasing tendency with response to a stimuli. It also possesses a dual-phase continuity other than interpenetrating at the molecular level. As a result, the IPN system is widely preferred in the field of cancer therapy with zero-order drug delivery method that retains minimized fluctuations. The potentiality of this IPN system makes it a vast research area to diagnose and treat cancer and related diseases. The complexity and synergistic nature of this IPN system overcome the drawbacks of the individual polymeric carriers for cancer diagnosis and treatment, thus making it as a unique drug delivery vehicle. The comprehensive view of IPN classification, methods of preparation, their applications in cancer treatment and mechanism of drug release and action are explicitly focussed on in this chapter.

Keywords

Interpenetrating polymer network · Biocompatible · Synergistic · Carrier molecule

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9.1 Introduction

Interpenetrating polymer network ensembles the alloys of cross-linked polymers that are formed by synthesizing and/or cross-linking one polymer on the other without a covalent bond formation which can be detached only by breaking the chemical bonds between them (Myung et al. 2008; Sperling 2005). The synergistic nature of this polymeric multicomponent system will possess a unique drug release profile (Kim et al. 2004). The IPN system containing sulphur, natural rubber, with partially reacted resins of phenol formaldehyde is first found by Aylsworth in 1914 and is first termed in the 1960s by Miller while studying polystyrene network. The IPN system is known as a polymer alloy due to its peculiar nature that deviates from the other system such as (Lohani et al. 2014):

- IPN swells, but not dissolves in solvent as a polymer blend.
- IPN involves both chemical linkage and cross-linking, while polymer complex or graft copolymers involve either one of them.
- IPN has a bi-continuous structure with improved properties in terms of its toughness, morphology and strength.

This IPN system is nontoxic, biodegradable as well as biocompatible that predominantly employs them in the drug delivery applications. For targeted and sustained drug release applications, the attractive physicochemical properties of IPN find a distinct position relating to the preparation of capsules, tablets, hydrogels, micro- and nanoparticles, etc. The tremendous involvement of IPN in the biomedical field encouraged the researchers in developing smart drug release strategies on the target site (i.e.) stimuli-responsive drug release approach at the desired site (Reddy et al. 2008; Alsuraifi et al. 2018). This stimulus signal can be either external (induced artificially) or internal (physiological condition) depending upon the target site. This in turn permits it to be applied as a self-regulated mechanism for an effective as well as for a secure targeted drug delivery.

The major advantages of this IPN system are given below:

- The synergistic properties of natural and synthetic polymers expose an improved mechanical strength and a high-phase stability of the desired final product with high biocompatibility (Jain et al. 2013; Wu et al. 2007).
- The incessant zero viscosity of the hydrogel prevents the phase separation-blended polymers in the IPN system (Isiklan 2006).
- The stable interlocked networks of the polymers with the reacting components prevent the thermodynamic incompatibilities, and on the applied stress, the phase detached remains to be together (Bhardwaj et al. 2012; Margaret et al. 2013).

Cancer being a dreadful disease needs a suitable perception for its proper diagnosis and treatment. The conventional treatment results in the burst release and inverse reaction of drug molecules (Chamundeeswari et al. 2018). The ability of IPN to encapsulate or incorporate drug molecules within themselves enables an

advanced targeted drug delivery for the cancer treatment at a predetermined rate. This facilitates a zero-order drug delivery pattern with reduced fluctuations. The greater drug payload, nontoxicity, stability and sustainability, increased half-life of systemic circulation and therapeutic index, site-targeted action avoiding non-specific reactions and greater biodistribution and biodegradability make the IPN system to serve as a promising source for the cancer treatment (Raj et al. 2018; Soman et al. 2014).

9.2 Classification of IPN Systems (Fig. 9.1)

9.2.1 Based on the Chemical Bonding

Based on the bond that cross-links the polymers to get entangled, IPN system is classified into two types (Murugesh and Mandal 2012):

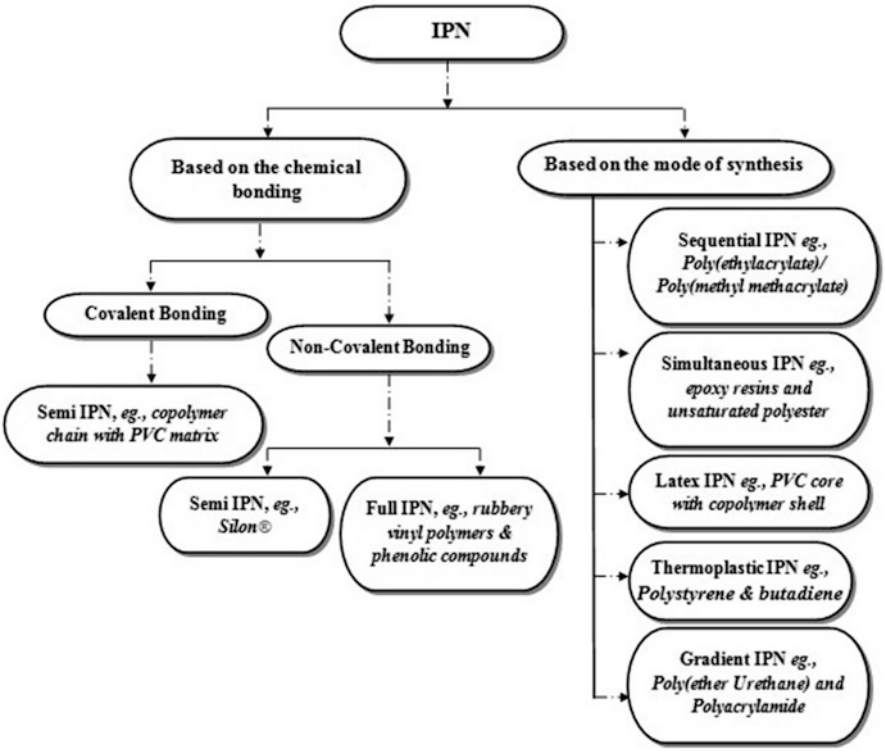

Fig. 9.1 Schematic classification of IPN system. The properties of the IPN system vary according to the individual property of the polymeric system used. This makes the formation of different types of IPN system that can be differentiated based on their chemical bonding and their mode of synthesis

9.2.1.1 Covalent Bonding

Semi IPN: Single IPN system forms by cross-linking two discrete polymers.

9.2.1.2 Non-covalent Bonding

Semi IPN: Only one polymer molecule will get cross-linked to the other polymer system to form a single IPN system.

Full IPN: Independent cross-linking of two or more polymer networks occurs to produce completely entangled IPN system.

9.2.2 Based on the Mode of Synthesis

Sequential IPN: Sequence of reaction occurs to produce an IPN system. Firstly, monomer I get polymerize with the cross-linkers I to produce a first polymer network; sequentially, the monomer II swells with the cross-linkers II and polymerizes with the first polymer network to form an IPN system (Sperling and Hu 2003).

Simultaneous IPN: In simultaneous IPN formation, simultaneous reaction of polymerization and cross-linking of monomer I and II occur. The one-step reaction without any interfering routes will produce a complete intercalated IPN system (Kiguchi et al. 2004).

Latex IPN: Latex IPN possesses a core and shell structure. It is prepared by polymerizing the monomer II on the latex seed of cross-linked polymer network I along with the activators and cross-linkers. The morphology of the produced IPN system depends on the path of polymerization (Chikh et al. 2011).

Thermoplastic IPN: The thermoplastic IPN flows at an elevated temperature (similar to thermoplastic elastomer), and the cross-linking of polymers occurs through physical bonding than the chemical bonding (Ignat and Stanciu 2003).

Gradient IPN: For the formation of gradient IPN, the monomer I is allowed to swell monomer II network surface following the polymerization of both the networks. The monomer II concentration varies against the monomer I (Karabanova et al. 2005) (Fig. 9.2).

9.3 Methods for IPN Synthesis

The preparation of an IPN system by any method employs three major steps such as:

- Three-chemical immiscible-phase formation
- Coating agent deposition
- Rigidization of coating agent

Some of the methods used for preparing IPN system are given below:

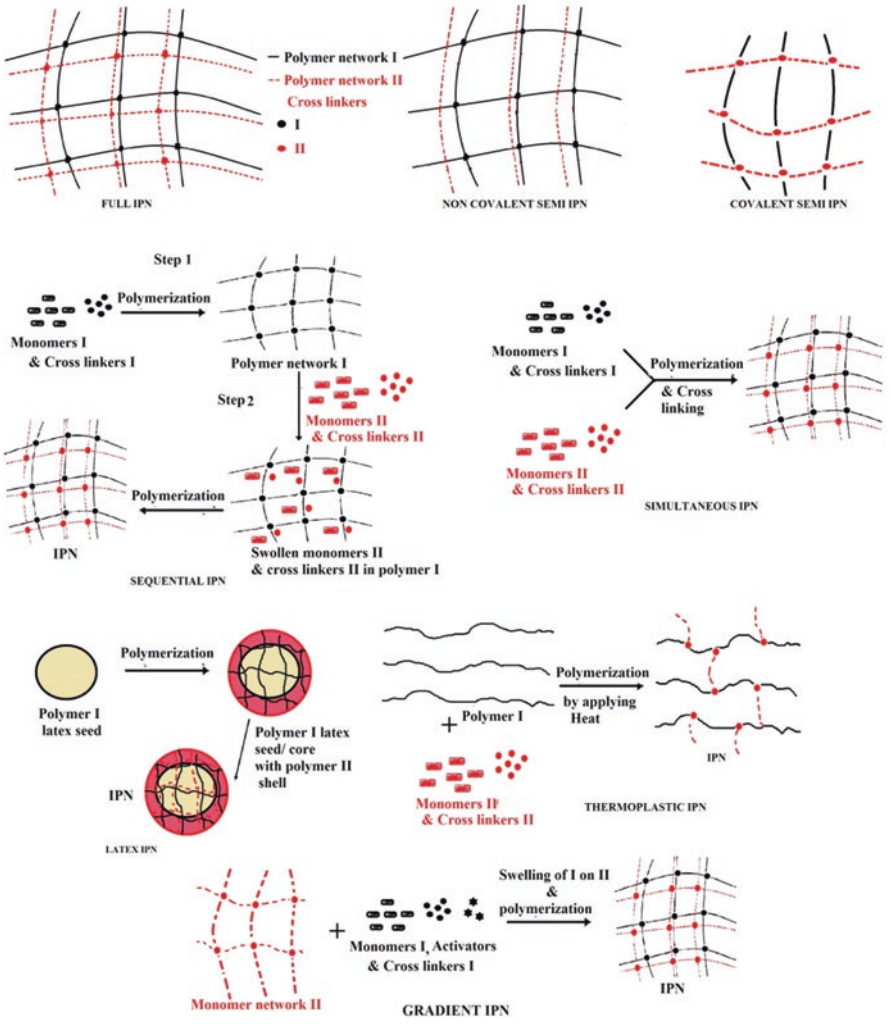

Fig. 9.2 Pictorial representation of different IPN system. The morphology of different IPN varies according to method adopted for its synthesis. This can enable sufficient encapsulation of drug molecules with the advantage of using it in the targeted drug delivery for cancer treatment

9.3.1 Casting Evaporation

The casting evaporation technique relies on the heating of polymers and casting it to produce an intercalated polymeric structure. To produce a sequential IPN gel, the polymer I and the cross-linkers I are heated to dissolve the polymer, and subsequently, polymer II and the cross-linkers II are added, heated and then cast. This will produce a cross-linked IPN system (Kosmala et al. 2000).

9.3.2 Emulsification Cross-Linking

This technique utilizes a phase separation technique, in which emulsions (w/o or o/w) are cross-linked together to form an intercalated IPN system. The w/o emulsion is produced by dispersing water-soluble polymers in aqueous solution and then mixing with an oil phase. In case of o/w emulsion, aqueous polymeric phase is mixed with the aqueous phase containing another polymer. Then they are cross-linked to produce an IPN system (Banerjee et al. 2010; Bhattacharya et al. 2013). The emulsion polymerization technique is usually preferred for preparing nano-IPN system.

9.3.3 Mini-Emulsion/Inverse Mini-Emulsion Technique

In mini-emulsion technique, hydrophobic monomeric droplets are dispersed in water (oil in water). A semi-IPN system is obtained by polymerizing and cross-linking the hydrophobic monomeric droplets (obtained by sonicating polymers with specific initiators) using cross-linkers I and by adding cross-linkers II. The second polymer is polymerized and cross-linked to form a full-IPN system. The hydrophilic monomers can be polymerized and cross-linked by inverse mini-emulsion technique. This technique follows mini-emulsification of hydrophilic monomeric droplets in hydrophobic phase (water in oil), i.e., inversion of mini-emulsification technique. Both these techniques use a high shear stress (Banerjee et al. 2010; Landfester 2006).

9.3.4 Coacervation Phase Separation

Coacervation is one of the physicochemical methods of microencapsulation technique. They can be simple or complex process. The simple coacervation process is the partial desolvation (by adding solvents or by changing temperature) of polymer in a ternary or a binary system (Gander et al. 2002). While in complex process, two oppositely charged polymers react to form a complex system (Lazko et al. 2004).

9.3.5 Multiorifice-Centrifugal Process

This method is a physicomechanical process that depends on the impact of centrifugal force. The apparatus consists of a rotating cylinder with three grooves in which the lower and the upper grooves are meant to carry the polymer molecules. The intermediate groove is the aperture through which the final film is formed by the rotation of the cylinder (Venkatesan et al. 2009).

9.3.6 Pan Coating

Pan coating is also a physicomechanical process in which the polymer solution is sprayed over the tumbled mass on the mixer. This method is suitable for making micro-IPN system (Burgess and Hickey 2007).

9.3.7 Air Suspension Coating

Air suspension coating, a physicomechanical process, consists of an air distribution plate, a nozzle, a coating chamber and a control panel. The polymer solution is sprayed from the coating chamber over the core/seed material (Das et al. 2011).

9.3.8 Spray Drying and Spray Congealing

The spray dryer consists of an atomizer, air heater, cyclone, blower, spray chamber and product collector. In this technique, the polymeric solution or the coating material is mixed with core material, and a hot stream is flown from the atomizer following solidification (Takahashi et al. 2005; Vyas and Khar 2002). In spray congealing, the polymeric solution is used as a melt.

9.4 Strategies for Drug Release Using IPN Systems for Cancer Treatment

The drug molecules bind either physically or chemically to the IPN system. They can also bind through electrostatic or through hydrophobic interactions. The drug release mechanism from the IPN system depends on the binding force. The drug release majorly occurs through:

9.4.1 Degradation-Controlled Monolithic System

The degradation-controlled drug release involves the degradation of the polymeric matrix for the controlled release of the drug molecules. In this case, the drug molecules are finely distributed on the polymeric matrix, such that there will be a slow degradation of matrix occurring for the controlled release of drug molecules. The dissolution of the matrix over time is the rate-limiting step for degradation-controlled drug release system (Von Burkersroda et al. 2002). It occurs through surface or bulk erosion. For a homogeneous bulk degradation mechanism, the drug release rate will be initially slow following a rapid release due to the bulk degradation. The system geometry does not affect the release rate and it highly depends on the degradation rate. The surface gets degraded inwardly in the surface erosion mechanism (Saralidze et al. 2010; Grassi and Grassi 2005).

The drug release rate can be given by the following equation:

$$\mathrm{Mt} / \mathrm{M}\infty = 1 - \left[\left(1 - t / t\infty\right)\right]^3$$

where

M_t = amount of drug released at time t
M_∞= amount of drug released at time of complete degradation

9.4.2 Diffusion-Controlled Monolithic System

The diffusion is the ability of a drug molecule to affect the external environment when exposed to a stimulus. It can be either a reservoir-type or a matrix-type diffusion system. The permeation of water in the polymer causes swelling of the polymeric matrix, thereby increasing the pore size of the matrix and diffusion of the drug molecules (Stevenson et al. 2012). The diffusion-controlled monolithic system involves diffusion of drug molecules with polymeric matrix degradation. The rate of drug release depends on the heterogeneous or homogeneous polymeric degradation mechanism. The reservoir type involves degradation of polymeric matrix only after the drug is diffused out (Singh et al. 2011). The diffusion rate depends on Fick's law of diffusion.

9.4.3 Erodible Poly-Agent System

In this type of mechanism, the drug molecules are bonded chemically to the matrix such that the drug molecule-polymer hydrolysis will be rapid compared to the polymer degradation. The rate-limiting step depends on the hydrolysis of drug-polymer matrix (Singh et al. 2011).

9.5 Stimuli-Responsive IPN System

The non-specific drug release can be achieved by the local drug release by diffusion and through degradation of the IPN system. In order to make it target-specific and finely tuned controlled drug release, stimuli-responsive smart drug delivery system will increase their applicability in the cancer therapy. This triggered drug release will control the rate of consistent drug release at the target site. The major stimuli that trigger the drug release include:

9.5.1 pH-Responsive Drug Release

Oral drug delivery is the most preferred non-invasive drug delivery route. However, it possesses a series of demerits such as premature drug release due to the acidic condition in the GI tract and the enzymatic degradation of the drug molecules. Therefore, pH-responsive smart drug delivery system will overcome the drawbacks to serve as an efficient cancer therapy system (Dai et al. 2008). The anionic and neutral polymers are found to possess less response to the acidic pH. The ampholyte and electrolyte polymers are found to response to the external pH changes. The cationic polymers like chitosan can exhibit a higher response to the lower acidic pH. Depending upon the isoelectric point, swelling and dissolution of the polymers, it readily responds to the acidic pH of the GI tract (Ahmed et al. 2009). Many anti-cancer drugs like doxorubicin and 5-fluorouracil are successfully synthesized as a pH-responsive smart drug delivery system for tumour cells (Qi et al. 2015).

9.5.2 Enzyme-Responsive Drug Release

The drug release can also be effectively achieved by fabricating an external enzyme-responsive smart system. The hydrogels synthesized from the polysaccharides can be used in case of any colon cancer treatment due to the active enzymes present in the GI tract. However, the polymer degradation can also cause pH fluctuations henceforth affecting the drug release activity (Jain et al. 2007; Sinha and Kumria 2001).

9.5.3 Temperature-Responsive Drug Release

The thermal-sensitive natural and synthetic polymers are found to be a valuable source for the synthesis of a smart temperature-responsive IPN drug delivery system. They involve in the transition to a more hydrophobic component from a hydrophilic one due to the temperature trigger that is also a reversible process. The IPN hydrogels can be two types based on its thermal sensitivity: upper critical solution temperature and lower critical solution temperature hydrogels (Klouda and Mikos 2008; Zhang et al. 2004a, b). Different polymers like alginate and chitosan are utilized for the thermal-responsive drug delivery system for cancer treatment (Guilherme et al. 2005). There are also dual- or multi-responsive drug release system fabricated for targeting tumour cells.

9.5.4 Electro-sensitive Drug Release

External stimuli like electrical signal can be used to trigger the drug delivery system for the target-specific action. Polyelectrolytes are widely used hydrogels for electro-sensitive drug release (Murdan 2003). On applying electric signal, the hydrogels

release active agents by the deformation of the system. The moieties that respond in terms of applied electric field are formulated within the IPN-drug complex. The complex system is implanted subcutaneously and is directed using an external electric field. The electric potential conduction patch is externally applied on the gel over the skin. In response to the applied stimulus, the carrier system delivers the active agent at the appropriate site. The major mechanism of drug release on the applied electric pulse includes diffusion, erosion due to electric pulse, de-swelling and electrophoresis of active drug molecules. The drug release rate at varying physiological states is found to be challenging for the electrostimulated drug release system (Kim et al. 2002; Liu et al. 2008).

9.6 Targeting Mechanism of IPNs on Tumour Cells

9.6.1 Active Targeting

The active targeting by the micro- or nano-IPN system involves the binding of the specific ligands to the overexpressed protein receptors on the surface of the non-dividing cells or tumour cells (Nacev et al. 2010). This targeting mechanism along with the stimuli-responsive drug release will enhance the cellular uptake of the active agents to the target site. The stabilized carrier molecules by PEGylation along with the small-molecule ligands like transferrin, growth factors, antibodies, peptides, etc. help in the active binding of the ligand molecules to the target-specific receptors (Danhier et al. 2010; Pérez-Herrero and Fernández-Medarde 2015). The direct binding of ligands to the target site prevents the off-site drug delivery such that reducing the adverse impact of the drug release to the healthy cells (Sun et al. 2014). The mechanism of active targeting of carrier molecule is shown in Fig. 9.3.

9.6.2 Passive Targeting

The passive targeting mechanism of IPN system on the tumour cells is primarily based upon the enhanced permeability and retention effect. The cancer or tumour tissues possess a leaky vasculature with irregular angiogenesis (Chrastina et al. 2011). The drug-IPN complex enters the endothelial interstitial space and accumulates on the specific cancer site, while small drug molecules can diffuse away from the accumulated target site, and the EPR effect is found to be size dependent varying with different patients (Acharya and Sahoo 2011; Lee et al. 2010).

9.7 IPN-Based Dosages for Drug Delivery Systems for Cancer Therapy

IPN, a complex of two or multiple polymers in network form (Sperling 1977, Mundargi et al. 2008), is highly an efficient carrier for delivering the cancer-curing drugs in a controlled manner that delivers patient compliance and reduces adverse

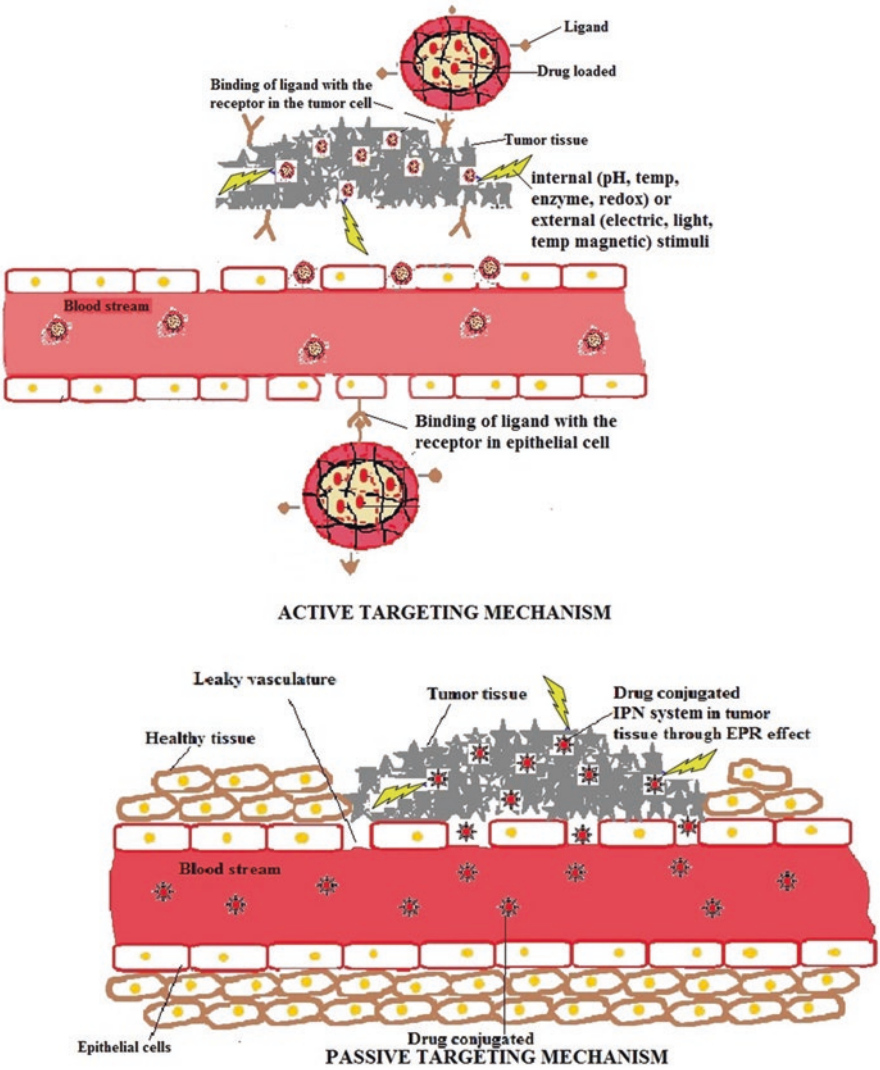

Fig. 9.3 Targeting mechanism on cancer cells. Targeting can be by either by active or passive mechanism. The active mechanism occurs by the direct binding of the ligand molecules to the specific protein in the cancer cell surface, and passive mechanism occurs by the efficient accumulation of IPN system in the tumour site by EPR effect

reactions (Liu et al. 2007). The amount of drug to be distributed at the target site is important for the successful implementation of cancer therapy. The basic designing of the IPN drug delivery system is in the form of zero-order pattern with reduced fluctuation (Jain et al. 2011).

9.7.1 Microspheres

Microspheres are a type of colloidal drug delivery system with less than 200 μm particle size. The major advantage of the microsphere-based drug delivery system is its minimized toxicity in the non-targeted cells and its augmented effectiveness (Suzuki 1994). For tumour vascular endothelial cells, microsphere is one of the selective drug delivery systems (Rajput and Agrawal 2010). It is widely used as carrier during liver transplantation or surgery (Sharma et al. 2007). By using the process of embolization, the microspheres can be incorporated into the peritumoural vessels, and 95% of the doses can be targeted. Cytotoxin-loaded microspheres for breast cancer, enteric-coated pancreatin microsphere for pancreatic cancer, radioactive microsphere, magnetic microspheres, microsphere as cancer vaccine delivery system and drug-eluting microspheres are some examples of microspherical drug delivery system (Rajput and Agrawal 2010). Chitosan-polyethylene oxide-g-acrylamide intermolecular rigid network, an IPN-based microspherical drug delivery system, is developed for the delivery of capecitabine, the antineoplastic drug for enhancing the time of drug delivery by forming a network (Agnihotri and Aminabhavi 2006).

9.7.2 Transdermal Membranes

Transdermal technology is one of the promising drug delivery system which is applied in breast cancer treatment. For the effective use of this drug delivery system, transdermal patches are engineered for targeted delivery of drugs to the cancer cells, thus avoiding the side effects of the drugs to the non-cancerous cells and minimizing the dosage of drugs. The drug is provided through the skin. The major advantages of using transdermal patches include site-specific drug delivery to the target site, providing maximum bioavailability. Transdermal patch includes a linear, compartment, adhesive, permeable membrane and a backing (Tan 2010).

9.7.3 Tablets

IPN matrix tablets can be prepared by wet granulation method or covalent cross-linking method (Mandal et al. 2010) and compressed to tablets for the sustained release of anticancer drugs. The release of drug is maintained by the swelling capacity of the IPN matrix, and the drug release is prolonged for a long time (Vineet et al. 2012).

9.7.4 Capsules

IPN-reinforced capsules can be prepared using the micron-sized colloidosomes of polymethyl methacrylate-co-divinyl benzene microgels which leads to the

formation of structures with a raspberry core-shell morphology (Kweon et al. 2008). It was found that the cell proliferation was greatly decreased when the anticancer drugs such as 5-Fu and paclitaxel are encapsulated with additional advantage of sustainable release and free drugs causing side effects are not available (Iqbal et al. 2017). Also, a study indicates that the nucleolin aptamer-capped fluorescein-loaded mesoporous silica nanocapsules specifically target the cancerous cells (Frank et al. 2013).

9.7.5 Nanoparticles

Huge-potential anticancer drugs can be released in a controlled manner by using the IPN device-thermally active nanoshells (Mayet et al. 2014). Drugs that find difficulty to cross the blood-brain barriers can be crossed easily with the help of nanoparticles and can deliver the anticancer drugs in tumour sites (Koziara et al. 2004). In a study, it was found that the lipid cationic nanoparticle coupled with integrin-targeted ligand induces apoptosis in the tumour cells and shows reversion of the metastatic tumours (Hood et al. 2002). The most important features of nanoparticles-mediated IPN drug delivery system are its bioavailability and drug-targeting capacity (Dubin 2004; Dimendra et al. 2012).

9.7.6 Hydrogels

There exists a lot of disadvantages with the synthetic polymers, and so natural polymers such as hyaluronic acid and collagen are widely applied for the sustained release of anticancer drugs (Mayet et al. 2014). In a study, anticancer drugs such as 5-fluorouracil, bleomycin A2 and mitomycin C are incorporated into the hydrogel matrix (collagen-poly (HEMA) hydrogel) for controlled-release formulation (Jeyanthi and Rao 1990). Also, hydrogel-based drug delivery system increases the gene therapy and chemotherapy efficacy by maximizing the half-life of the anticancer drug and inducing sustained release of drugs. In addition to this, hydrogels are used as a substitute for tissues in tumour microenvironment reconstruction (Mohammadmajid et al. 2017).

9.7.7 Sheet

Sheeting is one of the potential method for the IPN-based drug delivery system (Jain et al. 2011). For enhanced anticancer drug delivery, ruthenium complex-loaded monolayer-layered double-hydroxide ultra-thin nanosheets are used which act as theranostic agent for light-switchable cancer imaging and increase the luminescence lifetime for photodynamic therapy (Shanyue et al. 2018).

9.7.8 Sponges

Nanosponges are porous, colloidal, 1 micrometer-sized tiny meshlike carriers that can be used to incorporate both hydrophilic and lipophilic drugs with improved anticancer drug bioavailability and solubility at the targeted site. Various factors such as temperature, degree of substitution, polymer used, type of drug and the method of preparation affect the formulation of nanosponges. The methods used to prepare nanosponges include ultrasound-assisted synthesis, emulsion solvent diffusion method and solvent method. Cyclodextrin-based nanosponge is one of the best available anticancer drug delivery methods (Tukaram et al. 2017). In a study, sponges are developed using freeze-drying alginate-oxidized nanocellulose with a cross-linker in which the addition of novel carboxyl group leads to the formation of mechanically stable alginate-based sponge structure. Further, mechanical strength was induced by oxidized cellulose nanocrystals. The advantages of sponges include increased compression strength, ultrahigh porosity, concomitant water absorption and retention (Babu et al. 2013).

9.7.9 Films

Anticancer drug delivery using nanofilm structures can hold proteins, dendrimers or nanoparticles with accurate controlling capacity. Nanofilm is one of the promising techniques in which the anticancer drug with DNA is synthesized and arranged with peptide by layer-by-layer deposition method (Younghyun et al. 2014). Radical solution polymerization is another technique used to prepare full-IPN film. The concentration of polymeric material and extent of cross-linking are the two factors to be considered while preparing a film (Rodkate et al. 2010).

9.7.10 Calcifiable Matrix System

Elastin and collagen are the basic components of the connective tissues. These basic components along with IPN matrix can be used as a calcifiable matrix system for effective drug delivery system in bone cancerous tissues and tissue calcification (Meaney 1995; Stolzoff and Webster 2016). The clinical fate and therapeutic efficiency of the biomaterials are affected by the calcification (Schoen 1992) which depends on various chemical factors related to the cells (Wada et al. 1999).

9.8 IPN-Induced Cancer Therapeutics

Different anticancer drugs complexed with the IPN are widely investigated for the targeted and controlled drug delivery system. Some of the anticancer drugs are given below:

9.8.1 5-Fluorouracil

5-Fluorouracil is the broadly studied anticancer drug for pancreatic, breast and gastric cancer treatment (Longley et al. 2003; Dickson and Cunningham 2004). For example, the microsphere of IPN hydrogel (pH and temperature sensitive) containing N-isopropylacrylamide and sodium alginate is analyzed for the drug release rate and gives 90% 5-fluorouracil release within 12 h (Reddy et al. 2008). The hybrid multifunctional and photothermal-responsive Au in IPN-PNIPAAm nanosystem is found to possess biocompatibility even in the low concentration employed for the cellular imaging purposes (Zhao et al. 2011). It is also found that the natural polymeric system possesses higher swelling and drug-releasing properties with higher pH-responsive drug release (PAsp and starch containing semi-IPN system in colon 5-FU delivery) (Liu et al. 2011).

9.8.2 DOX Hydrochloride

DOX hydrochloride generally acts by the intercalation of DNA. Hence, it is used majorly in soft tissue sarcoma, hematological malignancy and carcinoma treatment. There are only fewer reports found in the DOX delivery by the IPN system with reduced toxic effect. One of the examples for IPN-based DOX release is the hydrogel containing hydrophilic gelatin, and hydrophobic divinyl ester is found to exhibit 85% drug release rate in 6–10 days with a lesser burst release rate (Brayfield 2014; Mohamed et al. 2011) (Table 9.1).

Table 9.1 IPN-based therapeutic drugs for cancer treatment. Different anticancer drugs are selectively bound to the IPN systems like semi and full IPN that produced sufficient drug release and action at the target site

Drug	IPN system	Synthesis method
5-Fluorouracil	IPN nanogels	In situ polymerization and cross-linking (Zhao et al. 2011)
	Semi-IPN hydrogels	Free radical polymerization (Rao et al. 2008)
	IPN hydrogels	Sequential polymerization (Zhang et al. 2004a, b)
	Semi-IPN microspheres	w/o emulsification (Sekhar et al. 2011)
Doxorubicin hydrochloride	IPN pluronic P105 micelles	Ultrasonic (Husseini et al. 2002)
	IPN hydrogels	Emulsion cross-linking (Mohamed et al. 2011)
	Semi-IPN hydrogels	Free radical polymerization (Jaiswal et al. 2013)
Capecitabine	Semi-IPN microspheres	Emulsion cross-linking and free radical (Agnihotri and Aminabhavi 2006)
Oxaliplatin	Semi-IPN microspheres	Direct polymerization (Chen et al. 2008)

9.8.3 Capecitabine

Capecitabine is a prodrug which on administration will get converted into 5-FU. This drug is widely utilized for cancer treatments such as breast and colorectal metastatic cancer. This drug possess serious side effects like nausea, cardiac damage, dermatitis, vomiting, etc. Hence, only 2.5 g/m^2 is recommended per day. An IPN system of 82–168 μm hydrogel microsphere is prepared using glutaraldehyde cross-linked poly(ethylene oxide-g-acrylamide). Chitosan gives 74% drug release at the intestinal pH and at 1.2 pH (Agnihotri and Aminabhavi 2004; Agnihotri and Aminabhavi 2006).

9.8.4 Oxaliplatin

The hydrophilic oxaliplatin antitumour drug with half-life approximately 10–25 mins is used for the colorectal cancer treatment in the advanced state. A higher antitumour activity is found by a pH and thermal-sensitive semi-IPN nanosystem with 70% within 48 h of administration (Chen et al. 2008).

9.9 Biomedical Applications of IPN-Based Drug Delivery System

IPN, a widely used biomaterial, is used in the controlled-release drug delivery system. IPN-based drug delivery system is basically designed to transport drugs with minimum fluctuation, with specific time period and at a predetermined rate. The existence of various biological and physical characteristics such as biodegradability, excellent swelling capacity, enhanced solubility of hydrophobic drugs, weak antigenicity, imparting drug stability in the formulations, biocompatibility and drug targeting increases the use of IPN drug delivery system for various biomedical applications that include bioengineered tissues, cartilage scaffolds, bone substitutes, cancer therapy, etc. (Jain et al. 2011).

9.9.1 Bioengineered Tissue

Replacement of tissues which are impaired can be executed with the principles of tissue engineering, an emerging field. IPN-related materials which are purely natural, biodegradable, mechanically stable and biocompatible (George et al. 2008) are used as biomaterials for the development of bioengineered tissues (Chen et al. 2002). Such type of biomaterials favours cell proliferation and cell adherence. Collagen is a widely used biomaterial, and so it is used in generating bioengineered tissues such as blood vessels, heart valves and ligaments (Auger et al. 1998). The hemostatic feature of collagen enhances the blood-clotting mechanism and in turn can be used in tissue repairing process. In bone tissue-engineering process,

collagen-hydroxyapatite composites which are highly porous scaffolds are used immensely. The collagen-hydroxyapatite composites are biocompatible in nature, and the scaffold's histocompatibility is not affected by hydroxyapatite (Liu et al. 2003). For load-bearing artificial tissues, hydrogels synthesized using double-network techniques are used (Yasuda et al. 2005) which exhibit the property of low-friction resistance and biocompatibility and one of the best scaffolds for the cells cultured (Azuma et al. 2007). A tough scaffold is necessary for the cell culture for implanting the engineered tissues within the body that enhances the repairing and regeneration process in living organs (Yasuda et al. 2005). While introducing poly (N,N0-dimethylacrylamide) [PDMAAm] to the body, it leads to the automatic repairing process in cartilage with signs of no inflammation (Hago and Li 2013). The anisotropic mechanical property exhibited by the liquid crystalline DN gel and cellulose-based DN gel is essential for the anisotropic functioning in the human system (Imabuchi et al. 2011). The calcification of implantable bioprosthetic heart valve can be induced by using collagen and elastin as controlled cardiovascular drug delivery device (Park et al. 2000).

9.9.2 Bone Substitutes

In human system, bone is one of the most powerful regenerating tissue that gains wide importance in the field of tissue engineering. Most of the orthopaedic problems can be treated using the composite form of collagen with other polymers. Acquired and congenital orthopaedic defects can be cured with combined bone graft material made up of demineralized bone collagen and porous hydroxyapatite (Takaoka et al. 1988). The resultant osteoinductive material, the combined form of grafted demineralized bone collagen and hydroxyapatite, is used as a bone substitute and also for expressing biological activity by using the combined IPN as a carrier of bone morphogenetic protein (BMP). The bone is also regenerated using the enzymatically degradable IPN (edIPN), which is non-fouling in nature and made up of poly(AAm-co-EG/AAC) that helps in introducing the cell signalling domain (Ho et al. 2007). Peptide-modified IPNs of poly(acrylamide-co-ethylene glycol/acrylic acid) functionalized with an Arg-Gly-Asp (RGD) containing 15 amino acid peptides are used in the regeneration of bone in the peri-implant region (Barber et al. 2007). Water-swellable IPN having both ionic polymer and thermoplastic polymer is used for repairing natural cartilage in the joints (Gupta and Ravi-Kumar 2000).

9.9.3 Cartilage Scaffolds

Using freeze-drying process, semi-IPN scaffolds made up of alginate and chitosan are prepared with the cross-linking agent $CaCl_2$, and this scaffold plays an important role in the cartilage tissue engineering (Tigli and Gumusderelioglu 2009). The IPN PVA/GE hydrogels, prepared by freeze-thawing method with varied mechanical and physical properties such as the swelling property and absorbing capacity, are

used for exudative wounds, and it shows the importance of scaffolds in tissue engineering (Rani et al. 2010).

9.9.4 Cancer Treatment

IPN-based nanoparticles are used in treating various stages of cancer; more specifically, IPN nanoshells are introduced for the leaky vasculature of cancer. For example, PEG polymeric nanoparticle is used for treating neoplasms since the PEGylated nanoparticles get stacked in the tumour cells (Auger et al. 1998). IPN in the form of chitosan and collagen as biodegradable polymer scaffold is used as an alternative substrate for in vitro culture of human epidermoid carcinoma cells (HEp-2). Here, glutaraldehyde acts as the cross-linking agent. The cultured HEp-2 cell is used for testing anticancerous drugs (Shanmugasundaram et al. 2001; Atyabi et al. 2008).

9.10 IPN System for Different Tumour Cells

Conventional chemotherapy is not a promising field in destroying the tumour cells since it has side effects. Drug targeting can be achieved using different types of IPN systems for varied tumour cells.

9.10.1 Lung Cancer

Paclitaxel-loaded PLGA microspheres, camptothecin-loaded PEGylated microspheres and nanosponges are some examples of IPN-based drug delivery system for curing lung cancer. No toxicity is associated with the delivery of paclitaxel using the PLGA microspheres (Rajput and Agrawal 2010). It is found that human serum albumin and gelatin constitute the biodegradable nanoparticle that acts as a good pulmonary drug carrier (Dimendra et al. 2012). Also, nanosponges are applied in delivering the anticancer drug to the targeted site in the lungs (Tukaram 2017).

9.10.2 Breast Cancer

The occurrence statistics of breast cancer is high among women. Adriamycin-loaded albumin microspheres, cytotoxin-loaded microspheres, transdermal patches, mitoxantrone-loaded albumin microspheres, oligonucleotides combined with nanoliposomes and polylactic-acid-encapsulated microspheres with IL-12, TNF-alpha and granulocyte macrophage-colony stimulating factor are some examples of IPN-based drug delivery system for breast tumour regression. When cytotoxin-loaded microspheres are administered intra-arterially, the conjugate is carried to the capillary bed and the drug is delivered at the targeted site. Mitoxantrone-loaded albumin microspheres greatly minimize the toxic effect of the drug (Rajput and Agrawal

2010). Additionally, transdermal patches deliver the drug to the cancerous sites by undergoing some modifications for drug penetration with lesser side effects (Tan 2010). Recently, it is found that oligonucleotides combined with nanoliposomes target the cancer cells and deliver the nucleic acids, thus stopping the generation of alpha folate receptor (Dimendra et al. 2012).

9.10.3 Liver Cancer

Phosphorus-32 microspheres, poly-lactide-co-glycolide microspheres, Y-90 microsphere, degradable starch microspheres with iodized oil and SIR-Spheres ^{99m}Tc-labelled microspheres can be cited as examples of IPN-based drug delivery system for targeting hepatocellular carcinoma cells. Y-90 microspheres loaded with oxaliplatin, fluorouracil and leucovorin are studied in hepatocellular carcinoma cells. ^{99m}Tc-labelled microspheres are widely applied in the field of neoplastic lesions imaging, and SIR-Spheres are used for treating metastatic liver tumours (Rajput and Agrawal 2010).

9.10.4 Pancreatic Cancer

Enteric-coated pancreatin microspheres, pH-sensitive histidylated oligolysine with the drug liposome complex and antisense technology are some of the IPN-based drug delivery system for pancreatic cancer treatment. Enteric-coated pancreatin microspheres are used to treat the pancreatic cancer that reduce the occlusion of the pancreatic duct and weight loss (Rajput and Agrawal 2010). Antisense technology (use of oligonucleotides) is used for treating pancreatic cancer, and the pH-sensitive histidylated oligolysine with the drug liposome complex enhances the drug delivery to pancreatic cells without inducing the toxic effect (Dimendra et al. 2012).

9.10.5 Bladder Cancer

Chlorin e6 loaded in polystyrene microspheres and poly paclitaxel microspheres are two examples for the IPN-based drug delivery system for bladder cancer therapy. Chlorin e6 loaded in polystyrene microspheres provides the intracellular localization site to destroy the carcinoma cells by photodynamic process, and poly paclitaxel microsphere is a potential therapy for superficial bladder cancer (Rajput and Agrawal 2010).

9.10.6 Brain Cancer

Brain consists of a blood-brain barrier that stacks the entry of foreign particles to the brain cells, and this phenomenon acts as a blocking process for the entry of

anticancer drugs. To overcome this blood-brain barrier, drugs are loaded with IPN system. Poly(methylidene malonate) loaded with 5-fluorouracil microsphere shows a sustained drug delivery system, and so it is widely used to treat malignant tumour (Rajput and Agrawal 2010). Poly(valerolactone-allylvalerolactone) loaded with temozolomide acts as a nanosponge drug delivery system (Tukaram 2017).

9.10.7 Colorectal Cancer

Methotrexate-loaded guar gum microspheres, Eudragit P-4135F-based microspheres and poly(D,L-lactic-co-glycolic acid) microspheres with interleukin-12 gene are IPN-based drug delivery system for targeting the colorectal cancerous cells. Guar gum microspheres have the ability to carry the drug and control its release when it reaches the colon, and Eudragit P-4135F-based microsphere is a pH-dependent colon drug delivery system (Rajput and Agrawal 2010).

9.11 Challenges in Cancer Treatment Using IPN System

A novel drug delivery system is highly applicable in the cancer diagnosis and treatment. Cancer treatment lays many difficulties in the proper fabrication of the effective drug delivery system. The cancer cells are found to have a defense mechanism through altered targets, elevated drug metabolism, efflux pump overexpression or self-repairing capacity (Gottesman 2002). The challenges associated with the IPN system in cancer treatment include inability of the polymeric matrix to effectively release the active components at the target site, absence of cohesiveness, reduced-phase molecular interactions (due to less efficient interfaces), heterogeneity, kinetic profiles of interpenetrated polymers and various other parameters in process like operating condition, reactor type and the mechanism behind the IPN formation (Somya et al. 2015).

9.12 Conclusion and Future Perspectives

Thus, the propensity of the IPN system has made it to be an effective agent for the controlled drug delivery system for cancer diagnosis and treatment. Though it has attained a remarkable position in the biomedical field, advanced work has to be carried out in order to bring them to the large-scale in vivo cancer treatment from preclinical and in vitro tests. The standardization of stimuli-responsive smart drug delivery IPN system is necessary to enhance the properties to readily serve as promising drug carrier for the cancer treatment. The production of novel polymers and the cross-linkers with Good Manufacturing Practice are also essential to pave an everlasting position for the IPN system in the drug delivery field.

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