ISSN No:-2456-2165

Injectable Hydrogels Drug Delivery System for Cancer Therapy

Chetan D. Tangade; J.V. Vyas; Dr. V.V. Paithankar; Dr. A.M. Wankhade

Abstract:- These issues can be successfully avoided with injectable hydrogels by releasing medication locally at the tumor site. The benefits of local toxicity on the tumor have prompted studies into whether hydrogels are appropriate for drug delivery. Different hydrogel drug delivery systems, such as heat-, pH-, light-, and dual-sensitive hydrogels, have been developed in accordance with different cancer types and stages. Recent developments in hydrogels and other drug delivery technologies are highlighted in this review. In conclusion, as we learn more about injectable hydrogels for cancer treatment at a site, their efficacy and durability as treatments improve. Promising avenues for future research include smart delivery systems that react differently to stimuli at different times based on alterations in the tumor site's microenvironment. Because there are numerous polymer systems to choose from that have diverse chemical properties and excellent performance,there has been an increase in interest in Injectable hydrogels have been used in cancer therapy in recent years.To address the shortcomings of the available treatments, several research teamsare developing ablation systems appropriate for thermal and photothermal ablation, radiation therapy, and chemotherapyThe initial polymers' structure and properties are frequently categorized by origin or syntheticity—are the main topics of our work, which reviews and discusses the most recent developments in injectable hydrogel technology.

Keyword:- *Polyphosphazenes (PPZ), Camptotechin (CPT), Tumor Cell Lysates 3 (TLR3), Nanocapsule-Based Hydrogels (NBL), Blood-Brain Barrier (BBB), Doxorubicin (DOX).*

I. INDRODUCTION

Injectable hydrogels are hydrophilic polymer networks in three dimensions that have a strong affinity for bodily fluids. These networks can be injected or administered intravenously using a drug syringe. Therapeutic drug delivery and tissue engineering have been proposed using injectable hydrogels in the biomedical field.[1]

Depending on how they gel, hydrogels can be categorized as physically or chemically cross-linked.The addition of chemical compounds can create new chain linkages by means of heat radiation or light, or it can be done through a particular process that involves the formation of Schiff bases, Clicks on azide-alkyne (CuAAC), Michael-type Addition, and Diels-Alder cycloaddition. Three-dimensional structures that can serve as platforms for engineering van tissues. or controlled can be created by encasing the required medications within the gel during the hydrogel's formation. Because of their longer physical stability, more stable crosslinking content, and longer degradation time, hydrogels are stronger than other materials. Nonetheless, certain chemical elements, such as the mixture of monomers, photoinitiators, organic solvents, or catalysts, seem to limit the in vivo application.[2]

The upper limit for injectable drugs has been set at 0.05 Pa·sthrough the Food and Drug Administration (FDA) in the US. After gelation, there was a noticeable quick increase in this value, which continued to rise over time. Other crucial structural elements like porosity (e.g., pore size) strictly determine the mechanical properties of the entire hydrogel. G. distance between intersections). The duration of hydrogel integrity will be extended by increasing the concentration or attachment rate, which will also increase the mechanical strength. That being said, this will determine how much the hydrogel's porosity decreases and how the film releases in response to the delivery of solutions or medications that will restrict the flow of nutrients and encourage cell growth in the tissue-engineered tissue. Thus, there needs to be a careful consideration of balance between these parameters. Injectable hydrogel intended for medical use needs to meet specific criteria, includingstability, non-toxicity, biodegradability, biocompatibility, and suitable general and viscoelastic properties. Injectable hydrogels that are biocompatible must not cause cancer, be toxic, or harm the body while they are degrading. Nucleic acids, peptides, and carbohydrates generally break down spontaneously into innocuous byproducts.[3]

Cancer treatment is one of the most studied applications of injectable hydrogels. Actually, administering chemotherapy to treat cancer frequently results in excessive cytotoxicity. To get around this problem, drug hydrogels can be used to deliver chemotherapy drugs into the body and provide controlled, targeted release at the tumor site.[4,5]

ISSN No:-2456-2165

II. SYNTHETIC INJECTABLE HYDROGELS

A. Polyphosphazenes

Synthetic Injectable Hydrogels (PPZ) are a class of organic-inorganic hybrid macromolecules consisting of nitrogen and phosphorus atoms arranged in repeat, with single and double bonds occurring alternately. Their skeletons may be branching or linear. Phosphorus atoms are bonded to two organic groups, just like the aryl and alkyl moieties of amino acids.

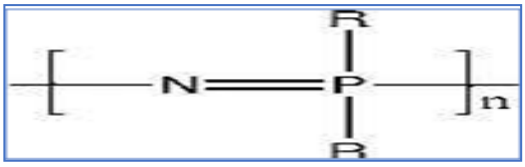

Fig. 1: Representation of Polyphosphazenes. X=O,NH; R and R1=Alkyl, Aryl, amino acid are provided in figure (1). [6]

PPZ can be produced from a variety of materials; the majority of materials related to biotechnology are made via ring-opening polymerization and macromolecular modification.Because of its aqueous solution's capacity to experience a sol–gel transition with temperature, PPZ is being considered as a potential material for injectable hydrogel formulations. Though PPZ gels at body temperature, it is actually sold at room temperature or lower. The ratio of hydrophobic to hydrophilic substituents can be changed to reverse this change. Moreover, numerous PPZ hydrogels that are sensitive to hydrolysis have been created with minimal toxicity from the breakdown products, which typically consist of free organic side groups, ammonium, H3PO4, and others. Because these derivatives have been demonstrated to have a very long degradation time, reducing biomedical relevance, the use of cyclic PPZ samples instead should be suitably investigated. Numerous research teams have created a range of PPZ injectable hydrogels, despite the fact hat many PPZ polymers are not yet commercially accessible. sRNA or cytotoxic drugs have been successfully delivered to cancer cells both in vitro and in vivo using PPZ-based hydrogels..

Injectable hydrogels derived from Camptotechin (CPT) prodrugs have been suggested as an additional alteration to the way PPZ is used to treat lung conditions, such as lung cancer. Magnetothermal ablation and cancer diagnosis have both benefited from the incorporation of ferrite superparamagnetic iron oxide nanoparticles into hydrogel samples.[8]

B. Polaxamers

Injectable hydrogels derived from Camptotechin (CPT) prodrugs have been suggested as an additional modification to the use of PPZ for the treatment of lung and lung cancer. Magnetothermal ablation and cancer diagnosis have both benefited from the incorporation of ferrite superparamagnetic iron oxide nanoparticles into hydrogel samples. Diagrammatic illustration of poloxamers. Figure (2) gives the values for x: 2–130 and y: 15–67.[9,10]

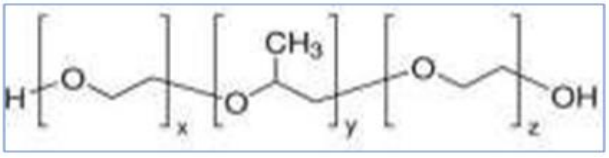

Fig. 2: Schematic Representation of Poloxamers. x:2–130;y:15–67. [9,10]

Because of its PPO element tongue, PF127 (PEO/PPO balance 70/30) is one of the most widely used poloxamers in biomedical applications. It can form micellar nanocarriers of lipophilic drugs during hydrogel network or reverse thermal gelation. At 4 °C, about 20 weight percent of the aqueous content of PF127 has a low viscosity state. Owing to micellar packing and entanglement, half of the gel is obtained when heated to room temperature or body temperature. Thus far, PF127 injectable hydrogels have been proposed as drug and crystal carriers for the treatment of hematological disorders and cancers. It's interesting to note that this system has been shown to reverse the majority of drug reactions in MCF-7/ADR cells due to its ability to increase intracellular drug escaping from the cell membrane pump. Cytotoxic drug-loaded nanoparticle carriers, such as micelles or polymeric nanoparticles, were added to the hydrogel in order to improve the drug release profile. This method was used to create poly (D, L-lactide-co-glycolide) nanoparticles loaded with doxorubicin. (DOXPLGA) and 5-fluorouracil (5-FU) can be delivered simultaneously for the in vivo and in vitro treatment of melanoma. Thermal and photothermal effects are generated when metal nanoparticles (like copper or gold) are employed as nanocarriers.[11]

Finally, to prepare a good depot system for cancer and cancer treatment, it is worth mentioning the addition of cyclodextrin (α-CD) to the hydrogel network.

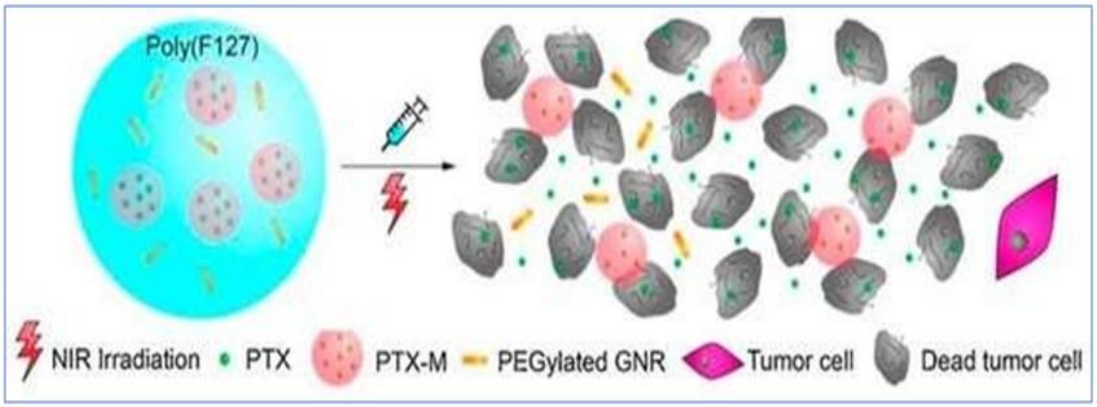

Fig. 3: Schematic Representation of the PTX-NPs/AuNRs/gel-mediated Photothermal–Chemotherapy.[12]

C. Polyesters

A new approach to administering hydrophobic medications that may be able to treat high dosages of cancer at the point of no return is thermosensitive in situ gels, which are based on amphiphilic copolymers of biodegradable polyesters and polyethylene glycol (PEG). Limitations are often associated with the use of these medications. Nevertheless, the main disadvantage of these materials is that their limited use in biomedicine stems from the fact that the product's acid degradation can change the environment's pH. [13]

This class of polymers has the benefit of being highly biodegradable, which enables the creation of biocompatible and stimuli-responsive delivery systems. In addition, it permits targeted or improved delivery into the body, which can be applied to hydrophobic medication targets and cancerous regions. The principal limitation of these materials, though, may stem from the product's acid degradation, which modifies the pH of the surrounding environment and limits the materials' use in biomedicine.[14]

Numerous biodegradable polymers, each with distinct biological characteristics, have been used to create hydrogels. A sketch of the principal polyester structures utilized in this context can be found in Figure (4).[15]

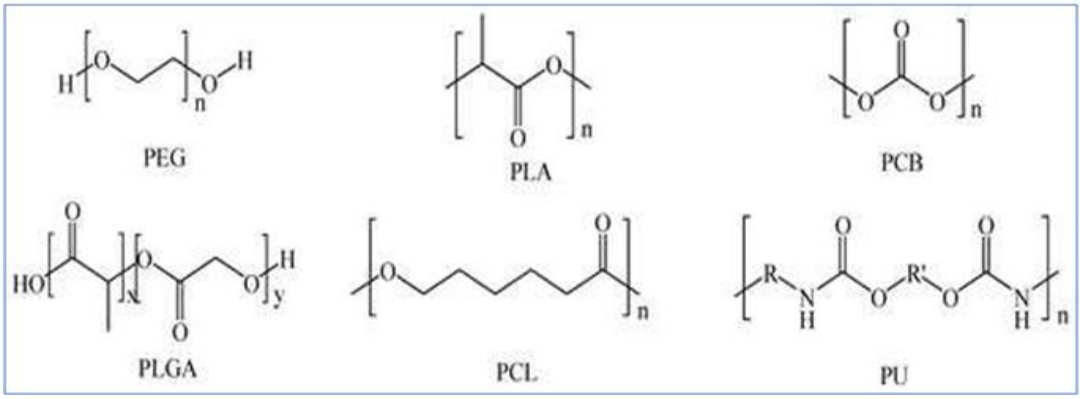

Fig. 4: Diagram illustrating the Primary Biodegradable Polyesters and Poly (Ethylene Glycol) (PEG). Polylactide (PLA), Polycarbonate (PCB), Poly(Lactide-Co-Glycolide) (PLGA), Poly(ε-Caprolactone) (PCL), and Poly(Urethane) (PU).[15]

Injection thermo sensitive PLA-PEG-PLA has been used for the local delivery of cisplatin (CisPt) and gemcitirib (GEM) to foster synergy in the treatment of pancreatic cancer.Nevertheless, three hydrogels (PLA-PL-PLA) are produced when poly (D, L-lactide) PLA is partially combined with pluronic L(PL) for intra peritoneal intestinal treatment.[16]

The PLGA-PEG-PLGA gels show a transition temperature between 10 and 40°C at polymer concentrations of 15-20wt percent, according to data reports. When the temperature drops, amphiphilic copolymers [17] flow freely, but when the temperature rises to body temperature, they gel. Polyoctadecanedioic anhydride, methoxypolyethylene glycol, and d,l-lactic acid oligomers were combined to create A thermosensitive amphiphilic triblock copolymer that can be used in oncology locally. In particular, lyophilized powders containing paclitaxel (PTX) loaded LA oligomer nanoparticles can be stored and subsequently reconstituted at room temperature in aqueous media to form hydrogel at the injection site.[18]

In vivo experiments on osteosarcoma have suggested the use of PLGA-PEG-PLGA gel as a carrier for topotecan (TPC), CisPt, DOX, and methotrexate (MTX).due to the ease with which micellar aggregation networks form when polymer concentration increases (Pharmacis 2019, 11, 486 8/56).[19]

ISSN No:-2456-2165

Drugs or drug nanoparticles can be loaded into injectable, thermosensitive hydrogels. More accurately, 2-methoxyestradiol (ME) and cytarabine (CYT), which are used to treat leukemia and cancer, respectively, are released when certain surfactants interact with ionic compounds. In contemporary therapies, DOX is combined with sRNA poly(ethyleneimine)-lysine (PEI-Lys) complexes to further promote PLK1 silencing, tumor apoptosis, and osteosarcoma cell cycle regulation.[20]

Hydrophobic and hydrophilic drug releases in one go are a competitive development in the pharmaceutical and biomedical industries, as they show the differences in the clinical survival rates for medication therapy alone. Granulocyte-macrophage colony-stimulating factor, which is continuously released by the device, attracts, grows, and develops dendritic cells and macrophages at the injection site, rendering it a valuable therapeutic tool for melanoma.[21]

Granulocyte-macrophage colony-stimulating factor, which is continuously released by the device, encourages the recruitment, development, and proliferation of dendritic cells and macrophages at the injection site and so treats melanoma effectively. The process of producing amphiphilic block copolymers with PEG side chains involves the use of ε-caprolactone.[22]

A supramolecular hydrogel that could be injected to release PTX, DOX, and CisPt in bladder and lung tumors was created by synthesizing MPEG-b-PCL copolymer diblock with a-CD. Within these systems, α-CD is exclusively integrated into linear polymer chains. The ensuing supramolecular complexes are frequently assembled into dense arrays created by host interactions stemming from π-π stacking of polymer chains.[23]

These systems have drawn particular interest because of their advantageous characteristics, like thixotropy and reversibility, as well as their capacity for encapsulation, which results in fewer side effects and a cancer treatment that lasts longer. Ethylene glycol-b-poly (ε-caprolactone-co-1,4,8-trioxa [4.6] spiro-9-undecanone) and diblock copolymer preparation of (PEG-PCL) host-guest inclusion complex injectable nanocomposite surface modified with materials based on α-cyclodextrin, PTX/PEG-PCL nanoparticles, and gold nanorods.[24]

To do this, PCLA-PEG-PCLA triblock copolymer was created by ring-opening copolymerization of ε-caprolactone and LA in the presence of PEG and tin (II) 2-ethylhexanoate. In order to produce non-anticoagulant heparin prodrugs loaded into thermosensitive hydrogels for anti-metastatic therapy and as GEM carriers for the treatment of pancreatic cancer, amphiphilic copolymers have been specially conjugated with heparin.[25]

An alternative strategy that has been proposed as a means of preventing diabetic complications after breast cancer surgery is the development of a dihydroxyacetone polycarbonate (pDHA) and PEG-based biodegradable polymeric biomaterial. In order to create physically cross-linked injectable hydrogels that can form triblock copolymers and continuously and locally deliver Herceptin, vitamin E and D functionalized polycarbonates are used as hydrophobic building blocks in the treatment of breast cancer. Making a biodegradable polymeric biomaterial based on PEG and dihydroxyacetone polycarbonate (pDHA) is an additional tactic. This approach has been suggested as a way to stop diabetic complications following breast cancer surgery. Vitamin D and E functionalized polycarbonates serve as hydrophobic building blocks for physically cross-linked injectable hydrogels that can form triblock copolymers and continuously and locally deliver Herceptin for the breast cancertreatment.[26]

D. Polyacrylates

The production of self-sustaining injectable hydrogels after injection under UV irradiation can be accomplished without using heat gelation by using light-induced free radical polymerization involving acrylate monomers and/or functionalized macromonomers.

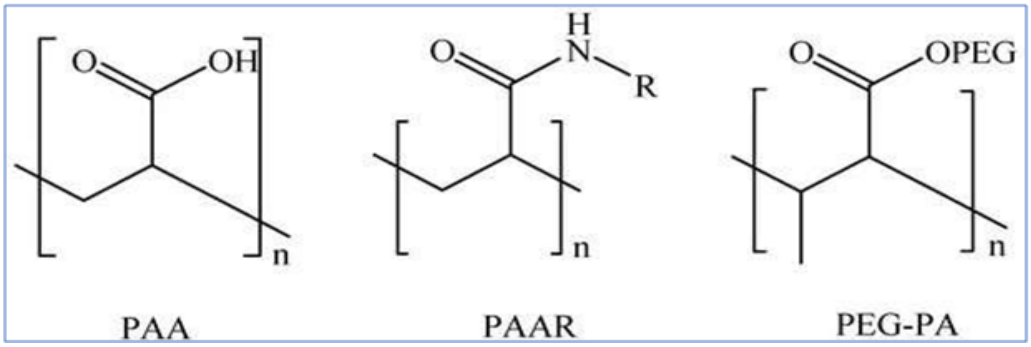

Fig. 5: Diagram Illustrating the Primary Acrylate Polymers. PEG-PA: PEGylated poly (Methacrylic Acid); PAA: Poly (Acrylic Acid); PAAR: N-Alkyl Poly (Acrylic Amide).[27]

ISSN No:-2456-2165

This class of materials consisted primarily of PEG acrylate polymers (PEG-PA), which were created to enable the introduction of PEG characteristics (e.g. PEG. improved mechanical properties, greater drug loading capacity, non-cytotoxicity, non-immunogenicity, and the capacity to lessen opsonization) inside a hydrogel network. The pH-sensitive and near-infrared hydrogel was efficiently loaded by the host-guest interactions catalyzed by the adamantane-modified DOX prodrug. Along with in vivo trials treating murine sarcoma, its effectiveness was evaluated against HeLa (cervix) and MCF7 (breast) cancer cells in vitro. Alternatively, thermo responsive supra molecular poly (N-acryloyl glycinamide-co-acrylamide) (PNAm) hydrogels were prepared by utilizing radical photopolymer, which included DOX and polydopamine-coated gold nanoparticles.[28]

E. Synthetic Polypeptide

Because they are both biocompatible and biodegradable, peptides are naturally occurring synthetic materials that are particularly interesting. The chemical diversity of this class of compounds is another advantage. The synthetic polypeptides that result from the synthesis of 21 natural amino acids, as well as monomers derived from other sources, are shown in Figure. (6).[29]

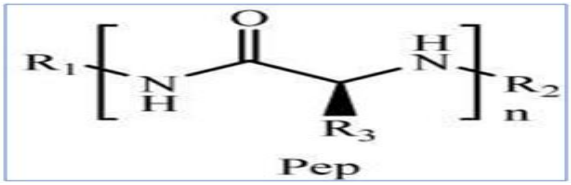

Fig. 6: Schematicre Presentation of Synthetic Polypeptides.[29]

The medication contains cytotoxic molecules that encapsulate bioactive ingredients for the treatment of various tumors. Ion gelation has been specifically suggested for the production of Ce6 cells from cancer cells and the induction of immune responses in mice in good health. Hydrogels for TMP-2 and DOX-based therapies for lung, breast, and cervical cancer as well as for DOX or gene (CDN) delivery through immune system stimulation are made using the thermogel process. Furthermore, Pep hydrogel was loaded with the DOX liposome formulation for the combination of losartan (LST). Peptide groups can also be coupled with oligoethylene glycols (OEG) or PEG derivatives to form pegylated or block copolymers, which is another technique for creating hydrogel starting materials. These hydrogels have demonstrated their applicability in the preparation and administration of medications in various clinical settings involving cytotoxic drugs. They can release information or activate the immune system in reaction to physical stimuli like cellular redox state and pH temperature.

Thermogels composed of poly (1-EG4-SS-Cys) diblock copolymer and PEG were used as reducing agents. Hydrogels with superior shear-thinning properties were also produced by a physical synthesis method employing PEG44-NH2 as the macroinitiator.

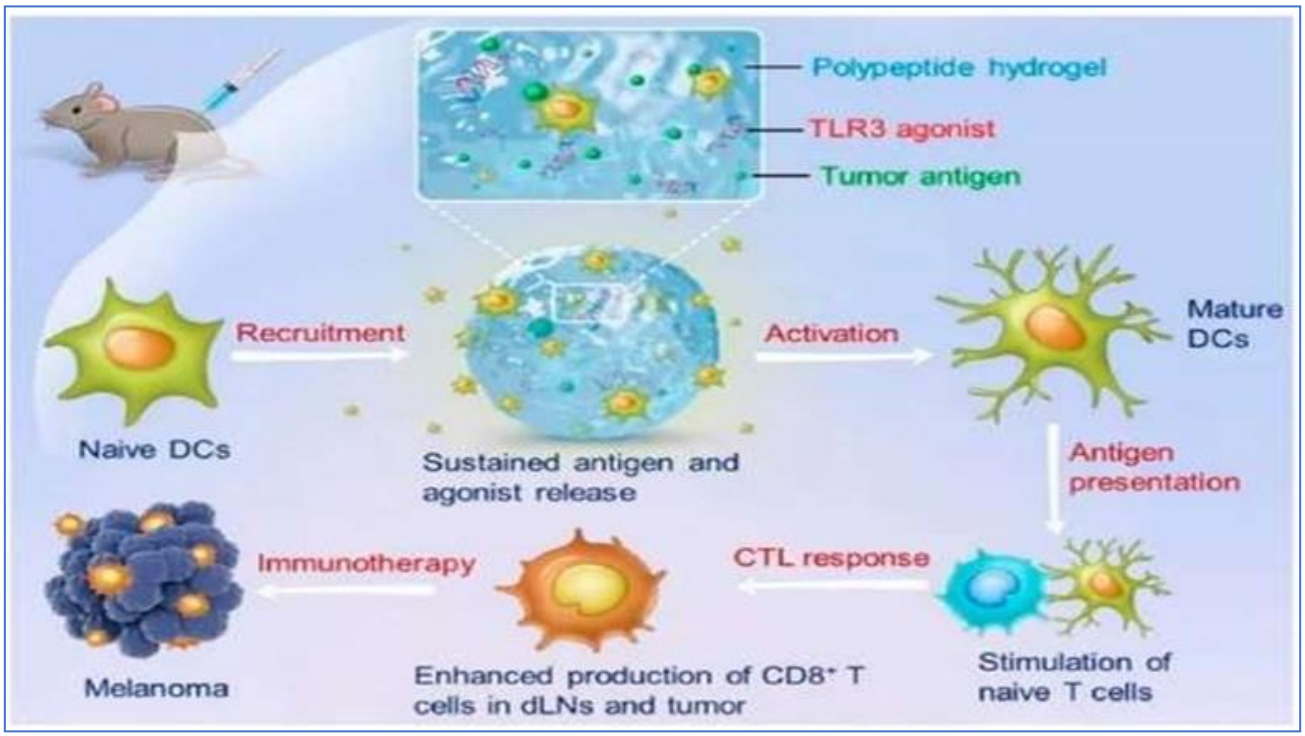

Fig. 7: Dendritic Cells (DCs) are Modulated in Vivo through the Prolonged Release of Tumor Antigens and Tumor Cell Lysates 3 (TLR3) agonist from a Polypeptide Hydrogel (7). This Results in a Potent Cytotoxic T-Lymphocyte (CTL) Response.[30]

ISSN No:-2456-2165

F. Dendrimers and Other Systems

Synthetic branched polymers known as dendrimers are created by adding monomer units to the generation 0 core during a series of reaction steps. They have a spherical structure, nanometer size, and low polydispersity index. These materials have unique qualities that make them suitable for use in pharmaceutical applications. These characteristics include the hydrophobic inner surface's affinity for various drug molecules, a range of functional groups that lend themselves well to research, and the capacity to pass through cell membranes through paracellular and endocytic pathways. Derivatizing heparin residues allows for the determination of the desired behavior. ToImproved biodistribution and increased solubility PEGylated PAMAM injectable hydrogels were tested as 5-FU carriers or pH-and redox-sensitive DOX delivery vehicles for the treatment of head and neck and oral child cancer, respectively. pH-sensitive PVA/GO hybrids loaded with CPT-CD complexes and hydrogels based on lipid nano capsules that can cross the blood-brain barrier are other injectable hydrogels for cancer therapy. The biocompatible properties of carbon nanostructures are utilized in the second method.[31]

III. TYPES OF INJECTABLE HYDROGELS USED IN MEDICINE DELIVERY, TISSUE ENGINEERING AND OTHER FIELDS

A. Thermosensitive Hydrogels

The volume of hydrogels that change in response to temperature changes are said to be temperature-sensitive. In gels, there are always certain amounts of hydrophobic and hydrophilic groups. Changes in temperature can have an impact on the hydrophobic interactions between these groups. In addition to creating cross-linked three-dimensional networks, hydrogels have a high capacity to absorb water. (A) The hydrogel swells at concentrations of 129 mg (xerogel) to 80,000 mg (damp gel). The stress-strain curves (i–v) of different hydrogels. Hydrogen bonds that form between macromolecular chains cause variations in gel structure and volume. What is meant by the low temperature test (LCST) is the temperature at which the volume changes. Under these conditions, gels expand in liquid. The gel shrinks when it reaches LCST. By combining them with medication and heating them to high temperatures, its special products can be injected into the body or used as medicinal products.

A thermosensitive doxorubicin (DOX) delivery system was developed in one study using PECT hydrogels. Unlike hydrogels based on free DOX diffusion, which have rapidly cleared drugs and poor drug permeability in tissues, PECT hydrogels encapsulate drug-loaded nanoparticles that self-polymerize. The PECT gel exhibits a sol-gel transition following in vivo injection. When the temperature goes above 28°C, viscosity significantly increases. At 37°C, the viscosity of hydrogels varies from sol to gel. By means of the EPR effect, the loaded nanoparticles disintegrate from the hydrogel and travel to the tumour. Drugs that are released intracellularly have a lower toxicity and stronger antitumor effects. As opposed to intravenous (I. VIII. In the context of tumors, thermosensitive hydrogels loaded with nanodrugs are efficient drug delivery vehicles.Drug delivery using thermosensitive hydrogels is a promising method due to its high loading efficiency with two or more components. It is thought that the Polo-like kinase 1 (PLK1) gene plays a major role in the regulation of meiosis and mitosis among tumor cells. By using RNA interference based on PLK1shRNA, these targets' activity in tumors may be reduced. The co-delivery hydrogel approach of DOX and PLK1shRNA/PEI-Lys was developed for the treatment of osteosarcoma. The anti-tumor effects of DOX may be enhanced, as per this model, by the hydrogel's PLK1shRNA/PEI-Lys. An effective eutectic hydrogel is created when DOX and PLK1shRNA/PEI-Lys are combined.[32]

B. PH-sensitive hydrogels

Tumor glycolysis will cause the surrounding tissue to become more acidic, lowering the extracellular matrix's pH in the tissue. Polymer gels that change in volume in response to changes in the pH and ionic strength of their surrounding environment are known as pH-sensitive hydrogels. One approach uses oxidized pullulan (OP) and dihydrocaffeic acid (CS-DA) grafted onto chitosan. Hydrogels loaded with doxorubicin were compared to traditional cancer treatments, and their anti-inflammatory qualities were examined. Response of hydrogels for local cancer therapy to pH variations in tumor tissue. Drug release is caused by the pH dropping as glycolysis takes place in the tumor area. When comparing the morphology of the hydrogel at pH 7.4 to pH 5.5, significant degradation of the hydrogel produced a larger pore. Over 80 percent of the DOX was liberated from the hydrogel after 60 hours at pH 5.5. To test the hydrogel's anti-tumor properties, Hct116 cells—a type of colon tumor—were added. At pH 5 and pH 7, DOX is released from the hydrogel continuously and steadily. It is possible for DOX to be released for longer than three days in both scenarios. Recent research has demonstrated that aspirin can inhibit cyclooxygenase, which in turn inhibits carbon monoxide synthase. It can also decrease survival, inhibit nuclear transcription factors, proteasomes, and genes that activate calcium-activated neutral proteasomes.[33]

Aspirin and the combination medication were used to demonstrate that while the drug released more slowly in simulated regular juice, it released more quickly in gastric juice. The oscillation is very good, as evidenced by the oscillation rate reaching 90% after 12 hours of oscillation.To further transform the polymer into an anti-inflammatory biosensor, dexamethasone phosphate was added to molecularly imprinted polymer nanospheres and subsequently transferred into a pH-sensitive hydrogel. Since an antibiotic may produce an acidic environment, the pH-sensitive hydrogel can release the medication quickly at pH 6.0~7.4 to prevent inflammation. This variation destroys hydrogels that are pH-sensitive. Innovative thinking was prompted by drugs used to treat cancer.[34]

C. Photosensitive Hydrogels

Two categories of photosensitive hydrogel processes exist based on the characteristics of the photosensitive material. The first is to immediately add photosensitive molecules to the temperature gel in order to cause it to reach the temperature change stage by converting light energy into electrical energy. The hydrogel then develops light sensitivity in this manner [35]. Among these, compounds containing ruthenium, nitrophenyl, and coumarin eliminate photosensitive groups and hydrophobic end bonds through the use of aryl methyl bonds and only light. The ester group degrades in the presence of ultraviolet or near-infrared light. It makes one more light-sensitive. The gel separates as the hydrophobic and hydrophilic ends become different. The cis-trans structure is changed to regulate azobenzene compounds.[35,36]

A creative idea for regulated medication delivery and localized distribution is printable hydrogel. It is a significant technological advancement to achieve 4D drug distribution in both space and time. Loading medications into the three-dimensional hydrogel space allows for dynamic drug release. This procedure allows for the control of the release of various drugs at different times. This is one of the 4D medications that comes with extra time. [37,38]

D. Dual Sensitive Hydrogels

Drug release under control and multidrug hydrogels have drawn increased interest. Hydrogels that are sensitive to pH and temperature, in particular, have been thoroughly researched. The body's pH and temperature are two crucial biological and chemical components. Dual-responsive hydrogels that are sensitive to both pH and temperature are made of a two-piece hydrophilic polymer network. It typically consists of two or more pH- and temperature-responsive monomers or polymers. For local cancer treatment, the relationship between pH sensitivity and temperature is crucial. Modified doxorubicin prodrug nanoparticles (PDNP) loaded into a novel pH-sensitive, thermoresponsive hydrogel for improved tumor control over free DOX.[39]The pH and temperature can be changed to suit the environment of bodily fluids, and this kind of hydrogel is supported by both. Applying two or more materials through interaction also improves control release accuracy in addition to strengthening the hydrogel's mechanical strength. Because of these qualities, stimuli-responsive hydrogels can be used for a range of medical diagnostic purposes, such as cancer detection and anticancer drug delivery.[40,41]

IV. CONCLUSIONS

Drug delivery, biosensors, tissue engineering, and bioimaging are just a few of the medical applications for hydrogel systems. Hydrogels appear to be very popular worldwide; the market is predicted to grow from $10 billion in 2017 to $15 billion in 2020. Because they offer a regulated release time and area, injection hydrogels have shown to be effective drug delivery tools. Consequently, therapeutic drugs have a better therapeutic index of pain.Many products are currently on the market, including poloxamer 407 (LeGOO®), PLGA-PEG-PLGA (ReGel®), CS/organophosphate (BST-Gel®), and poly (vinyl methyl ether) co-maleic anhydride. Commercial hydrogel for vascular injury, oncology, cartilage repair, and vaccine adjuvants is called Gantrex® hydrogel. Prior to implementing the benefits of injectable hydrogels in clinical settings, the primary concerns related to measurement, sterilization, shelf life, and consumer compatibility (professional and/or patient) need to be addressed. A few formulations, like radiopaque PEG hydrogels (TraceIT® and SpaceOAR®), are presently undergoing clinical trials. These formulations help reduce radiation dose by improving target definition for radiation therapy. The use of injectable medications in the treatment of cancer has shown a lot of promise, but developing new models and design concepts is a continuous process that will improve the efficacy of injectable medicine. to more accurately translate hydrogel findings from science.

REFERENCES

[1]. Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA. Hydrogels in regenerative medicine. Advanced materials. 2009 Sep 4;21(32-33):3307-29.
[2]. Kim SH, Tan JP, Nederberg F, Fukushima K, Colson J, Yang C, Nelson A, Yang YY, Hedrick JL. Hydrogen bonding-enhanced micelle assemblies for drug delivery. Biomaterials. 2010 Nov 1;31(31):8063-71.
[3]. Yan C, Pochan DJ. Rheological properties of peptide-based hydrogels for biomedical and other applications. Chemical Society Reviews. 2010;39(9):3528-40.
[4]. Bae WK, Park MS, Lee JH, Hwang JE, Shim HJ, Cho SH, Kim DE, Ko HM, Cho CS, Park IK, Chung IJ. Docetaxel-loaded thermoresponsive conjugated linoleic acid-incorporated poloxamer hydrogel for the suppression of peritoneal metastasis of gastric cancer. Biomaterials. 2013 Jan 1;34(4):1433-41.
[5]. Appel EA, del Barrio J, Loh XJ, Scherman OA. Supramolecular polymeric hydrogels. Chemical Society Reviews. 2012;41(18):6195-214.
[6]. Li Y, Rodrigues J, Tomás H. Injectable and biodegradable hydrogels: gelation, biodegradation and biomedical applications. Chemical Society Reviews. 2012;41(6):2193-221.
[7]. Shinde UP, Yeon B, Jeong B. Recent progress of in situ formed gels for biomedical applications. Progress in polymer science. 2013 Mar 1;38(3-4):672-701.
[8]. Bin Imran A, Esaki K, Gotoh H, Seki T, Ito K, Sakai Y, Takeoka Y. Extremely stretchable thermosensitive hydrogels by introducing slide-ring polyrotaxane cross-linkers and ionic groups into the polymer network. Nature communications. 2014 Oct 8;5(1):5124.
[9]. Andreyev J, Ross P, Donnellan C, Lennan E, Leonard P, Waters C, Wedlake L, Bridgewater J, Glynne-Jones R, Allum W, Chau I. Guidance on the management of diarrhoea during cancer chemotherapy. The Lancet Oncology. 2014 Sep 1;15(10):e447-60.
[10]. Huebsch N, Kearney CJ, Zhao X, Kim J, Cezar CA, Suo Z, Mooney DJ. Ultrasound-triggered disruption and self-healing of reversibly cross-linked hydrogels

for drug delivery and enhanced chemotherapy. Proceedings of the National Academy of Sciences. 2014 Jul 8;111(27):9762-7

[11]. Bakaic E, Smeets NM, Hoare T. Injectable hydrogels based on poly (ethylene glycol) and derivatives as functional biomaterials. RSC advances. 2015;5(45):35469-86.

[12]. Wu X, He C, Wu Y, Chen X, Cheng J. Nanogel-incorporated physical and chemical hybrid gels for highly effective chemo–protein combination therapy. Advanced Functional Materials. 2015 Nov;25(43):6744-55.

[13]. Yang Z, Gao D, Cao Z, Zhang C, Cheng D, Liu J, Shuai X. Drug and gene co-delivery systems for cancer treatment. Biomaterials science. 2015;3(7):1035-49.

[14]. Xu Q, He C, Zhang Z, Ren K, Chen X. Injectable, biomolecule-responsive polypeptide hydrogels for cell encapsulation and facile cell recovery through triggered degradation. ACS applied materials & interfaces. 2016 Nov 16;8(45):30692-702.

[15]. Chen Y, Zhang F, Fu Q, Liu Y, Wang Z, Qi N. In vitro proliferation and osteogenic differentiation of human dental pulp stem cells in injectable thermo-sensitive chitosan/β-glycerophosphate/hydroxyapatite hydrogel. Journal of Biomaterials Applications. 2016 Sep;31(3):317-27.

[16]. Norouzi M, Nazari B, Miller DW. Injectable hydrogel-based drug delivery systems for local cancer therapy. Drug discovery today. 2016 Nov 1;21(11):1835-49.

[17]. Chen X, Liu Z. A pH-Responsive Hydrogel Based on a Tumor-Targeting Mesoporous Silica Nanocomposite for Sustained Cancer Labeling and Therapy. Macromolecular Rapid Communications. 2016 Sep;37(18):1533-9.

[18]. Chen X, Liu Z, Parker SG, Zhang X, Gooding JJ, Ru Y, Liu Y, Zhou Y. Light-induced hydrogel based on tumor-targeting mesoporous silica nanoparticles as a theranostic platform for sustained cancer treatment. ACS applied materials & interfaces. 2016 Jun 29;8(25):15857-63.

[19]. Castro V, Rodríguez H, Albericio F. CuAAC: An efficient click chemistry reaction on solid phase. ACS combinatorial science. 2016 Jan 11;18(1):1-4.

[20]. Dey P, Hemmati-Sadeghi S, Haag R. Hydrolytically degradable, dendritic polyglycerol sulfate based injectable hydrogels using strain promoted azide–alkyne cycloaddition reaction. Polymer Chemistry. 2016;7(2):375-83.

[21]. Gačanin J, Kovtun A, Fischer S, Schwager V, Quambusch J, Kuan SL, Liu W, Boldt F, Li C, Yang Z, Liu D. Spatiotemporally controlled release of rho-inhibiting C3 toxin from a protein–DNA hybrid hydrogel for targeted inhibition of osteoclast formation and activity. Advanced Healthcare Materials. 2017 Nov;6(21):1700392.

[22]. Casey J, Yue X, Nguyen TD, Acun A, Zellmer VR, Zhang S, Zorlutuna P. 3D hydrogel-based microwell arrays as a tumor microenvironment model to study breast cancer growth. Biomedical Materials. 2017 Mar 15;12(2):025009.

[23]. Bardajee GR, Hooshyar Z, Farsi M, Mobini A, Sang G. Synthesis of a novel thermo/pH sensitive nanogel based on salep modified graphene oxide for drug release. Materials Science and Engineering: C. 2017 Mar 1;72:558-65.

[24]. Bu Y, Shen H, Yang F, Yang Y, Wang X, Wu D. Construction of tough, in situ forming double-network hydrogels with good biocompatibility. ACS Applied Materials & Interfaces. 2017 Jan 25;9(3):2205-12.

[25]. Casey J, Yue X, Nguyen TD, Acun A, Zellmer VR, Zhang S, Zorlutuna P. 3D hydrogel-based microwell arrays as a tumor microenvironment model to study breast cancer growth. Biomedical Materials. 2017 Mar 15;12(2):025009.

[26]. Mathew AP, Uthaman S, Cho KH, Cho CS, Park IK. Injectable hydrogels for delivering biotherapeutic molecules. International journal of biological macromolecules. 2018 Apr 15;110:17-29.

[27]. Yu S, He C, Chen X. Injectable Hydrogels as Unique Platforms for Local Chemotherapeutics-Based Combination Antitumor Therapy. Macromolecular Bioscience. 2018 Dec;18(12):1800240.

[28]. Qi C, Liu J, Jin Y, Xu L, Wang G, Wang Z, Wang L. Photo-crosslinkable, injectable sericin hydrogel as 3D biomimetic extracellular matrix for minimally invasive repairing cartilage. Biomaterials. 2018 May 1;163:89-104.

[29]. Ahmad R, Kaus NH, Hamid S. Synthesis and characterization of PLGA-PEG thymoquinone nanoparticles and its cytotoxicity effects in tamoxifen-resistant breast cancer cells. Springer International Publishing; 2020.\

[30]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.

[31]. Bykov VJ, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. Nature Reviews Cancer. 2018 Feb;18(2):89-102.

[32]. Castelletto V, Edwards-Gayle CJ, Greco F, Hamley IW, Seitsonen J, Ruokolainen J. Self-assembly, tunable hydrogel properties, and selective anti-cancer activity of a carnosine-derived lipidated peptide. ACS applied materials & interfaces. 2019 Aug 13;11(37):33573-80.

[33]. Chen CH, Kuo CY, Chen SH, Mao SH, Chang CY, Shalumon KT, Chen JP. Thermosensitive injectable hydrogel for simultaneous intraperitoneal delivery of doxorubicin and prevention of peritoneal adhesion. International journal of molecular sciences. 2018 May 4;19(5):1373.

[34]. Zhang Z, He CL, Xu QH, Zhuang XL, Chen XS. Preparation of Poly (L-glutamic acid)-based Hydrogels &ITvia&IT Diels-Alder Reaction and Study on Their Biomolecule-responsive Properties. ACTA POLYMERICA SINICA. 2018 Jan 1(1):99-108.

[35]. Xu Q, Guo L, Sigen A, Gao Y, Zhou D, Greiser U, Creagh-Flynn J, Zhang H, Dong Y, Cutlar L, Wang F. Injectable hyperbranched poly (β-amino ester) hydrogels with on-demand degradation profiles to match wound healing processes. Chemical science. 2018;9(8):2179-87.

[36]. Yu S, Wang C, Yu J, Wang J, Lu Y, Zhang Y, Zhang X, Hu Q, Sun W, He C, Chen X. Injectable

bioresponsive gel depot for enhanced immune checkpoint blockade. Advanced Materials. 2018 Jul;30(28):1801527.
[37]. Bai Y, Li S, Li X, Han X, Li Y, Zhao J, Zhang J, Hou X, Yuan X. An injectable robust denatured albumin hydrogel formed via double equilibrium reactions. Journal of Biomaterials Science, Polymer Edition. 2019 May 24;30(8):662-78.
[38]. Nezhad-Mokhtari P, Ghorbani M, Roshangar L, Rad JS. Chemical gelling of hydrogels-based biological macromolecules for tissue engineering: Photo-and enzymatic-crosslinking methods. International journal of biological macromolecules. 2019 Oct 15;139:760-72.
[39]. Batista RA, Espitia PJ, Quintans JD, Freitas MM, Cerqueira MÂ, Teixeira JA, Cardoso JC. Hydrogel as an alternative structure for food packaging systems. Carbohydrate polymers. 2019 Feb 1;205:106-16.
[40]. Chang G, Zhang H, Li S, Huang F, Shen Y, Xie A. Effective photodynamic therapy of polymer hydrogel on tumor cells prepared using methylene blue sensitized mesoporous titania nanocrystal. Materials Science and Engineering: C. 2019 Jun 1;99:1392-8.
[41]. Chen Y, Hao Y, Huang Y, Wu W, Liu X, Li Y, Gou M, Qian Z. An injectable, near-infrared light-responsive click cross-linked azobenzene hydrogel for breast cancer chemotherapy. Journal of Biomedical Nanotechnology. 2019 Sep 1;15(9):1923-36.