INTERPENETRATING POLYMER NETWORK (IPN)
MICROPARTICLES AN ADVANCEMENT IN NOVEL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 \( \mu \text{m} \). Interpenetrating polymer network (IPN) is regarded as one of the most useful novel biomaterial containing two polymers, each in network form. The excellent biocompatibility and safety due to its physical characteristics such as impart stability of the drug in the formulations, improves solubility of hydrophobic drugs, excellent swelling capacity and its biological characteristics, like biodegradability, impart bioavailability, drug targeting in a specific tissue. The potential applications of IPN as drug delivery systems specially for the controlled release drug delivery systems. This article aims to provide a comprehensive review of merits, features, methods of microencapsulation, mechanism of drug release from microspheres, classification and problems occurs with different IPN.

Keywords: Interpenetrating polymer network, microspheres, biomaterial, drug targeting.

INTRODUCTION

During the past decades, a diversity of polymer-based pharmaceutical carrier systems have been developed as a new means of the controlling temporal or distributional drug delivery. These controlled drug release systems offer numerous advantages in comparison with conventionally administered drugs in dosage forms, such as improved efficiency and reduced toxicity. Polymeric cross-linked carrier matrices, such as microparticles, hydrogels and supramolecular polymer aggregates are typical examples of common drug delivery devices\[^1,2\]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One of such approach is using microspheres as carriers for drugs. Microspheres are solid,
approximately spherical particles ranging 1- 1000 µm in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microsphere matrix\cite{3}. The reason behind the development of controlled drug delivery systems is to make a therapeutic agents do its best when administered into the body. This means a high therapeutic efficacy with minimal toxicity successful application of many therapeutic agents are hampered by a multitude of problems. Drugs administered normally distribute throughout the body interacting not only with the target cells but also with the normal healthy cells which often results in toxic effects. Conventional therapy requires frequent administration of the therapeutic agent to the patient which reduces patient compliance. Systemic administration of the drug often requires high concentrations to maintain a therapeutic effect because of the dilution effect and the difficulty of drug placement in the target site. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount for the right period of time thereby causing little toxicity and minimal side effects. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug\cite{4}. An interpenetrating polymer network (IPN) is any material containing two polymers, each in network form. An IPN is a composite of at least two polymers, exhibiting varied characteristics, which is obtained when at least one polymer network is synthesized or crosslinked independently in the immediate presence of the other\cite{5} or in other words an IPN is a combination of at least two polymers chains each in network form, of which at least one is synthesized and/or cross-linked in the immediate presence of the other without any covalent bonds between them\cite{6}.

**INTERPENETRATING POLYMER NETWORK (IPN)**\cite{7}

An interpenetrating polymer network (IPN) is any material containing two polymers, each in network form. The three conditions for eligibility as an IPN are as follows:

1. The two polymers are synthesized and/or crosslinked in the presence of the other.
2. The two polymers have similar kinetics.
3. The two polymers are not dramatically phase separated.
IPNs that have only one polymer crosslinked (where the polymers are synthesized separately) or where the polymers have vastly different kinetics are still considered to be IPNs.

**MERITS OF IPN**\(^8\)

In modern era polymer IPN systems gaining huge popularity due to its following inherent advantages:

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

b) IPN is also attractive in producing synergistic properties from the component polymers. For example, when a hydrophilic gelling polymer is interpenetrated with a relatively hydrophobic gelling polymer, the resultant IPN hydrogel is expected to have an improved capability of immobilizing a drug.

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

d) IPN enhances the mechanical properties of the final product.

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

**FEATURES OF IPN**\(^9\)

The ideal characteristics of an IPN are as follows:

a) An ideal IPN can suppress creep and flow.

b) IPN can swells in solvents without dissolving.

c) IPNs are distinguishable from blends, block copolymers, and graft copolymers.

d) To keep the Separate phases together when the blends are subjected to stress.

e) These systems differ mainly because of the number and types of crosslinks that exist in the system.

f) Materials formed from IPN share the properties that are characteristic of each network. However; homopolymer alone cannot meet the divergent demand in terms of both properties and performance. Therefore, a composite or an ideal IPN of two or three different polymers would be a better choice.
g) Polymer comprising two or more polymer networks which are at least partially interlaced on a molecular scale but not covalently bonded to each other and cannot be separated unless chemical bonds are broken.

h) 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.

i) Hence, IPN based systems have gained good potential to develop the controlled release delivery of drugs$^{[10]}$.

METHODS OF MICROENCAPSULATION$^{[11]}$

1. Coacervation Phase Separation:

Microencapsulation by coacervation phase separation is generally attributed to the National Cash Register (NCR) Corporation and the patents of Green et al. The general outline of the process consists of three steps carried out under continuous agitation:

- Formation of three immiscible chemical phases
- Deposition of coating material, and
- Rigidization of the coating material

a) Incompatible polymer addition: It involves liquid phase separation of a polymeric coating material and microencapsulation can be accomplished by utilizing the incompatibility of dissimilar polymer existing in a common solvent.

b) Non-solvent addition: A liquid that is non-solvent for a given polymer can be added to the solution of the polymer to induce phase separation. The resulting immiscible liquid polymer can be utilized to effect microencapsulation of an immiscible core material.

c) Salt addition: There are two types of coacervation: Simple and Complex.

Simple coacervation involves the use of only one colloid (e.g., Gelatin in water) and involves the removal of the associated water from around the dispersed colloid by agents with greater affinity for water such as alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form coacervate.

Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are frequently used, and the coacervation is accomplished mainly by charge neutralization of the colloid carrying opposite charges rather than by dehydration.
d) Polymer-polymer interaction: The interaction of oppositely charged polyelectrolytes can result in the formation of a complex having such reduced solubility such that phase separation occurs.

e) Solvent evaporation: The processes are carried out in a liquid manufacturing vehicle. The microparticles coating material is dispersed in volatile solvents, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in a coating polymer solution. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microparticles. The mixture is then heated if necessary to evaporate the solvent for the polymer. In this case, in which the core material is dissolved in the polymer solution, polymer shrinks around the core. In case in which the core material is dissolved in the coating polymer solution, a matrix type microparticle is formed. The solvent evaporation technique to produce microparticles is applicable to a wide variety of core materials. The core materials may be either water soluble or water insoluble materials.

2. Multiorifice-Centrifugal Process: The south west research institute has developed a mechanical process for producing microparticles that utilizes centrifugal forces to hurl, a core material particle through an enveloping microencapsulation membrane therapy effecting mechanical microencapsulation. Processing variable include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity of the coating material and the viscosity and surface tension of the core material. This method is capable of microencapsulating liquids and solids of varied size with diverse coating materials.

3. Pan Coatings: The microencapsulation of relatively large particles by pan coating method has become wide spread in the pharmaceutical industry and solid particles greater than 600µm in size are generally considered essential for effective coating. The coating is applied as solution or as an automized spray to the desired solid core material in the coating pan. Usually, to remove the coating solvent, warm air is passed over the coated materials during coatings are being applied in the coating pans.

4. Air Suspension Coating: The process consists of dispersing of solid, particulate core material in a supporting air stream and the spray coating of the air suspended particles. Within coating chambers, the particles are suspended on an upward moving air stream.
The design of the chamber and its operating parameters effect a re-circulating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is sprayed to the moving particles.

5. Spray Drying and Spray Congealing: Spray drying and spray congealing are similar in that both involve dispersing the coating material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, where by relatively rapid solidification of the coating is affected. The principle difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in case of spray drying is effected by rapid evaporation of the solvent in which the coating material is dissolved, whereas in spray congealing it is accomplished by thermally congealing the molten coating material or by solidifying the dissolved coating by introducing the coating-core material mixture into a nonsolvent. Removal of the nonsolvent or the solvent from the coated product is then accomplished by sorption, extraction or evaporation techniques.

6. Polymerization: The method involves the reaction of monomeric units located at the interface existing between a core material and a continuous phase in which the core material is dispersed. The continuous and the core material supporting phase is usually a liquid or a gas, and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid or solid-gas interface.

7. Melt-dispersion technique: In this technique the coating material is melted by heating upto 80°C. The drug is suspended in it and then emulsified in water containing emulsifying agent at 80°C under stirring. Microparticles are formed as the temperature of the system reaches to room temperature.

8. Emulsion-cross-linking method: Cross-linking microparticles is prepared by emulsion-cross-linking method. One polymer is dissolved in suitable solution by continuously stirring until a homogeneous solution is obtained. After this, second polymer is dispersed in above polymer solution and stirred overnight to obtain a homogeneous solution. Then, drug is added in the above polymer solution. This solution is slowly added to light liquid paraffin containing 1% (w/w) span-80 under constant stirring at 400 rpm speed for 10 min. to this w/o emulsion, cross-linker is added slowly and stirring is continued for 3 hrs. The hardened microparticles are separated by filtration.
and washed with n-hexane. Finally, the microparticles are washed with 0.1 M glycine solution to mask the unreacted cross-linker and distilled water to remove the unreacted cross-linker. The microparticles are dried at 40°C for 24 h and stored in desiccators until further use.

**MECHANISM OF DRUG RELEASE**

Theoretically, the release of drugs from biodegradable microspheres can be classified broadly into four different categories. But in actual practice, the mechanism is more complex and an interplay of different mechanisms may operate.\(^{[12]}\)

**Degradation controlled monolithic system**

In degradation controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout. The drug is strongly to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is slow initially and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device.

Release from a sphere is governed by the equation, where \(M_t\) is the amount of the agent released at time \(t\), \(M_\infty\) is the amount at time \(t_\infty\) is the time for total erosion. Progesterone release from poly (glycolic-co-lactic acid) polymer films containing 10 weight% steroids is an example of this type of release.

\[
\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{t}{t_\infty}\right)^3
\]

**Diffusion controlled monolithic system**

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release and has to be taken into account. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism.

**Diffusion controlled reservoir systems**

Here the active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that
remains as such till the complete, release of drug and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery.

Erodible poly-agent system

In this case the active agent is chemically attached to the matrix and the rate of biodegradation of the matrix is slow compared to the rate of hydrolysis of drug polymer bond. Assuming that the rate of diffusion of the active agent from the matrix to the surrounding is rapid, the limiting step is the rate of cleavage of the bond attaching drug to the polymer matrix\cite{13}.

**CLASSIFICATION OF IPN\cite{14}**

![Figure 1](image)

**Figure 1**
Classification of Interpenetrating Polymer Network

1) **BASED ON CHEMICAL BONDING\cite{15}**

A) Covalent IPN

i) **Semi IPN**: A covalent semi-IPN contains two separate polymer systems that are crosslinked to form a single polymer network. This covalent semi-IPN is similar to a non-covalent IPN because one of the polymer systems can be crosslinked without networking with the second linear system. However, the two systems tend to be networked for better property development. These covalent semi-IPNs are developed with organic-inorganic composite materials.
B) Non-Covalent IPN

i) Semi IPN: A non-covalent semi IPN is one in which only one of the polymer system is crosslinked.

ii) Full IPN: A non-covalent full IPN is one in which the two separate polymers are independently crosslinked.
II) BASED ON ARRANGEMENT PATTERN\textsuperscript{[16]}

A) Novel IPN: Polymer comprising two or more polymer networks which are at least 
partially inter-locked on a molecular scale but not co-valently bonded to each 
other and can not be separated unless chemical bonds are broken.

B) Sequential IPN: In sequential IPN the second polymeric component network is 
polymerized following the completion of polymerization of the first component 
network.

C) Simultaneous IPN: Simultaneous IPN is prepared by a process in which both 
component networks are polymerized concurrently, the IPN may be referred to as 
a simultaneous IPN.

D) Semi IPN: If only one component of the assembly is cross linked leaving the 
other in a linear form, the system is termed as semi-IPN.

PROBLEMS OCCURING WITH IPN MICROSHERES\textsuperscript{[16]}

Non-Covalent IPN

The problem with the non-covalent systems, which can also be a problem with the 
covalent systems, is the lack of an effective interface. This problem could stem from 
several factors including surface energy phenomena and lack of molecular interactions 
between phases. Organic-Inorganic associations show several polymers that can interact 
with the inorganic phase. These polymers are proposed to hydrogen bond with the 
inorganic phase, creating an interface between the two materials. However, the key to 
having non-covalent organic-inorganic materials is not only utilizing a polymer that can 
have hydrogen bonding between the two phases but also to have low loading of the 
inorganic phase. Low loading of the inorganic phase will result in an increase in the 
overall material properties without sacrificing the interfacial bonding.

Covalent IPN

However, covalent IPN materials can have similar problems with the interface as 
the non-covalent materials. Again, similar to the non-covalent systems, a general lack of 
cohesiveness between the two phases can exist at molecular weight loadings higher than 
10\%. This problem with the gross phase separation at the interface is under investigation 
by researchers. Utilization of a variety of intermolecular bonding forces seems to 
 improve upon the overall separation problems of the material. For example, by utilizing a
polymer with a covalently bound silicate material that can also hydrogen bond with the organic polymer backbone creates more opportunities for better interfacial interactions.

CONCLUSION

IPN has numerous advantages as a biomaterial and is widely used as carrier systems for the delivery of drug and protein in the form of microspheres. The study of IPN for drug delivery systems may lead to a better understanding of critical diseases. The concepts of high swelling capacity, specificity and sensitivity play an important role in targeting delivery of drugs. By understanding the nature of drug delivery systems and their durability in the body, which can interact with the systems, can be identified. IPN has various advantages as a biomaterial and is widely used as carrier systems for delivery of the short biological half life drugs. There has been a spiky growth in the speed of discovery and development of IPN over the past few years. Current articles support the theory that IPN can provide the resources to deliver drugs at a prolonged controlled release to specific targets. Once optimized, these targeted hydrogel microspheres will provide the better treatment options. So, it can be inferred that IPN based microspheres for various drug delivery system are expected to become a useful matrix substance for various therapeutic applications in the future.

REFERENCES


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