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ADVANCEMENT OF NANOEMULSION FORMULATION IN DRUG DELIVERY SYSTEM FOR ANTICANCER DRUG

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Abstract: Nanoemulsion can be defined as Novel drug delivery system to improve delivery of therapeutic agent. They are thermodynamically stable, isotropic in nature. It is type of emulsion where two immiscible liquid i.e.,oil and water phase are mixed with the help of cosurfactant to form a single phase. The size of nanoemulsion is 20-200nm. The nanoemulsion may be prepared by both high and low energy emulsification method such as High Pressure homogenization method, ultrasonic emulsification, micro-fluidization method phase inversion temperature method etc. The advantage of nanoemulsion include biocompatibility, controlled drug release, drug targeting, improves, bioavailability and prolonged stability. These feature makes them appropriate for delivering anticancer therapeutics agents. Designing of nanoemulsion formulation highly depends upon the nature and site of tumour. They are considered to be an effective nanocarriers for targeting to cancer cells.Nanoemulsions have the ability to delivering large concentration of chemotherapy drugs to cancerous tissue without have an effect on cells and organ in the systemic circulation. Various nanoemulsion preparation available in the markets for the treatment of various type of cancer such as Paclitaxel, Chlorambucilnanoemulsion, Tocotrienolnanoemulsion, Piplartinenanoemulsion, Doxorubicin nanoemulsion etc.

INDEX TERMS: Anticancer, drug, nanoemulsion, therapeutic agent, tumour.

1.INTRODUCTION:

Nanoemulsion may be defined as novel drug delivery system focus to improve delivery of therapeutics agent [1]. They are thermodynamically stable, isotropic in nature [2]. It is type of emulsion where two immiscibleliquid i.e., water phase & oil phase are mixed together to formed a single phase with the help of an appropriate surface active agents.The size range of nanoemulsion is 20-200nm[3].There are three main components used in the preparation of nanoemulsions are oil, surfactant and cosurfactants.Advantages of nanoemulsion formulations include enhanced biocompatibility, controlled drug release, drug targeting,improves bioavailability and stability for a prolonged time period. These feature makes them appropriate for delivering of anticancer therapeutic agents.[4].Disadvantages of nanoemulsion are use of a huge concentration of surface active agentsand cosurfactant essential for stabilizing the nanodroplets,mean solubilizing capacity for high-melting materials,the surfactant should be safe for using pharmaceutical applications,Nanoemulsion stability is effected by environmental parameters such as temperature and pH[5].These parameters change upon Nanoemulsion delivery to patients.Designing of nanoemulsion formulations highly depends on the nature and various of formulation such as liquid, sprays, foams, creams, ointment and gels, they show best outcomes for the future of cosmetics, diagnostics, drug therapies and biotechnologies[6]. Nanoemulsion have applications in various regions such as in cancer treatment, in drugtargeting, as a mucosal vaccine, as a vehicle for Transdermal drug delivery and lipophilic drug as a self-nanoemulsifying and solid self-emulsifying drug delivery system[3]. Nanoemulsion composed of oil phases, surface active agents, active pharmaceutical ingredients and excipients. The oil phases are generally natural or synthetic lipid, fatty acids, The most commonly used oils for parenteral preparation are purified soybean, corn, castor, peanut cottonseed, sesame. Squalene had been reported for formulating stable nanoemulsions with smaller droplet Size[7]. Nanoemulsion can be designed to perform particular tasks for desired delivery, prolonged blood circulation and target specific site binding[4]. Cancer is a highly fatal disease in the world[8].Cancer caused by a series of consecutive mutations in genes so that these mutations can change thecell function. There are a several types of cancer affecting the health of all human societies. Generally Prostate and breast cancer comprise a major portion cancer in Men and women. And the blood cancer and cancer related to the brain and lymph are occurred in children[9].Cancer is a second major cause of death after COVID-19 in the United States and the National cancer institute has projected that abouts 2.001,140 new cancer cases and 6111,720 cancer death cases occur in the U.S. The occurrence of cancer cases

is predicted to increase to 12.8 %in 2025 compared to 2020. The new publication from NCRP projected the burden of cancer to 29.8 million DALYs by2025 in India[11]. Currently a nanoemulsion is to improve the delivery of therapeutic agents, are in extensive investigations as drug carriers[12].

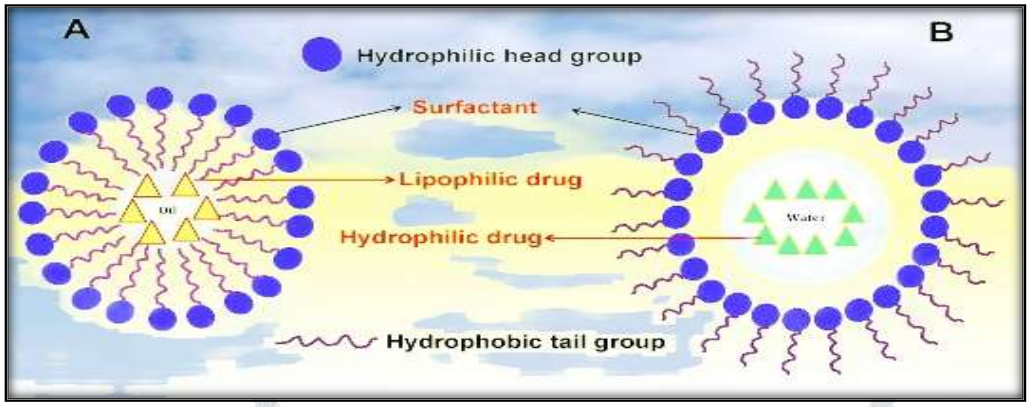


Fig1:Structure of nanoemulsiona)oil-in-water b)water-in-oil.

The occurrence of cancer cases is predicted to increase to 12.8 %in 2025 compared to 2020. The new publication from NCRP projected the burden of cancer to 29.8 million DALYs by2025 in India[11]. Currently a nanoemulsion is to improve the delivery of therapeutic agents, are in extensive investigations as drug carriers[12]. Nanoemulsionshave the ability to delivering high concentration of chemotherapy drugs to cancerous tissueswithout have an effecton cells and organ in the systemic circulation[13].Various nanoemulsion preparation available in the market for the treatment of various types of cancer such as Paclitaxel,Chlorambucilnanoemulsion, Tocotrienolnanoemulsion,Piplartinenanoemulsion, Doxorubicin nanoemulsion etc[4].

MANUFACTURING METHODS & FORMULATION OF NANOEMULSION

There arevarious method to manufacturing the nanoemulsion i.e., High energy emulsification and Low energy emulsification. In high energy emulsifications methods, mechanical devices deliver need a large disruptive force while in low energy emulsification, no need of any external force [14]

[A]High-energy Emulsification methods: Nanoemulsions can be formed by high energy method through utilizing mechanical energy input by using ultra sound generator, high pressure homogenizers,and high shear stirring[15].The size of globule of the dispersed phase in the nano-emulsions formulated by high pressure homogenizer reduces with homogenization cycles,the reduces the surface tension, the increases the surfaceactive agents adsorption rate and the decrease the viscosity ratio[2].

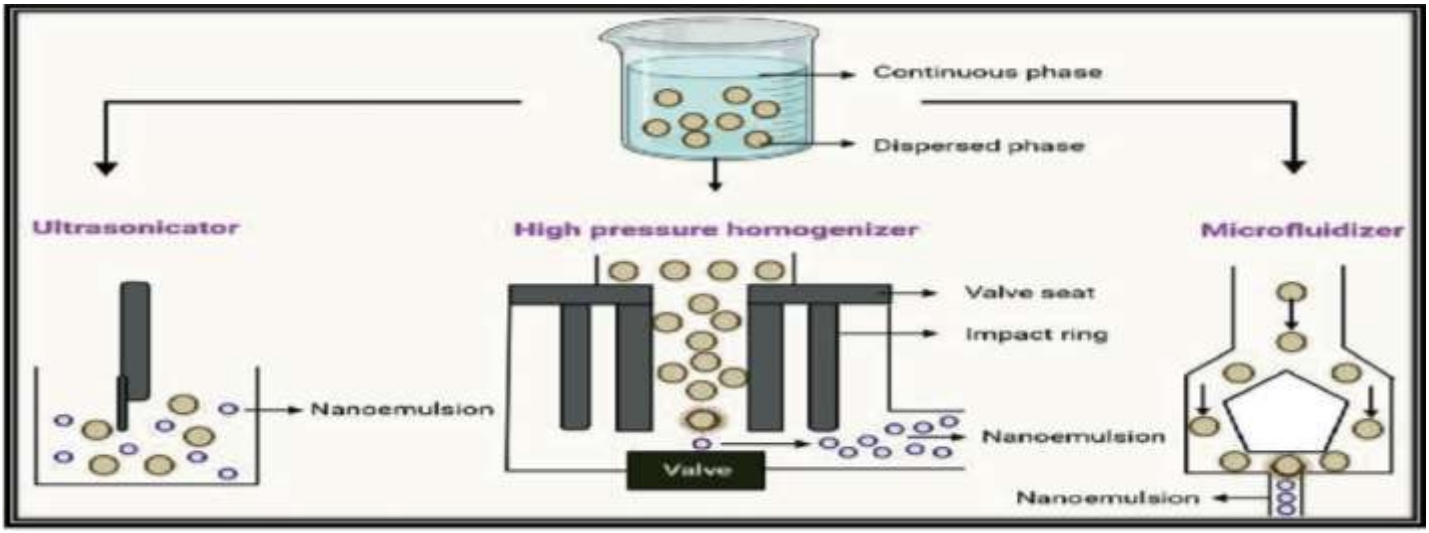


Fig:2: Different types of High-energy emulsification methods a]Ultrasonicatorb] High pressure homogenizerc] Microfluidizer

High-pressure homogenization: High -pressure homogenizers deliver high energy and provide uniform flow to formulate smallest globules sizes. Therefore,high pressure homogenizers are broadly used to formulate the nanoemulsions. HPH are used to generate extensively disruptive force that they formed nanoemulsions acutely low particles globules sizes (up to 1nm)[16]

Ultrasonic emulsification: As a suitable method for small scale test, emulsion is prepared by ultrasonic irradiations is an operative method for reducing the mean droplet diameter size (MDDS). Various nanoemulsions formulation was formed by this method are shown in table.[17]

Microfluidization method: A nanoemulsions are prepared by forcing the coarse emulsion through an air driven microfluidizer furnish with a Y- and Z-type interaction chamber. Some formulations are prepared by this method such as Tocotrienol nanoemulsion, Docetaxel nanoemulsions are shown in table [18]

METHOD	FORMULATION NAME
1.Ultrasonic emulsification	Paclitaxel, Perflurocarbon,Fisetinnanoemulsion,Lycopene nanoemulsion,Paclitaxel and curcumin nanoemulsion, chlorambucil nanoemulsion,Methotrexate nanoemulsion
2.High –pressure homogenization method	Tocotrienol nanoemulsion, Folic acid tagged protein nanoemulsion, Tributyrin oil & Docetaxel nanoemulsion
3.Microfluidization method	PEG400 with Paclitaxel,Dacarbazine nanoemulsion

[B]Low energy emulsification: The low energy emulsification method involves phase inversion temperature, emulsion inversion point, and spontaneous emulsification. This method formed more uniformly and smallerglobules by using physicochemical characterize of the system.[15]

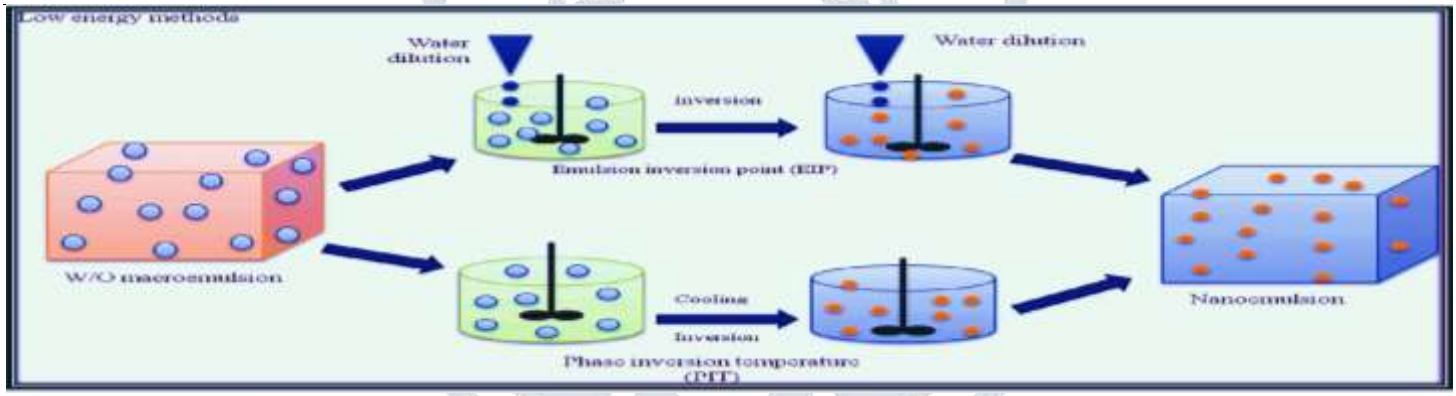


Fig:3: Low energy emulsification methods.

Phase inversion temperature method:PIT is type of low-energy emulsification method for formulating nanoemulsions which make changes in the special curvature of surface-active agents at constant composition by changing the temperature. In this method, nanoemulsions are prepared by the development of microemulsions at its PIT followed by instant cooling to room temperature which can be divided into three major steps:

1. Non-ionic surface-active agents, oil and water are stirred at room temperature to formed a coarse emulsion
2. The mixture is then gently heated up to around or above the PIT.
3. The solution is quickly cooled to the room temperature with continuous stirring, ensuring in the formation of o/w nanoemulsions.[19]

Paclitaxel nanoemulsion, Piplartinenanoemulsion, Cyanide photodynamic therapy is the nanoemulsion formulation prepared by this method.

Solvent displacement method: Nanoemulsions can be prepared this method at room temperature by pouring the organic phase containing oil dissolved in a solvent, like ethanol or acetone, into aqueous phase containing surface active agents. Emulsification occurs due to diffusion of organic solvent, which may be removed by vacuum evaporation. A high ratio of solvent to oil is needed to prepare small sized droplets. Solvent displacement method does not required heating, nor the presence of an organic solvent and LC or ME as a phase.[20]

Some nanoemulsion formulation were prepared by this method such as Doxorubicin nanoemulsion, Cheliensisinnanoemulsion, Drimysangustifolia with Drimysbrasiliensis, Betulinicnanoemulsion.

METHOD	FORMULATION NAME
1.Phase inversion temperature method	Paclitaxel nanoemulsion,Piplartinenanoemulsion, Aluminium-ptthalocyanine chloride photodynamic therapy, Cyanine photodynamic therapy
2.Solvent displacement method for preparing nanoemulsion	Doxorubicin nanoemulsion, Cheliensisinnanoemulsion,Drimysangustifolia with Drimysbrasiliensis,Betulinicnanoemulsion,Caeffine

1.Paclitaxel – Paclitaxel (PTX) is a derivative of taxane. Paclitaxel is one of the most essential anticancer drugsenhanced in the past 20 yearsas per reports of the National Cancer Institute (NCI). Paclitaxel hasshowedanti-tumour activity against a different type of cancers,

such as ovarian carcinomas, breast cancer, non-small cell lung cancer (NSCLC), and AIDS-related Kaposi sarcoma, ovarian carcinomas [21]. The chemical structure of paclitaxel is represented in Figure 3.The molecular weight of paclitaxel is 853 Dalton and it has a very less aqueous solubility (<1mg/ml). Besides, the compound don't carry any functional groups that can be ionized or t allow for salt formation to improve its aqueous solubility.Solubility of paclitaxel in another commonly usedsolvents [e.g., poly(ethylene glycol), propylene glycol, ethanol, etc.] is also limited[22].

PTX is an anti-microtubulin agent with a specific mechanism of action & they reach its antitumor effect by enhancing tubulin dimerization and obstructing depolymerization of the microtubules [23]. Paclitaxel binds to and preserved microtubules, and paclitaxel-bound microtubules inhibit depolymerization, even upon treatment under cold temperatures or with calcium ions. Therefore, paclitaxel medications promotetubulin polymerization and inhibit the development of mitosis[24].

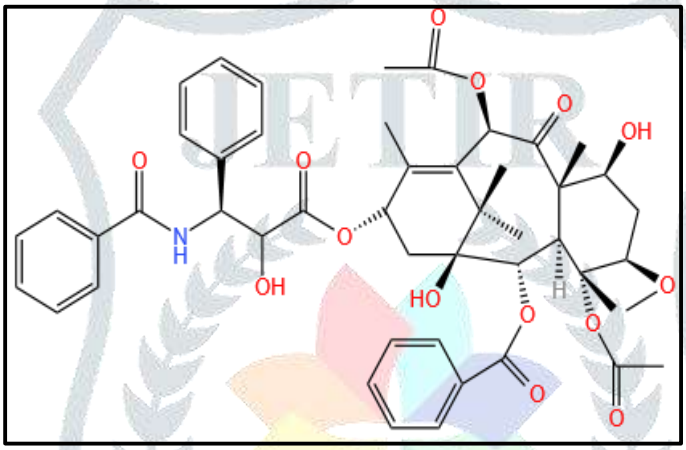


Fig:4-Chemical structure of Paclitaxel.

2.Tocotrienol nanoemulsion: This nanoemulsions was prepared by high pressure homogenization method. And Tocotrienol is an anti-neoplastic agents, are derived from natural phytonutrients and used in clinical experience.The anti-neoplasticeffects of tocotrienols were reported in numerous cancer cell lines including liver, pancreatic[14], breast ,liver and bladder cancers [25].Tocotrienols were reported to target the hallmark of cancer through pro-apoptotic (caspase-8, Bid, Bax, mitochondrialmembrane permeability), cell cycle arrest (cyclin D1, p21, p27), modulation of growth factors (EGF-dependent PI3K pathway, TGF-β), and anti-metastatic properties(E-cadherin, MMP-9, EMT, CXCR4) anti-angiogenesis (VEGF, VEGFR-2) [26]

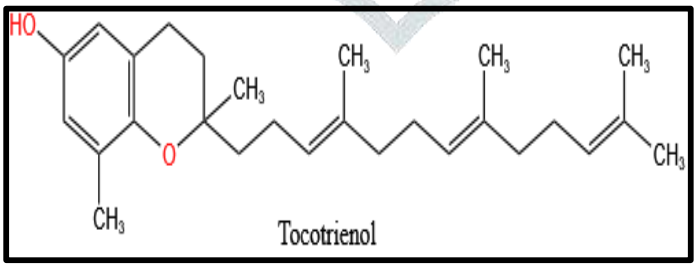


Fig:5: Chemical structure of Tocotrienol

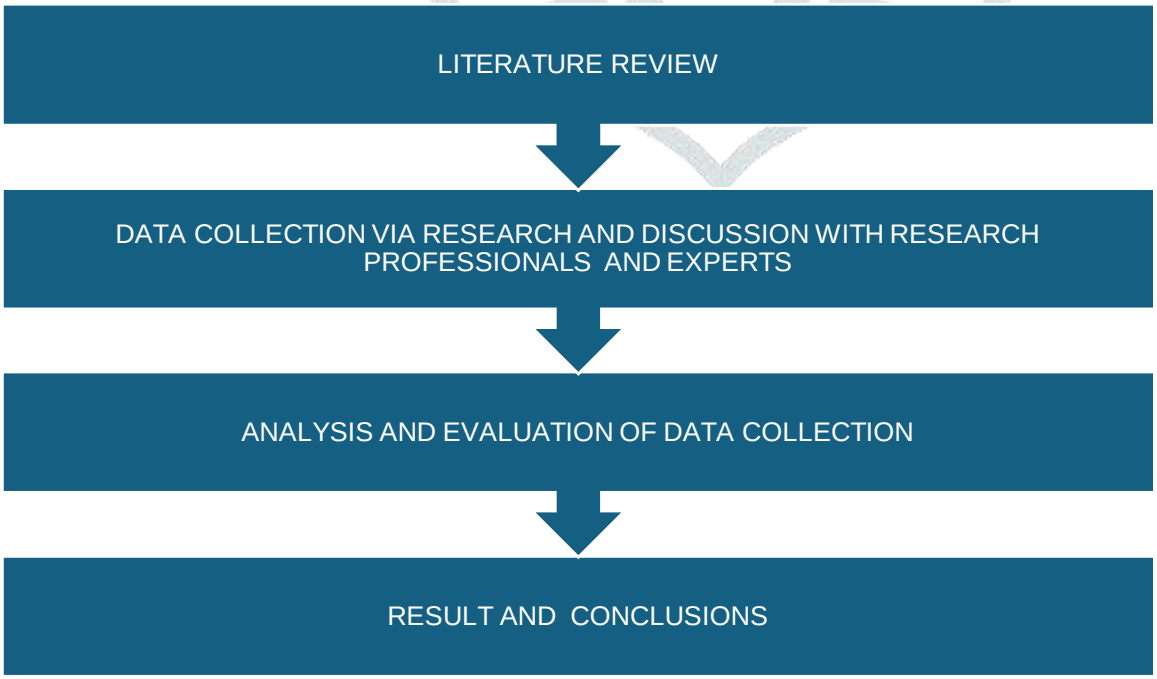
3.Cheliensisinnanoemulsion: These nanoemulsion was prepared bysolvent displacement method.Cheliensisinis isolated from *Goniothalamuscheliensis*as a novel anticancer drug, formulated in lipid nanoemulsions. The lipid emulsions were filtered through a 0.8pm filter, then freeze-dried, and then subjected to gamma sterilization. It should be help to overcome many stability issues in the formulation .[2]

2.LITERATURE REVIEW

S.NO	PAPER	AUTHOR	YEAR	RESEARCH WORK
1.	*Nanoemulsion-Based Drug Delivery for Anticancer Agents: Recent Advances and Challenges.*	**Brahmbhatt, H., et al.**	2018	A comprehensive review of the advancements and challenges in the use of nanoemulsions for cancer drug delivery, including formulation techniques, drug loading, and stability.
2.	*Nanoparticle-Based Nanoemulsion Formulations for Cancer Drug Delivery.*	**Yallapu, M. M., et al.**	2019	This paper explores the potential of nanoparticle-stabilized nanoemulsions for efficient drug delivery to cancerous tissues, highlighting the advancements in formulation techniques.
3.	*Nanoemulsions for Drug Delivery: A Promising Approach for Cancer Therapy.*	**Khadka, P., et al.**	2019	This review article presents the advancements in nanoemulsion-based drug delivery systems and their applications in cancer treatment, particularly in overcoming the limitations of conventional therapy.
4.	*Recent Advances in Nanoemulsion-Based Drug Delivery for Cancer Treatment.*	**Patel, M. P., & Patel, V. S. (2020).**	2020	This paper focuses on the advancement in the formulation of nanoemulsions for the targeted delivery of anticancer agents and the technological progress made in improving their efficiency.
5.	*Nanoemulsions: A Review of the Recent Advances in Cancer Therapy.*	**Garg, T., Rath, G., & Sharma, R. K.**	2020	The review provides an overview of recent advancements in the design and application of nanoemulsions for anticancer drug delivery, emphasizing novel drug encapsulation and delivery strategies.
6.	*Recent Innovations in Nanoemulsion-Based Drug Delivery for Cancer Treatment.*	**Chakraborty, S., & Sharma, A. K.**	2020	The review discusses innovations in nanoemulsion formulations that improve the delivery and efficacy of anticancer agents, along with targeting strategies for reducing side effects.
7.	*Nanoemulsions as Drug Delivery Systems for Cancer Therapy: A Review of Recent Innovations.*	**Fakhri, S., et al.**	2020	This paper reviews the recent developments in the design of nanoemulsions, focusing on their applications in cancer treatment and the mechanisms behind their improved drug delivery performance.
8.	*Therapeutic Potential of Nanoemulsions for Targeted Delivery of Anticancer Drugs.*	**Gorain, B., et al.**	2020	The article reviews the therapeutic potential of nanoemulsions in enhancing the delivery of anticancer drugs, with a particular focus on

				tumor-specific targeting and overcoming challenges in traditional therapies.
9.	*Nanoemulsions as a Versatile Platform for Cancer Drug Delivery.*	**Chaudhury, A., & Jain, A.**	2020	This literature review focuses on the versatility of nanoemulsions in drug delivery systems, discussing their applications in anticancer therapy and the potential advantages they offer over traditional methods.
10.	*Nanoemulsions for Cancer Therapy: Current Status and Future Directions.*	**Mishra, S., & Soni, V.**	2021	This review examines the use of nanoemulsion systems to improve the delivery and bioavailability of anticancer drugs and addresses challenges such as stability and targeted delivery.

3.RESEARCH METHODOLOGY



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