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A Review of Hydrogel Based Control Release System on Cancer Treatment

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Abstract: Hydrogels have been used for applications such as wounds, burns, dressings, contact lenses, tissue engineering applications, to name a few. The potential application of hydrogels for localized cancer therapy has also been widely explored. The review covers the principles of hydrogels and their classification.Hydrogels are classified based on their activation stimuli such as pH, temperature, magnetism, light, and ultrasound are discussed in detail. The basic design and mechanism of action of some stimuli-responsive hydrogels are presented with some studied examples. Finally, a summary of commercialized and patented hydrogels has been offered for cancer treatment.
Keywords: Cancer therapy, Hydrogels, injectable hydrogel, pH sensitive hydrogels

I. INTRODUCTION

Cancer is the second most common cause of death in the world. About 1 in 4 people develop cancer at some point in their lives. Cancer is this a serious problem that affects the health of all and human societies. Unfortunately, it is a disease that varies from tissue to tissue, and this diversity represents a great challenge for its specific diagnosis, monitoring the effectiveness of the treatment[23,24]. Among men, the highest cancer rates are found in the prostate,lung and prostate bronchi, colon and rectum and bladder[25,36]. In women, the prevalence of cancer is higher in the breast, bronchi, colon and rectum, uterine body and thyroid, respectively. In children, types of The most common cancers are blood cancers and cancers related to the brain and lymph nodes, respectively. Cancer occurs through a series of successive mutations in genes, so that these mutations change cellular functions. Chemical compounds play a clear role in the formation of genetic mutations and cancers in cells. In addition, smoking contains many carcinogenic chemicals that cause lung cancer.[12,37]

II. CONTROL RELEASE SYSTEM

Controlled drug release technology represents one of the scientific fields that it develops more rapidly in which chemists and chemical engineers contribute to the care of human health. These administration systems offers several advantages over dosage forms conventional, including improved efficiency, reduced toxicity and improved patient compliance and comfort[6,10]. These systems often use synthetic polymers as drug carriers. By doing so, the treatments that otherwise it would not be possible to use conventional now. Even the introduction of the first clinical controlled release systems were developed less than 25 years ago. All controlled release systems aim to improve the effectiveness of drug therapy. him improvement can take the form of increased therapeutic activity in relation to the intensity of side effects, a reduction in the number of drug administration required during the treatment or elimination of the need for a administration of specialized medication[5,16,26]

A. Hydrogel

Hydrogels are three-dimensional (3D) polymer networks whose hydrophilic structure allows the absorption of large amounts of water (thousand times its dry weight).Hydrogels made from synthetic polymers are currently attracting more interest than natural polymers due to their longer lifetime, greater water absorption capacity,improved mechanical properties, and fine degradability[13]. According to the type of crosslinking between the polymers, hydrogels can be classified into physical hydrogels, held together by non-covalent and reversible interactions, and chemical hydrogels, connected by non-reversible covalent bonds. various stimuli, and the ability to easily bind to hydrophilic and hydrophobic therapeutic compounds, have made them important candidates in biomedical application. In the therapeutic field, drug delivery approaches require tremendous improvements to achieve safe delivery systems to achieve the desired therapeutic effect and avoid side effects[29]. Hydrophilic polymer networks capable of absorbing large volumes of water and subject to appropriate swelling and shrinkage to facilitate controlled drug release are called hydrogels. Hydrogels are promising, fashionable, intelligent and "smart" drug delivery vehicles that meet the specific needs of targeting drugs to specific sites and control drug release[14,27].

B. Properties of hydrogel

1) .Swelling behaviour: The hydrogel polymer has chains that are linked to each other chemically or physically. Easy changes Environmental factors can rapidly respond to alter changes in the hydrogel. Different types of factors are pH, electrical signal and enzymatic or ionic species, which lead to a different physical structure of the gel.[18,39]
2) Mechanical resistance : This is an essential characteristic of hydrogel, which is mainly used in the biomedical and pharmaceutical industry as a substance for tissue engineering, drug delivery, tendon healing, wound dressing and replacement of cartilage The mechanical properties of a material can be adjusted and changed according to its purpose. The degree of cross-linking can be altered by scaling the material to produce a stiffer gel.[18,42]
3) Biocompatibility Hydrogels should be non-toxic and biocompatible, making them particularly useful in biomedical applications. In vivo toxicity testing and cytotoxicity testing are the concepts used mainly in polymers regarding these qualities.[17,20]
4) Polymer : Hydrogels are produced from natural and synthetic polymers.Natural polymers are chitosan, gelatin, alginates, fibrin.Synthetic polymers such as vinyl acetate, acrylic acid.Hydrogels are widely used in cancer treatment due to their biocompatibility, ability to hold large amounts of water and drug delivery potential.[11,30]

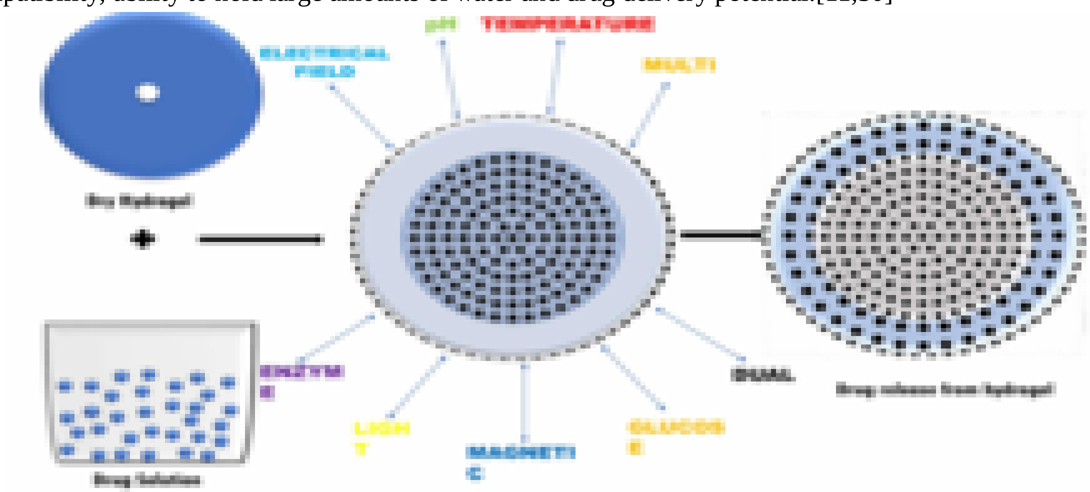

Fig.1 Drug release from hydrogel

C. Hydrogels in oral Therapy

Chemotherapy drugs are generally hydrophobic in nature and exhibit low bioavailability, requiring the administration of high doses. The oral administration of anticancer drugs presents problems such as low drug solubility, drug degradation when exposed to the acidic and enzymatic environment of the stomach, low bioavailability, first-pass metabolism, and strong binding of protein leading to non-specific biological protein. To solve these problems, some specialized biopolymers have been developed, such as gelatin, collagen, chitosan, PLGA, hyaluronic acid, etc. were used to develop an oral chemotherapy delivery platform that prevents drug degradation and provides enhanced bioavailability at the cancer target site. presented such a system in which Hydrophobic therapeutics were loaded into a nanoscale polyanionic hydrogel for oral delivery[9,15]. Nanoscale hydrogels have been designed to overcome physicochemical challenges such as low solubility and low permeability in the oral delivery of the anticancer drug Doxorubicin.Another oral delivery system has been studied from in which a pH-responsive hydrogel was formulated with zein-coacrylic acid using N,N-methylene bisacrylamide for cross-linking, which was further loaded with chemotherapy drugs such as rutin and 5-fluorouracil. In this study, the -OH and -NH2 groups present in zein is thought to bind to the -COOH groups present in the acrylic acid monomer and form acid-sensitive amide groups, thus imparting a pH-sensitive nature to the hydrogels. The hydrogels showed the highest degree of swelling in an acidic environment, which led to a higher drug release due to the larger surface area exposed for swelling.

D. Injectable Hydrogel For Local Cancer Therapy

Nanoparticle-loaded injectable hydrogels have been studied to enable localized delivery of one or more drugs, overcome biological barriers, reduce dosage and avoid systemic side effects.

A similar system was introduced by in which an injectable hydrogel composed of lipid nanocapsules loaded with lauroyl-gemcitabine (GemC12) is proposed for the local treatment of glioblastoma.Injectable hydrogels have been studied for the localized co-delivery of chemotherapy[3]. One such approach is presented by in which the localized injection of a hydrogel loaded with programmed cell death protein ligand 1 (αPDL1) is proposed to reprogram the tumor microenvironment from pro-tumoral to anti-tumoral with prolonged administration of αPDL1 to stimulate the immune system. the mechanism of crosslinking of the hydrogel. Inflammation present in the tumor microenvironment has been reported as one of the reasons driving tumor development, the reduction of which has been proposed to improve antitumor immune response and immune checkpoint blockade therapy[4,34].The hydrogel also acts as a reservoir for prolonged localized delivery of αPDL1, thereby reducing systemic side effects. The combined effect of these two factors led to the inhibition of primary and distant tumor growth in the CT26 tumor model studied. Similar immunotherapy systems have been described for cancer immunotherapy, obstructive nephropathy, immunochemotherapy, and chronic kidney disease[40,41].

E. pH Sensitive Hydrogels

The change in pH results in a change in the charge present on the polymer chain, which is then responsible for phenomena such as cross-linking, swelling, collapse and drug release. The pH-responsive behavior of hydrogels can be controlled modulating factors such as polymer loading, polymer concentration, dissociation constant, degree of ionization, and nature of pendant groups. The pendant groups are charged at a specific pH and develop repulsions between them, resulting in the swelling of the hydrogel. Thus, pH-responsive hydrogels are formulated considering the pH of the administration site. pH-responsive hydrogels have also been evaluated in combination with nanoparticles for localized antitumor therapy. Injectable nanoparticle-loaded hydrogels have been reported to exhibit sustained drug release and therapeutic efficacy with localized therapy.. The pH-controlled release of DOX was found to lead to tumor tissue targeting, cellular uptake, and therapeutic efficacy while reducing systemic toxicity at the same administered dose of intravenous injection.[7,32]

F. Temparature Sensitive Hydrogels

Thermosensitive polymers have part hydrophilic and hydrophobic interactions between them and the balanced interactions within these groups determine the response to temperature change. The interactions of these groups in the polymer structure with water molecules change with changes in temperature, resulting in changes in the solubility of the polymer[8]. This change in solubility of the interconnected polymer network leads to the formation of a sol phase (liquid liquid) and a gel phase (liquid non-liquid). Other types of hydrogels are cooling gels, in which the sol phase exists above the UCST, . Changes in the ratio of hydrophilic and hydrophobic moieties in the polymer structure lead to a change in the inherent UCST/LCST.Heat-responsive hydrogels have several advantages such as rapid sol-gel transition,avoidance of flash release due to gelation, absence of crosslinking agents, controlled drug release[28,35]

G. Chemotherapy drug delivery

Doxorubicin As an anthracycline compound, DOX uses four distinct mechanisms to exert their anticancer activity: (A) Development of DNA cross-linking by linking to DNA base pairs, which change the structure of DNA and suppresses cell replication (B) Suppression of topoisomerase II function to inhibit it relinking of DNA strands, causing DNA breaks, growing apoptosis and errors in DNA synthesis (C) Increased generation of ROS to mediate damage to lipids, proteins and DNA (D) Induction of DNA damage and The promotion of oxidative damage can induce apoptosis by DOX. However, previous experiments have shown that Changes in the molecular profile of cancer cells can cause it resistance to DOX chemotherapy.[19,21,22]

III. APPLICATION

Wound healing - Modified polysaccharide present in cartilage is used in the formation of hydrogels to treat cartilage defects. For example, gelatin and polyvinyl alcohol (PVA) hydrogels have been formulated, as well as blood coagulants[31].
Industrial Applicability - Hydrogels are used as absorbents for industrial effluents such as methylene blue dye. Another example is the adsorption of dioxins by hydrogel beads.[20,42]
Tissue engineering - Micronized hydrogels are used for this deliver macromolecules (phagosomes) into the cytoplasm of antigen-presenting cells. This property is also used in cartilage repair. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose, and other natural products.[1,2]

Drug delivery to the gastrointestinal tract - Hydrogels deliver drugs to specific sites in the digestive tract. Drugs loaded in colon-specific hydrogels show tissue specificity and a change in pH or enzymatic actions trigger drug release. They are designed to be highly swollen or degraded in the presence of microflora.

Ocular administration - Chitoni et al. described ophthalmic inserts composed of silicone rubber hydrogel. Cohen et al. developed an in situ gelation system of gluconic acid alginate for the ophthalmic delivery of pilocarpine.

Transdermal delivery - Swellable hydrogels can be used as a controlled release device in the field of clothing. Hydrogel-based formulations are being explored for transdermal iontophoresis to achieve better product permeability

IV. FUTURE PERSPECTIVE

Hydrogel-based controlled drug delivery system has a promising future and utility in the field of pharmaceutical and tissue engineering. The use of “smart” hydrophilic polymers certainly constitutes a great revolution in the delivery of therapeutic products. Their flexible nature and biocompatibility are one of the important and demanding features that not only cover almost the entire pharmaceutical and biomedical field, but are also used in biosensing devices, microchips, etc. Furthermore, exposing intelligence to its environment certainly provides improved methods for the administration of heat-stable substances. With such inherent properties, versatile nature and new advanced, hydrogel will surely show more potential and excellent applications in biomedical and pharmaceutical technology.

V. CONCLUSION

Three-dimensional networks of interconnected polymers called hydrogels should be seriously considered as supports or matrices for cells in tissue engineering,self-healing materials,and delivery systems for pharmaceuticals and biomolecules.A potential application of high-strength hydrogels is advanced medicine, especially cancer treatment. Hydrogels have a significant therapeutic impact on ophthalmic drug delivery. They deliver small molecules or large proteins, are 90% water, provide sustained drug release over days or months, are completely absorbed after administration, and remain visible during monitoring.

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