

Recent Trends on Hydrogel in Human Body

Vijay Singh Jatav, Himmat Singh and Santosh Kumar Singh

Gyan vihar school of pharmacy, Suresh Gyan vihar university, Jaipur, Rajasthan, India.

ABSTRACT

Hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are crosslinked polymer networks that absorb substantial amounts of aqueous solutions. Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial. Several techniques have been reported for the synthesis of hydrogels like co polymerization/crosslinking of co-monomers using multifunctional co-monomer, which acts as crosslinking agent. Chemical initiator initiates the polymerization reaction. Some applications are used of hydrogels in human body. Corgel™ may be useful in surgical and transcatheter applications including vascular surgery, cardiology, ophthalmology, orthopedics, aesthetics, ENT, drug delivery, tissue engineering and regenerative medicine. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. New synthetic methods have been used to prepare homo- and co-polymeric hydrogels for a wide range of drugs, peptides, and protein delivery applications.

Key Words: Hydrogels, Corgel, Polyvinyl Alcohol, Starch.

INTRODUCTION

Hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are superabsorbent (they can contain over 99% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. Hydrogels are crosslinked polymer networks that absorb substantial amounts of aqueous solutions.^{1,2}

Hydrogel-forming natural polymers include proteins such as collagen and gelatin, and polysaccharides such as alginate and agarose. Synthetic polymers that form Hydrogels are traditionally prepared using chemical polymerization methods. There are many approaches based on genetic engineering and biosynthetic methods to also create the unique Hydrogel materials.³

PREPARATION METHODS OF HYDROGELS

Hydrogels are polymeric networks. This implies that crosslinks have to be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution. The various methods for crosslinking are as follows:

Crosslinking of Polymers: - In this method chemically crosslinked gels are formed by radical polymerization of low molecular weight monomers, or branched homopolymers, or copolymers in the presence of crosslinking agent. This reaction is mostly carried out in solution for biomedical applications.⁴

Copolymerization/Crosslinking Reactions: - Copolymerization reactions are used to produce polymer gels, many hydrogels are produced in this fashion, for example poly (hydroxyalkyl methylacrylates).

Crosslinking by High Energy Radiation: - High energy radiation, such as gamma and electron beam radiation can be used to polymerize unsaturated compounds. Water soluble polymers derivatized with vinyl groups can be converted into hydrogels using high energy radiation.⁵

Crosslinking Using Enzymes: - Recently a new method was published using an enzyme to synthesize PEG-based hydrogels. A tetrahydroxy PEG was functionalized with addition of glutaminyl groups and networks were formed by addition of transglutaminase into solution of PEG and poly (lysine-cophenylalanine).⁶

Several techniques have been reported for the synthesis of hydrogels

- A chromia alumina hydrogel was prepared as in the preceding example except that ammonium nitrate was substituted as ammonium sulfate as base exchange

*Address for correspondence:
E-mail: jatavvijay@rediffmail.com

solution. A portion of washed hydrogel was impregnated in 13 liters of an aqueous solution maintaining 775 g of copper acetate and 223 g of potassium acetate. The impregnated hydrogel was dried in 100% steam at 260-270° F. and tempered 4 hours at 1100° F. in a hydrogen atmosphere.⁷

- Polyvinyl Alcohol–Gelatin Hydrogel was prepared, In short, 2.5 g of gelatin was dissolved in 100 mL of a 10% aqueous solution of PVA. Concentrated hydrochloric acid (HCl, 0.05 mL) was added, and the resulting dispersion was stirred (using a overhead stirrer at 100 ± 5 rpm) at 70°C for a half-hour to carry out the esterification reaction between PVA and gelatin.⁸
- Hydrogel sheets based on poly(vinyl alcohol) (PVA) and poly(vinyl acetate) (PVAc) have been prepared by the technique of acetalization of PVA using formaldehyde and grafting of acrylic acid onto PVAc by gamma irradiation. PVA hydrogel (PVAB) sheets have been prepared in geometrically stable shapes by compression moulding process.⁹
- Semicrystalline crosslinked poly (vinyl alcohol) hydrogels in the form of films were prepared by electron beam irradiation and a subsequent slow dehydration process at $25 \pm 1^\circ$, using various drying agents.¹⁰

As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acids, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds.

- The synthesis of hydrogel in industry is consist of solution and reversed suspension and reversed emulsion polymerizations. Figure:1 shows a block diagram of a generic solution polymerization process. This figure represents the major procedure of super absorbent polymer manufacturing in the laboratory and industrial scales¹¹.

COMMON USES FOR HYDROGELS

- Currently used as scaffolds in tissue engineering. When used as scaffolds, hydrogels may contain human cells in order to repair tissue.¹²
- Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.¹³⁻¹⁵
- As control-release delivery systems.¹⁶

- Provide absorption, desloughing and debriding capacities of necrotics and fibrotic tissue.

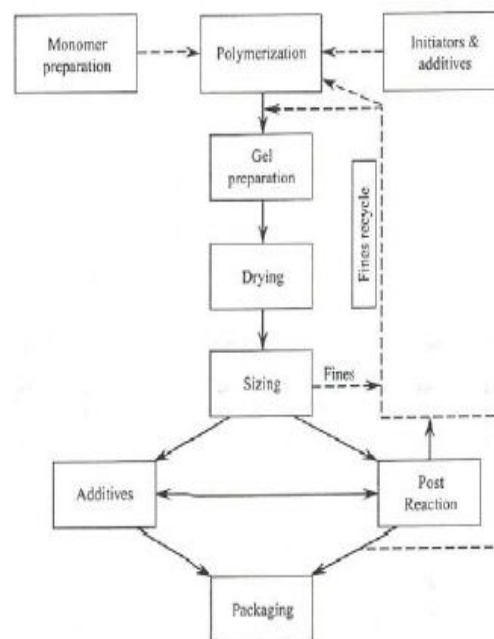


Fig. 1: Hydrogel preparation block diagram (solution polymerization procedure)^[11]

- Hydrogels that are responsive to specific molecules, such as glucose or antigens can be used as biosensors as well as in DDS.¹⁷
- Used in disposable diapers where they "capture" urine, or in sanitary napkins
- Contact lenses (silicone hydrogels, polyacrylamides)¹⁸

Common ingredients are e.g. polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups. Natural hydrogel materials are being investigated for tissue engineering, these materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers-

PROPERTIES OF HYDROGEL

Hydrogels are water swollen polymer matrices, with a tendency to imbibe water when placed in aqueous environment. This ability to swell, under biological conditions, makes it an ideal material for use in drug delivery and immobilization of proteins, peptides, and other biological compounds. Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial. These networks, have a three dimensional structure, crosslinked together either physically (entanglements, crystallites), or chemically (tie-points, junctions). This insoluble

crosslinked structure allows immobilization of active agents, biomolecules effectively, and allows for its release in well-defined specific manner. Thus the hydrogels biocompatibility and crosslinked structure are responsible for its varied applications.¹⁹

ADVANTAGES

- Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity.
- Hydrogel is more elastic and stronger than available hydrogels of similar softness. Poly (methyl acrylate-co-hydroxyethyl acrylate) hydrogel implant material of strength and softness.
- Hydrogel-based microvalves have a number of advantages over conventional microvalves, including relatively simple fabrication, no external power requirement, no integrated electronics, large displacement (185 μm), and large force generation (22 mN).
- Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
- Natural hydrogel materials are being investigated for tissue engineering, these materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers.^{20,21}

DISADVANTAGES

- The main disadvantages are the high cost and the sensation felt by movement of the maggots.
- Its disadvantage include thrombosis at anastomosis sites and the surgical risk associated with the device implantation and retrieval.
- Hydrogels are nonadherent; they may need to be secured by a secondary dressing.
- Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions.

APPLICATIONS OF HYDROGELS

Applications of Hydrogels in Drug Delivery

Advances in recombinant protein technology have identified several protein and peptide therapeutics for disease treatment. Thus hydrogels are primarily used for encapsulation of bioactive materials and their subsequent controlled release. Hydrogel based delivery devices can be used for oral, ocular, epidermal and subcutaneous application. These applications are discussed in detail below.^[22]

Drug Delivery in the GI Tract: - The ease of administration of drugs and the large surface area

for absorption makes the GI tract most popular route for drug delivery. Hydrogel-based devices can be designed to deliver drugs locally to specific sites in the GI tract.

Rectal Delivery: - This route has been used to deliver many types of drugs for treatment of diseases associated with the rectum, such as hemorrhoids. This route is an ideal way to administer drugs suffering heavy first-pass metabolism. An indomethacin poly vinyl alcohol (PVA) hydrogel used for rectal administration. The release of indomethacin from the PVA hydrogel agreed with the Fickian diffusion model for 10 hr. Rectal administration of indomethacin hydrogels to rats yielded high indomethacin plasma concentrations, without producing a sharp peak, and a sustained-release effect. In dogs, the indomethacin hydrogel produced a similar sustained-release effect; however, the indomethacin plasma concentration was relatively low compared with that of an indomethacin suppository.^[23]

Ocular Delivery: - Drug delivery to the eye is difficult due to its protective mechanisms, such as effective tear drainage, blinking, and low permeability of the cornea. Thus, eye drops containing drug solution tends to be eliminated rapidly from the eye and the drugs show limited absorption, leading to poor ophthalmic bioavailability. Due to the short retention time, a frequent dosing regimen is necessary for required therapeutic efficacy.²²

Transdermal Delivery:- Polyurethane hydrogel drug reservoirs for use in transdermal drug delivery systems. A drug reservoir for use in a transdermal drug delivery system, comprising a layer of a polyurethane hydrogel having a drug formulation comprising at least one permeation enhancer absorbed therein.^[24] Drug delivery to the skin has been generally used to treat skin diseases or for disinfections of the skin. In recent years, however a transdermal route for the delivery of drugs has been investigated. Swollen hydrogels can be delivered for long duration and can be easily removed. These hydrogels can also bypass hepatic first-class metabolism, and are more comfortable for the patient.

The hydrogel type polyurethane (PU) foams were prepared from diisocyanate and polyol with/without hydrophilic moiety for wound dressing to protect infection from outside and to heal skin wound. Biomaterials with hydrogel properties, such as alginate and hyaluronic acid, and antimicrobial agent (silver sulfadiazine, AgSD) were also incorporated in the polyurethane foam. The PU foams have good properties such as mechanical strength, swelling ratio, and cell adhesion for applying to wound dressing.^[25]

Subcutaneous Delivery:- Among the varied possible pharmaceutical applications of hydrogels, the most substantial application is probably in

implantable therapeutics. Leading to inflammation, Carcinogenicity and immunogenicity. They have high water content, environment similar to biological tissue, making them relatively biocompatible.

Thus hydrogels are an ideal material to be used for delivery of proteins and peptides. Hydrogel formulations for subcutaneous delivery of anticancer drugs have been proposed. For example, crosslinked PHEMA was applied to cyratatine (Ara-C) Current studies on implantable hydrogels are leading towards the development of biodegradable systems, which don't require surgical removal once the drug has been administered²³⁻²⁸

Application of Hydrogels to Fix Bone Replacements

Provided are orthopedic fasteners and replacements such as nails, screws, pins, hip and knee replacements, etc., coated with hydrogels and other biocompatible/biodegradable materials which expand in the presence of liquids. Useful coating materials include methacrylate, hyaluronic acid esters, and crosslinked esters of hyaluronic acid resulting from the esterification of hyaluronic acid with polyhydric alcohols

Replacements can be thus coated, even those made of stainless steel, metal alloys, titanium, or cobalt-chromium, treatment of the surfaces to improve metal-polymer adhesion.^{29-31.}

Hydrogel for Repairing, Regenerating Human Tissue

Regenerating healthy tissue in a cancer-ridden liver, healing a biopsy site and providing wounded soldiers in battle with pain-killing, infection-fighting medical treatment are among the myriad uses the scientists foresee for the new technology. Formulating hydrogels as delivery vehicles for cells extends the uses of these biopolymers far beyond soft-contact lenses into an intriguing realm once viewed as the domain of science fiction, including growing bones and organs to replace those that are diseased or injured. Hydrogels are formed from networks of super-absorbent, chain-like polymers. Although they are not soluble in water, they soak up large amounts of it, and their porous structure allows nutrients and cell wastes to pass right through them.³²⁻³⁴

PRODUCTS OF HYDROGEL NANO DOX™ HYDROGEL

Nanotherapeutics, a privately held specialty biopharmaceutical company, announced that it has submitted its first Investigational New Drug (IND) application to the FDA. a topical doxycycline hydrogel for chronic wounds. The randomized double-blind study will assess the safety and efficacy of the product on the healing rates of non-

infected diabetic ulcers of the lower extremity. "Diabetic ulcers are the primary cause of amputations of the leg, foot, or toe. Two-thirds of all lower extremity .We believe that NanoDOX™ is a unique formulation that holds significant promise for the millions of people suffering from diabetic ulcers," said Weaver H. Gaines, Chairman of the Board. "

NanoDOX™ Hydrogel, the company's leading pharmaceutical product in development, is an alternative topical formulation of doxycycline. Nanotherapeutics developed the product with its proprietary particle stabilization technology and formulated it to improve the topical delivery of doxycycline to increase local efficacy of the drug.^{28, 35}

FUCOIDAN-CHITOSAN HYDROGEL™

Hydrogels are ideal biopolymeric pharmaceutical forms for the treatment of skin Wounds.

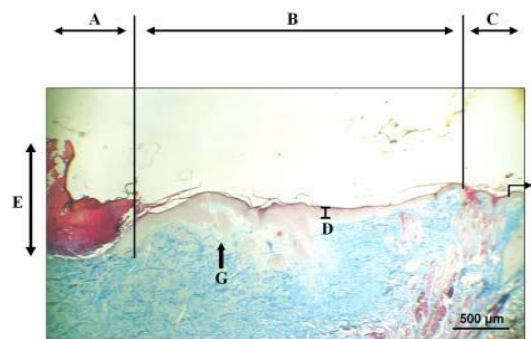


Fig. 2: The scheme of the microscopic evaluation of the wound area. A-the eschar area of the wound, B-the wound epithelial elongation, C-non-burned epithelial area, wound epithelium thickness (the healing area of the wound) E-the eschar thickness of the wound, F-non-burned epithelium thickness, G- the papillary structures as called rete pegs or finger like projections^[37]

They have low interfacial tension, high molecular and oxygen permeability, good moisturizing and mechanical properties that resemble physiological soft tissue Low gel hardness ensures that the minimum work is required for removal of gels from the container and the applicability onto the desired site. Low hardness decrease the retention time of gel formulation on the wound and therefore, a hydrogel formulation should have an appropriate hardness value for the effective treatment of wounds.^{36,37}

CORGEL BIOHYDROGEL™

The patented hyaluronan (hyaluronic acid) based biocompatible hydrogel is based on di-

hydroxyphenyl linkages of tyramine substituted hyaluronan. Corgel™ may be useful in surgical and transcatheter applications including vascular surgery, cardiology, ophthalmology, orthopedics, aesthetics, ENT, drug delivery, tissue engineering and regenerative medicine.³⁸

RECENT TRENDS OF HYDROGEL

Microparticles of Poly methacrylic acid and novel semi-interpenetrating network composed of Poly methacrylic acid-alginate (PMAA) were prepared and their application in oral insulin delivery was evaluated. The release kinetics at pH 7.4 exhibited sustained release of insulin for more than 5 hrs in case of PMAA microparticles whereas burst release of insulin (90% of total insulin loaded) within 1 hr of study was observed in the case of PMAA-alginate microparticles.³⁹

The new type of hydrogel system *HYPAN* (which is known under the trademark *HYPAN™*) is described in some detail here, emphasizing its grades and those properties potentially useful in controlled drug delivery systems. A physical network of crystalline clusters, which fully replace the covalent network typical of other hydrogels, distinguishes *HYPAN* hydrogels. As a result, *HYPAN* hydrogels can be processed by a number of methods unusual for hydrogels, such as extrusion and injection molding.⁴⁰

Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature sensitive, which are used for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. The liposomal drug delivery system developed here enables controlled release of vasodilator and would allow an appropriate time for beginning irradiation treatment to be defined.⁴¹

SUMMARY AND CONCLUSION

Hydrogels are superabsorbent natural or synthetic polymers. Hydrogel-forming natural polymers include proteins such as collagen and gelatin, and polysaccharides such as alginate and agarose. The various methods of preparation of hydrogels are crosslinking of Polymers, Copolymerization/Crosslinking Reactions, Crosslinking by High Energy Radiation and Crosslinking Using Enzymes. This insoluble crosslinked structure allows immobilization of active agents, biomolecules effectively, and allows

for its release in well-defined specific manner. Hydrogel based delivery devices can be used for oral, ocular, epidermal and subcutaneous application. Hydrogels are orthopedic fasteners and replacements such as nails, screws, pins, hip and knee replacements, etc. Products of hydrogel are nano dox™ hydrogel, fucoidan-chitosan hydrogel™, corgel biohydrogel™, etc. Recent developments in the field of polymer science and technology has led to the development of hydrogel for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Novel semi-interpenetrating network composed of Poly methacrylic acid-alginate (PMAA) were prepared for oral insulin delivery. New synthetic methods have been used to prepare homo- and co-polymeric hydrogels for a wide range of drugs, peptides, and protein delivery applications. Hydrogels are also used in regenerating human tissue cells.

REFERENCES

1. David B. Troy, Paul Beringer, "Remington: The Science and Practice of Pharmacy. Published by Lippincott Williams & Wilkins, 2005. Twenty-First Editions. P.NO. 294,756,867,868.
2. <http://www.thefreedictionary.com/hydrogel> (Accessed in Nov. 2010)
3. <http://en.wikipedia.org/wiki/Gel>
4. Peppas N.A.: Hydrogels in Medicine and Pharmacy, Vol. 1. Fundamentals, CRC Press, Boca Raton, FL, 1986, 180.
5. Malcolm B. Huglin, M.B.Z., *Swelling properties of copolymeric hydrogels prepared by gamma irradiation*. 1986. p. 457-475.
6. Sperinde, J.J. and L.G. Griffith, *Control and Prediction of Gelation Kinetics in Enzymatically Cross-Linked Poly(ethylene glycol) Hydrogels*. 2000. p. 5476-5480.
7. William A. S. and Robert C. W., Method of hydrogel preparations, US Patent 2773839, 1956.
8. Pal K., Banthia A.K., Majumdar D.K., Preparation and Characterization of Polyvinyl Alcohol-Gelatin Hydrogel Membranes for Biomedical Applications. *AAPS PharmSciTech*. 2007; 8(1).
9. Gupta S.C., Baheti G.L., and Gupta B.P., Application of hydrogel system for neutron attenuation, Radiation Physics and Chemistry, 2000, 59(1), p. 103-107.
10. Peppas N.A., Crystallization of polyvinyl alcohol-water film by slows dehydration, European polymer J., 1976, 12(8), p. 495-498
11. Alaei J., Hasan S., Boroojerdi & Rabiei Z., Application of hydrogels in drying

- operation, *Petroleum & Coal*, 2005, 47 (3), p. 32-37.
12. Ma, Peter X., and Jennifer Elisseeff, eds. *Scaffolding in Tissue Engineering*. New York: C R C P LLC, 2005.
 13. Qiu Y. and Park K., *Triggering in Drug Delivery Systems*, *Advanced Drug Delivery Reviews*, 2001, 53(3), p. 321-339.
 14. Liang-chang Dong, Allan S. Hoffman, A novel approach for preparation of pH sensitive hydrogel for enteric drug delivery, *J. of control. Rel.* 1991, 15(2), p. 141- 152.
 15. Luke M. G., Declan M. D., Michael J.D. N., James E. K., John G.L., Austin H., Clement L. H., Lower critical solution temperature control and swelling behaviour of physically crosslinked thermosensitive copolymers based on N isopropylacrylamide, *European Polymer Journal*, 2006, 42(10), p. 2540-2548.
 16. CS Satish, KP Satish, HG Shivakumar, Hydrogels as controlled drug delivery systems: Synthesis, crosslinking, water and drug transport mechanism, *Year* 2006,68(2), p. 133-140.
 17. Ting-Yu Liu, Shang-Hsiu Hu, Dean-Mo Liu, San-Yuan Chen, I-Wei Chen Biomedical nanoparticle carriers with combined thermal and magnetic responses *Nano Today*, 2009, 4(1), p. 52-65.
 18. Subbaraman L.N., Glasier M.A., Senchyna M., Jones L., Stabilization of lysozyme mass extracted from lotrafilcon silicone hydrogel contact lenses., *Optom Vis Sci.* 2005, 82(3), p. 209-14.
 19. Lin, C.C. and Metters A.T., Hydrogels in controlled release formulations: Network design and mathematical modeling, *Advanced Drug Delivery Reviews*, 2006, 58(12-13), p. 1379-1408.
 20. *Handbook of Pharmaceutical Excipients*, A. Wade and P.J. Weller ed., The Pharmaceutical Press, London, 1994, p. 229-232.
 21. *British Pharmacopoeia 2002*, the Stationary Office, London, 2002, p. 2092-2094.
 22. http://etd.lsu.edu/docs/available/etd-07032007-25943/unrestricted/Datta_thesis.pdf
 23. Kazuhiro M., Atsushi N., Shinichi F., Katsuaki M., Suong-H. H. and Ikada Y, Evaluation of polyvinyl Alcohol Hydrogel as a Sustained-Release Vehicle for Rectal Administration of Indomethacin, *Journal Pharmaceutical Research* , 1989, 6(4).
 24. Polyurethane hydrogel drug reservoirs for use in transdermal drug delivery systems, and associated methods of manufacture and use, US Patent 5902603, May 11, 1999.
 25. Preparation of wound dressing using hydrogel polyurethane foam., *Trends in Biomaterials and Artificial Organs*, 2001.
 26. Patel, V.R. and M.M. Amiji, Preparation and Characterization of Freeze-dried Chitosan-Poly (Ethylene Oxide) Hydrogels for Site-Specific Antibiotic Delivery in the Stomach. *Pharmaceutical Research*, 1996. 13(4): p. 588-593.
 27. Yadavalli, V.K., et al., Microfabricated protein-containing poly (ethylene glycol)Hydrogel arrays for biosensing. *Sensors and Actuators B: Chemical*, 2004. p. 290-297.
 28. Hoffman, A.S., *Hydrogels for biomedical applications*. *Advanced Drug Delivery Reviews*, 2002. 54(1): p. 3-12.
 29. <http://www.lbl.gov/TechTransfer/techs/lbn12398.html>
 30. <http://lib.bioinfo.pl/meid:234060>
 31. <http://www.sciencedirect.com/science?>
 32. Kobayashi, T., et.al., Motility and growth of human bone-marrow mesenchymal stem cells during ex vivo expansion in autologous serum. *J Bone Joint Surg Br*, 2005, 87-B: 1426-1433.
 33. <http://www.medicalnewstoday.com/article/s/77312.php>
 34. <http://www.sciencedaily.com/releases/2007/07/070719011146.htm>
 35. <http://www.medicalnewstoday.com/article/s/120545.php>
 36. <https://denshi.pharm.or.jp/home/pubpharm/pubview.asp?p=b080735>
 37. Deshpande A.A., *Drug Dev. Ind. Pharm.*, 18, P.no 1225-1279 (1992).
 38. <http://www.lifecore.com/MoreAboutHyaluronan/CorgelBioHydrogel/tabid/65/Default.aspx>.
 39. Parakh S.R., Jagdale S.C. * and Deokar V. D *Advanced Insulin Delivery Systems: Present Trends And Future Directions*, *Pharmainfo.net*, 2005, 3(2).
 40. <http://jba.sagepub.com/cgi/content/abstract/3/4/552>
 41. Stoy J Biomater, New Type of Hydrogel for Controlled Drug Delivery Appl.1988; P.no.552-604.