

# Nanoemulsion for delivery of anticancer drugs

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## Competing interests

The authors declare no conflicts of interest.

## Author contributions

Virender Kumar was responsible for writing original draft; Vandana Garg was responsible for review and editing; Harish Dureja was responsible for supervision and methodology.

## Abbreviations

PEG, polyethylene glycol; TPLe, two-bottle formula of lipid nanoemulsion.

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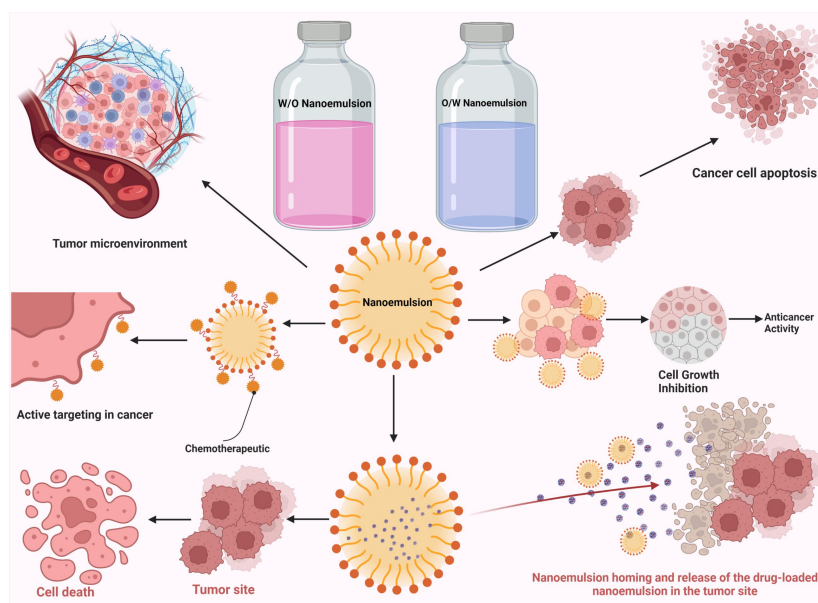
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## Abstract

Cancer refers to a collection of diseases that have abnormal cell growth as their hallmark. This inability of cytotoxic agents to distinguish between rapidly dividing healthy cells and rapidly multiplying cancerous cells produces the most notorious adverse effects of cytotoxic anticancer agents. As an essential tool in nanotechnology, nanoemulsions have therapeutic and clinical applications. Currently, nanoemulsions are considered to be one of the most feasible nano-carriers for delivering lipophilic antineoplastic agents with targeted delivery. In addition to solving water-solubilization issues, these formulations deliver specific targeting to cancer cells and might even be developed to overcome multi-drug resistance. Nanoemulsions overcome the problems associated with conventional drug delivery systems, such as low bioavailability and noncompliance. A review of nanoemulsion in cancer therapeutics is presented here to shed light on the current position of this technology.

**Keywords:** nanoemulsion; cancer; targeted delivery; cytotoxic agents; nano-carriers



### Highlights

1. Nanotechnology has become a common tool to enhance the effectiveness of anticancer substances, despite the uncertainty surrounding the development of nanodrugs and the difficulties associated with creating powerful bioactive from natural sources.
2. Recently, nanoemulsions have gained attention as potentially useful drug delivery systems. In addition to having a high solubilization capacity, nanoemulsion are thermodynamically stable, easy to prepare and absorb large amounts of drugs.
3. Nanoemulsions entrapping anticancer agents are described in this article.
4. Bioavailability, biodistribution, therapeutic activity, drug targeting and stability can all be improved by the application of nanoemulsion-based delivery systems for anticancer agents.

### Background

Nanotechnology is very important in developing a miniature drug delivery system. Nanotechnology is essential to achieve a drug's safe, most effective and efficient action [1]. Better stability and absorption, quantitative transfer of drug, controlled release of drug and pharmacodynamics activity in the desired manner are the properties related to nanotechnology [2]. Nanoemulsion is an isotropic system that is thermodynamically stable [3]. With the help of emulsifiers, two immiscible liquids are mixed into one phase to prepare nanoemulsion [4]. Nanoemulsions are used to improve the release of active pharmaceutical ingredients [5]. Nanoemulsions are generally considered safe-level excipients which overcome physical instability and physiological limitations for drug delivery, physical properties like the size of particles, preparation techniques, thermodynamic stability, etc. [6]. Nanoemulsions are either oil in water dispersion or water in oil dispersion, i.e., nanosized emulsions with about 200 nm droplets size [7]. To produce a stable emulsion, one should consider many factors to control throughout taking all compositions together to

make fine droplets by applying suitable shear force by composition to be added or used [8]. Nanoemulsions were designed to perform specific tasks for desired delivery drugs, prolonged blood circulation, imaging capability, target-specific binding capability, etc. [9]. Depending on the active and passive targeting mechanisms, these characteristics can be tuned to help deliver the drug/imaging agents to the specific site of interest. This nanoemulsion can be used to deliver the drug efficiently in cancer. In cancer treatment, nanoemulsion can be an excellent carrier to transfer the drug to the targeted site by enclosing it into a closed structure in its core, which enhances the drug's bioavailability and reduces the undesired action of the drug on other cells or tissues [10]. The use of nanoemulsion as a small delivery vehicle, because without nanoformulations, more than 99% of drugs used against tumors do not reach the targeted site because of the lack of transport to carry them to the cancer cells [11]. Drugs developed over decades to treat cancer fail because of their poor solubility and non-specific toxicity [12]. Safe tumor treatment can be made using nanoemulsion cancer therapy. Solubility, toxicity and other problems related to drugs used in cancer treatment can be minimized using nanoemulsions [13]. Patients with cancer are still unable to be cured primarily because of drug resistance. There are numerous determinants of drug resistance in cancer which includes heterogeneity of tumour, growth kinetics and microenvironment of tumour. This resistance in cancer can be overcome by using combination therapy, by blocking checkpoints of immunotherapy and using nanoformulations like nanoemulsion, as shown in Figure 1 [14]. Nanoemulsions are modified with ligands of different natures to focus on components present on the surface of neoplasm cells or avoid resistance mechanisms to multiple drugs [15].

Nanoemulsions possess numerous advantages, i.e., when the drug is formulated as nanoemulsions, it improves solubility, bioavailability, and drug efficacy. The enclosed nanoemulsion system encapsulates the drug entity and lowers the toxicity and irritant nature of the drug. It consists of smaller droplets with a larger surface area that enhances solubility and absorption. Nanoemulsions are available as different formulations like liquids, lotions, foams, sprays, etc. It is an

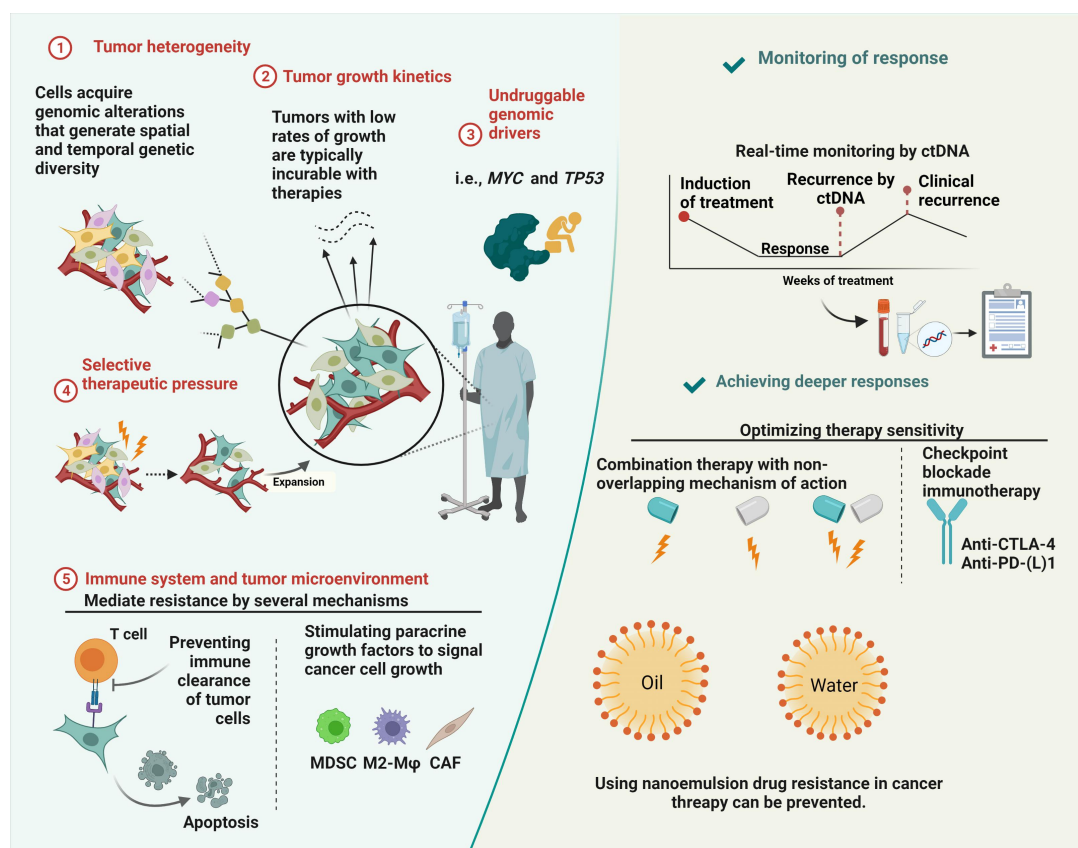


Figure 1 Drug resistance in cancer and methods for combatting resistance in cancer

excellent option to intake oil-soluble supplements in cell culture techniques [16]. Various advantages of nanoemulsion are shown in Figure 2.

### Formulation and preparation methodology of nanoemulsions

The method used in the formulation of nanoemulsion (A) high energy emulsification (B) low energy emulsification [17].

#### A. High energy emulsification

In this technique, microfluidization, homogenization, jet dispersion technique, ultrasonic treatment and high-amplitude ultrasonic technique are used. The size of droplets of the dispersed phase in the nanoemulsion prepared by the high-pressure homogenizer decreases with homogenization cycles, the decrease of surface tension, the increase of surfactant adsorption rate and the reduction viscosity ratio [18].

#### Ultrasonic emulsification

It is a very effective technique to minimize the size of droplets. An ultrasonic generator is meant to generate and supply energy into the mixture using an ultrasonic probe. Piezoelectric quartz crystal is used in the instrument, which works on the alternating current supply; it can contract and expand with the response current. The mechanical vibration is generated due to altering voltage. This vibration is supplied to the liquid via a sonicator and causes cavitation and breaking droplets into smaller and smaller droplets. The formation and collapse of droplets are meant as cavitation [19].

**Paclitaxel.** The paclitaxel nanoemulsion was formulated using ultrasound technology to examine the effect of the paclitaxel with C6-ceramide on the therapeutic activity of human glioblastoma cells when administered as a nanoemulsion formulation based on oil in water emulsification. Pine nut oil is used as a constituent. When administered to human malignant glioma cells, paclitaxel with ceramide observed a significant increase in cytotoxicity compared to administration alone. In tumors of the ovary, breast and pancreas, the nanoemulsion is administered into the tumor tissue by therapeutic ultrasound, which gets converted to microbubbles locally. To get the accumulation of nanoemulsion on tumor tissue, ultrasound imaging was used. Using ultrasound imaging, paclitaxel nanoemulsion administered via systemic injection can be observed for the breast,

ovarian and pancreatic tumors, indicating that ultrasound-triggered drugs were effectively released from the nanodroplets accumulated by cancer [20].

**Perfluorocarbon.** Tumor treatment using perfluorocarbon, the drug in nanoemulsion, can be delivered to solid tumors while monitoring nanocarriers' biodistribution through ultrasound and  $^{19}\text{F}$  magnetic resonance imaging. In the perfluorocarbon nanoemulsion stabilized by the block copolymer, perfluorobutane is used as a droplet-forming compound. To optimize the drug carrier, the studies of imaging the drug carrier nanoparticle for its tumor accumulation and other properties, such as extravasation of drug-containing nanoparticles, provide a new direction for optimizing drug nanocarriers. In vivo fluorescence microscopy was used to study the degree of extravasation of polymer micelles, nanoemulsions and nanoemulsion encapsulated drugs, diffusion in tissues, internalization of tissue cells and uptake of the reticuloendothelial system [21].

**Fisetin nanoemulsion.** Because of the low water solubility of natural flavonoid fisetin, its administration is complicated. Incorporating fisetin into nanoemulsions enhances its solubility, bioavailability and efficacy. The study of pharmacokinetic properties of formulation allows the development of the best nanoemulsion with a higher bioavailability and minor toxicity. According to studies, when the fisetin nanoformulations such as nanoemulsion were administered intravenously, there was no remarkable variation in the free administration. On intraperitoneal administration of fisetin, 24 times increased in the relative bioavailability of fisetin compared to free fisetin. In addition, compared with free fisetin (223 mg/kg), it shows the anticancer activity of nanoemulsion of fisetin at about 5–6 times smaller doses of lung cancer [22].

**Lycopene nanoemulsion.** One of the potent drug carriers in cancer treatment is lycopene and gold nanoparticles. However, the extreme instability and poor bioavailability of lycopene limit its application in the body. A nanoemulsion system containing lycopene and gold nanoparticles was formulated, and the possible synergistic effect on the inhibition of the HT-29 colon cancer cell line was studied. Tween 80 was used as an emulsifier to prepare lycopene-nano-gold nanoemulsion. When the doses of gold nanoparticles and lycopene are 250 times and 120 times lower than the combined treatment, lycopene-nano-gold nanoemulsion can provide synergistic effects, proving the potential of nanoemulsion in the treatment of colon cancer [23].

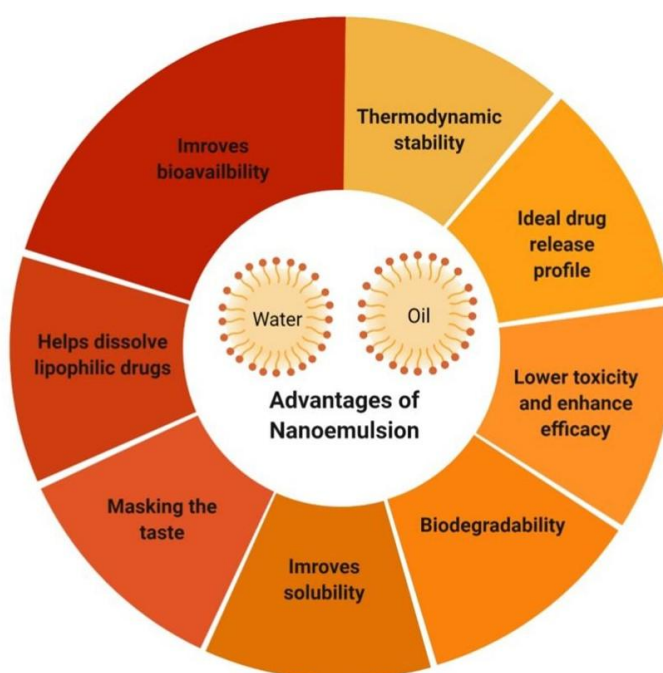


Figure 2 Advantages of nanoemulsion

**Paclitaxel and curcumin nanoemulsion.** Combining paclitaxel with curcumin in the nanoemulsion formulation provides the ability to get better on the multiple drug resistance. The combination of curcumin with paclitaxel formulated as nanoemulsion with flaxseed oil can be administered to the targeted tumor tissue more efficiently and with less cytotoxicity. Nuclear factor-kappa B was inhibited by the curcumin administration and was also found to be effective in downregulating multidrug resistance. It is found that the cytotoxic effect of the augmented formulation of curcumin and paclitaxel was increased on the wild-type cancer cells and also able to perform apoptosis on resistant cells. This combination therapy has essential prospects for treating cancer in the ovary [24].

**Chlorambucil nanoemulsion.** Chlorambucil nanoemulsion was found to be effective against ovarian cancer. The cytotoxic activity of chlorambucil was enhanced when administered as a nanoemulsion. Apoptosis activity was also enhanced in nanoemulsion compared to the aqueous administration of the drug. The studies show that the chlorambucil formulation as a long-circulating nanoemulsion improves the drug's pharmacokinetic profile and increases the half-life with polyethylene glycol (PEG) emulsification [25].

**Methotrexate nanoemulsion.** Dodecyl methotrexate, a lipophilic derivative of methotrexate associated with lipid nanoemulsions, was prepared. The lipid nanoemulsion was prepared for four hours by sonicating phosphatidylcholine, triolein and cholesterol oleate. The methotrexate dodecyl ester and lipid nanoemulsion were combined by subjecting methotrexate dodecyl ester and the previously prepared lipid nanoemulsion to additional co-sonication. The lipophilic derivative-dodecyl methotrexate is stable and the absorption of the preparation by tumor cells is significantly higher than that of methotrexate, resulting in a significant increase in cytotoxicity [26].

#### High-pressure homogenization method

To produce nanoemulsions uses of a high-pressure homogenizer is preferred. To produce the smallest size of particles about 1nm. Depending upon the type of equipment used and the procedure and conditions, the droplets being produced. The processing condition affects the droplets, such as the number of cycles, temperature, time taken, energy utilized by the system, formulation composition, etc. Cavitation force, hydraulic shear force, strong turbulence, etc., are incorporated in the high-pressure homogenization technique to produce highly tiny droplets of nanoemulsion [27].

**Tocotrienol nanoemulsion.** In vitro, vitamin E rich in tocotrienols has been partially proven to have anticancer activity on murine tumor cells. Tocopherols have also been shown to increase the anticancer activity of statins. Using high-pressure homogenization technology, a viscous mixture of tocotrienol-rich fractions with medium-chain triglycerides in 70% and 30% respectively as oil, containing 9% W/W simvastatin [28]. Dissolve and prepare nanoemulsion symmetry technology by high pressure. Studies show that tocotrienol nanoemulsion formulation releases about 20 percent of simvastatin under synchronized conditions. The parenteral administration of formulation was a feasibly better choice of administration for chemotherapy. There is a great need to effectively prevent skin damage caused by long-term sun radiation exposure. Using nanoemulsion formulations for cancer therapy on the skin is the most efficient strategy to enhance the safety and efficacy of the anticancer compounds from natural sources such as soy isoflavone to use nanoemulsion formulations to improve their skin delivery. The red palm oil (Tocomin) fraction rich in nano-emulsified tocotrienols (T3) was evaluated to produce the best nanoemulsion delivery system for skin photoprotection. Physical and chemical properties and light stability studies show that the nanoemulsion formulated with Solutol HS15 (a surfactant) and tocopheryl PEG succinate as co-surfactants is remarkably better than using Lutrol F68 as co-surfactants. The reaction of skin drugs evaluated in vitro to evaluate skin irritation and cytotoxicity, the SHS15-TPGS nanoemulsion with a ratio of 60:40 was recognized as the leading Tocomin nanoemulsion local platform. Antiphotocarcinogenic molecule in Tocomin nanoemulsion in cream and liquid forms shows the sustained release of the drug with higher

compatibility and gives excellent protection from ultraviolet B radiation.

**Folic acid tagged protein nanoemulsions.** A high-pressure homogenizer was used to prepare folate-labeled protein nanoemulsion, and it was found that it was preferably incorporated on the A20 cell line, which expresses folate receptor- $\alpha$ . The carbon monoxide releasing molecule is added to the initial formulation oil phase. The folic acid functionalized nanoemulsion loaded with carbon monoxide releasing molecule showed significant antitumor effects and improved survival of the mice with subcutaneous lymphoma tumors. The developed nanoemulsion has also been shown to have good tolerance to these immunologically active mice. Therefore, the results indicate that folic acid-labeled protein nanoemulsion can be easily used in cancer treatment and has a significant ability to deliver drugs to cells [29].

**Tributylin oil & Docetaxel nanoemulsion.** Docetaxel has anticancer activity and can be used to treat cancer. Tributyrin was found to be a very good solubilize for the docetaxel. The synergistic effect of docetaxel with tributyrin may not be providing good anticancer activity—formulation based on nanoemulsion of tributyrin and docetaxel being studied in mice. The docetaxel was founded with antimitotic training in or without nano-formulation; intravenous administration of nanoemulsion formulation of docetaxel and tributyrin shows toxicity [30].

#### Microfluidization method

Microfluidization is used to produce nanosized particles. The microfluidization process utilizes a microfluidizer that consists of the forceful insertion of the drug into the interaction chamber. Then, the liquid in the chamber is split into two strands and merged at super high speed. This process is continuously repeated for times to get the desired size of particles to produce a good nanoemulsion. Compared with other droplets colliding at high speed, this is the main force of microfluidization. High shear and cavitation forces can reduce the droplet size. The high-yielding technique of formulating uniform nanoemulsions incorporates pressurized microfluidic instruments to decompose concentrated emulsions into concentrated emulsions. The fast-flowing flow of the premixed emulsion is driven by rigid stainless steel microchannels, which are manufactured using photolithography and micromachines [31].

**PEG400 with Paclitaxel.** Successfully developed a new type of lipid nanoemulsion mediated by PEG400 as a delivery vehicle for paclitaxel. The preparation contains a drug dissolved in PEG400 solutions (25 mg/mL) and a 20% lipid emulsion mixed to form a paclitaxel-loaded nanoemulsion. Compared with traditional A2780 cell lines or B cap-37 tumors in mice, this two-bottle formula of lipid nanoemulsion (TPLE) loaded with paclitaxel can remarkably decrease the extraction of reticuloendothelial system organs and the increase tumor uptake. More effective antitumor effect: lipid nanoemulsion loaded with paclitaxel. TPLE does not cause hemolysis and venous irritation and shows the same cytotoxicity as paclitaxel to HeLa cells. Its LD50 is 2.7 times of paclitaxel, which has excellent and safe. In addition, compared with traditional paclitaxel-loaded lipid nanoemulsions, TPLE exhibited significantly faster paclitaxel release, with a more significant proportion of paclitaxel in the phospholipid layer and a smaller proportion in the oil phase. In the clinical application of cancer treatment, a new two-bottle formulation of paclitaxel drug carrier, studies proved its feasibility and potential advantages as a nanoemulsion formulation [32].

**Dacarbazine nanoemulsion.** The high fat-soluble drug dacarbazine nanoemulsion was prepared. The study reported that dacarbazine nanoemulsions of about an average of 131 nm are more effective than dacarbazine suspensions of about an average of 5,470 nm. The application of dacarbazine nanoemulsion can reduce the tumor volume by up to 10 times for topical use compared with the dacarbazine suspension preparation, using a human melanoma cell in a xenograft model of mice. Dacarbazine nanoemulsion suspension is more effective in treating and preventing tumor growth. The preparation method of dacarbazine suspension is as follows: first,



dissolve it in ethanol, add it to a solution of high performance liquid chromatography grade water, polysorbate 80 and soybean oil & then homogenize it at 25 °C for 60 seconds. With the help of a microfluidizer, the dacarbazine nanoemulsion was prepared from the suspension [33].

### B. Low energy emulsification

In low-energy emulsification, the inversion of phase, solvent replacement and spontaneous emulsification is used. The phase inversion method of making emulsion is the function of the composition of components with the temperature or vice versa. The temperature changes by keeping the composition constant, or the constituents' design is altered by consistently controlling the temperature. The positive curvature can be observed at room temperature in the mixture of water, oil and a non-ionic surfactant. In this method, rapid temperature change can formulate a stable emulsion; and it will also reduce the formation of coalescence [34].

### Phase inversion temperature method

The phase changes by applying a higher temperature to the microemulsion in this process. On change in the temperature, the solubility of the surfactant also varies. Based on this phenomenon of temperature change, the solubility of surfactants like polyethoxylated surfactant changes their affinity for water and oil. Due to the dehydration of the Polyoxyethylene groups, polyethoxylated surfactants tend to become lipophilic when heated. This process leads to the preparation of nanoemulsions using the Phase inversion temperature method. This inversion temperature technique is combined with oil, water and non-ionic surfactant at room temperature. The mixture usually contains oil in water microemulsion with excess oil & a surfactant monolayer, exhibiting a positive curvature. This coarse emulsion is gradually heated to make the polyethoxylated surfactant lipophilic. The surfactant gets dissolved in the oil phase, & the oil in water O/W emulsion transforms into water in oil (W/O) type emulsion. The surfactant monolayer shows a negative curvature at this stage [35].

### Spontaneous emulsification method

It consists of 3 steps: (a) Prepare a homogeneous organic solution composed of oily and lipophilic surfactants and hydrophilic surfactants in water, (b) induce the organic phase into the aqueous phase under continuous magnetic stirring to form an oil in water type emulsion, (c) using evaporation under reduced pressure water phase is removed [36].

**Paclitaxel nanoemulsion.** For the treatment of solid tumors, paclitaxel is a potent antineoplastic agent. Oral use is restricted due to poor water solubility. Oil in water nanoemulsion where internal phase surfactant: Capryol 90, emulsifier: Tween 20 and external phase is water used provides excellent oral bioavailability. In vitro studies for the effects of the paclitaxel formulation as nanoemulsion on breast cancer morphology, proliferation and DNA fragmentation. A decrease in half-maximal inhibitory concentration 50 and anti-proliferation activity by nanoemulsion of paclitaxel suggests that this may cause the increased absorption of paclitaxel via oil core. About 55.9% increment in the absolute oral bioavailability of drug with sustained-release profile as nanoemulsion. By reviewing the actual results of this study based on stability studies, Caco-2 permeability, cell proliferation analysis and pharmacokinetic characteristics, it can be concluded that oral nanoemulsions are impressive compared to currently available injectable chemotherapeutic formulations [37].

**Piplartine nanoemulsion.** Piplartine is an anticancer agent found as an alkaloid in black pepper. It is complicated to have the oral administration of the piperine because of its low solubility and improper formulation. Prepare oral pipeline nanoemulsion, and evaluate its toxicity, pharmacokinetics and efficacy. The optimized nanoemulsion is prepared by self-emulsification and homogenization-ultrasonic processing methods. Compared with pure Piplartine, nanoemulsions loaded with Piplartine show enhanced dissolution, cell permeability and cytotoxicity. Formulating

piplertin into a nanoemulsion will not hinder its absorption in cancer cells. Compared with free Piplartine, the oral bioavailability of nanoemulsion loaded with Piplartine is increased by 1.5 times. At 10 mg/kg, nanoemulsion showed significant antitumor activity in melanoma mice [38].

**Aluminium-phthalocyanine chloride photodynamic therapy.** Phototherapy for cancer consists of light and molecular O<sub>2</sub> with a photosensitizer. It causes stress by the oxidative mechanism in cancer cells. Aluminum-phthalocyanine chloride, a hydrophobic photosensitizer, has excellent potential in antitumor photodynamic therapy. Hydrophobic molecules certainly aggregate, so they need to be enclosed in the nanoformulations to enhance the action and pharmacokinetic drug profile, which causes a quenching effect on the luminescence nature of the drug in aqueous media. A nanoemulsion containing aluminum-phthalocyanine chloride has been developed, a hydrophobic phthalocyanine derivative. The preparation has robust photodynamic activity in an aqueous medium. Regardless of whether it is a monolayer or a sphere, it can effectively reduce the in vitro viability of the MCF7 adenocarcinoma cell line. A stable aluminum chloride phthalocyanine nanoemulsion was developed using a spontaneous emulsification technique, with more excellent phototherapeutic action on tumor tissue in vitro [39].

**Cyanine Photodynamic therapy.** Phototherapy is one of the best cancer treatments. The local therapeutic process does a lot in minimizing the toxicity of anticancer therapy. New drug carrier formulation as a photodynamic therapeutic agent of cyanine dyes photosensitizers has great clinical significance in cancer phototherapy. All nanocapsules with different shell thicknesses and average size < 200 nm show good infra-red-786 encapsulation ability. The light manifests the cell culture results and dark cytotoxicity and incandescence of the drug molecules carried in the multi-layer drug carrier [40].

### Solvent displacement method for preparing nanoemulsion

In this method of preparing nanoemulsion, the oil phase is dissolved in some organic solvent such as acetone and added to the aqueous phase containing a surfactant at room temperature. The higher amount of dilution of oil leads to smaller droplets. After that, the organic solvent can be removed using a suitable procedure like evaporation [41].

**Doxorubicin nanoemulsion.** A safe and effective lipid nanoemulsions formulation was designed for the antitumor delivery of Adriamycin. A nanoemulsion was prepared in an aqueous system using doxorubicin, lecithin, soybean oil, and medium-chain triglycerides by solvent diffusion method. The DOX-loaded nanoemulsion (doxorubicin/nanoemulsion) and polyethylene glycol – modified nanoemulsion (doxorubicin/ polyethylene glycol/nanoemulsion) were prepared by solvent diffusion method. Based on the toxic effect on cell and cell uptake in vitro in human lung cancer, nude mice carrying lung cancer cell tumors were used to further test theirs in vivo biodistribution, antitumor activity and cardiotoxicity. Passive targeting to nanoemulsion to the cancer cells invivo and better accumulation of the formulation into the tumor tissue by administration into the tumor cells in vitro. Results of antitumor activity analysis showed that the nanoemulsion loaded with doxorubicin has similar therapeutic effects as the commercially available doxorubicin. In addition, the toxicity of doxorubicin, especially its cardiotoxicity, is reduced [42].

**Cheliensisin nanoemulsion.** Cheliensisin is a new anticancer drug derived from natural sources, formulated in lipid nanoemulsions. The lipid emulsions are filtered from a 0.8µm filter, then lyophilized, and then subjected to gamma sterilization. It will help to overcome any stability issues in the formulation [43].

**Drimys angustifolia Miers with Drimys brasiliensis Miers.** The cytotoxic effects of volatile oils from *D. Angustifolia* and *D. brasiliensis* were evaluated in the nanoemulsion formulation. In the study of the toxicity of formulation on glioma cell and bladder cells in vitro, the results show that *D. Angustifolia* is rich in bicyclogermene (19.6%) and *D. brasiliensis* rich in cyclochromone (18.2%), cell effectivity treats cancer [44].

**Betulinic nanoemulsion.** Angiogenesis inhibitors can be encapsulated using the nano emulsification technique to administer and deliver the drug. Many are used clinically for cancer treatment, including bevacizumab, sorafenib, sunitinib, pazopanib and everolimus, which can reduce toxicity and improve the therapeutic effect. The betulinic acid nanoemulsion provides an anti-inflammatory and anti-angiogenesis impact on the body. Administration of the drug can be achieved by combining short PEG chains with the camptothecin via ester bond formation leads to producing a liposome. This doxorubicin is encapsulated in this liposome or nanocapsule, which helps in dual-drug delivery. Anticancer activity can be increased in vivo by adding esterase or lowering pH, i.e., pH < 5, doxorubicin and camptothecin released rapidly [45].

**Caffeine.** Recently, caffeine has been studied to treat various types of cancer after oral administration. Caffeine was found to be effective in the treatment of some skin cancer, such as cancer caused by radiation from the sun. It is also a formulation for the transdermal delivery of drugs for skin cancers. The oil phase titration method may prepare other caffeine W/O nanoemulsions. For the penetration studies, the skin penetration test was carried out in vitro with the skin of rats as a permeable membrane on Franz diffusion cells. The comparison is made between the formulation and aq. Solution of the drug on the graphical curve representation for skin penetration in vitro [45].

## Conclusion

A promising new strategy in cancer treatment is nanoemulsions. In order to meet a variety of demands, nanoemulsions can be designed to encapsulate hydrophilic and hydrophobic molecules. By contrast, nanoemulsions have the advantage of being able to target tumor cells and avoid multidrug resistance. In cancer therapy, there is much uncertainty, largely because most anticancer drugs fail to work because healthy cells and tissues are adversely affected and cancer cells develop resistance mechanisms. It is essential to study innovative solutions in order to create anticancer drugs that are safe and efficient, to go through every phase of clinical trials and to be approved. Developing a formulation of this type is of critical importance in cancer therapy since this multifactorial illness accounts for a substantial share of deaths and no fully viable treatment has yet been found.

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