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Hydrogels as Controlled Drug Delivery System: A Brief Review of Properties Classification and Synthesis

Hina Shoukat [a] Sobia Noreen [b] Saima Asghar [c]

Abstract *Hyrogels are carriers of novel drug delivery system, and these polymeric networks have ability to hold large amount of water, but they do not dissolve in water. These polymeric networks may be crosslinked either through chemical or physical crosslinking method. Without changing their three-dimensional structure hydrogels undergo the swelling mechanism Hydrogels are used as drug delivery carriers because of their distinctive properties. They have three dimensional configurations and have water-soluble cross-linked network of polymers. Hydrogels have porous structure and by changing the cross-linker concentration we can modify their affinity for water. Because of their unique properties these are used for various medical purposes like cellular immobilization, tissue engineering, diagnostics and regenerative medicines.*

Key Words: Novel Drug Delivery System, Polymeric Network, Cross Linked Network

Introduction

Drug delievry system is a device or carrier that provides the active therapeutic moeity in body and is responsible to control time, site and rate inj which drug releases in the body.It is a system which is intended to modify the safety and efficacy of active ingredient (Jain, 2008).The ability and efficacy of therapeutic active ingredient is affected by method it is being administered (Reddy & Swarnalatha, 2010). Most commonly used delievry system includes tablets ,pills,lozenges ,inhalers ,emulsions ,suspensions, syrups and elixirs.But these have various disadvantages like they does not meet the required therapeutic level, reduced toxicity,drug degradation, and drug loss. By incorporating traditional drug delievry system into novel drug delievry system helps to improve efficacy ,safety , and patient compliance (Allen & Cullis, 2004).

Hyrogels are cariers of novel drug delievry system and these polymeric network have ability to hold large amount of water but they do not dissolve in water. These polymeric network may be crosslinked either through chemical or physical crosslinking method. Without changing their three dimensional structure hydrogels undergo the swelling mechanism (Ahmed, 2015; Hennink & van Nostrum, 2012).

Hydrogels are used as drug delivery carriers because of their distinctive properties. They have three dimensional configurations and have water-soluble cross-linked network of polymers. Hydrogels have porous structure and by changing the cross-linker concentration we can modify their affinity for water. Because of their unique properties these are used for various medical purposes like cellular immobilization , tissue engineering ,diagnostics and regenerative medicines (Hoare & Kohane, 2008).

Hydrogels have three-dimensional structure with two or multi component system having cross linked polymeric chains with hydrophilic functional groups

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which interact with biological fluids or water and have soft or rubbery nature that resembles living tissue. Swelling characteristics of hydrogels are due to hydrophilic functional groups and they are insoluble in aqueous media due to presence of covalent bonds (Ahmed, 2015).

In recent years, hydrogels have gained appreciable importance as controlled drug delivery system due to its desirable features(Ganji & Vasheghani-Farahani, 2009). Problems related to conventional drug delivery system such as variation in plasma drug level and not able to maintain therapeutic window are overcome by novel drug delivery system(NDDS) (Gothoskar, 2004).NDDS includes hydrogels ,liposomes ,noisome , Nano particles , vesicles, micro particles , micelle, dendritic polymers .For controlled drug delivery system , hydrogels fit best to attain the pharmaceutical needs (Bheemidi, Tiruckovela, & Varanasi, 2011; Peppas, Bures, Leobandung, & Ichikawa, 2000)

Hydrogels can be formed either from natural or synthetic polymers. Natural polymers are obtained from plants and animals ,these are proteins that are collagen or polysaccharide (Patil, Rane, Bakliwal, & Pawar, 2011). Hydrogels have ability to imbibe large amount of water approximately up to thousand times its dry weight in water. Hydrophilic nature oh hydrogels is due to presence of chemical groups like sulphonic, carboxyl and hydroxyl group. Hydrogels cross linking network may be formed either of homo or co polymers. When hydrophobic and hydrophilic polymers are copolymerized it will form semi inter penetrating network or inter penetrating network (IPN). Hydrogel's porosity can be controlled by their density of cross links and affinity for aqueous medium. Thus, porous structure affects the entrapment of drug and their subsequent release from the cross-linked network. Hydrogels can be fabricated as Nano particles, micro particles, slabs, films and beads

Novel Drug Delivery System

The safety and efficacy of therapeutically active ingredient is affected by its administration method (Reddy & Swarnalatha, 2010). The basic purpose of developing novel drug delivery system is to enhance the effectiveness and bioavailability of drug and to minimize or reduce toxicity and harm full side effects (Kaparissides, Alexandridou, Kotti, & Chaididou, 2006). Figure 1 demonstrates the classidication of drug delievry system:

Carrier technology helps to deliver the drug to the body in a more effective manner. Carriers which control the release features and absorption of drug include macro particles, liposomes and Nano particles (Vasir, Tambwekar, & Garg, 2003). Following is the different type of carriers:

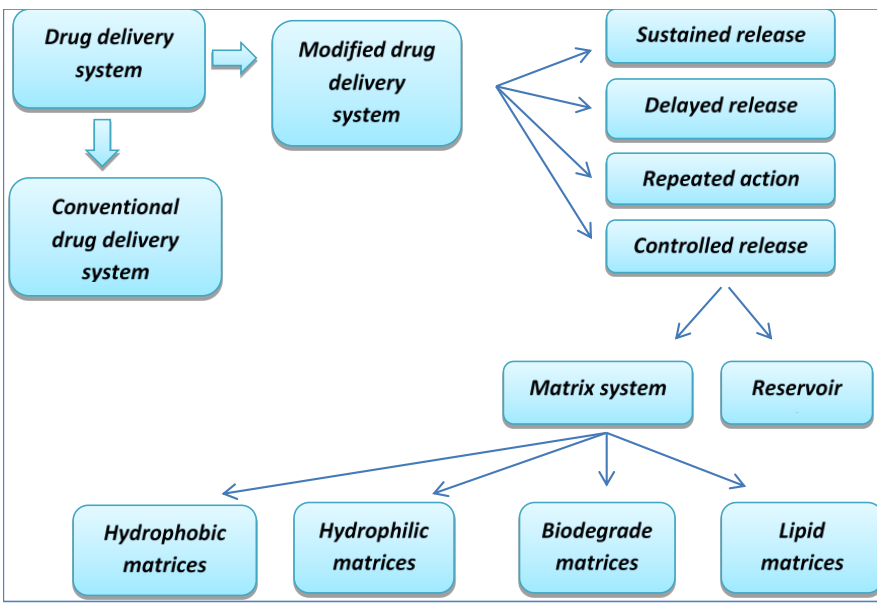

Figure 1: Classification of Drug Delievry system

Micro Particles

Size of micro particles ranges from 1-200 µm. They have ability to deliver the drug in a controlled manner and effectively at the target site. They are widely used for delivery of DNA in gene therapy. Drug from the micro particles releases at constant rate and in a sustained and controlled manner (Jyothi, Roy, Prasanhti, & Vajrapriya, 2016).

Liposomes

Liposomes are microscopic in nature act as carrier of peptides, proteins and in various infections and carriers. They have ability to deliver biotechnology products like cloned genes, recombinant proteins and oligonucleotides. Hydrophilic core of hydrogels is encapsulated by phospholipid bilayer. They have ability to entrap therapeutically active ingredient insides its inner core while hydrophobic agent into lipid membrane (Chonn & Cullis, 1995).

Dendrimers

Dendrimer word is derived from two Greek words "Dendron" means tree and "meros" means parts (Noor, Mahmood, Afreen, & Uzma, 2014). Dendrimers have three-dimensional structure and their size ranges from 2 to 10nm. Dendrimers have ability to overcome problems like poor solubility, permeability and toxicity (Garg, Singh, Arora, & Murthy, 2011).

Nano Particles

Size of these submicron sized microparticles ranges below 1000nm in them drug is either attached or entrapped to the matrix system (Soppimath, Aminabhavi, Kulkarni, & Rudzinski, 2001).They have various morphologies like nano capsules, nano spheres(Jung et al., 2000). By conjugating Nano carriers with the drug ,controlled delivery of drug can be achieved by changing in physiological environment that includes temperature, pH or through physical environment(Wilczewska, Niemirowicz, Markiewicz, & Car, 2012).

Polymeric Micelle

Polymeric micelles are colloidal dispersion and these are formed by self-assembling of amphiphilic block co polymer , having particle size monomer ,at which micelles are formed and they are known as critical micelle concentration (CMC) (Torchilin, 2007).

Hydrogels

Hydrogels are carriers of novel drug delivery system, and these polymeric networks have ability to hold large amount of water, but they do not dissolve in water. These polymeric networks may be crosslinked either through chemical or physical crosslinking method. Without changing their three dimensional structure hydrogels undergo the swelling mechanism Ahmed, 2015; Hennink & van Nostrum, 2012).

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Classification of Hydrogels

Hydrogels are classified on following basis as shown in figure 3 (Ahmed, 2015; Yang, Chu, & Fix, 2002; Zhai, Li, Yi, & Ha, 2000)

According to Source

For fabrication of hydrogels both synthetic and natural sources are used:

Natural Hydrogels

These are fabricated by cross linking natural polymers:

Examples

alginate, chitosan, xanthan gum, dextran, fibrin, gelatin.

Synthetic Hydrogels

These are fabricated by cross linking synthetic polymers. They may be biodegradable, stable, stimuli dependent and peptide.

Examples Poly vinyl pyrollidone (PVP), poly lactic acid (PVA), poly vinyl alcohol(PVA)(Ilić-Stojanović, Nikolić, Nikolić, & Petrović, 2017).

On the Basis of Method of Cross Linking

These are classified as following:

Physically Cross-Linked Hydrogels

These hydrogels are linked by physical or non-covalent interaction like hydrogen bonding through mutual bonding of chains of polymers (Nikolić, Ilić-Stojanović, Petrović, Tačić, & Nikolić, 2019).

Chemically Cross-Linked Hydrogels

These hydrogels are linked through permanent covalent bonds (Hennink & van Nostrum, 2012).

On Basis of Polymer Composition

Non-Ionic Hydrogels

These hydrogels swell due to polymer interactions and water.

Homo-Polymer Hydrogels

These hydrogels are fabricated by single type of monomer. While more than single type of monomer units undergoes rearrangement to fabricate co-polymers. These monomers may be arranged either in block or random form or in any other configuration. In case of interpenetrating network one polymer is cross linked to another via chemical bond (Dragan, 2014).

On Basis of Network Electric Charge

Ionic Hydrogels

These hydrogels may be cationic, anionic, or ampholytic.

Cationic hydrogels exhibit swelling when medium is transferred from acidic to basic medium while anionic hydrogels show maximum swelling in basic medium. Ampholytic hydrogels contains both positive and negative charges and are balanced at certain pH (Omidian & Park, 2010).

Neutral Hydrogels

These hydrogels do not possess charged groups in their structure and swell by interaction of polymer network
and water (Zdravković, Nikolić, Ilić-Stojanović, & Nikolić, 2017).

On the Basis of Stimuli Responsive

Conventional Hydrogels

Swelling characteristics of these hydrogels are independent of changes in the external environment. Conventional hydrogels do not possess any charge. They undergoes the swelling process but do not dissolves in water (Rosiak & Yoshii, 1999).

Smart Hydrogels

Stimuli responsive or smart hydrogels shows alterations in their volume in response to change in internal or external stimuli resulting in pronounced changes in physical nature which is favorable for the delivery of drug at the target site. The external stimuli can be pH, ionic strength, temperature, ultrasonic sound, electric current, type of solvent (Ahmed, 2015) as shown in figure 4. Different parameters such as force applied, shape recovery, response speed determines the response of hydrogels to various external stimuli (Ahmed, 2015).

Hydrogel Preparation

Hydrogels are polymeric structure exhibiting hydrophilic properties. Monomer, initiator and cross-linking agent are three basic parts of hydrogel formulation as shown in figure 5. Diluents such as water and other solutions can be used to enhance hydrogel properties and to control heat production during formulation. Non-reactive ingredients and unnecessary products are produced during preparation, so hydrogel washing is needed to remove impurities. Hydrogels are prepared by using polymerization techniques including bulk polymerization, solution polymerization or suspension polymerization (Ahmed, Aggor, Awad, & El-Aref, 2013)

Bulk Polymerization

It is simplest method as it involves one or more kind of monomer and monomer soluble initiators. Type of monomer and solvents used decided to select suitable initiator. Cross-linking agent is added in minute amount in hydrogel preparation. Chemical catalyst, radiation and ultraviolet rays are used to initiate the polymerization reaction. To make homogeneous

hydrogel the monomers of bulk polymerization produces glassy, transparent and hard matrix which become soft and flexible when immersed in water (Seidel & Malmonge, 2000)

Solution Polymerization

Neutral or ionic monomers are incorporated in solution polymerization technique in addition with multifunctional cross-linking agent. Redox initiator system or UV irradiation is used to initiate the polymerization. Solution polymerization has advantage over bulk polymerization due to presence of solvent which serve as heat sink. Water, benzyl alcohol, ethanol, water-ethanol are typically used solvents. If amount of water during polymerization is in excess than water content correspond to equilibrium swelling then phase separation take place thus results heterogeneous hydrogel (Ahmed et al., 2013)

Suspension Polymerization

In the hydrocarbon phase monomers and initiator both are dispersed as homogeneous mixture. Continuous agitation and addition of suspending agent is required due to thermodynamically unstable dispersion. Suspension polymerization has advantage over others as the final product is powder or microspheres, so there is no need of grinding. Particle size and shape of resin is affected by rotor design, agitation speed, viscosity of monomers and dispersant type (Ogata, Nagayoshi, Nagasako, Kurihara, & Nonaka, 2006)

Swelling Behaviour and Drug Loading into Hydrogels

Hydrogel polymeric chains absorb water in the presence of aqueous solvent. Association, dissociation and attachment of ions on polymer chains cause hydrogel to swell (Khalid, Qadir, Massud, Ali, & Rasool, 2009). Hydrogel swelling affects the release of drug from the vehicle. Hydrogel swelling can be modified by changing monomer composition and pH of the system in the case of pH sensitive hydrogel (Watts & Lllum, 1997).

Factors Affecting the Hydrogel Swelling

- The important factor that affects the hydrogel swelling is cross-linking ratio. It is ratio of moles of cross-linking agent and polymer repeating units.
- With high cross-linking ratio, hydrogel structure will become tighter and swelling rate will be less as compared to lower cross-linked hydrogel.
- High cross-linking makes the polymeric chain relatively less acidic due to reduced mesh size, concealed the carboxylic groups, hinders the process of ionization and reduced the mobility of polymer chain as a result lowers swelling rate (Khalid et al., 2009). The chemical structure of polymer can also affect the rate of hydrogel swelling.
- Hydrophilic group bearing hydrogels swell at higher rate as compared to hydrophobic groups containing hydrogel. In the presence of water, the hydrophobic groups collapse, thus reducing their exposure to water.
- Swelling of stimuli responsive hydrogel can be affected by their specific stimuli (Peppas et al., 2000).

Basically, hydrogel based system has been used to deliver hydrophilic, small drug molecules which are soluble in aqueous solvent and hydrogel matrix. But macromolecules and hydrophobic substances can also be entrapped in hydrogel polymeric system (Hoare & Kohane, 2008). There are two approaches for drug loading into hydrogel system (Lin & Metters, 2006).

1. *In-situ* loading.
2. Post loading

In-Situ Loading

In this method monomer is completely mixed with drug molecules, an initiator and in the presence or absence of suitable cross-linking agent allowed to polymerize thus trapping the drug in hydrogel network. Hydrogel matrix formation and drug loading is accomplished simultaneously (Zarzycki, Modrzejewska, & Nawrotek, 2010). Hydrogel swelling, diffusion, covalent bond cleavage, and reversible drug-polymer interactions controlled the drug release in these system (Lin & Metters, 2006)

Post Loading

In the second method, hydrogel network is developed and then prepared hydrogel discs are allowed to swell to equilibrium in drug solution to trap the drug molecules. In case of inert hydrogel system, diffusion process serves as main driving force for drug loading and kinetics of release is determined by gel swelling and diffusion (Lin & Metters, 2006).

Hydrophobic drug delivery is very problematic. Different approaches have been used to enhance hydrophobic drug entrapment into hydrogel. Simplest

technique is the formation of solid molecular dispersion of hydrophobic drug, exploiting the increased solubility of poorly soluble compounds in amorphous form rather than crystalline form. Other basic approaches are incorporation of hydrophobic domains, introducing cyclodextrin, and grafting of hydrophobic side chains (Zahedi & Lee, 2007)

Conclusion

Current research in the field of hydrogels as intelligent materials with remarkable applications is focused on basic principles of hydrogels. Recent developments in the field of both natural and synthetic polymeric materials have resulted in the development of various hydrogels sensitive to pH, temperature, light, and electric field which are used for many applications especially in biomedicine and biomedical fields. However, use of natural polymers and advent of biodegradable and biocompatible hydrogels could have a promising application in the field of biotechnology. Hydrogel become promising material in drug delivery system and biomedical field because of remarkable properties such as tunable biological, chemical and physical characteristics, versatility in fabrication, resemblance with extracellular fluid and biocompatibility. Fabrication of sophisticated hydrogels from natural and synthetic sources has potential applications in drug and gene delivery, regeneration medicines, cell therapy, stem cell and cancer research which will improve patient care and quality of life.

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Appendix

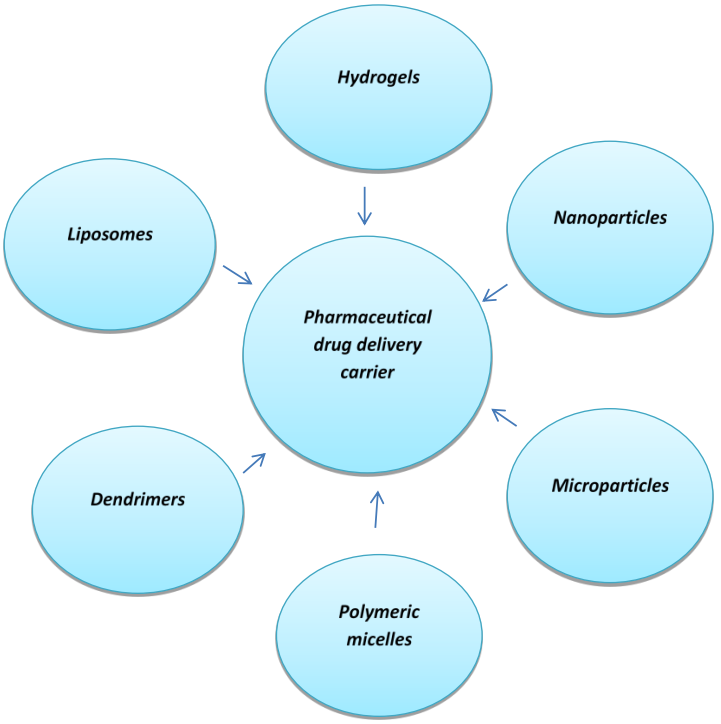

Figure 2: Pharmaceutical Drug Delivery Carriers

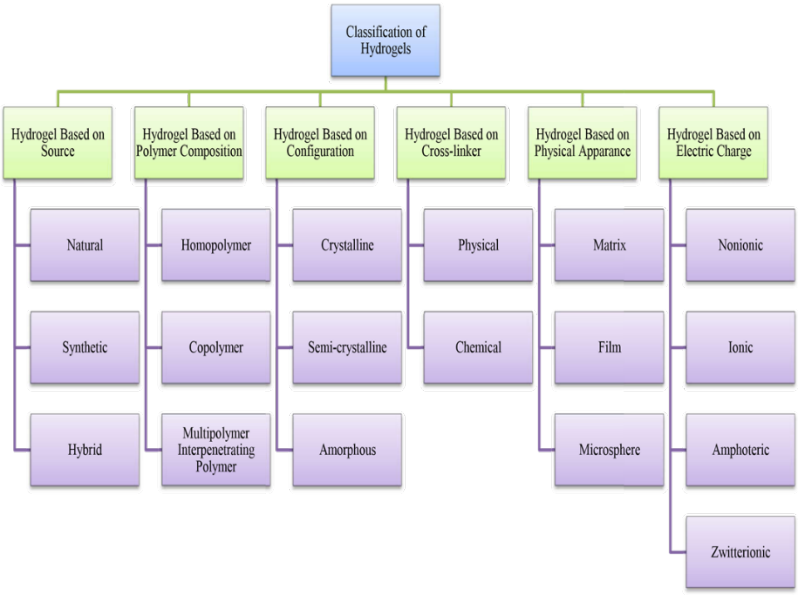

Figure 3: Classification of Hydrogel

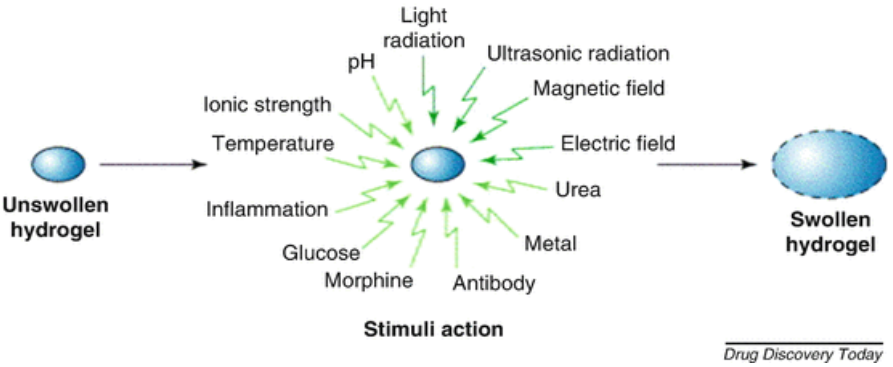

Figure 4: Chemical and Physical Stimuli Responsive Hydrogels

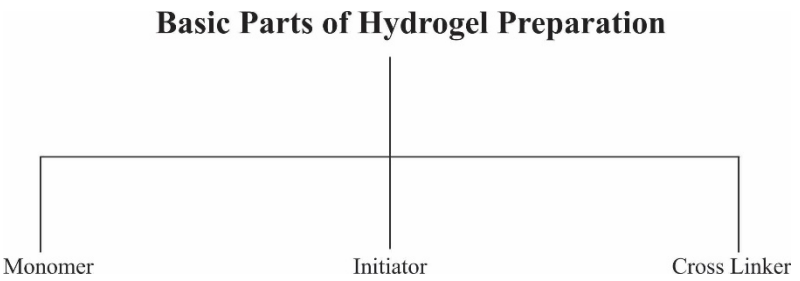

Figure 5: Basic Parts of Hydrogel