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# SELECTED DRUG DELIVERY SYSTEMS BASED ON NANOEMULSION

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## ABSTRACT

A nanoemulsion is recognized as an emulsion with a droplet size ranging from 20 to 200 nm. It can provide greater encapsulation efficiency for delivery. Nanoemulsions have unique characteristics such as extremely small size, biocompatibility, relative stability, ability to solubilize high quantities of hydrophobic compounds, ability to reduce toxicity of cytotoxic drugs and ability to protect drugs from hydrolysis and enzymatic degradation under physiological conditions. Nanoemulsions can be used in many drug delivery systems. This paper summarises utilization of selected nanoemulsions as anti–inflammatory, anti–cancer and anti–microbial in some drug delivery systems.

**Keywords:** nanoemulsion, drug delivery systems, anit–cancer, anit–inflammatory, anti–microbial, wound healing.

## INTRODUCTION

In the last few years an increasing number of investigations concerning the use of nanoscale structures for drugs and genes delivery purposes have been reported. Nano–carriers have been investigated for delivery of drugs to the specific anatomical sites such as brain [1] eyes [2] lungs [3] intestine [4] nose [5] and skin [6]. Nanoemulsions are also recognized as antimicrobial oil–in–water emulsions containing naonometersized droplets stabilized with surfactants [7]. According to the report more than 40% of the new drug candidates do not have adequate water solubility which affects their bioavailability and therapeutic index significantly [8]. Nanodelivery systems are fast becoming important approaches in delivering lipophilic compound and improving physical and chemical stability of active ingredients

within formulations. They possess many important attributes such as ease to prepare, composed of food– grade generally recognized as safe (GRAS) and/ or FDA approved ingredients thereby, ability to reduce toxicity and adverse side effect and ability to protect encapsulated compounds against degradation [9]. However, nanoscale colloid drug delivery systems have been reported to have great potential for enhancing bioavailability of poorly water–soluble drugs resulting in significant increase in solubility stability drugs [10–13]. Nanoemulsions have several advantages in biological applications such as carriers for targeted drug delivery, non–toxic disinfectant cleaner, improving oral delivery of poorly soluble drugs, vehicles for transdermal delivery and antimicrobial activities [14]. These unique characteristics of nanoemulsions highlight them as suitable drug carriers with improved targeting properties. It has been demonstrated that with the help of nanoemulsions as delivery systems the retention time of drugs in the body can be increased thereby reducing the amount of drug required for a therapeutic treatment. There are many nanocarriers for drug delivery such as liposomes nanoemulsions drug nanocrystals and polymeric micelles [15–18]. Nanoemulsions had significant long circulation period in bloodstream. Due to this characteristic it was found that tumor targeting can be achieved by surface modification [19]. Many research works have been reported using noemulsions to deliver drugs by various routes of administration such as intravenous oral ocular and gene delivery systems for therapeutic needs [20–32]. This review paper is an attempt to highlight some drug delivery systems using nanemulsion formulations.

**Selected studies on anti–inflammatory nanoemulsions**

Inflammation plays a fundamental role in the immune response of the human body to microbes injury.microbes injury. Recent studies have demonstrated that inflammation is a key not only in infection and cancer but also to autoimmune diseases such as rheumatoid arthritis multiple sclerosis type I diabetes and Crohn's disease or certain neuro–degenerative conditions [33–36]. Nanoemulsion delivery systems have been shown to increase bioavailability and efficacy of a number of compounds such as anti–inflammatory agents [37–38]. Tang et al. [39] investigated activities of novel aspirin oil–in water (O/W) nanoemulsion and water–in–oil–in–water (W/O/W) in values of 20 mg/ml and 10 mg/ml respectively as anti–inflammatory on paw edema rats induced by carrageenan injection. The results revealed that oral administration of nanoemulsion and nano multiple emulsion containing aspirin (60 mg/kg) significantly reduced paw edema induced by carrageenan injection. Both nanoformulations decreased the number of abdominal constriction in acetic

acid–induced animal model. Moreover, the nanoemulsion demonstrated an enhanced anti–inflammatory effect compared to the control animal model. The study suggested that nanoemulsion and nano multiple emulsion produced pronounced anti–inflammatory which may assist as new nanocarriers in the treatment of inflammatory disorders and alleviating pains. In another study Hemmila et al. [7] investigated dermal inflammatory effect of topical application of a nanoemulsion compound (NB–201) on burn wound infection using Sprague–Dawley rats models. NB–201 and NB–201 placebo 5% mafenide acetate solution or 0.9% saline (control) was applied onto the wound at 16 and 24 hours after burn injury. Skin sample was harvested 32 hours postburn for quantitative wound culture and determination of inflammatory mediators in tissue homogenates. The results approved that treatment with NB–201 significantly decreased levels of proinflammatory cytokines as well as degree of hair follicle cell apoptosis in skin compared to saline–treated controls. Uveitis is an umbrella term used to describe wide ranges of inflammatory conditions occurring inside the eye [40]. The term literally means inflammation of the uvea (vascular pigmented middle coat of the eye wall) composed of iris, ciliary body and choroid. However adjacent structures such as the sclera retina and optic nerve may also be involved [41–43]. Vaidehi et al. [40] used tacrolimus nanoemulsion for Uveitis treatment and they found that tacrolimus nanoemulsion administered topically is a promising therapeutic approach to treat uveitis

**Selected studies on anti–cancer nanoemulsions**

Cancer is considered as one of the most fatal diseases worldwide. One of the major issues facing cancer treatment is the poor bioavailability and adverse side effects of anticancer drugs. This phenomenon can be overcome using nanoemulsion drug loaded formulations [44]. In addition, nanoemulsion drug loaded formulations approved to be better methods for anticancer drugs delivery [45–46]. Caffeine has been investigated for the treatment of various types of cancers in many research works [47–51]. There is also some evidence that dermally applied caffeine can protect the skin from skin cancer caused by sun exposure [50]. They evaluated transdermal delivery of anticancer drug caffeine from water–in–oil nanoemulsions using invitro skin permeation profile of optimized nanoemulsions of anticancer drug caffeine formulation. Significant increase in permeability parameters was observed in nanoemulsion formulations as compared to aqueous solution of caffeine. The results suggested that w/o nanoemulsions are good carriers for transdermal delivery of caffeine. Breast cancer is a malignant growth that begins in the tissues of the breast which over the course of a lifetime results in one out of eight women being diagnosed with one of several types of breast cancer.

Kakumanu et al. [17] evaluated nanoemulsion of water–soluble of the highly lipid–soluble drug tamoxifen (TAM) in breast cancer treatment. They found that the nanoemulsions of TAM which had 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 which suggested that a nanoemulsion compared to a suspension preparation of TAM (with particle sizes greater than 6000 nm) increased its anticancer properties relative to breast cancer. Dacarbazine (DAC) is one of anticancer drugs that have been used to treat various types of cancers. Kakumanu et al. [52] used an epidermoid carcinoma xenograft mouse model to test whether there is an increased efficacy of DAC as a nanoemulsion on reducing tumor size. Tumors were induced in 5–week–old nude mice by subcutaneous injection. The mice were treated with a suspension of DAC (0.1 mg/kg) a nanoemulsion of DAC (0.1 mg/kg) or nano–control in a period of 40 days. The results showed that the final tumor size of mice receiving the nanoemulsion was significantly reduced compared to the suspension of DAC and untreated sample. The final tumor size of mice receiving the nanoemulsion of DAC topically was also significantly reduced compared to the suspension of DAC topically. These results could be attributed to the reduction in particle size of the nanoemulsion in comparison with the suspension. The natural flavonoid fisetin (3347–tetrahydroxyflavone) has shown antitumour activity [53]. Pharmacokinetic studies in mice revealed that the fisetin nanoemulsion injected intravenously (13 mg/kg) showed no significant difference in systemic exposure compared to free fisetin. When the fisetin nanoemulsion was administered intraperitoneally a 24–fold increase in fisetin relative bioavailability was noticed compared to free fisetin. Additionally the antitumour activity of the fisetin nanoemulsion in Lewis lung carcinoma bearing mice occurred at lower dose (36.6 mg/kg) compared to free fisetin dose of 223 mg/kg.

**Selected studies on wound healing and anti–microbial nanoemulsions**

Antimicrobial activities of some pharmaceutical materials are investigated in many research works [54–57]. Hemmila et al. [7] examined bacterial growth in burn wound using male Sprague–Dawley model using NB–201 (NB–201 is an antimicrobial nanoemulsion formulation consists of emulsification of vegetable oil and water with surfactant and alcohol). At 8 hours after injury the burn wound was inoculated with $1 \times 10^6$ colony–forming units (CFUs) of *Pseudomonas aeruginosa*. The wound was treated with the nanoemulsion compound of NB–201, NB–201 placebo, 5% mafenide acetate solution or 0.9% saline (control) at 16 and 24 hours after burn injury. Skin was harvested 32 hours postburn for

quantitative wound culture and determination of inflammatory mediators in tissue homogenates. They found that NB–201 decreased mean bacterial growth in the burn wound by 1000–fold in the animal having bacterial counts greater than $10^5$ CFU/g. Liu et al. [58] evaluated clinical effect of alum–borneol nanoemulsion on wound surface of superficial second–degree and the change of the epidermal growth factor (EGF) in the process of wounds healing on scald model rat. They found that the wound healing rates of alum–borneol nano–emulsion group on the 3rd 7th and 10th day were higher than that of blank nanoemulsion group. Danielli et al. [59] evaluated the antifungal activity of the pure oil of *Stenachaenium megapotamicum* and its nanoemulsion. Compared with pure volatile oil the nanoemulsion significantly increased the fungi susceptibility against dermatophytes tested. An improvement in the effect of substances involved in a nanoparticulate system due to the small particle size was discussed [60]. According to Donsi et al. [61] a reduction in particle size to less than 200 nm activates mechanisms of passive transport through the cell membrane and may justify the increased activity of the oil in nanoparticulate system. Similarly, other studies have attempted to develop nanoparticles capable of carrying volatile oils also are being performed [62]. In another study, a nanoparticle system protected the oil against evaporation besides decreasing the pronounced odor and improving its stability [63]. Nuchuchua et al. [64] improved the integrity of oils thus increasing the vaporization and consequently prolonging the repellent activity previously described for volatile oil of the species tested. In conclusion, *S. megapotamicum* volatile oil presented strong and selective antifungal activity against dermatophytes including *S. dimiatum* whose treatment is more difficult. The nanoemulsion developed with volatile oil showed the ability of nanoparticulate system to improve the activity of the oil significantly increasing the susceptibility of *E. floccosum* and *T. rubrum* isolates representing a promising alternative for the treatment of infections caused by these pathogens. Soybean oil–in–water nanoemulsion was determined for its effectiveness against *Streptococcus mutans* and *Lactobacillus casei* by live/dead staining. Moreover, *in vitro* antimicrobial effectiveness of the nanoemulsion against planktonic *Streptococcus mutans* (*S. mutans*) and *Lactobacillus casei* (*L. casei*) was studied [65]. Candida albicans and mixed cultures were determined by serial dilution techniques for the evaluation of minimum inhibitory concentration and minimum bactericidal concentration (MIC/MBC). The results showed that the nanoemulsion had notable antimicrobial activity against biofilm organisms. Up to 83.0% were killed within 1 min. The dilutions of the nanoemulsion ranging from 243 to 19683 were effective against planktonic (*S. mutans*) and (*L. casei*) and the nanoemulsion showed reductions of bacterial counts significantly.

**Table 1 Selected nanoemulsions composites applications**

| S. no | Name of nanoemulsion composite | Application | Reference |
|---|---|---|---|
| 1 | Dorzolamide hydrochloride nonoemulsion | Antiglaucoma drug | Hussein et al [66] |
| 2 | Aceclofenac nanoemulsion | Topical application | Choudhury [67] |
| 3 | Nebulized nanoemulsion | Respiratory drug Delivery | Amir Amani [68] |
| 4 | Based gel of COX-2 inhibitors nanoemulsion | Inflammatory efficacy enhancement | Lala and Awari [69] |
| 5 | silymarin nanoemulsion | *Anti carbon tetrachloride-induced hepatic damage* | Rabea Parveen [70] |
| 6 | *Paclitaxel and etoposide with a cholesterol-rich nanoemulsion* | Tumor growth inhibition | Iara et al [71] |
| 7 | *Cashew nut shell liquid (CSNL) nanoemulsion* | *Inhibitor of human MCF-7 breast cancer cell proliferation* | Amal Al-Hazzani et al [72] |
| 8 | *Tocotrienol-Rich Fraction of Palm Oil nanoemulsion* | Anticancer and Blood Circulation Activities | Alaadin Alayoubi et al [73] |
| 9 | Curcuma comosa *Nanoemulsions* | Increasing *In Situ* Intestinal Absorption of Phytoestrogenic Diarylheptanoids | Jian Su et al [74] |

**Table 2 Selected nanoemulsions composites and the main findings of application**

| S. no | Nanoemulsion name | Finding | Reference |
|---|---|---|---|
| 1 | Azithromycin: essential oil based nanoemulsion | Cinnamon oil enhanced the solubility of Azithromycin to greater extent because it is highly lipophilic in nature. The Nanoemulsion composite had substantial potency against both gram-positive and gram-negative organisms. | Nirmalaet al[75] |
| 2 | Curcuminnanoemulsion | The developed formulations did not show any toxicity and found safe for intranasal delivery for brain targeting. Moreover, the nanoemulsion showed higher flux and permeation across sheep nasal mucosa. | Sood et al[76] |
| 3 | Soybean oil-in-water nanoemulsion | The results showed that the nanoemulsion has effective anti-cariogenic activity against cariogenic microorganisms. | Karthikeya et al[77] |
| 4 | Meloxicam - based gel nanoemulsion | Absorption studies demonstrated a higher permeation of meloxicam from nanoemulsion gel, than the drug solution. FTIR and DSC studies supported stratum corneum lipid extraction as a possible penetration enhancer mechanism for Meloxicam -nanoemulsion gel. CLSM studies confirmed the permeation of the nanoemulsion gel formulation to the deeper layers of the skin (up to 130 µm). | Khurana et al[78] |
| 5 | Cetylpyridinium chloride nanoemulsion | The nanoemulsion exposed to Waterline biofilms for 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours showed high reduction of colonies, and very low counts after 12 hours and 24 hours (67 colony-forming units/mL) were observed. Exposures for 48 hours and 72 hours showed no or few visible colonies (2 colony-forming units/mL). The nanoemulsion employed improves efficacy against microorganisms more than unemulsified components. | Karthikeyan et al [79] |

## CONCLUSION

In summary, this review paper presents the efficacy of some nanoemulsions as ant–inflammatory anti–cancer and anti–microbial drug delivery systems. This presentation can be considered as a basis for studying more nanoemulsions and their effectiveness in various fields of drug delivery systems.

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