REVIEW ON TREATMENT OF ENDOMETRIOSIS BY HYDROGEL CONTAINING LETROZOLE

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Abstract

Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial-like tissue outside the uterus, causing pain, infertility, and other complications. Current treatments, including hormonal therapies and surgery, offer limited efficacy and often lead to recurrence or side effects. Letrozole, an aromatase inhibitor, has emerged as a promising therapeutic agent due to its ability to reduce estrogen production, a key factor in the progression of endometriosis. However, systemic administration of letrozole can lead to adverse effects. To enhance the therapeutic outcomes and minimize side effects, the development of a localized delivery system is essential. In this study, we propose a letrozole-loaded hydrogel formulation designed for sustained and targeted drug release directly to endometriotic lesions. Hydrogels, known for their biocompatibility, tunable release profiles, and ability to maintain high local drug concentrations, serve as an ideal carrier for letrozole. The hydrogel formulation was evaluated for its physical properties, drug release kinetics, and in vitro cytotoxicity against endometriotic cells. Results demonstrated a sustained release of letrozole over a prolonged period, with significant suppression of estrogen production and reduced proliferation of endometriotic cells. Furthermore, the biocompatibility of the hydrogel was confirmed, with minimal toxicity to surrounding healthy tissue.

Keywords-

Endometriosis, treatment of endometriosis, hydrogel, endometrial injury, endometrial repair, delivery system, uterine, letrozole.

Introduction

clinical treatment strategies especially for moderates to severe injuries, often fail to provide satisfactory therapeutic effect and pregnancy outcome. With the development of reproductive medicine and materials engineering researchers have developed bioactive hydrogel materials, which can be as a physical anti adhesion barrier along or as functional delivery system for intrauterine injury treatment by loading stem cell or various active substances.

Endometriosis can start at a person's first menstrual period and last until menopause. There is no cure, but symptoms can be treated with medicine.

The endometrium is a unique tissue within the female reproductive system that un undergoes cyclic procese of growth, differentiation shading, and renewal in each menstrual cycle successful embryo implantation in the uterus relies on high quality embryos and a receptive endometrial environment.

Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia .Endometriosis is very common debilitating disease that occur in 6 to 10% of the general female population in

women pain, infertility, or both the frequency is 35-50%. Endometriosis management evidence based update treatment pharmacoceutical hormone treatment and non-hormonal treatment.

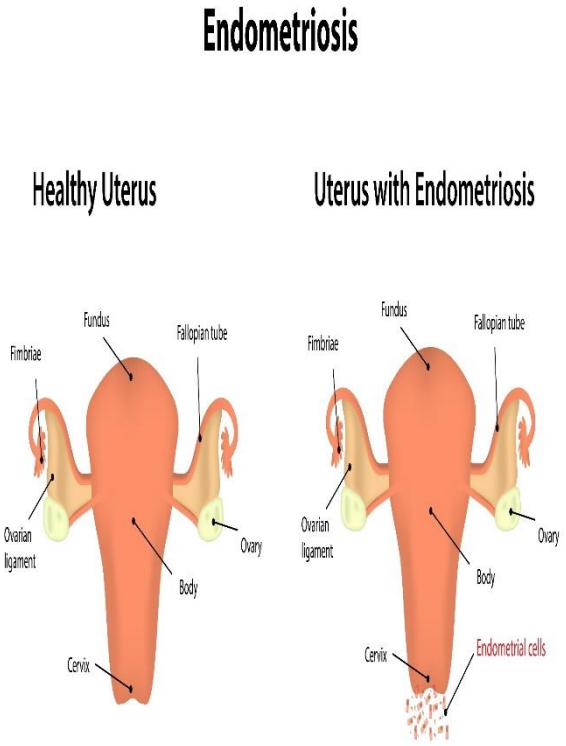


Fig.1 endometriosis (a)healthy uterus .(b) uterus with endometriosis

Symptoms

Endometriosis often causes severe pain in the pelvis, especially during menstrual periods. Some people also have pain during sex or when using the bathroom. Some people have trouble getting pregnant.

Some people with endometriosis don't have any symptoms. For those who do, a common symptom is pain in the lower part of the belly (pelvis). Pain may be most noticeable:

- during a period
- during or after sex
- when urinating or defecating.

Some people also experience:

- chronic pelvic pain
- heavy bleeding during periods or between periods
- trouble getting pregnant
- bloating or nausea
- fatigue
- depression or anxiety.

Symptoms often improve after menopause, but not always.

Endometriosis symptoms are variable and broad, meaning that healthcare workers may not easily diagnose it. Individuals with symptoms may not be aware of the condition.

Causes

Endometriosis is a complex disease that affects many women globally from the onset of their first period (menarche) through menopause, regardless of ethnic origin or social status. Many different factors are thought to contribute to its development. At present endometriosis is thought to arise due to:

- Retrograde menstruation is when menstrual blood containing endometrial cells flows back through the fallopian tubes and into the pelvic cavity at the time that blood is flowing out of the body through the cervix and vagina during periods. Retrograde menstruation can result in endometrial-

like cells being deposited outside the uterus where they can implant and grow.

- Cellular metaplasia is when cells change from one form to another. Cells outside the uterus change into endometrial-like cells and start to grow.
- Stem cells can give rise to the disease, which then spreads through the body via blood and lymphatic vessels.

Other factors may also contribute to the growth or persistence of ectopic endometrial tissue. For example, endometriosis is known to be dependent on estrogen, which increases the inflammation, growth and pain associated with the disease. However, the relationship between estrogen and endometriosis is complex since the absence of estrogen does not always mean the absence of endometriosis.

Prevention

At present, there is no known way to prevent endometriosis. Enhanced awareness, followed by early diagnosis and management may slow or halt the natural progression of the disease and reduce the long-term burden of its symptoms, including possibly the risk of central nervous system pain sensitization. Currently there is no cure.

Diagnosis

A careful history of menstrual symptoms and chronic pelvic pain provides the basis for suspecting endometriosis. Although several screening tools and tests have been proposed and tested, none are currently validated to accurately identify or predict individuals or populations that are most likely to have the disease. Endometriosis can often present symptoms that mimic other conditions and contribute to a diagnostic delay. Ovarian endometrioma, adhesions and deep nodular forms of disease often require ultrasonography or magnetic resonance imaging (MRI) to detect. Histologic verification, usually following surgical/laparoscopic visualization, can be useful in confirming diagnosis, particularly for the most common superficial lesions. The need for histologic/laparoscopic confirmation should not prevent the commencement of empirical medical treatment.

Treatment

Treatments to manage endometriosis can vary based on the severity of symptoms and whether pregnancy is desired. No treatments cure the disease.

A range of medications can help manage endometriosis and its symptoms.

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics (painkillers) like ibuprofen and naproxen are often used to treat pain.

Hormonal medicines like GnRH-analogues and contraceptive (birth control) methods can also help control pain. These methods include:

- pills
- hormonal intrauterine devices (IUDs)
- vaginal rings

- implants
- injections
- patches.

These methods may not be suitable for those wanting to get pregnant.

Fertility medicines and procedures are sometimes used for those having difficulty getting pregnant because of endometriosis.

Surgery is sometimes used to remove endometriosis lesions, adhesions and scar tissues. Laparoscopic surgery (using a small camera to visualize inside the body) allows doctors to keep incisions small.

Discuss your treatment options with a health care provider.

Treatments are based on individual preferences and effectiveness, side effects, long-term safety, costs and availability.

Raising awareness can help people to be diagnosed early. Early treatment can slow or halt the natural progression of the disease and reduce the long-term symptoms.

In addition to talking to their doctor, people may find additional advice and emotional assistance in local patient support groups.

Some treatments are associated with side effects, and endometriosis-related symptoms can sometimes reappear after therapy ends. The choice of treatment depends on effectiveness in the individual, adverse side effects, long-term safety, costs, and availability. Most current hormonal management is not suitable for persons suffering from endometriosis who wish to get pregnant, since they affect ovulation.

Success in reducing pain symptoms and increasing pregnancy rates through surgery are often dependent on the extent of disease. In addition, lesions may recur even after successful eradication, and pelvic floor muscle abnormalities can contribute to chronic pelvic pain. Secondary changes of the pelvis, including the pelvic floor, and central sensitization may benefit from physiotherapy and complementary treatments in some patients. Treatment options for infertility due to endometriosis include laparoscopic surgical removal of endometriosis, ovarian stimulation with intrauterine insemination (IUI), and in vitro fertilization (IVF), but success rates vary.

Hydrogel formulation technique :

Hydrogels are a class of hydrophilic three dimensional polymeric network with biocomptibility as well as the capability of absorbing water and encapsulation, which have potential applications as a promising intrauterine controlled release delivery system.

Hydrogel is a kind of bioinspired, superhydrophilic materials with unique characteristics, such as excellent biocompatibility,biodergradability, porosity, swelling and cross linkage.these unique physiochemical properties of bioinspired hydrogels enable their promising application as novel delivery platform and alternative therapies for endometrial injury. Hydrogels have a variety of use cases, including contact lenses, delivering doses of medication

within the body, moisturizers, water storage in soil, cleaning polluted water and As gelling and thickening agents. A hydrogel is gel made of a type of plastic that can bind water. Our hydrogel implant can be easily and quickly destroyed, either with uv light or a special solution, so that recipients don't have to have an invasive and risky operation should they decide to reverse the procedure.

Current research in the treatment of iua is focused on the repair of the endometrium by using hydrogel as a matrix loaded with various bioactive substances. In later section, we will summarize the recent studies according to different sources of biomaterial based hydrogel delivery system. When hydrogel used in the biomedical field, the design principles are often based on the specific microenvironment and application requirements of the target disease.

Hydrogels are three-dimensional (3D) structured networks of crosslinked hydrophilic polymer matrices capable of holding a large amount of water (> 10%by definition) and displaying useful characteristics such as softness, toughness, biocompatibility, stretchability, and deformability. The crosslinking among the hydrophilic functionalities facilitates their structural integrity and prevents their immediate dissolution in the aqueous environment. Their ability to entrap and preserve a substantial amount of water or biological solutions, and the unique combination of softness and flexibility are similar to natural soft tissues, and thus make them promising materials to mimic their properties. Additionally, they show exceptional physicochemical properties, including swelling and permeability, as well as distinct mechanical and optical properties, together with biocompatibility, which have made them a flexible tool for applications such as imaging, diagnosis, and treatment.

Hydrogels can be fabricated into thin films or molded into any shape, length, size, or different architectures, depending on the requirement. The high water absorption of hydrogels arises due to the presence of hydrophilic functionalities such as –OH, –COOH, –CONH–, $–NH_2$, SO_3H, *etc.* For many advanced applications, these hydrogel networks are designed with diverse polymers of natural or synthetic origin to form a hybrid structure, which is utilized to support, protect or attach new functionalities to the hydrogel structure. Most of the polymers that are used for hydrogel preparation are non-toxic and are considered suitable for many biomedical applications, from skin patches to implants, and they have been successfully implemented in all the sectors.

Recent advances in the medical field have utilized numerous hydrogel-based products for the treatment of patients. For example, polysaccharide (chitosan, alginate, cellulose, *etc.*) based hydrogels have been extensively utilized for wound dressing, poly(2-hydroxyethyl methacrylate) [p(HEMA)] is typically used for contact lenses hyaluronic acid (HA) hydrogels for drug delivery systems, and protein (gelatin, collagen, and fibrin)-based hydrogels or scaffolds have been used for tissue engineering. For the treatment of cancers or tumors, the drugs are

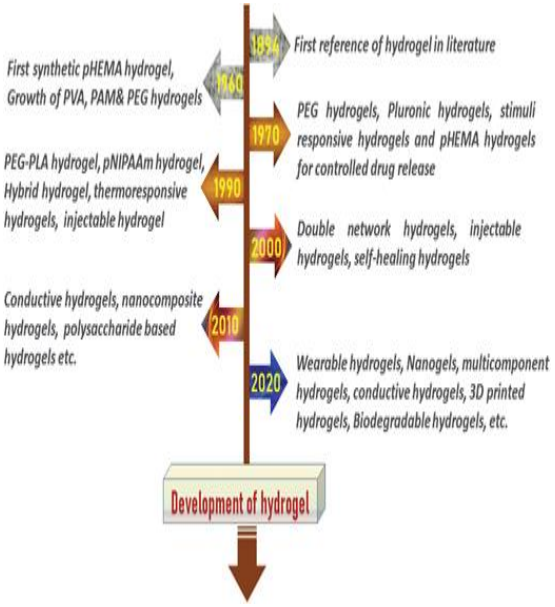
incorporated within a hydrogel and injected directly into the tumor site or adjacent areas, restricting the toxicity of the drugs to the localized area where tumor cells persist. For multidimensional applications, stimuli-responsive hydrogels that can be controlled by altering experimental conditions like temperature, surface charge, pH, and other biological conditions have been developed.

1.1.1 History

One of the first mentions of hydrogels appeared during the 19th century for colloidal gels prepared from inorganic salts. However, the use of gels was not highlighted until the first synthetic hydrogel on crosslinked poly-2-hydroxyethylmethacrylate (pHEMA) was found by Wichterle and Lim in 1954. Since then, the term "hydrogel" was regularly used to describe the three-dimensional network of hydrophilic polymers. During the 1960s, the soft contact lenses developed using the crosslinked macromolecular network of pHEMA were widely distributed around Western Europe. After successful trials, the Food and Drug Administration (FDA) approved the lenses designed using pHEMA in 1971, and hydrogels based on pHEMA were further applied to controlled drug delivery applications In 1967, Updike and Hicks used a polyacrylamide (PAM) based hydrogel to entrap enzyme glucose-oxidase to prepare sensors.

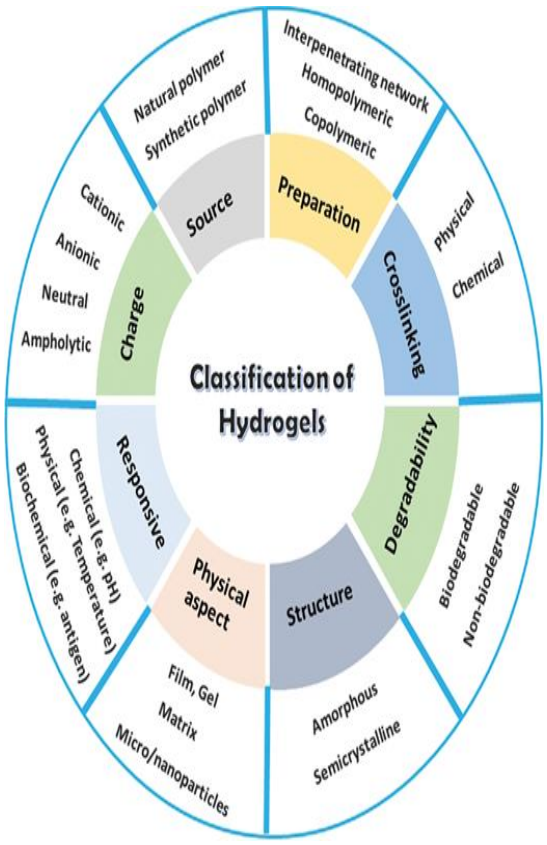
Figure 1.1 shows the schematic illustration of the significant growth of hydrogels over the years. The chemistry of hydrogels had a significant breakthrough in the sixties when diverse applications of hydrogels were reported for drug delivery, tissue engineering, skincare products, food products, and many other biomedical applications. In the 1970s, new hydrogel concepts were explored and materials such as acrylamides, *N*-vinylpyrrolidone, and vinyl acetate were applied in order to improve the biocompatibility. During the same period, Tanaka conducted experiments on PAM gels and reported that the gels tend to collapse upon changing the temperature or solvent composition.26 He explained the phenomenon based on mean-field theory and predicted the occurrence of critical endpoints in the phase equilibria.

Figure 1.1



1.1.2 Classification of Hydrogels

Hydrogels are categorized into many different groups depending on their origin, structure, preparation method, crosslinking mechanism, charge, responsive nature, physical aspect, and degradation. Figure 1.3 represents a broad classification of hydrogels formulated based on a literature survey.



1.1.2.1 Hydrogel Classification Based on Origin

Basically, hydrogels have been divided into two groups based on their origin, *i.e.*, natural and synthetic hydrogels. Recently, significant development has been achieved in designing hydrogels using natural biomass resources. Typically, natural hydrogels are prepared from polysaccharides like alginate, chitosan, agarose, HA, cellulose, *etc.* or proteins derived from biological sources (such as collagen, gelatin, elastin, fibrin, *etc.*). Proteins like collagen and elastin are natural constituents of the extracellular matrix (ECM) and often derived from animal tendons/skin or human sources (*e.g.* placenta), while polysaccharides for hydrogel preparation are derived from the shells of sea crustaceans, marine algae, and plants. Given the global energy crises and environmental concerns, polysaccharides have been widely investigated in biomedical research because of their non-toxic nature, low cost, biocompatibility and biodegradability. Additionally, they contain ample hydroxyl groups (OH), carboxyl acid groups (COOH), or amine (NH_2) groups that provide a convenient platform for anchoring with other groups, hydrogen bonding, functionalization, or chemical modifications that allow crosslinking.

Natural hydrogels are biodegradable materials with good biocompatibility and low toxicity. The molecular structures of natural hydrogels (derived from the ECM) have the inherent properties that can naturally support cell adhesion and proliferation. Other hydrogels produced from plant-based materials are readily available and avoid any kind of viral infections that may have animal origins. However, the undefined structures of these materials allow limited control on the mechanical properties (like rigidity and flexibility), and the difficulty in reproducibility in large-scale production has narrowed their use in many biomedical applications.

Hydrogel Classification Based on the Preparation Method

Hydrogels have been broadly classified as homopolymeric, copolymeric, and interpenetrating polymer network (IPN) hydrogels based on the preparation method. Homopolymeric hydrogels represent polymer networks that are created from a single polymer with the same repeating monomers, whereas copolymer

hydrogels contain multimonomeric polymer(s) with minimum one hydrophilic polymer, arranged in block, random, or alternating configurations. In contrast, IPN hydrogels are made from two independently crosslinked natural or synthetic polymers confined in the network structure. If one component is crosslinked and the other is not, it is called semi-IPN. Pescosolido *et al.* synthesized an injectable hydrogel from the IPN of two polysaccharides, *i.e.*, calcium alginate and dextran-HEMA. The IPN hydrogels were completely degradable and exhibited favorable characteristics for the delivery of targeted drugs and tissue engineering applications. To expand the scope of these polysaccharides, more efforts were made to enhance the stability of polysaccharides by hybridizing with PVA *via* semi-IPN. More recently, Wang *et al.* formulated a unique gelatin–alginate IPN hydrogel *via* physical crosslinking, which exhibited a water content of 79%. The obtained gel exhibited significantly improved mechanical properties compared to pure gelatin hydrogl.

1.Hydrogel types Based on Crosslinking

There are many ways to crosslink hydrophilic polymer chains to form stable polymer networks of hydrogels. The crosslinking regulates water absorption and helps to uphold the 3D structure of hydrogels in swollen states. Among various crosslinking procedures, physical and chemical crosslinking are the most commonly used methods to fabricate hydrogels. Physically crosslinked hydrogels can be fabricated under very mild conditions without the need for crosslinking agents that may cause toxicity to cells or tissues. There are many techniques for producing physically crosslinked hydrogels, such as hydrogen bonding, charge interactions, ionic/electrostatic interactions, stereo-complexing, freezing–thawing, protein interactions, hydrophobic interactions, and crystallization. Chemically crosslinked hydrogels consist of a covalently crosslinked network and the bonds are much stronger and often more stable than those of physically crosslinked hydrogels. The chemical crosslinks are produced in a number of ways, such as copolymerization of multifunctional monomers,

Hydrogels may be further classified into four groups based on their charge on the crosslinked chain, such as anionic, cationic, neutral, and ampholytic. The charge of the overall network is based on the charge present on the individual polymers that constitute the network structure. Figure shows the different crosslinking methods recently adopted for the preparation of hydrogels.

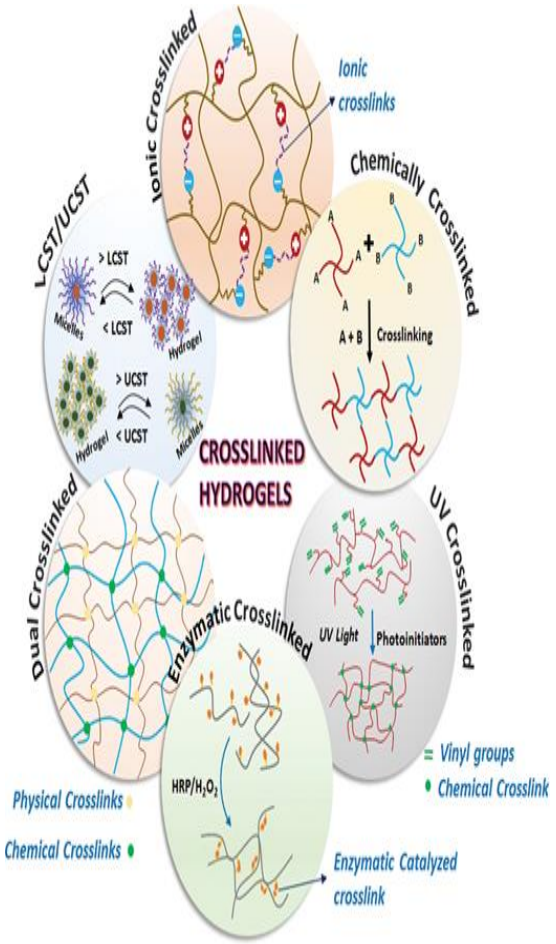


Fig.2 Crosslinked Hydrogels

Crosslinking approaches adopted for hydrogel preparation. The diagram represents the most commonly used crosslinking methods such as physical crosslinking (ionic crosslinking), chemical crosslinking, LCST/UCST, UV-based crosslinking, dual crosslinking and enzyme crosslinking.

2.Crosslinking by Ionic or Electrostatic Interactions

In general, ionic or electrostatic crosslinking occurs due to the molecular interconnection between the anionic and cationic polyelectrolytes. For example, the positively charged amine groups of chitosan, a natural polymer, and the negatively charged phosphate groups of glycerol phosphate disodium salt can form electrostatic crosslinking to formulate chitosan-based hydrogels. Similarly, alginate (an anionic polysaccharide) composed of mannuronic and glucuronic acid monomers was crosslinked with divalent cations like magnesium (Mg^{2+}), calcium (Ca^{2+}), barium (Ba^{2+}), *etc.* The cations tend to specifically crosslink with the guluronate blocks of alginate with an appropriate coordination degree between the divalent ions and form an inter-polymer junction with adjacent blocks, leading to the formation of alginate-based hydrogels. This method is frequently utilized to encapsulate drugs and proteins due to easy crosslinking procedures.

3.Crosslinking by Hydrophobic Interactions

Hydrophobic interactions play a crucial role in designing tough hydrogels for large biological systems. The hydrophobic interactions can be formed by incorporating hydrophobic structural units into the hydrophilic polymer chain. Usually, the hydrogel formed by hydrophobic interactions exhibits high toughness due to the flexible movement of junction zones in the hydrogel network, which helps to dissipate energy efficiently and upsurge fraction toughness. Hydrophilic interactions have been actively use in associative thickeners like hydrophobically ethoxylated urethanes.

4.Crosslinking by Enzyme-catalyzed Reactions

Enzymatic crosslinking is another technique that is currently gaining much attraction as it provides the opportunity to manipulate the gel formation by regulating the enzyme characteristics. The formation of gels depends on many parameters, like a specific type of enzymes, their structural arrangement, physiological conditions, *etc.* Compared to physical and chemical crosslinking methods, enzyme-catalyzed hydrogel formation is simple and carried out under mild physiological conditions. For example, no toxic chemicals, no high temperatures, high efficiency, and no harmful radiation are involved in the crosslinking process. The majority of enzymes that are currently employed in the crosslinking process are similar to the enzymes that carry out catalytic reactions in the body. Moreover, other cytotoxic effects and unexpected by-products that arise during chemical or photo-crosslinking methods are avoided as a result of substrate-specific enzyme reactions .

5.Crosslinking by Crystallization

In this process, the crystallites present or that form in the polymer chain serve as building blocks for physical crosslinking in the network, consequently resulting in the formation of a hydrogel. The PVA solution undergoes repeated freezing and thawing cycles to form a hydrogel. The properties of the resultant gel depend on many factors like molecular weight, concentration of solution, freezing time and temperature, number of cycles, *etc.*

6.Hydrogel Classification Based on Degradability

Hydrogels have been categorized into biodegradable and non-biodegradable based on their degradation. The hydrogels synthesized from natural polymers such as chitosan, alginate, agarose, fibrin, *etc.* are completely biodegradable. Degradable gels made from water soluble polymers such as PVA, PEG, PAM, and polyvinylpyrrolidone (PVP) degrade by the breaking of virtual or covalent crosslinks. For many biomedical applications, the biodegradable aspect is the primary criterion for the use of the material inside the body. Recently Heng *et al.* reported the development of a biodegradable hydrogel based on pectin aldehyde and poly(*N*-isopropylacrylamide-stat-acylhydrazide) as a drug carrier for antitumor therapy. In contrast, non-biodegradable hydrogels are prepared with synthetic polymers.

Advantages:

- Absorbency
- Flexibility
- Adhesion
- Biocompatibility
- Stimuli responsiveness
- Drug delivery
- Wound care
- Screen protection

Disadvantages:

can be hard to handle

usually mechanically weak.

May difficult to load drug and cells and then crosslink in vitro as a prefabricated matrix.

May be difficult to sterilize.

Material & methods:

Methods:

Methods A: Solubility

Methods B: Swelling measurment

Methods C: Scanning Electron Microscopy

Methods D: Light scattering

Methods E: Sol- gel analysis

Methods F: Rheology

Methods G: Free radical polymerization

Methods H: Cross linking

Methods I: Freeze drying

Methods J: Gas blowing

Methods K: Ionic interaction

Methods L:Hydrogen bonds

Methods M: Hydrophobic interaction

Material: hydrogel can be made from natural polymers, synthetic polymers, or a combination of the two. Some common natural polymers used to make hydrogel include

- cellulose,
- chitosan,
- starch,
- pectin,
- lignin,
- alginate,
- gelatin,
- hyaluronic acid,
- heparin
- fibrin

Synthetic polymers:

- polyvinyl alcohol
- polyethylene glycol
- acrylate polymers
- polyurethane
- pol(lactide- co- glycolide

other material:

- acrylic acid
- acrylamide
- oxidized starch

Drug profile letrozole:

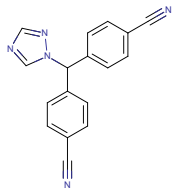
An injectable agarose hydrogel composed of polydopamine and letrozole AHPL FOR Synergistic photothermal and endocrine therapies of endometriosis.

Letrozole, or CGS 20267,is an oral non-steroidal type II aromatic inhibitor first described in the literature in 1990. It is a third generation aromatic inhibitors.

Letrozole was granted FDA approval on 25july 1997

Type : small molecule

Groups approved, investigational



Weight 285.3027

Chemical formula C17H11N5

Letrozole a drug that can inhibit aromatase enzyme and in some studies on animal models (rats, mice and baboons) it has led to the reduction in the size of endometriotic implants . Letrozole is a drug that inhibits the aromatase enzyme by competitively binding to the cytochrome P 450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Elevated levels of aromatase have been found in endometriotic lesions . Therefore, aromatase inhibitors maybe effective in treating endometriosis related pelvic pain.

Mechanism of action

Letrozole is a non-steroidal type II aromatase inhibitor. It blocks the active site, and therefore the electron transfer chain of CYP19A1. This competitive inhibition prevents the conversion of androgens to estrogen. This action leads to a reduction in uterine weight and elevated leuteinizing hormone. In postmenopausal women, the action of aromatase is responsible for the majority of estrogen production. With reduced availability of estrogen, estrogen-dependant tumors regress. Third generation aromatase inhibitors do not significantly affect cortisol, aldosterone, and thyroxine levels.

Conclusion

letrozole-loaded hydrogel formulations present a promising approach for the localized treatment of endometriosis, offering potential for improved therapeutic efficacy and reduced systemic side effects. Further in vivo studies are required to validate these findings and optimize the formulation for clinical application.Introduction; Endometrium is the inner most layer of the uterus. This layer comprises epithelial and stroma. A receptive endometrium with proper thickness is essential for successful embryo implantation, however endometrial injury caused by intrauterine procedures often leads to pathophysiological changes in its environment, resulting in subsequent female infertility. Among diverse treatment methods of endometrial injury, hydrogel are a class of hydrophilic three dimensional polymeric network with bicompability as well as the capability of absorbing water and encapsulation, which have potential applications as a promising intrauterine controlled release delivery system. The human endometrium is complex and dynamic tissue with more than 400 cycles of proliferation and shedding during a woman's reproductive years. Endometrium can be divided into outer functional and inner basal layer,endometriosis is common gynecological disease in woman of chidbearing age. Commonly used treatment methods, such as endocrine and surgical therapies, display poor therapeutic effect.

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