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Review Article

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CHITOSAN-BASED INTERPENETRATING POLYMER NETWORK (IPN) HYDROGELS: A POTENTIAL MULTICOMPONENT ORAL DRUG DELIVERY VEHICLE

Preeti K Suresh*, Satish K Suryawani and Divya Dewangan

University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India.

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ABSTRACT

Multicomponent drug delivery systems have found several potential diagnostic and therapeutic applications. Among these the interpenetrating polymeric network (IPN) has emerged as one of the most useful novel biomaterial, which is entanglement of polymer networks with at least one network synthesized and/or cross-linked in the presence of the other. The development of IPN is attractive because they provide free volume space for the easy encapsulation of drugs in the three-dimensional network structure which are obtained by cross-linking of two or more polymer network. This review focuses on the IPN hydrogels based on chitosan for oral drug delivery applications. Chitosan is a natural, biodegradable, nontoxic, mucoadhesive and biocompatible polymer and has found diverse pharmaceutical applications. Chitosan based IPN hydrogels have garnered immense attention as a vehicle for oral drug delivery. The suitability of chitosan based IPN hydrogels as potential oral delivery vehicle stems from their capability of imbibing large amount of body fluid without solubilisation and potential for encapsulation of large amount of drugs, adaptability to be combined with specific responsive polymer(s). This review also summarizes IPN and various multicomponent polymeric materials for developing drug delivery vehicle.

Keywords: Double network, biodegradable, biocompatible, biomaterial, multicomponent.

INTRODUCTION

With the discovery and synthesis of large number of new therapeutic moieties, a need for development of special vehicle for their delivery has also come into view. New systems are needed to deliver genetically engineered pharmaceuticals, *viz.* protein and peptides and to improve the therapeutic efficacy and safety of drugs administered by conventional method. In the recent years, considerable attention has been focused on development of new drug delivery systems.[1]

The oral route of drug delivery remains the preferred and most patient-convenient means of drug administration. Oral administration presents a series of attractive advantages over other routes of drug delivery. These advantages are particularly relevant for the treatment of pediatric patient and include the avoidance of pain and discomfort associated with injection and the elimination of possible infections caused by inappropriate use or reuse of syringe. Moreover, oral formulations are less expensive to produce, because they do not need to be manufactured under sterile conditions.[2] But the major problem is that oral route is burdened with physiological variability which makes drugs ineffective for the treatment of various diseases.[3] Over the past 20 years, advances in oral modified-release technologies have been largely driven by development of improved biocompatible and biodegradable polymeric materials for controlling release rates.

In the recent years interpenetrating polymeric network (IPN) hydrogels have generated considerable interest as a biomaterial vehicle for drug delivery.[4] IPN hydrogels encompasses the advantages of both the conventional dosage forms as well as novel drug delivery systems by offering a biocompatible, convenient and stable drug delivery system for molecules as small as non-steroidal anti-inflammatory drugs or as large as proteins and peptides.

Hydrogels are the three-dimensional network polymers that are known to swell in aqueous solutions. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility.[5] Polymeric hydrogels are of considerable interest as biomaterials in drug delivery research. IPNs are defined as a combination of two polymers in network form, at least one of which is synthesized and/or cross-linked in the immediate presence of the other.[6,7]

INTERPENETRATING POLYMERIC NETWORK (IPN)

IPNs are unique “alloys” of cross-linked polymers in which at least one network is synthesized and/or cross-linked in the presence of the other.[8] IPNs are also known as entanglements of polymer networks that are ideally held together only by permanent topological interactions.[9] The inter-network entanglements are permanent because of chemical cross-linking and cannot be separated. Many

***Corresponding Author:**
Preeti K Suresh
University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur-492 010, Chhattisgarh, India.
Contact no:- +91-9827938427
Email: preeti_venugopalan@yahoo.co.in, suresh.preeti@gmail.com

researchers suggested that IPN formation enable the enhancement of performance of hydrogels.

Generally IPNs are created for the purpose of combining individual properties of two or more polymers. In some cases, entirely new properties are exhibited by the IPN that are not observed in either of the two single networks alone.[10] The development of interpenetrating network polymers is attractive because IPNs provide free volume space for the easy encapsulation of drugs in the three-dimensional network structure which are obtained by cross-linking of two or more polymer network.[11] Various properties of IPNs such as porosity, bio-adhesiveness, elasticity, swelling and stimuli-responsive behavior can be controlled by the appropriate choice of the network-forming polymers and suitable cross-linking agent and its proportion.[12,13]

IPN can be prepared by using various matrices such as poly urethane, poly butadiene, methacrylic acid, L-lysine, glutamic acid, poly vinyl alcohol, carboxymethyl cellulose, poly acrylic acid, gelatin , poly vinyl pyrrolidone, alginate, dextran, xanthane, guar gum, chitosan, polyethylene glycol etc. for various applications.[3,11,14-21]

These biocompatible, nontoxic and biodegradable polymers are now acquiring unique place for biomedical application for various purposes such as cartilage scaffolds, biological tissue graft, tissue engineering, wound dressing and for drug delivery.[22-24]

TYPES OF IPNS

There are primarily two classification schemes used to describe IPNs viz., by synthesis and by structure.[25]

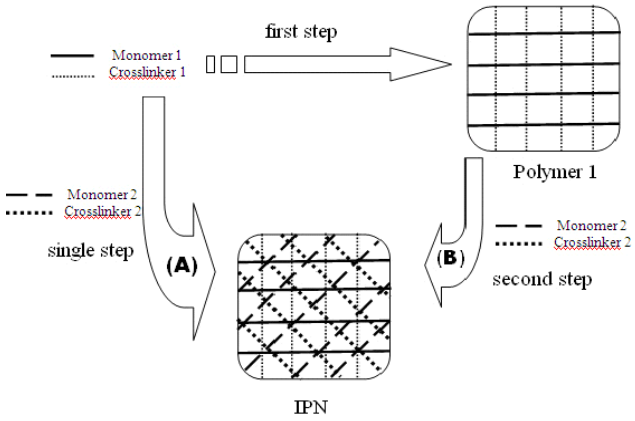
By synthesis

- ***Simultaneous interpenetrating networks (SINs):*** Two different combination of monomers and/or prepolymer plus the cross-linkers and initiators are mixed, followed by simultaneous polymerization via non-interfering reactions (Figure **1a**). Both combinations of monomer and/or prepolymers form two different intercalated networks to make the IPN. Interference is minimized if one of the polymerization processes involves chain polymerization while the other involves step polymerization kinetics.[5, 14]
- ***Sequential interpenetrating networks:*** In this class IPN is synthesized from mixture of different combination of monomer and/or prepolymer in sequential mode. Initially monomer 1 is polymerized with cross-linker 1 to produce a network. Subsequently, monomer 2 along with cross-linker 2 is swollen in and then polymerized in a sequential mode to make the IPN (Figure **1b**).

By structure

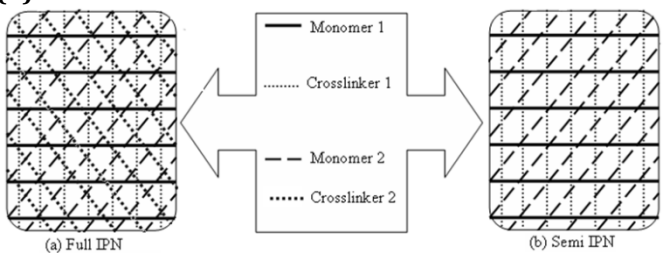
- ***Full IPNs:*** They comprise of two or more networks that are ideally juxtaposed, which generate many entanglements and interactions between the networks (Figure **2a**).[26]
- ***Homo-IPNs***: These IPNs are a special type of full-IPN, where the two polymers used in the networks are same or identical.
- ***Semi IPNs***: In these IPNs only one component of the assembly is cross linked to form network and other component is present in a linear (non-crosslinked) form (Figure **2b**).[27]
- ***Latex IPNs:*** These IPNs are prepared in the form of latex which have a core and shell structure. The polymers are synthesized by emulsion polymerization of monomer 2 together with the cross-linker and activator in the original seed latex of cross-linked polymer 1. The morphology of the IPN depends upon how the IPN components are polymerized.[5]

Figure 1. Schematic diagram for the synthesis of: (A) Simultaneous IPN and (B) Sequential IPN



- ***Gradient IPNs:*** In this case, a film can be made with polymer network 1 predominantly on one surface and polymer network 2 on the other surface, with a composition gradient existing throughout the interior.[5]
- ***Thermoplastic IPNs:*** These materials contain physical cross-links rather than chemical cross-links (like ionic and hydrogen bond). As such they are hybrids between polymer blends and IPNs. Such cross-links may utilize block copolymers, ionomers, and/or semicrystalline polymers. Being thermoplastic, they flow at elevated temperatures.[28]

Figure 2. Schematic representation of: (a) Full IPN and (b) Semi IPN



CHARACTERISTIC FEATURES OF IPNS:

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

INTERPENETRATING POLYMER NETWORK MATRICES

Some of the applications of different types of natural and synthetic IPN matrices are presented in Tables **1** and **2**. The interpenetrating polymer matrices have specific properties which can be utilized for various applications. Natural polymers have biocompatible, biodegradable, non-immunogenic and nontoxic properties making them suitable candidates for biomedical applications. Chitosan is a derived polysaccharide polymeric material found abundantly in nature that is amenable to easy IPN preparation and in the recent years it has rightly generated great interest as a polymeric vehicle for drug delivery.

Table 1. Types of natural IPN matrices

Matrices	Application(s)	Reference(s)
Cellulose derivatives	Hydrogel for controlled release of ciprofloxacin	17
Chitosan and derivatives	Oral delivery of insulin	20
Dextran	Controlled release of theophylline	3
Egg albumin	Controlled release of cefadroxil	11
Gelatin	Controlled release of cefadroxil, hydrogels for wound healing, thermosensitive hydrogel	11, 62, 63
Guar gum	Enzyme sensitive hydrogel	64
Poly (L-lysine)	Hydrogel for protein delivery	15
Sodium alginate	Beads for controlled release of cefadroxil	11

Table 2. Matrices for various types of synthetic IPN matrices

Matrice(s)	Application(s)	Reference(s)
Acrylamide	Controlled release of theophylline	3
Acrylic acid	Corneal epithelial wound healing, Electrical responsive hydrogel	18, 73
N-isopropylacrylamide	Thermosensitive hydrogel	13, 63, 68
Poly(2-ethyl-2-oxazoline)	Thermosensitive hydrogel	71
poly(2-hydroxyethyl methacrylate)	Contact lenses, wound dressing	69, 70
Poly(caprolactone)	Tissue engineering scaffolds	22
Poly(styrene)	Tissue engineering scaffolds	22
Poly(vinyl alcohol)	For controlled release, immobilization of enzymes	16, 67
Poly(vinylpyrrolidone)	Adhesive film	66
Polydimethylsiloxane	As elastomer	72
Polyethylene glycol and derivatives	For drug delivery, wound healing, pH and temperature sensitive film	21, 62, 65
Polyurethane	Prosthetic teeth, controlled drug delivery	14

CHITOSAN AS IPN COMPONENT

Sources

Chitosan is a polysaccharide that is obtained by alkaline deacetylation of a naturally occurring polysaccharide, chitin.[29] Chitin occurs abundantly in nature as ordered crystalline microfibrils forming structural components in the exoskeleton of arthropods or in the cell walls of fungi and yeast.[30,31] Production of chitosan from these sources is inexpensive and easy.

Chemical structure

Chitosan is a linear co-polymer polysaccharide consisting of β (1–4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D-glucosamine) units (Figure **3**).[31,32] Chemically chitosan is poly[β-(1–4)-2-amino-2-deoxy-D-glucopyranose]. It is an interesting polysaccharide primarily due to the presence of the amino functionality, which could be suitably modified to impart desired properties and distinctive biological functions including solubility and bioadhesivity.[33]

Properties of Chitosan

Properties of chitosan depends on a number of parameters such as the molecular weight, degree of deacetylation, sequence of the amino group (D-glucosamine residues) and the acetamido groups (N-acetyl-D-glucosamine) and the purity of the product. The properties of commercial chitosan have been summarized in Table **3**.[31]

Figure 3. Structure of chitosan

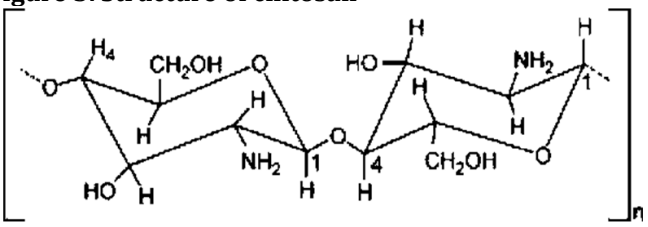


Table 3. General properties of commercial Chitosan

Parameter	Value
Molecular weight	10- 10,000 kDa
Viscosity of 1% solution in 1% acetic acid	200- 2000 cps
Moisture content	6-7%
Degree of deacetylation	60-95%
Solubility	Sparingly soluble in water, soluble in acidic solutions, insoluble in ethanol and most organic solvents

Chitosan is metabolized by certain human enzymes, especially lysozyme, and is considered biodegradable.[34] It is also biocompatible, non-immunogenic, non-carcinogenic, nontoxic and mucoadhesive polymer, which makes it a suitable candidate for biomedical applications, such as wound management, tissue engineering and drug delivery vehicle.[30,35-39] Chitosan also shows permeation enhancer properties and it is able to enhance the paracellular route of absorption, which is important for the transport of hydrophilic compounds such as therapeutic peptides and antisense oligonucleotides across the membrane.[40-42]

Chitosan has generated considerable interest as a bioadhesive material. The mucoadhesive properties of chitosan have been illustrated by its ability to adhere to porcine gastric mucosa in vitro, and hence it could be useful for in site-specific drug delivery. Important mechanism of action was suggested to be ionic interactions between positively charged amino groups in chitosan and the negatively charged mucus gel layer in addition to adhesion by hydration. The interactions are strong at acidic and slightly acidic pH levels, at which the charge density of chitosan is high. Increase in molecular weight of chitosan results in stronger adhesion.[43]

Chitosan also displays additional biological properties viz., regenerative effect on connective gum tissue and accelerates formation of osteoblast. It is also hemostatic, fungistatic, spermicidal, antitumor, anticholesteremic and immunoadjuvant.[44]

Chitosan hydrogel preparation

The preparation of chitosan hydrogel has been reviewed by Bhattarai *et al*, 2010.[45]

By physical association networks

- *Ionic complexes or ion gelation:* Cationic amine group present in chitosan form ionic complexes with anionic molecule (tripolyphosphate) and metal molecules such as Pt(II), Pd(II), Mo(VI).[46, 37]
- *Polyelectrolyte complexes:* In this method instead of small metal ions, large macromolecule which have anionic group bind cationic amine group of chitosan to form polyelectrolyte complexes such as carboxymethyl cellulose, alginate, chondroitin sulfate, hyaluronic acid, or heparin, pectin, dextran sulfate, xanthan, gelatin,

albumin, fibroin, keratin, and collagen, polyacrylic acid.[47,48]

- *Physical mixture and secondary bonding:* Hydrogels can be formed by polymer blends between chitosan and other water-soluble nonionic polymers, such as PVA and polyethyleimine. Hydrogels are formed by physical interaction between two chains in network form.
- *Thermoreversible hydrogel and hydrophobic associations:* Hydrogels prepared by aggregation of chitosan-based co-polymers or by neutralization with polyol salts show promising thermoreversible gelation properties in aqueous media.

By cross-linked networks

- *Chemical cross-linking:* Chitosan hydrogels can be prepared by the use of various cross-linkers such as glutaraldehyde, formaldehyde, genipin, diglycidyl ether, diisocyanate, diethyl squarate, phloretic acid, etc. [49-51] Cross-linked polymers form a network which is stable and swell in aqueous fluid to form hydrogel.
- *Interpenetrating polymer networks:* IPNs also use cross-linker to form hydrogels but instead of single network, more than two networks of different polymers are used. Both networks physically entangle to each other but it may possible to crosslink single network (semi IPNs) or both networks (full IPNs).[4,23,24]

CHITOSAN BASED IPN HYDROGEL

A variety of synthetic and natural polymers have been used for preparing IPN hydrogel as drug carriers, which are summarized in Tables **4** and **5**. Drug delivery systems have capitalized on their wide-ranging hydrophobic and hydrophilic components, and their polymer–polymer, polymer–drug, polymer–solvent, or polymer–physiological medium interactions.[45]

Table 4. Chitosan based semi-interpenetrating polymer networks as drug delivery vehicle

Additional polymers	Cross-linkers	Biomedical applications	References
Alanine	GA	Oral controlled release of chlorpheniramine	74
Alginate	GA	Oral controlled release of drug	11
Dextran-g-acryl amide	GA	Oral controlled release of theophylline	3
Glutamic acid	GA	Beads for controlled release of chlorpheniramine	74
Glutamic acid, Glycine	GA	Oral controlled release of chlorpheniramine	75
Glycine	GA	Oral controlled release of chlorpheniramine	76
Hydroxyl ethyl cellulose	GA	Oral controlled release of isoniazide	77
Methyl cellulose	GA	Oral controlled release of theophylline	4
N,N-dimethyl acrylamide	GA	Oral controlled release of chlorthiazide	55
Polaxamer 407	UV	Sponge for wound dressing	23
Poly(aniline)	GA	Biosensor film	78
Poly(dimethylsiloxane), Polyethylene glycol	HAD	Bioadhesive Film	79
Poly(ethylene oxide)-g-acrylamide	GA	Oral controlled release of capecitabine	80
Poly(N-isopropylacrylamide)	MBA	Oral pH, temperature sensitive release of cAMP	72
Polyethylene glycol	GA	Oral controlled release of isoniazide	81
Polyvinyl pyrrolidone	GA	Controlled release of amoxicilline	56

GA – glutaraldehyde, UV – ultraviolet radiation, MBA – N,N'methylenebisacrylamide, HAD – hexamethylene-1,6-di-(aminocarboxysulfonate), cAMP – cyclic adenosine 30, 50-monophosphate

Table 5. Chitosan based full-interpenetrating polymer networks as drug delivery vehicle

Additional polymer(s)	Cross-linker(s)	Biomedical application(s)	Reference(s)
Acryl amide-g-poly (vinyl alcohol)	CAN and GA	Oral controlled release of cefadroxil	53
Gelatin	GA	Microsphere for nasal delivery of propranol HCl	82
Poly(acrylic acid-co-acrylamide)	MBA	Superporous hydrogel for oral delivery of insulin	20
Poly(N-vinylpyrrolidone) and poly(acrylic acid)	MBA and GA	Oral controlled release of amoxicilline	12

GA – glutaraldehyde, MBA – N,N'-methylenebisacrylamide, CAN – ceric ammonium nitrate

To exploit attractive features of chitosan, a number of IPN hydrogels have been developed for various applications. Recently chitosan based hydrogel as oral delivery vehicle for drugs, enzymes and other biological molecules have been potentially targeted in advanced drug delivery field.

The suitability of chitosan based IPN hydrogels as potential oral delivery vehicle can be attributed to the following:

- Capable of imbibing large amount of body fluid.
- Ability to absorb body fluid to form swelled mass.
- Insolubility of IPN in body fluid renders it a suitable vehicle for drug delivery.
- Has potential for encapsulation of large amount of drugs.
- Drugs diffuse from swelled IPN hydrogel in specific manner which enables controlled release of drug.
- Chitosan can be combined with specific responsive polymer(s) in IPN to explore their environment responsive properties:

  Enzyme sensitivity: some polymer degraded by specific enzyme present in body such as pectin, guar gum, dextran, carrageenan.[52]

  pH sensitivity: some polymers swell in response to pH and they show pH responsive drug delivery such as poly(acrylamide), poly(methacrylate), alginate, poly(methyl acrylamide), Poly vinyl pyrrolidone.[53-56]

  Thermosensitivity: some polymers change shrinkage and swelling properties in response to temperature change such as Poly(2-ethyl-2-oxazoline), N-isopropyl-acrylamide.[57]

Limitation of chitosan based IPN hydrogel

- Generally glutaraldehyde is used as a cross-linker which is toxic, and carcinogenic to human body at particular concentrations.
- At acidic pH of stomach chitosan depolymerizes leading to high release rate at acidic medium making it unsuitable as intestinal delivery vehicle.
- Cross-linking of amine groups of chitosan can lead to decrease in its bioadhesive properties.

Method of preparation

Chitosan based IPN hydrogel for oral application can be prepared in the form of microsphere, beads or disc. Their

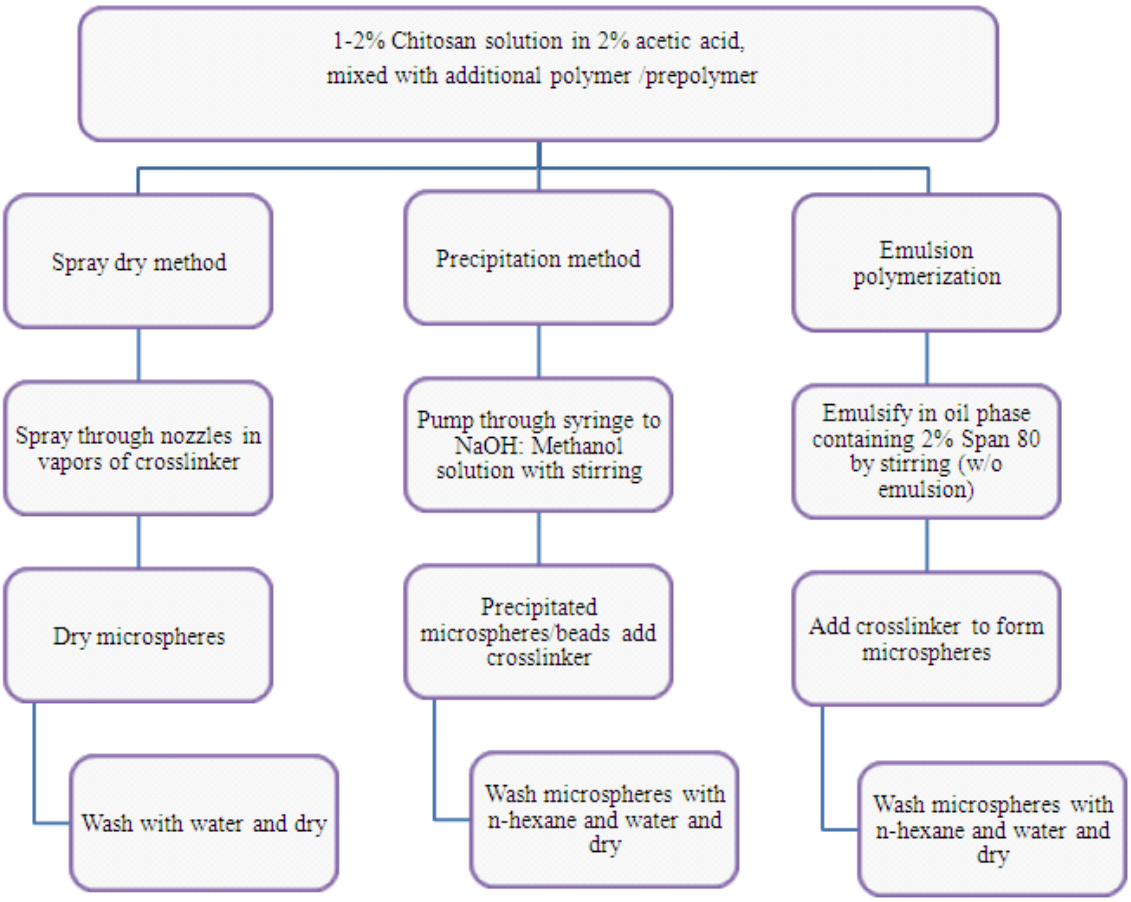
general preparation methods can be categorized as spray drying method[58], precipitation method[51] and emulsion polymerization method[4, 24] (Figure **4**).

Drug loading

Drugs can be loaded into IPN hydrogels by two methods:

- Direct incorporation of drugs in polymer solution before cross-linking to form hydrogels[4, 24]
- Absorption of drugs by IPN hydrogels from drug solution and subsequent drying[20]

Figure 4. Preparation method of Chitosan based IPN microspheres



Control of characteristics of Chitosan-IPN

Chitosan IPN hydrogels have several properties which make it a suitable vehicle for drug delivery. Chitosan properties can be modified by formation of IPN hydrogel by combination with other polymers. Chitosan IPN hydrogels are prepared by cross-linking of chitosan and additional polymers. The use of a bifunctional agent can block amino groups and turn chitosan structures more inert and resistant.

IPN properties such as porosity, elasticity, degree of swelling and responsive behavior to a stimulus can be tuned by the appropriate choice of the network-forming polymers and suitable cross-linking agent and its proportion. Among the various factors, selection of polymers primarily depends on intention of application of IPN hydrogels.

Chitosan can be prepared by deacetylation of chitin with different grade of molecular weight. The higher the degree of deacetylation in chitosan, the higher would be the degree of covalent cross-linking but it is found to be independent of the molecular weight of chitosan.[59] Degree of cross-linking controls the release characteristics of drugs from IPN hydrogels.

The major disadvantage of hydrogels of hydrophilic polymeric matrix is their low mechanical strength due to their high water content, particularly after swelling. This can be overcome by using acrylic acid, methacrylic acid, poloxamer and acryl amide, which not only increase mechanical strength but also alter physiochemical properties of IPNs.[3, 23]

pH sensitive IPN hydrogel can be prepared by using poly(acrylic acid), poly(methacrylamide), ethyl cellulose and alginate. Poly(acrylic acid) show pH dependent drug release since poly(acrylic acid) swells to a higher degree at higher pH. Carboxyl group present in poly (acrylic acid) is ionized at basic pH and water absorption increases resulting in high swelling behavior. Drug release from hydrogel into the solution is swelling-controlled.

Drug release from hydrogel by diffusion and diffusion rate increased with swelling of IPN hydrogels. Chitosan is a weak base with a pK value of about 6.2–7.0 and, therefore, is insoluble at neutral and alkaline pH values. At low pH chitosan show higher swelling behavior since amine groups are ionized at acidic pH.[60]

Enzyme sensitive hydrogels have been prepared by using polymers that degraded by enzyme present in GIT tract. Pectin, dextran and carrageenan are example of such polymers. They are degraded by enzyme present in colon and show colon specific drug release behavior.[52, 61]

Mucoadhesive properties of IPN hydrogel can be modified by use of chitosan derivatives and use of mucoadhesive polymer such as poly(acrylic acid, hydroxy propyl methyl cellulose, hydroxy ethyl cellulose, gelatin, etc. Existence of O-carboxymethyl chitosan (O-CMC) enhanced the mucoadhesive force of the chitosan-IPNs.[20]

Drug entrapment efficiency and drug release depends upon amount of cross-linker used and ratio of chitosan to polymers. Drug entrapment efficiency increases with increase in cross-linking density, while drug release rate

decreases with increase in cross-linking.

CONCLUSION

Chitosan based IPN hydrogels are effective and suitable vehicle for the controlled delivery of drugs. It encapsulate large amount of drug and release them in body from swelled matrix in a controlled manner. Chitosan is nontoxic, biodegradable, non-mutagenic and biocompatible, which makes it suitable vehicle for oral delivery of drugs.

Properties of chitosan with conjunction to other additional polymer have been explored. With IPN hydrogels, it is possible to combine synergistic properties of two or more polymers. Two different types of polymer properties such as hydrophilic and hydrophobic behavior have been combined. Hydrophilic polymer show swelling behavior in body fluid while hydrophobic polymer prevents it. By controlling ratio of the two polymers, it is possible to control the swelling of hydrogel and thus release rate of drug from hydrogel.

In IPN hydrogel, specific individual properties of various polymers can be explored, viz., pH-responsive, thermo-responsive and enzyme-responsive properties.

Various chitosan derivatives can be utilized for making IPN hydrogel to explore their highly specified properties to improve the utility of delivery vehicle for various purposes.

FUTURE PROSPECTS

The field of chitosan based IPN hydrogel has immense scope to explore their properties, which makes them suitable vehicle for oral delivery of bioactive molecules especially for localized and controlled delivery of drugs. The potential of chitosan derivatives for IPNs remains to be explored. Mucoadhesive properties of novel derivative of chitosan such as thiolated chitosan, o-carboxymethyl chitosan, etc. are reported to be very high. Chitosan derivatives having environmental responsive behavior offer opportunities for oral controlled drug delivery.

Cross-linker choice will be obligatory for the formulation of oral controlled delivery vehicle. Currently used cross-linker glutaraldehyde has a number of disadvantages. Among the various novel biocompatible natural cross-linkers, genipin appears to be the alternative and most suitable choice for preparation of chitosan based IPN hydrogels.

DECLARATION OF INTEREST

The authors report no declarations of interest.

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