Vol 6|Issue 2| 2016 |52-56.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

NANOHYDROGEL DRUG DELIVERY: A REVIEW

Raisey Jose, K. Krishnakumar, B. Dineshkumar, Smitha K Nair*

Dept.of Pharmaceutics, St James College of Pharmaceutical Sciences, Chalakudy
St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized Centre), Chalakudy

ABSTRACT

Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fluids, and thus resemble, to a large extent, a biological tissue. They are insoluble due to the presence of chemical (tie-points, junctions) and/or physical crosslinks such as entanglements and crystallites. These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as pH, ionic strength and temperature. The aim of this article is to present a concise review on the applications of hydrogels in the pharmaceutical field, hydrogel characterization and analysis of drug release from such devices.

Key words:

INTRODUCTION

Nanotechnology has become a buzzword in pharmaceutical sciences and efforts are ongoing to extend its application in various streams of pharmaceutical sciences. Nanotechnology has dramatically influenced drug delivery research over the last two decades and several nanoscale technologies/carriers have been and are being explored for improving therapeutic performance of drugs. The nanoscale technologies can be broadly classified into: lipid-based nanocarriers, polymeric nano carriers, inorganic nanocarriers and drug nanoparticles or nano suspensions. All these colloidal nanocarriers are extensively being studied in drug delivery research and have demonstrated great potential in improving drug delivery by various routes of administration.

Most of the pharmaceutical companies today are oriented toward designing new pharmaceutical dosage forms of existing drugs rather than discovering new drug products. Utilization of the existing resource of marketed and patented drug substances with known therapeutic effects, and modification of their pharmaco-therapeutic characteristics by incorporation in suitable drug delivery system, has been the target of recent pharmaceutical development [1].

Gels are semisolid systems in which a liquid phase is constrained within a three dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. The clarity ranges from clear to a whitish translucent. Gels are usually clear transparent semisolid containing the solubilised active substances. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains. When solvent used as continuous phases is water, the gel formed is called hydrogel [2].

Hydrogels have been used extensively in the development of the smart drug delivery systems. In 1960 Wichterle and Lim were discovered hydrogel of poly(2-hydroxyethyl methacrylate)from that time to till now hydrogels have been of great interest to biomedical scientist and widely involved in development of drug delivery system. Hydrogels are three-dimensional, hydrophilic, polymeric networks that can swell in water and hold a large amount of water while maintaining the structure. Their ability to absorb water is because of its crosslinking network structure which is formed by polymer bearing hydrophilic groups such as –OH, –CONH, –COOH, $–SO_3H$, and $–NH_2$. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites [3, 4]. In this review we are focused on conceptual points of hydrogels related to hygrogel types, their crosslinking,

***Corresponding Author Smitha K Nair** E mail: stjamespharmacyproject@gmail.com

polymers, application as well as developments.

Advantages

- Avoidance of first pass metabolism
- Convenient and easy to apply
- Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes &gastric emptying time
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intrapatient variations
- Ability to easilyterminate the medications, when needed
- A relatively large area of application in comparison with buccal or nasal cavity
- Ability to deliver drug more selectively to a specific site
- Avoidance of gastro-intestinal incompatibility
- Providing utilization of drugs with short biological half-life, narrow therapeutic window
- Improving physiological and pharmacological response
- Improve patient compliance
- Provide suitability for self-medication [5].

Limitations

• High cost.
• Low mechanical strength
• Difficult to load
• Difficult to sterilize
• Non-adherent
• In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions [6].

Classification of Hydrogel Products

The hydrogel products can be classified on different bases [7] as detailed below:

1. Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins

2. Classification according to polymeric composition

The method of preparation leads to formations of some important classes of hydrogels. These can be exemplified by the following:

Homopolymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.

Copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.

Multipolymer Interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer component, contained in a network form. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer.

Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

(a) Amorphous (non-crystalline).
(b) Semicrystalline: A complex mixture of amorphous and crystalline phases.
(c) Crystalline.

Classification based on type of cross-linking

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

Classification according to network electrical charge

Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the cross-linked chains:

- Nonionic (neutral).
- Ionic (including anionic or cationic).
- Amphoteric electrolyte (ampholytic) containing both acidic and basic groups
- Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

Hydrogel-forming natural polymers include proteins such as collagen and gelatine and polysaccharides such as starch, alginate, and agarose. Synthetic polymers that form hydrogels are traditionally prepared using chemical polymerization methods.

Formulation and Characterization of Hydrogel

Preparation of Nano-suspension by EPAS

Weighed amount of drug was dissolved in 10 ml of organic solvent. The resultant solution is sprayed though a fine nozzle into a heated aqueous solution 80-85^{o}C containing stabilizing surfactant and the mixture was continuously stirred magnetically. The organic solvent was allowed to evaporate and a Nanosuspension has formed. The rapid evaporation of the organic solvent produces high supersaturation and rapid precipitation of the drug in the form of a colloidal suspension. The colloidal suspension is centrifuged and freeze dried [8].

Preparation of Gel base

Weighed amount of powder (PVA, Carbopol, HPMC, etc)was sprinkled gently in beaker containing warm waterand continuously stirred magnetically until thin hazy dispersion without lumps formed. Remaining amount of

water was added on cold and mixing continue until smooth homogenous gel formed.

Preparation of hydrogel formulation

The gel base are neutralized and made viscous by the addition of triethanolamine and left overnight in the refrigerator to allow complete gel dispersion. To the prepared gel base, the Nanoparticle of drug prepared by EPAS technique is added at 10% w/w concentration was added by mean of gentle levigation with mortle and pestle.

Characterization for hydrogel

Physicochemical Evaluation of Gel formulations

The physical appearance, homogeneity, and texture of the prepared gels were tested by visual observations.

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of particles and no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

pH Value

2 gm of gel was stirred in distilled water until a uniform suspension was formed. The volume was made up to 50ml and the pH of solution was measured using a glass electrode pH meter at room temperature. Measurement were done on 1, 7, 14 days after the hydrogel preparation.

Drug Content

For assay of the drug in gels, drug was extracted from 1 g of each gel formulations with 20 ml of methanol for 30 min. The resultant mixture was filtered through membrane filter (pore size 0.45 mm). The absorbance of the sample was determined spectrophotometrically.

Accelerated stability studies

All the gel formulations with stabilized naproxen particles were subjected to a stability testing for three months as per ICH guidelines at a temperature of 40°C ± 2°C. All selected formulations were analyzed for the change in appearance, pH and drug content.

***In vitro* diffusion studies**

In vitro Permeation studies were conducted using pre-calibrated, upright Franz diffusion cells with an average surface area of 0.5cm^2 and receiver compartment volume of 2.5mL.Cellulose nitrate membrane (0.1 µm pore diameter) was soaked with isopropyl myristate to simulate the lipophilic properties of stratum corneum and mounted on diffusion cell. The gel formulation (1.0 g) was gently placed in the donor chamber and then fixed in between donor and receptor compartment of diffusion cell. The receptor chamber was filled with freshly phosphate buffer of pH 6.8. The diffusion cell was maintained at 37°C using a recirculating water bath and the solution in the receptor chambers was stirred continuously at 300rpm. The cells were allowed to equilibrate in the water bath for 1 h prior to experiment initiation. Care was exercised to remove any bubbles between the underside of the membrane and solution in the receiver compartment. Using a long needle, samples (0.5 ml) were removed from the receptor compartment at defined time intervals (30, 60, 120, 180, 240, 300 and 360 min). This volume was immediately replaced using blank, pre-warmed buffer. No interference of the other formulation components was observed. The samples withdrawn were UV spectrophotometrically estimated. Each formulation is performed in triplicate (n=3).

***In vitro* Release kinetic studies**

This kinetic model is generally used to analyse the release of hydrogel semisolid dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved. A more stringent test was used to distinguish between the mechanism of drug release. In order to ascertain the mechanism of drug release, the release data was fitted into the general equation

$$M_t / M_\infty = K t^n$$

Where

M_t is the amount of drug released at t

M_∞ is amount of drug released at infinite time

K is the constant incorporating characteristics of the polymer network system and the drug

n is the diffusional exponent indicative of the transport mechanism.

The release exponent takes various values depending upon different geometries.

Applications of hydrogels in drug delivery

Oral delivery of drug is cheap and allows maximum patient compliance. Through oral delivery system one can target mouth, stomach, small intestine and colon. The bioadhesive property of the hydrogels could help to deliver drugs to the oral cavity or at the specific sites of gastrointestinal tract (GIT). These hydrogels have been used to locally treat periodontal diseases, fungal and viral infections and oral cavity cancers. The rectal route of administration of drug is also gaining attention even though the patient acceptability is low. The main reason for this can be attributed to the rich blood supply to the region, which helps in increased bio-availability of the drug as the first-pass metabolism is partially bypassed. Rectal route of administration has been used for a long time for the local treatment of hemorrhoids [9].

Administration of aqueous drops in ocular cavity is the preferred way to administer drug in the ocular cavity. But most of the drug is removed from the ocular cavity due to tear drainage and blinking. In addition to this, the low permeability of the cornea

worsens the situation. Though the use of suspension and ointments increase the ocular retention time, they produce a gritty feeling thereby reducing the patient compliance. Human skin can be easily accessed by a person and has got a large surface area which makes it a potential site for administering drugs, both locally and systemically. Systemic delivery of drug by this route of administration helps in bypassing the first–pass metabolism and delivery of the drug for prolonged period of time at a constant rate. In addition to the above advantages, the hydrogels provide a soothing effect on the skin as compared to occlusive/oily feeling caused by the application of ointments. The delivery of drug to the ear cavity is mainly carried out by the use of aqueous or oil drops. The main limitation in the use ear drops is the retention time of the drops in the cavity while the person is standing. The use of hydrogel for the delivery of drugs to the ear cavity can be done easily. Lee and co-workers were successful in delivering recombinant human insulin-like growth factor I (rhiGF-1) locally using gelatin hydrogel. The group found that by delivering the rhiGF-1 by this method can be useful in the treatment of noise-induced hearing loss. Of late scientists are working on the local delivery of the drugs in the ear cavity using hydrogels

Recent Studies Based On Hydrogel

Shivani Nanda, *et.al*., studied on the development on PVA-CS hydrogel scaffolds using glutaraldehyde as a cross-linking agent by chemical crosslinking method in order to obtain biomimetic scaffolds for articular cartilage regeneration [10]. Gupta, et.al., studied to synthesize superporous hydrogels of rosiglitazone using chitosan and to study its swelling behaviour for application as a gastroretentive drug delivery system. The studies showed that chitosan-based superporous hydrogels can be used as a gastroretentive drug delivery system in view of their swelling characteristics in acidic pH [11]. Swatantra Kumar, et.al., studied to formulate and evaluate temperature-sensitive, controlled-release camptothecin hydrogel for anticancer drug delivery. Temperature-sensitive hydrogel based on chitosan/β-glycerophosphate (β-GP)/β-cyclodextrin (β-CD) was prepared by crosslinking method [12]. ParimalMaji, *et.al.,* studied on matrix type transdermal patches were prepared using alprazolam as a model drug and employing the combinations of chitosan-polyvinyl alcohol (CS-PVA) cross linked with Maleic anhydride. The patches were found to be free of any skin irritation [13]. Marija Glavas Dodov, *et.al.,* studied to formulate and evaluate rectal hydrogels containing DZP as a drug substance in combination with suitable co-solvents and preservatives. Prepared formulations were stable for four months at 26 °C (ambient temperature characteristic of the 2nd climate zone) [14].

CONCLUSION

There are numerous applications of these hydrogels, in particular in the medical and pharmaceutical sectors. Due to their high water contents and soft consistency hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. Recent advances in the development of neutral and ionic hydrogels for drug delivery applications have concentrated on several aspects of their synthesis, characterization and behavior. In the last few years, there have been new creative methods of preparation of hydrophilic polymers and hydrogels that may be used in the future in drug delivery applications. Synthesis of new polymers and crosslinkers with more biocompatibility and better biodegradability would be essential for successful applications. If the achievements of the past can be extrapolated into the future, however, it is highly likely that responsive hydrogels with a wide array of desirable properties can be made.

ACKNOWLEDGEMENT

None

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Shakti D, Pankaj K, Gilhotra RM, Vikashkumar K. Hydrogel-A Conceptual Overview. *International Journal of Pharmaceutical & Biological Archives*, 2(6), 2011, 1588-1597.
2. KirtiKumari, Sara UVS, Monika Sachdeva. Formulation and evaluation of topical hydrogel of mometasonefuroate using different polymers. *International Journal of Pharmaceutical and Chemical Sciences*, 2 (1), 2013, 89-100.
3. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in Pharmaceutical Formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, 50, 2000, 27-46.
4. Okay O. General Properties of hydrogels, hydrogel sensors and actuators. *Springer Series on Chemical Sensors and Biosensors*, 6, 2009, 1-14.
5. Chandira RM, Pradeeppasupathi A. Design, development and formulation of anti-acne dermatological gel. *Journal of Chemical and Pharmaceutical Research*, 2(1), 2010, 401-404.
6. Anisha S, Pramod KS, Vipin KG, Garima G. Hydrogels: A Review. *International Journal of Pharmaceutical Sciences Review and Research*, 4(2), 2010, 97-105.
7. Enas MA. Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2), 2015 105–121.
8. Senthilrajan D, Kumarappan C, Srinivasan R. Preparation And enhanced in-vitro diffusion profile of naproxen by EPAS technique in hydrogel formulation. *Digest Journal of Nanomaterials and Biostructures*, 8(1), 2013, 25-33.

9. Mini K. Pal, Banthia AK, Majumdar DK. Polymeric Hydrogels: Characterization and Biomedical Applications. *Designed Monomers and Polymers*, 12, 2009, 197-207.
10. Shivani Nanda, Nikhil Sood, Reddy BVK, Tanmay S. Markandeywar. Preparation and characterization of Poly(vinyl alcohol)-chondroitin sulphate hydrogel as scaffolds for articular cartilage regeneration. *Indian Journal of Materials Science*, 1, 2013, 1-8.
11. Vishal Gupta N, Shivakumar HG. Development of a gastro-retentive drug delivery system based on superporous hydrogel. *Tropical Journal of Pharmaceutical Research*, 9(3), 2010, 257-264.
12. Swatantra K, Singh K, Awani K, Satyawan S. Formulation of thermo-sensitive hydrogel containing cyclodextrin for controlled drug delivery of camptothecin. *Tropical Journal of Pharmaceutical Research*, 13(7), 2014, 1007-1012.
13. Parimal M, Arijit G, Sougata J, Nirmal M. Preparation and characterization of maleic anhydride cross-linked chitosan-polyvinylalcohol hydrogel matrix transdermal patch. *Journal of Pharma SciTech*, 2(2), 2013, 62-67.
14. Marija G, Katerina G, Maja S, Suzana T, Jasmina T, Marija D. Formulation and evaluation of diazepam hydrogel for rectal administration. *Acta Pham*, 55, 2005, 251-261.