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Nanoemulsions in Cancer Therapy

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ABSTRACT: Emulsions are two-phase mixtures of insoluble liquids in which a "continuous phase" surrounds discrete vesicles of the "dispersed phase". Nanoemulsions or mini-emulsions or ultrafine emulsions or submicron emulsions are transparent or translucent oil-in-water (o/w) or water-in-oil droplets with a mean droplet diameter in the range between 100 and 500 nm. Nanoemulsion-based delivery system is superior to conventional topical dosage forms, such as ointment and gels, in several respects. Nanoemulsions are composed of safe, well-characterized ingredients, combined in a proprietary manner to yield stable emulsion. Cancer is a class of disorders characterized by abnormal growth of cells proliferating in an uncontrolled way.The efficiency of anticancer drugs is limited by their unsatisfactory properties, such as poor solubility, narrow therapeutic window, and intensive cytotoxicity to normal tissues, which may be the causes of treatment failure in cancer. Nanoemulsions increase the solubility of drugs exhibiting poor water solubility through entrapment in the core of the nanoemulsion droplets.

KEYWORDS: Nanoemulsion; Cancer; Therapy; Emulsion; Formulation.

INTRODUCTION

Emulsions are two-phase mixtures of insoluble liquids in which a "continuous phase" surrounds discrete vesicles of the "dispersed phase". An emulsion is usually stabilized by some kind of surfactant system to prevent the dispersed phase from coalescing into a macroscopic phase [1, 2]. In drug delivery systems, the continuous phase is usually the aqueous phase, and the drug often is carried in (or is itself) the non-aqueous liquid phase of the emulsion. Many emulsions are of micron size scale but most can also be formulated on the nano-size scale Surfactant molecules, stabilizing emulsions are often the same that form micelles. Hydrocarbon or fluorocarbon liquids are generally employed as the dispersed phase, which most often carries a hydrophobic drug; thus the emulsion carriers must be dissolved or disrupted some how for quick release to transfer the drug to the target cells and tissues. More stable emulsions slowly deliver therapeutics by diffusion from the hydrophobic interior.

Nanoemulsions or mini-emulsions or ultrafine emulsions or submicron emulsions are transparent or translucent oil-in-water (o/w) or water-in-oil droplets with a mean droplet diameter in the range between 100 and 500 nm [3-9, 1]. Nanoemulsions are the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase by means of an appropriate surfactants or its mix with a droplet diameter approximately in the range of 0.5-100 um [10]. Unlike the thermodynamically stable micro emulsions, nanoemulsions are kinetically stable with great stability in suspension due to their small droplet size [11]. Nanoemulsions are submicron sized emulsions which are under extensive investigation as

drug carriers for improving the delivery of therapeutic agents. For the systemic delivery of biologically active agents for controlled drug delivery and targeting, they are by far the most advanced nanoparticle systems [10]. Advantages of nanoemulsions over macro emulsions or coarse emulsions include higher surface area and free energy without problems like inherent creaming, flocculation, coalescence and sedimentation associated with macro emulsions. Nanoemulsions can be formulated in a variety of formulations such as liquids, sprays, foams, creams, ointments and gels [11].Nanoemulsion show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. Nanoemulsion have applications in different areas such as in cancer treatment, in drug targeting, as a mucosal vaccine, as a vehicle for transdermal drug delivery and lipophilic drug as a self-nanoemulsifying and solid self-nanoemulsifying drug delivery system, etc.[10]

SUPERIORITY OF NANOEMULSIONS TO CONVENTIONAL DOSAGE FORMS

Nanoemulsion-based delivery systems is superior to conventional topical dosage forms, such as ointment and gels, in several respects.. Nanoemulsions are composed of safe, well-characterized ingredients, combined in a proprietary manner to yield stable emulsion Nanoemulsions increases the solubility of drugs exhibiting poor water solubility through entrapment in the core of the nanoemulsion droplets. Drug stability is always a prime concern in product development. Drugs which are promising at the time of discovery can be problematic to develop into commercially viable products due to stability concerns. Nanoemulsions could enhance the stability of chemically unstable compounds by protecting them from oxidative degradation and degradation by light. Nanoemulsions help in transporting agents to the target area. Nanoemulsions are effective in their own right against certain bacteria, fungi and viruses. These droplets accumulate in the epidermis and dermis, where they interact directly with and disrupt organisms at the site of the infection. Nanoemulsions typically exhibit a low potential for skin irritation. The unique size range of therapeutic nanoemulsions allows the droplets to traverse the pores and hair follicles of the skin and mucosal membranes, without disrupting normal tissues [12]. Nanoemulsions can also act as mucosal vaccine adjuvants. As with adjuvants in general, nanoemulsion adjuvants offer the possibility of achieving immunity with less antigen [13].Nanoemulsions may achieve the same benefits as liposomes in topical delivery, such as reduced side effects and improved physical stability, but at a much lower cost compared to liposomes due to the relative ease of scale-up and manufacturing of nanoemulsion-based formulations. Inherent anti-infective properties can be possessed by nanoemulsions, with the ability to kill pathogens, such as those present in wounds. The process by which nanoemulsions kill pathogens is by physical disruption of the cell wall and subsequent lysis of the organism and is not chemical, as with other types of antibiotic treatments. Nanoemulsion droplets when encounter lipids on a bacterial cell wall or a virus envelope, the surface tension of the nanoemulsion droplets forces the lipids of the organism and oil contained in the nanoemulsion droplets to merge. On a mass scale, this merging effectively disintegrates the membrane and kills the pathogen. Combining this inherent ability of nanoemulsions to kill certain pathogens by physical disruption with anti-infective compounds possessing other mechanisms of action may result in products with unique anti-infective properties, enhanced efficacy and greater safety.

Adjuvants in general are substances that enhance the effect of vaccines. Nanoemulsion-based adjuvants, administered as nose drops or by a simple nasal sprayer offer the possibility of non-irritating, needle-free vaccines. The nanoemulsion is uniquely capable of permeating the nasal mucosa loading vaccine antigen into immune-presenting cells. These cells then carry the antigen to areas of the body that initiate an immune response, including the lymph nodes, thymus and spleen producing both mucosal immunity and systemic immune response [14].

FORMULATION & MANUFACTURING OF NANOEMULSIONS

The methods used to produce nanoemulsions is divided into the high- and low-energy ones[15].High-energy methods include high-pressure homogenization and micro fluidization which can be used at both laboratory and industrial scale as well as ultrasonification which is primarily used at laboratory scale[15,16,18]. These high-energy methods are undesirable for labile drugs and macromolecules, such as proteins and nucleic acids although very effective in reducing droplet size. In case of labile molecules low-energy emulsification methods are preferred which include, spontaneous emulsification, the solvent-diffusion method and the phase-inversion temperature (PIT) method [15-17, 18, 19, 20]. A hydrophilic one can be solubilized in the aqueous phase and a lipophilic drug can be added to the oil phase. Co-solvents can be used, if needed, to aid drug solubilization. During high-pressure homogenization, the coarse dispersion of the oil and aqueous phase is passed through a small inlet orifice at an operating pressure(500–5000 psi), where the emulsion mixture is subjected to intense turbulence and hydraulic shear that produces a fine emulsion with an extremely small droplet size [21]. In Micro fluidization a high pressure positive displacement pump is used operating at very high pressures, up to 20,000 psi, which forces the emulsion product through the interaction chamber which consists of a series of microchannels. The emulsion flows through the microchannels on to an impringement area which results in very fine emulsion droplets [22]. The operating pressure, the number of passes of the coarse emulsion through the interaction chamber of the microfluidizer determines the particle size of the fine emulsion. The higher will be the operating pressure and the number of passes, the smaller the droplet size of the final emulsion. To remove any large particles present, the resulting nanoemulsion be filtered through a 0.2 μm filter under nitrogen resulting in a uniform nanoemulsion. High-energy emulsification methods produces both o/w and w/o nanoemulsions. In the low-energy emulsification methods, solvent diffusion and PIT generate o/w nanoemulsions, whereas spontaneous emulsification produces w/o nanoemulsions [15-17,18, 19, 20]. By rapid cooling of the microemulsion form in the phase-inversion zone, or dilution with water whatever the temperature, very stable o/w nanoemulsions can be produced [18]. Dilution with water is more practical and adaptable. It is preferred for industrial and pharmaceutical applications. It has recently been shown that under certain conditions, the PIT method can also produce w/o nanoemulsions [18]. The process involves inclusion of a lipophilic PEG-surfactant generating a microemulsion within the phase-inversion zone which upon dilution with suitable oil produces highly monodispersed w/o nanodroplets [18]. Nanoemulsions with an aqueous core have increasing demand for hydrophilic drug delivery and targeting, particularly for peptides/proteins [23].

NANOEMULSION & ANTICANCER THERAPY

Cancer is a class of disorders characterized by abnormal growth of cells proliferating in an uncontrolled way [24]. Cancer occurs at a molecular level when multiple subsets of genes undergo genetic alterations, either activation of oncogenes or inactivation of tumor suppressor genes. This leads to malignant proliferation of cancer cells, tissue infiltration, and dysfunction of organs [25]. Tumour tissues are characterized with active angiogenesis and high vascular density keeping blood supply for their growth, but they have a defective vascular architecture and this combined with poor lymphatic drainage, contributes to what is known as the enhanced permeation and retention (EPR) effect [26, 27]. Tumour genes, not stable with their development often show geno variation. The inherent complexity of tumor microenvironment and the existence of P-glycoprotein (Pgp) usually act as barriers to traditional chemotherapy by preventing drug from reaching the tumor mass. Meanwhile, delivery of the therapeutic agents in vivo shares physiological barriers, including hepatic and renal clearance, enzymolysis

and hydrolysis, as well as endosomal/lysosomal degradation [28, 29]. Many substances are under investigation currently for drug delivery and more specifically for cancer therapy technology. It helps to formulate the medicinal products with maximum therapeutic value and minimum or negligible range side effects. A major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue causing severe side effects and resulting in low cure rates. Thus, it is very hard to target the abnormal cells by the conventional method of the drug delivery system [24]. In addition, the efficiency of anticancer drugs is limited by their unsatisfactory properties, such as poor solubility, narrow therapeutic window, and intensive cytotoxicity to normal tissues, which may be the causes of treatment failure in cancer [30, 31]. Nanoemulsions are capable of delivering high concentration of chemotherapy drugs to cancerous tissues without affecting cells and organs in the systemic circulation. They have shown a strong potential for drug delivery in the treatment of cancer. In addition to their drug targeting application and their ability to improve bioavailability of drugs a variety of imaging methodologies can easily detect nanoemulsions. Formulation of lipophilic anticancer drugs in o/w nanoemulsions has proved to be highly advantageous. The oil phase of the emulsion acts as solubilizer for the liphophilc compound thereby enhancing the solubility of the drug in an emulsion system. Therefore less amount of the drug has to be administered in comparison to an aqueous solution. The pain associated with the intravenously administered drugs can be minimised by the lipid emulsion by exposing the tissue to lower concentration of the drug and by avoiding a tissue irritating vehicle [52].

ADVANCEMENTS IN THE FIELD OF NANOEMULSIONS FOR CANCER THERAPY

Tagne et. al work on the preparation of a water-soluble nanoemulsion of the highly lipid-soluble drug tamoxifen (TAM) suggests that a nanoemulsion compared to a suspension preparation of TAM increases its anticancer properties relative to breast cancer. Relative to a suspension of TAM, the nanoemulsion preparation demonstrated a greater zeta potential (increased negative charge) which is generally associated with increasing drug/membrane permeability. Also in comparison to suspensions of TAM with particle sizes greater than 6000 nm, nanoemulsions of TAM, having mean particle sizes of 47 nm, inhibited cell proliferation 20-fold greater and increased cell apoptosis 4-fold greater in the HTB-20 breast cancer cell line[32].

Primo et. al work evaluated the photophysical and in vitro properties of a second-generation photosensitizer drug (PS) widely used in systemic clinical protocols for cancer therapy based on Photodynamic Therapy (PDT), Foscan. Focusing on topical administration of Foscan and other photosensitizer drugs biodegradable nanoemulsions (NE) was employed as a colloidal vehicle of the oil/water (o/w) type. This formulation was obtained and stabilized by the methodology described by Tabosa do Egito et. al., based on the mixture of two phases: an aqueous solution and an organic medium consisting of nonionic surfactants and oil. The photodynamic potential of the drug incorporated into the NE was studied by steady-state and time-resolved spectroscopic techniques. The results of the study showed that the photophysical properties of PS were maintained after its incorporation into the NE when compared with homogeneous organic medium. The Foscan diffusion flux (J) was increased when this PS was incorporated into the NE, if compared with its flux in physiological medium. These parameters demonstrated that the NE can be potentially applied as a drug delivery system (DDS) for Foscan in both in vitro and in vivo assays, as well as in future clinical applications involving topical skin cancer PDT [33].

Kaneda et. al studied the perfluorocarbon nanoemulsions for quantitative molecular imaging and targeted therapeutics. They found liquid perfluorocarbon nanoemulsions make ideal agents for cellular and magnetic resonance molecular imaging. The perfluorocarbon core material is surrounded by a lipid monolayer. They can be functionalized with a variety of agents such as targeting ligands, imaging agents and drugs either individually or in

combination. Multiple copies of targeting ligands served to enhance avidity through multivalent interactions. The composition of the particle's perfluorocarbon core resulted in high local concentrations of (19)F. Lipophilic drugs contained within molecularly targeted nanoemulsions can result in contact facilitated drug delivery to target cells. The dual use of perfluorocarbon nanoparticles for both site targeted drug delivery and molecular imaging provided both imaging of disease states as well as conclusive evidence that drug delivery is localized to the area of interest [34].

Sarkar et. al studied the engineering of nanoemulsions for drug delivery. They found nanoemulsions which are usually spherical as a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies and biotechnologies. Nanoemulsions exist in a wide variety of forms that are dictated by the particle components. The longer-term properties of the particle depends on the composition of the adsorbed material lying at the dispersed droplet interface with the dispersion medium which has an impact on the partitioning and extraction of droplet contents. They have a very low surface tension and this produces a very large surface area. Nanoemulsions also include small meta-stable very small-scale emulsions. The surface properties and chemistry strongly influences behavior, processing, storage and formulation composition. These properties also have an impact on the longevity of a pharmaceutical preparation. The studies found out that nanoemulsion droplets based on fluorinated compounds finds a number of widespread biomedical roles and applications and that the developments in nanoemulsion technology are likely to lead to a much greater use of this medium in future pharmaceuticals[35].

Fang et. al studied the acoustically active perfluorocarbon nanoemulsions as drug delivery carriers for camptothecin, their drug release and their cytotoxicity against cancer cells. Camptothecin is a topoisomerase I inhibitor acting against a broad spectrum of cancers, however its clinical application is limited by its insolubility, instability, and toxicity. Fang et. al's work developed acoustically active nanoemulsions for camptothecin encapsulation so as to circumvent the delivery problems. Camptothecin in these systems showed retarded drug release. Camptothecin in nanoemulsions with a lower oil concentration exhibited cytotoxicity against melanomas and ovarian cancer cells. Confocal laser scanning microscopy confirmed nanoemulsion uptake into cells. Hemolysis caused by the interaction between erythrocytes and the nanoemulsions was also investigated. Formulations with phosphatidylethanolamine as the emulsifier showed less hemolysis than those with phosphatidylcholine [36].

Mendes et. al studied the uptake by breast carcinoma of a lipidic nanoemulsion. After intravenous injection a lipidic nanoemulsion concentrates in breast carcinoma tissue and other solid tumors and carries drugs directed against neoplastic tissues. Use of the nanoemulsion decreases toxicity of the chemotherapeutic agents without decreasing the anticancer action. Their work tested the hypothesis whether the nanoemulsion concentrates in breast carcinoma tissue after loco regional injection and the result concluded that with intralesional injection of the nanoemulsion, a great concentration effect can be achieved in breast carcinoma tissues. This injection technique may be thus a promising approach for drug-targeting in neoadjuvant chemotherapy in breast cancer treatment [37].

Fernando et. al in their study developed a new nano drug delivery system (NDDS) based on association of biodegradable surfactants with biocompatible magnetic fluid of maguemita citrate derivative. This formulation consisted of nanostructured colloidal particles in a magnetic emulsion. Their preliminary *in vitro* experiments showed that the formulation presents a great potential for synergic application in the topical release of photosensitizer drug (PS) and excellent target tissue properties in the photodynamic therapy (PDT) combined with hyperthermia (HPT) protocols. The physical chemistry characterization and *in vitro* assays were carried out by Zn(II) Phtalocyanine (ZnPc) photosensitizer incorporated into NDDS in the absence and the presence of

magnetic fluid. It showed good results and high biocompatibility. Their study results indicated that magnetic nanoemulsion (MNE) increase the drug release on the deeper skin layers when compared with classical formulation in the absence of magnetic particles. These results indicated the increase of biocompatibility of NDDS due to the great affinity for the polar extracellular matrix in the skin and also for the increase in the drug partition inside of corneocites wall[38].

Shakeel et. al studied the transdermal delivery of anti cancer drug caffeine from water in oil nanoemulsions. Nanoemulsion formulation of caffeine for transdermal delivery was developed and evaluated on the basis of investigations of caffeine for the treatment of various types cancers upon oral administration and also on the basis that dermal applied caffeine can protect the skin from skin cancer caused by sun exposure. W/O nanoemulsion formulations of caffeine were prepared by oil phase titration method. Thermodynamically stable nanoemulsions were characterized for morphology, droplet size, viscosity and refractive index. The in vitro skin permeation studies were performed on Franz diffusion cell using rat skin as permeation membrane. The in vitro skin permeation profile of optimized formulation was compared with aqueous solution of caffeine. The end results suggested that w/o nanoemulsions are good carriers for transdermal delivery of caffeine [39].

Huang et. al studied the antitumor immune responses induced by nanoemulsions encapsulated MAGE 1-HSP70/SEA complexation vaccine following different administration routes. The study had the purpose to compare the immune responses induced by nanoemulsions-encapsulated MAGE1 HSP70 and SEA NE(MHS) vaccine after following different administration routes and finding out different new and effective immune routes. The results suggested that this novel nanoemulsion carrier can exert potent anti-tumour immunity against antigens encapsulated in it. It indicated that the nanoemulsion vaccine adapted to administration via different routes including preoral may have broader applications in the future [40].

Hwang et. al developed water in oil (w/o) nanoemulsions for the intravesical administration of cisplatin. The nanoemulsion loaded with cisplatin was found active against bladder cancer cells. The nanoemulsion with the drug exhibited the complete inhibition of cell proliferation. Encapsulation of cisplation in nanoemulsions resulted in slower and more sustained release thereby suggesting that nanoemulsions are feasible to load cisplatin for intravesical drug delivery [41].

Ferenando et. al performed the synthesis and in vitro characterisation of a new class of drug delivery system denominated magnetic nanoemulsion. The association of biocompatible magnetic nanoemulsion fluids with colloidal nanoparticles resulted in a new drug delivery system for application in photodynamic therapy and magnetic hyperthermia treatment. It works in a synergic manner based on heat dissipation and/or photosensitization resulting in tumor damage after minimum drug doses [42].

Ganta et. al examined the co-administration of Paclitaxel (PTX) and curcumin (CVR) in nanoemulsion formulation to overcome multidrug resistance in tumor cells. They are inhibited of nuclear factor Kappa B as well as potent doen –regulator of ABC transporters in wild type SKOV3 and drug resistant (TR) human ovarian adenocarcinoma cells. The results of the study showed that the combination PTX and CVR therapy when administered in nanoemulsions formulations enhanced the cytotoxicity in wild type and resistant cells by promoting the apoptotic response [43].

Kakumanu et. al worked on the preparation of a water-soluble nanoemulsion of the highly lipid-soluble drug Dacarbazine (DAC). They worked on mouse xenograft model. They found out that relative to suspensions of DAC, the nanoemulsion preparation demonstrated a lower zeta-potential is associated with influencing drug membrane permeability. Their study proved that relative to suspensions of DAC, nanoemulsions of DAC were more efficacious. The result concluded that in the xenograft mouse model of melanoma, nanoemulsion suspensions of DAC are more efficacious in the treatment and prevention of tumor growth [44].

Ortiz et. al reported on the preparation of a water-soluble nanoemulsion of the highly lipid-soluble drug tamoxifen (TAM). Relative to a suspension of TAM, the nanoemulsion preparation demonstrated a greater zeta potential (increased negative charge) which has previously been associated with increasing drug/membrane permeability. The study also reported that relative to suspensions of TAM with particle sizes greater than 6000 nm, nanoemulsions of TAM, having mean particle sizes of 47 nm, inhibited cell proliferation 20-fold greater and increased cell apoptosis 4-fold greater in the HTB-20 breast cancer cell line. Thus, this work suggests that a nanoemulsion compared to a suspension preparation of TAM increases its anticancer properties relative to breast cancer [45].

Maestro et. al reported the new applications of nanoemulsions and the optimization of their preparation. Nano-emulsions are non-equilibrium systems which have characteristics and properties which depend not only on composition but also on the preparation method. Nanoemulsions are being developed into consumer products directly, mainly in pharmacy and cosmetics. The work emphasises that the recent applications of nanoemulsions have made the studies on optimization methods for nano-emulsion preparation a requirement [46].

Desai et. al examined the cytotoxicity and apoptosis enhancement in brain tumor cells upon co-administration of paclitaxel (PTX) and ceramide (CER) in nanoemulsion formulation. Objective of the study was examining augmentation of therapeutic activity in human glioblastoma cells with combination of paclitaxel and the apoptotic signalling molecule, C(6)-Ceramide(CER) when administered as oil in water nanoemulsions. Nanoemulsion was formulated with pine nut oil having high concentrations of essential polyunsaturated fatty acid. The results of the study show that oil in water nanoemulsions can be designed with combination therapy for enhancement of cytotoxic effect in brain tumor cells .PTX and CER can be used together to augment therapeutic activity in cases of aggressive tumor models such as glioblastoma especially [47].

Ichikawa et. al evaluated the effects of the formulation and particle composition of gadolinium (Gd)-containing lipid nanoemulsion (Gd-nanoLE) on the biodistribution of Gd after its intravenous (IV) injection in D(1)-179 melanoma-bearing hamsters for its application in cancer neutron-capture therapy. Gd-nanoLEs whose particles had an oily core (soybean oil, ethyl oleate, lipiodol, or triolein) and a surface layer of hydrogenated phosphatidylcholine, gadolinium-diethyl-enetriaminepentaacetic acid-distearylamide, and a co surfactant (Myrj 53, Brij 700, or HCO-60) were prepared by a thin-layer hydration-sonication method. Brij 700 and HCO-60 prolonged the retention of Gd in the blood and enhanced its accumulation in tumours as was revealed by bio distributing data. Soybean oil yielded the highest Gd concentration in the blood and tumor and the lowest in the liver and spleen among the core components employed. The maximum Gd level observed by the group in its study was greater than the limit required for significantly suppressing tumor growth in neutron-capture therapy [48].

Yosra et. al designed and optimized the self-nanoemulsifying drug delivery systems. Tamoxifen citrate is an antiestrogen for peroral breast cancer treatment but the drug delivery encounters problems of poor water solubility and vulnerability to enzymatic degradation in both intestine and liver. In an attempt to circumvent such obstacles tamoxifen citrate self-nanoemulsifying drug delivery systems (SNEDDS) were prepared. Preliminary screening was carried out to select proper ingredient combinations and all surfactants screened were recognized for their bioactive aspects. Ternary phase diagrams were constructed and an optimum system was designated. Three tamoxifen SNEDDS were compared for optimization. The systems were assessed for robustness to dilution, globule size, cloud point, surface morphology and drug release. The results of the study showed that the drug release from the selected formulation was significantly higher than other SNEDDS and drug suspension and that the prepared system could be promising to improve oral efficacy of the tamoxifen citrate [49].

Kuo et. al worked on neuroblastoma, the most common form of childhood cancer which may arise biochemical block of cellular differentiation and a resultant continuation of a proliferative state. Neuroblastoma often spontaneously reverts by undergoing partial differentiation and ultimate degeneration and may be associated with the generation of reactive oxygen species (ROS). The objective of their study was to investigate whether a subcutaneous injection and/or transdermal application of a nanoemulsion preparation of anti-oxidant synergy formulation (ASF) would reduce tumor growth rate in a neuroblastoma xenograph mouse model. The results of the study indicated that whereas suspensions of ASF were ineffective in decreasing tumor growth rate in the neuroblastoma mouse model, tumor growth rate was reduced on an average 65% by either subcutaneous injection or transdermal application of an ASF nanoemulsion preparation to the tumor. The data of the study suggested that subcutaneous and/or transdermal application of an ASF nanoemulsion preparation is effective in reducing tumor growth rate in this neuroblastoma mouse model [50].

Dias et. al studied the pharmacokinetics and tumor uptake of a derivatized form of paclitaxel associated to a cholesterol-rich nanoemulsion (LDE) in patients with gynaecologic cancers. LDE concentrates in cancer tissues after injection into the blood stream. The association of LDE to derivatized paclitaxel showed lower toxicity and increased anti tumoral activity thus has been tested in a B16 melanoma murine model. The conclusion of the study was that paclitaxel oleate associated to LDE is stable in the blood stream. It has a greater plasma half- life and AUC than those for paclitoxel cremophor. Compare to normal tissues more paclitoxel in malignant tissues. Therefore association of paclitaxel to LDE can lead to better treatment of gynaecologic cancers [51].

CONCLUSION

Nanoemulsions are useful in cancer therapy as they show high loading capacity, small particle size, good physical stability and preserved toxicity, greater zeta potential. They have great future application as they can be administered through various routes and have greater therapeutic stability, slower and more sustained drug release. They have largely shown that they are more efficacious in the prevention and treatment of tumour growth.

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