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Review on advanced and potential various Nanogel & hydrogel for breast cancer management

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ABSTRACT
Breast cancer remains one of the most devastating diseases in the world. Nanotechnology has the potential to revolutionize cancer diagnosis and treatment. (1) It is a breast cancer, the most common recurrent cancer in women and the leading cause of death with approximately 5 million deaths per year worldwide. Among women under 40, approximately 7% were diagnosed with BC, while among women under 35 the rate was less than 4%. There are currently fewer treatment options for Of these patients.(2) The purpose of this review is to present current issues in the treatment of breast cancer and to discuss nanoparticle-based targeting to overcome barriers associated with conventional drug treatment. (3) Conventional therapies are currently used to treat breast cancer, but they have many disadvantages, such as: B. low bioavailability, short circulation time and off-target toxicity.(4)Polymeric micelles are of great interest as an innovative drug delivery system for the diagnosis and treatment of breast Cancer As they offer many advantages over the traditional drug delivery system.(5)Nanomedicine is a scientific field that uses pharmacy and nanoscience. It uses materials, including organic and inorganic, such as nanoscale polymers and metallic structures, also called nanoparticles (NPs), to increase the effectiveness of drug delivery methods.(6) Breast cancer is one of the most difficult cancers in women. It is considered one of the deadliest tumors today. Modified nanomedicine could make major advances in breast cancer recurrence using implants.Advances have been made in breast reconstruction procedures following mastectomy and in early diagnosis and treatment of breast cancer. (8) In the last decade, great emphasis has been placed on developing applications of nanotechnology in breast cancer therapy. Cancer. Benefits of nanotechnologies that improve biological processes and promote better compatibility of biomaterials.(9)

Keywords: NPs, Nanohydrogel, TP, TPL, IMQ, EDC, GPA, drawbacks, liposomal carrier, herceptin-adorned PEGylated lecithin-inulin nanogel , IMQ, Fluorescent active gel.etc.

I. INTRODUCTION

Breast cancer is one of the most common cancers in women worldwide.(3) In 2016, a total of 246,660 new cases of breast cancer and 14% of breast cancer-related deaths were reported in the United States. Most deaths from breast cancer are due to drug resistance and the possibility of metastasis to distant organs such as lymph nodes, bones, lungs and liver. At the beginning of 2020, 2.3 million women were diagnosed with breast cancer, including approx.6 lakh were killed worldwide and this number rose to 7.8 million by the end of 2020. (4) Nanotherapeutics are a rapidly developing field that are being used to overcome problems associated with traditional formulations, including nonspecific biodistribution, lack of targeting, low water solubility, and poor oral bioavailability. (5) Currently, cancer research is focused on improving the treatment of BC with various new chemotherapeutic agents such as nanoformulations, liposomes, hydrogels, Exosomes, dendrites, microspheres, microvesicles, phytosomes, micelles, etc.. (2) The 10-year incidence of locoregional recurrence of stage I and II breast cancer in women after surgery is 4–18%, which may ultimately lead to great physical and mental suffering due to subsequent ulceration. With unpleasant odor, pain, and bleeding.18 Breast cancer is the most common malignancy in women and the second leading cause of cancer death in the United States. (6) There are more than twenty therapeutic nanomaterials approved for clinical use. Among them,

Lipid-based formulations, such as liposomal doxorubicin (Doxil/Caelyx) and liposomal daunorubicin (DaunoXome), are considered an important class of nanocarriers for use in cancer

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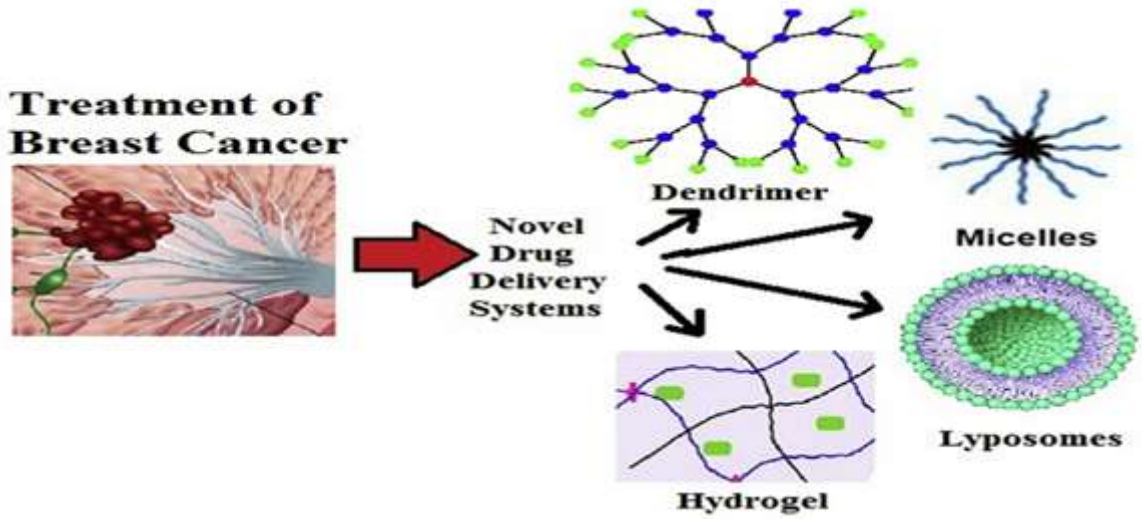
treatment. Paclitaxel (Abraxane) has a diameter comparable to liposomal drugs (130 nm) and was approved by the FDA in 2005 for the treatment of metastatic breast cancer.(8)To date, studies on targeted drug delivery for breast cancer have largely centered on pre-clinical studies using anti-HER2 antibody-linked liposomal drugs.(9)**Fig-1novel drug delivery system for breast cancer management.(11)**



Nanohydrogel

nanoparticle composed of a hydrogel with a network of cross-linked hydrophilic polymers is known as a **nanogel**.(16)

Among the various delivery systems, hydrogels have great potential to serve as ideal platforms for topical therapy. These are hydrophilic gels with a three-dimensional (3D) network structure composed of certain types of biocompatible natural or synthetic polymers. Hydrogel materials, which feature excellent biocompatibility and biodegradability, are being used as excellent new drug carriers in cancer treatment.

Hydrogel materials can be used as precise and controlled drug delivery systems capable of continuously and sequentially releasing chemotherapeutic drugs, radionuclides, immunosuppressive drugs, hyperthermic agents and phototherapeutic agents.(10)

Advantages

Hydrogel materials have multiple sizes and multiple delivery routes, which can be targeted to different locations and types of cancer.

1)Hydrogel can intelligently respond to environmental changes according to internal and external environmental stimuli.

2) Greatly improves the targeting of drugs, thereby reducing the dose of drugs and improving treatment effectiveness.(16)

Route of administration

- Pulmonary
- Nasal
- Parenteral
- Intra-ocular
- Oral

Benefits of Nanogel Drug Delivery Approach

- Provides protection from biodegradation of drugs inside the body. Physical properties like size of nanogels can be easily adjusted and maintained according to the desired delivery molecule.
- Low amount drug is required as well as quantity of doses is reduced.
- Improves the bioavailability of the drug molecule and reduce the toxicity of the drugs.
- Drugs loaded nanogels can be delivered inside the body with no adverse or side effects.(16)

❖ **Injectable thermo-responsive nano-hydrogel loading triptolide**

We are interested in the possible dual effectiveness of TP in the treatment of breast cancer. Tripterygium wilfordii Hook F. has been used in traditional Chinese medicine for hundreds

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of years and is said to have immunosuppressive and anti-inflammatory properties. Triptolide (TP), an extract of this Chinese plant, has been identified as a key chemical contributing to these properties (Qiu and Kao, 2003). Triptolide (TPL) is a diterpenoid tripepoxide Isolated from Tripterygium wilfordii.Hook F, commonly known as "Thunder God Vine" or "Lei Gong Teng", whose highly effective antitumor effects have been reported in many types of cancer. The clinical use of triptolide (TPL) in the treatment of cancer is significantly limited due to its toxicity and inefficient administration. A topical, thermosensitive, sustained-release hydrogel was developed for intratumoral administration of TPL.TPL@nano-gel led to lower systemic toxicity and higher antitumor efficacy compared to multiple injections of TPL.

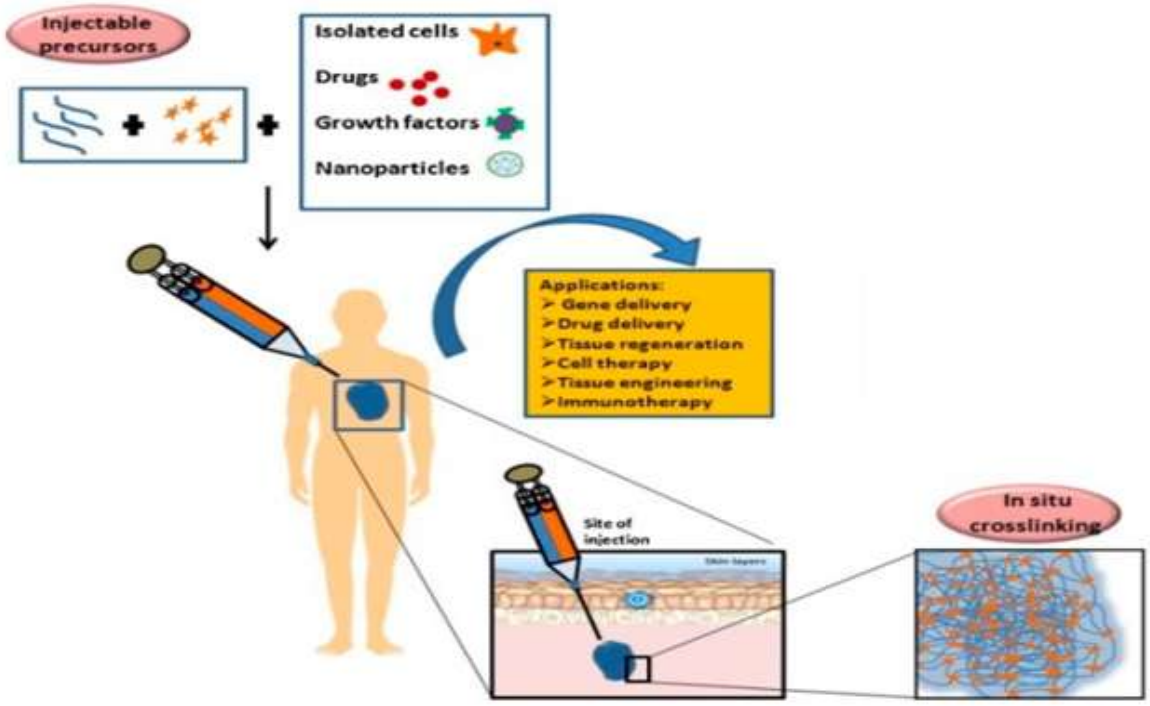

Fig-2 Injectable hydrogel.(4)

These findings indicate that this injectable thermo-responsive hydrogel carries great potential for TPL as a safe and effective cancer in therapy.A themoresponsive nano-hydrogel was fabricated for the sustained release of triptolide (TPL) in the localized treatment of breast tumor. Thermo-responsive hydrogels have been widely utilized in tumor treatment. Thermogels are also known as thermo-sensitive or thermo-responsive hydrogels.(11)

II. MATERIAL AND METHODS

N-Isopropylacrylamide (NIPAM) was purchased from Chengdu Huaxia Chemical Reagent Co. Ltd. (Chengdu, China). Acrylic acid (AAc), potassium persulfate (KPS), and N,N,N',N'-tetramethylethylenediamine (TEMED) were from Chengdu Kelong Chemical Reagent Co. Ltd. Bought.(Chengdu, China). Pluronic F68, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), and 4-(dimethylamino)pyridine (DMAP) were purchased from Aladdin Biochemical Technology Co. (Shanghai, China). Triptolide (TPL) was purchased by Chengdu Desita Biological Technology Co.Ltd. (Chengdu, China). Dimethyl sulfoxide (DMSO), heparin, gelatin, collagen, protease, endothelial cell growth supplement, 3-(4,5-dimethylthiazol-2-yl)-2, diphenyltetrazolium bromide (MTT), and Drabkina 525 reagent kit were purchased from Sigma. – Aldrich (St. Louis, United States). Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), phosphate buffered saline (PBS), penicillin-streptomycin and 0.Trypsin 25% (wt/vol) with 1 mmol/L EDTA was purchased from Invitrogen (Carlsbad, USA). All animal experiments were carried out in accordance with

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the rules of the Experimental Animal Administrative Committee of Chengdu University of Traditional Chinese Medicine (Chengdu, China).(12)

• **Structural characterization of p(NIPAAm-co-AAc)-g-F68 copolymer**

The molecular weight of p(NIPAAm-co-AAc)-g-F68 was determined by gel permeation chromatography.NMR spectrometry (AVANCE III HD 500 MHz spectrometer; Bruker, Germany) was used to characterize the synthesized p(NIPAAm-co-AAc)-g-F68 copolymer with DMSO-d6 as the solvent. Ultrapure water (0.02% sodium azide, pH 6.0) was used as the mobile phase at a flow rate of 1 mL/min at 25 °C.

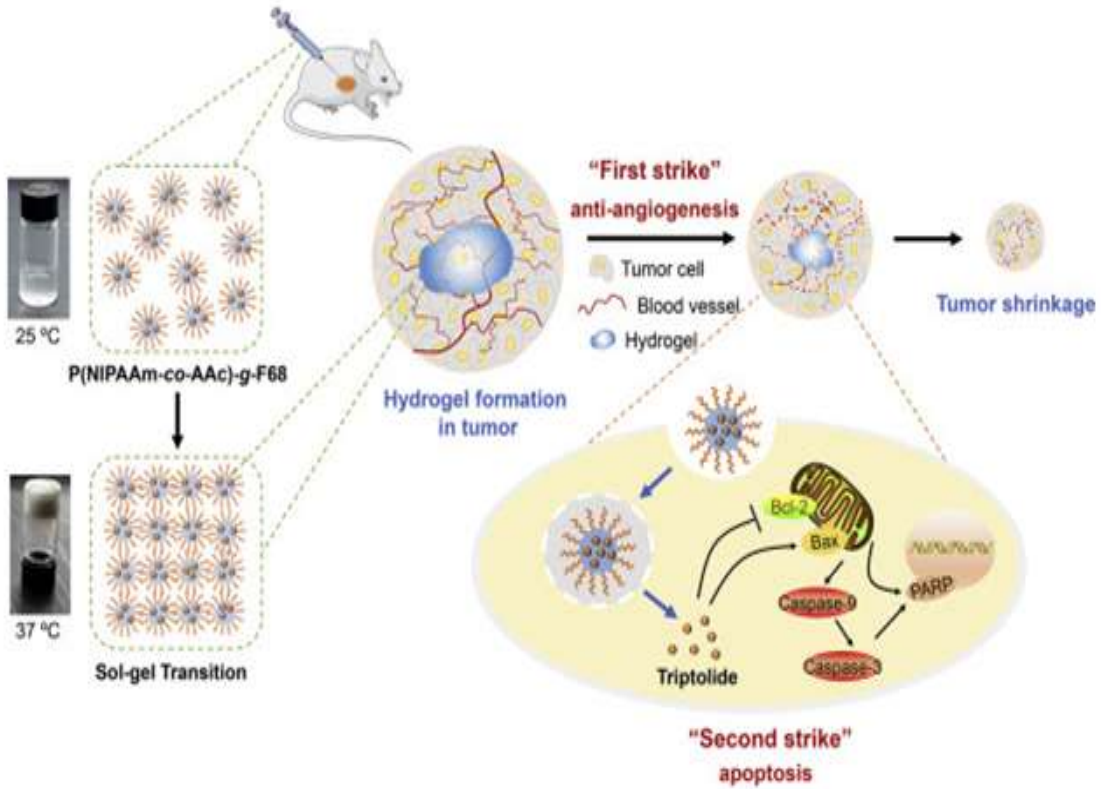

Fig 3 : injectable thermosensitive nano-hydrogel loading triptolide (TPL) composed by the self-assembly of p (NIPAAm-co-AAc)-g-F68 copolymer for localized tumor therapy.(12)

In vivo tumor inhibition effect of TPL@nano-gel

The dorsal subcutaneous part of BALB/c mice (4 weeks old) was inoculated with 4T1 mouse breast cancer cells (5 x 106 cells/mouse). The tumors were allowed to grow to approximately 200 mm3. Then, the xenografted mice were randomly divided intoFour groups, and Saline, blank gel, free TPL, and TPL nanogel (0.45 mg/kg) were intratumorally injected on days 1, 5, and 10. The weight was And the tumor volume([width] 2 × [length]/2) was recorded once every 2 days.On day 14, a portion of the mice (6 of Mice in each group) were sacrificed and photographed, and the Primary tumors were excised and weighed.

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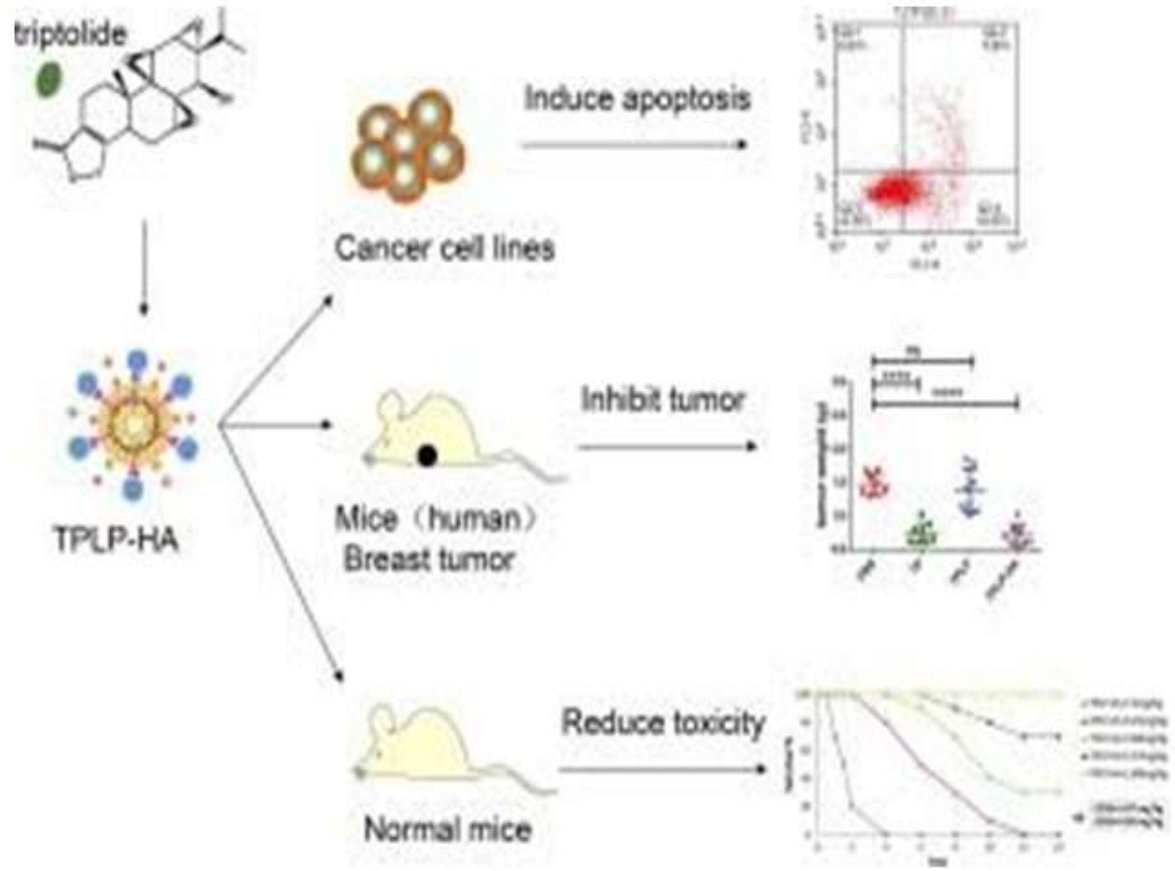

Fig-4 In tumor inhibition effect.

❖ **Multifunctional bioresponsive Fluorescent active nanogel composite for breast cancer**

Cancer is one of the most common causes of death worldwide. The most common types of cancer are lung, colon, prostate and breast cancer. Bioresponsive nanocomposites, easy to produce and rationally designed, are of great importance for the diagnosis and treatment of cancer. A traceable and bioresponsive fluorescent active nanogel composite was prepared by integrating creatinine-functionalized carbon dots (QDs) into a lecithin-inulin nanogel. The cellular uptake of Herceptin is increased. This caused To inhibit the proliferation of breast cancer cells and also reduce their viability.Such nanogel composites have great potential for image-based disease diagnosis and cancer treatment, as fluorescence imaging not only closely monitors changes in biological signals in vitro and in vivo. Overall, the Herceptin-decorated PEGylated lecithin-inulin composite nanogel could be a promising theranostic candidate for the treatment of HER-2 positive breast cancer.

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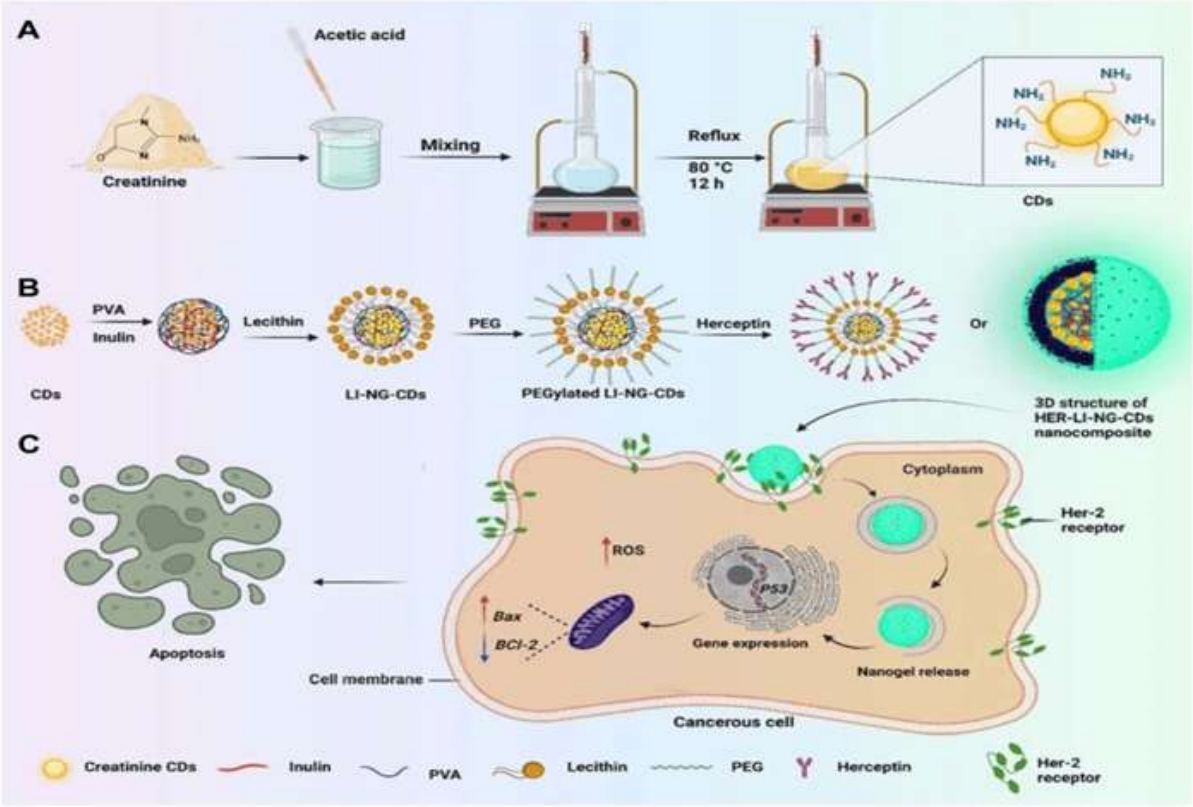

Synthesis of carbon dots fig-5

Material and method

Precursor materials containing 20 mL creatinine 0.2 mol L−1 and acetic acid 2.5 mol L−1 were refluxed at 80 °C with constant vigorous stirring for 12 h. During reflux processing, the solution color converted from colourless to yellow, indicating the formation of CDs. The obtained product was cooled to room temperature.(13)

Herceptin integrated nanogel

To prepare herceptin-integrated nanogel (Her-LI-NG-CDs), 150 µL of glutaraldehyde was added to 1 ml of prepared Nanogel in the previous step with very slow stirring, followed by a rest period of 5 min.

Finally, 15 µL of herceptin (45 mg ml−1) was added to the nanogel to complete the conjugation process.

Instrument

UV–vis absorption spectra were recorded by a Jenway spec-Trophotometer model 6705 (UK). Fluorescence spectra were Recorded by a fluorescence spectrophotometer F-2700-Hi-Tachi (Japan) equipped with a xenon lamp source. pH adjustment was performed using a digital pH-Meter model 632.

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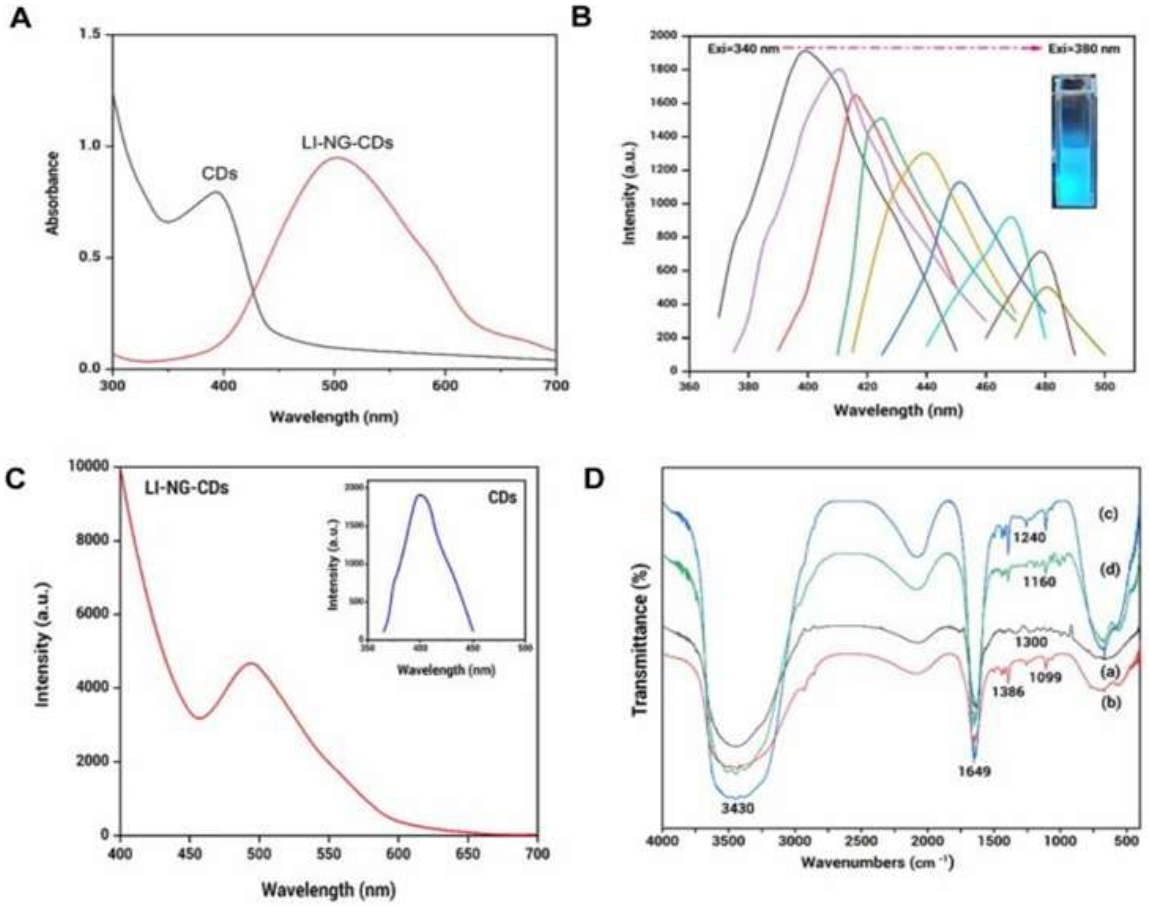

Fig: 6) The UV − vis spectra of CDs and the prepared nanogel. B The emission fluorescence spectra of CDs at diverse excitation wavelengths from 340 to 380 nm along with the photo of its bright blue luminescence color under UV light .(13)

❖ **Liposomal-Loaded Thermal-sensitive or Responsive Hydrogel**

To reduce the side effects of immune drugs and ensure sustained release of immune drugs in local parts of the body, we developed a thermoresponsive injectable hydrogel containing an imiquimod-loaded liposomal system. In animals, drug-containing liposomes combined with hydrogel can be effectively used in breast cancer treatment to delay tumor growth.

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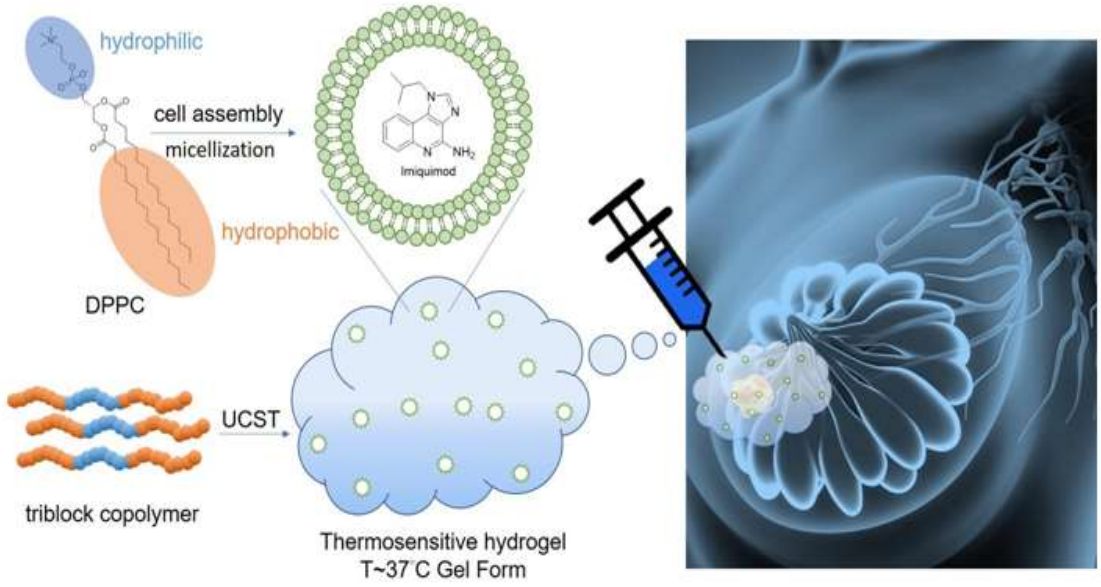

In 1893, it was proposed that the immune system could recognize tumors and control their growth. Since then, cancer immunotherapy has become an important research area in cancer treatment. Polymer-based carriers (micelles and liposomes). The liposomal carrier has a relatively higher drug loading capacity, which can solve the problem of poor drug delivery in the human body and increase the amount of drugaccumulated in the tumor microenvironment. Liposomal carriers can be equipped with acidic, basic or temperature-sensitive functional groups, allowing the delivery of the transported drug in a specific environment, for example in the slightly acidic environment (pH 6.5)(14).

Advantages

- To Achieve a sustained and slow release of immunotherapeutic drugs in the breast cancer tumor region and thus suppress the tumor's growth
- Utilizing the high drug-loading capacity and the long-term and slow release properties(14)

- **Materials and Methods**
- 1,2-Dipalmitoyl-sn-glycero-3-phosphatidylcholine was purchased from Avanti® Polar Lipids, INC in Alabama, USA. Imiquimod (IMQ) was purchased from Alfa Aesar in Lancashire, England.
- Phosphate buffer solution (0.01M) (PBS) was prepared from the of 137mM NaCl, 2.7 mM KCl, 10 mM Na2SO4, and 2 mM KH2PO4 in the 800 mL distilled water and then tune the pH to 7.4 with HCl solution.

Liposome preparation

1,2-Dipalmitoyl-sn-glycero-3-phosphatidylcholine and IMQ were dissolved in a methanol/dichloromethane solution and the organic solvent was removed by rotary evaporation to prepare the film. Then, phosphate buffer solution (PBS) was added to perform hydration in the ultrasonic device to form liposomes. Finally, the product was passed through a membrane filter with a pore diameter of 0.22 μm to obtain a liposome containing the active ingredient.(14)

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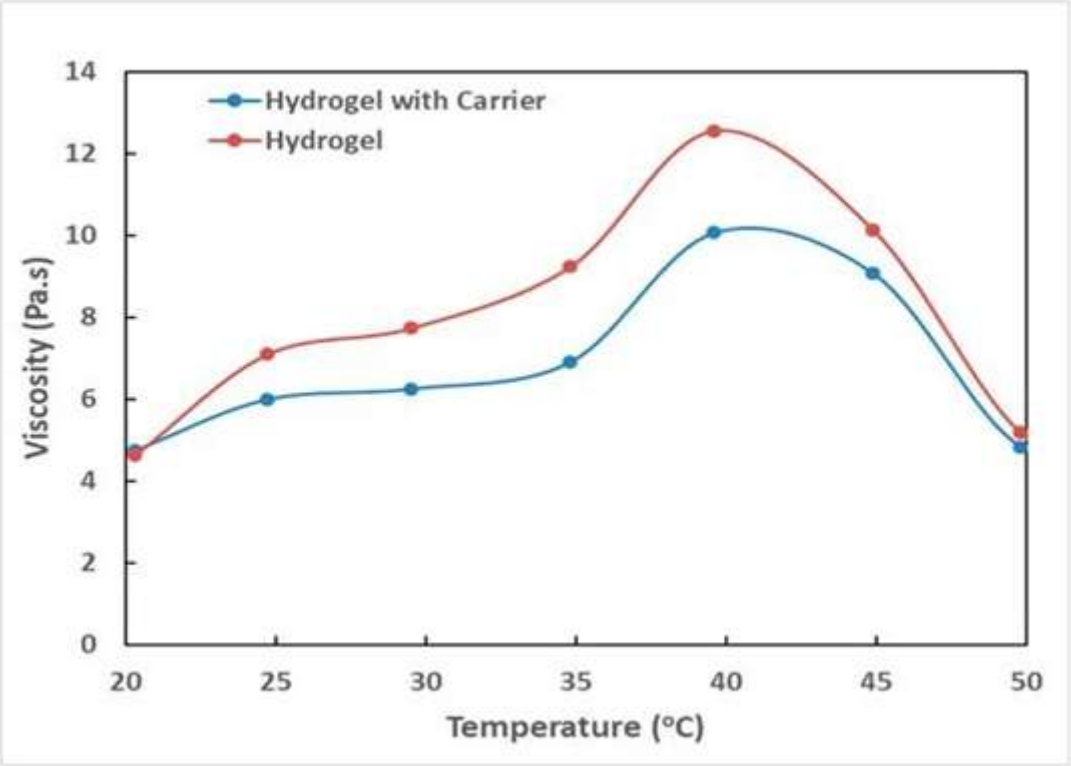
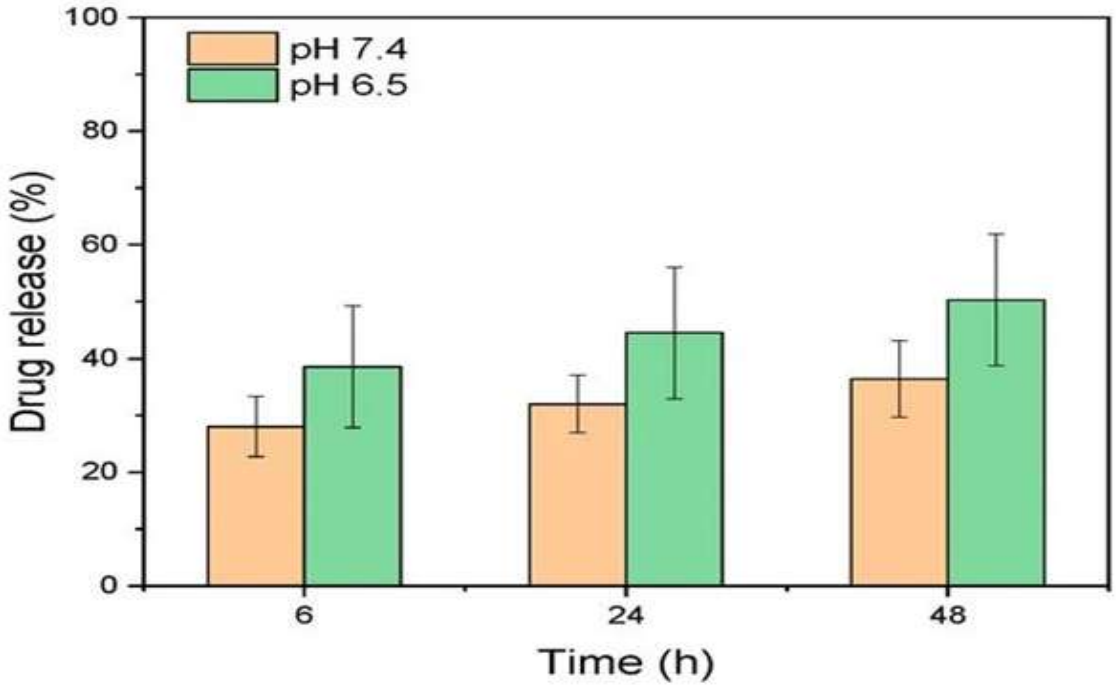


Fig:7 Analysis of the fluid viscosity of the hydrogel before and after mixing with IMQ-containing liposomes.(14)



Drug leakage and release of IMQ-containing liposomes in different pH environments. IMQ: imiquimod.(14)fig-8

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❖ **Tumor-Targeted Injectable Double-Network Hydrogel.**

The double-mesh hydrogel is created by injecting GPA precursor solutions into the resected mouse cavity, where gelation occurs rapidly. The temperature increase-induced polymerization of PEGDA is caused by near-infrared radiation and a second polymer network is then formed. Crosslinks between alginate and endogenous Ca2+ around the tumor. In this study, we designed and fabricated a polyethylene glycol acrylate-DN-alginate (GPA) nanocomposite hydrogel with 125I-modified gold nanorods (125I-GNR-RGDY) for the combined postoperative prevention of local recurrence and wound infection in breast cancer. Preparation of tumor-targeted nanocomposite hydrogel (125I-GPA) and synergistic treatment with PTT and brachytherapy for breast cancer relapse and wound infection.

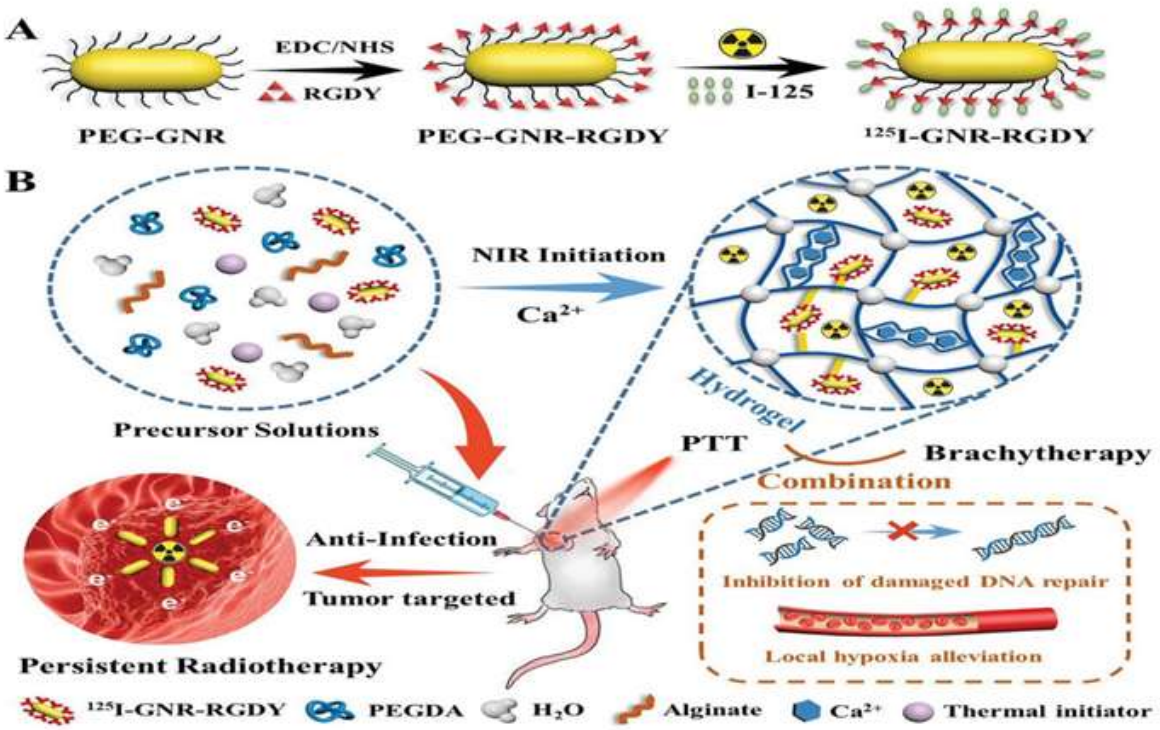

Fig-9 Nanocomposite double-network GPA hydrogel and their theranostic application for inhibition of postoperative breast cancer recurrence.(15)

- **Material and methods**

❖ Polyethylene glycol acrylate (PEGDA, Mn 700), sodium alginate (ALG),1-ethyl-3-(3-dimethylaminopropylcarboimidehydrochloride (EDC), N-hydroxysuccinimide (NHS), and 2,2′-azobis [2-(2-imidazolin-2-yl)propane] dihydrochloride (AIPH) were purchased from Sigma-Aldrich.

❖ PEG modified Au nanorods (GNR) was supplied by XFNANO (Nanjing) Co. Ltd. RGDY peptide was provided by GL Biochem (Shanghai) Co. Ltd. Iodine-125 (125I) radionuclide (500 mCi mL−1 in 0.1 m NaOH solution) was obtained from PerkinEmer (USA).(15)

❖ **Characterization of Nanocomposite Hydrogels**

❖ In this study, we aimed to design a tumor microenvironment-responsive hydrogel for synergistic inhibition of postoperative breast cancer recurrence and drug-resistant infection.

❖ The nanocomposite hydrogel was composed of GNR-RGDY and PEGDA–alginate (ALG) DN hydrogel (GPA). PEGDA and ALG monomers were added to GNR or GNR-RGDY precursor solution.

❖ Thermal induction of PEGDA polymerization led to formation of the first polymer network under conditions involving NIR irradiation based on the photothermal property of GNR. (15)

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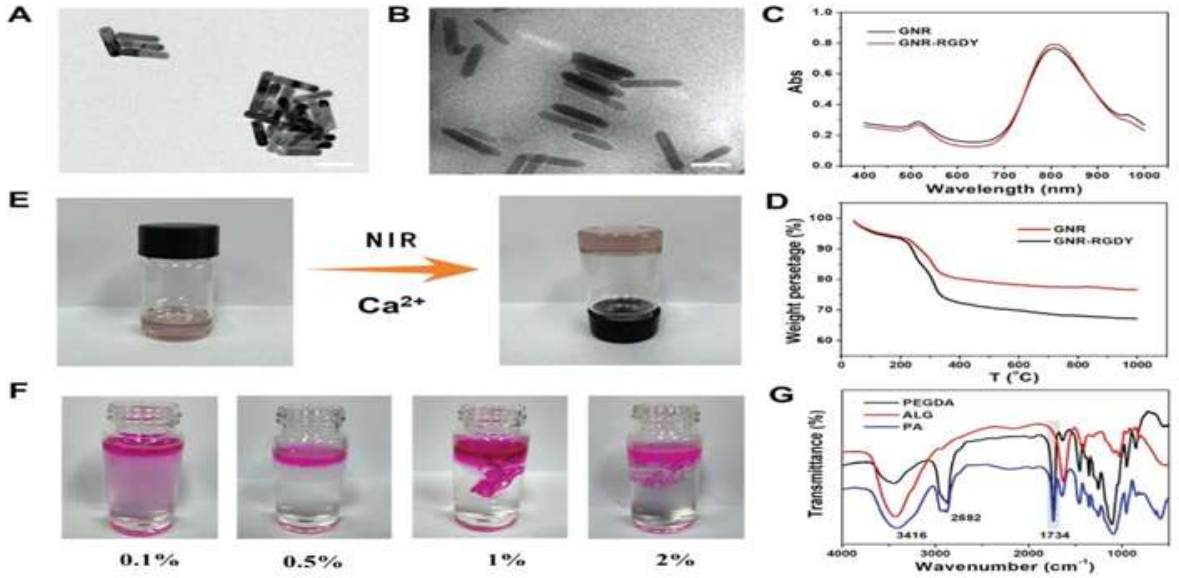

Fig-10 Structural characterization of the DN hydrogel was performed by Fourier transform infrared (FTIR) spectroscopy(15)

❖ **Drawbacks**

- It requires expensive techniques to completely remove the solvent sand surfactants at the end of the process.
- Sometimes, traces of surfactants can cause toxicity.(16)

III. CONCLUSION

Novel drug delivery system most potential compared to conventional therapy. Various nanogel and hydrogel potential effect on breast tomor.they also have less drawback as compared to conventional drug.

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