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Review Article

Nanoemulsions for drug delivery through different routes

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Utilising nanoemulsions as vehicles for carrying active pharmaceutical ingredients is emerging as a promising approach for the latters' targeted delivery. For drug molecules to be clinically effective, their administration by a route, which provides a proper channel for them to reach their target, is of prime importance. Further, they also need to be suitably protected in the biological milieu till they are delivered to the required site of action. Nanoemulsions with a mean droplet diameter of about 20-200 nm are extremely versatile in this regard. Due to their characteristic size and properties, which includes kinetic stability, they are very effective in enveloping and/or solubilising the drugs and successfully chaperoning them towards suitable targets. They also cause the drugs to be released in controlled and sustained modes, thereby reducing drug toxicity and dumping. Additionally, depending on the physiochemical properties of the drugs, nanoemulsions can be structurally engineered to maximize their solubilisation as per the required route of delivery, which is heavily dependent on the drug structure. Effective targeting can be achieved by incorporating suitable homing molecules on their surface, which in turn recognize and bind to specific receptors on the target molecules. This review focuses on the different routes by which drug loaded nanoemulsions can be administered, thus throwing light on the versatility of these vehicles for therapeutic and other related applications.

Key words: Nanoemulsions, therapeutics, oral route, parenteral delivery, transdermal application, intranasal administration.

Nanoemulsions, with a characteristic droplet size of 20-200 nm were developed around 20 years ago (Solans *et al*, 2005; Mason *et al*, 2006; Gutierrez *et al*, 2008; Anton *et al*, 2008). They are often referred to as mini (El Aasser & Sudol, 2004) submicron (Bivas-Benita *et al*, 2004), ultrafine (Nakajima, 1997) or fine dispersed emulsions, and appear transparent to the naked eye due to the inability of nanoparticles to scatter light (McClements, 2002). They can be used as novel formulations in areas of pharmaceutics, cosmetic science, food technology, etc (Sonneville-Aubert *et al*, 2004; Acosta, 2009; Sosnik *et al*, 2010). Their non toxic and non irritant nature makes them ideal therapeutic agents as they do not damage human and animal cells (Aboofazeli, 2010). Their long term physical stability confers an additional advantage.

Nanoemulsion formulations either involve oil droplets dispersed in aqueous medium (O/W) or the reverse (W/O) (Sadurni *et al*, 2005; Wulff-Perez *et al*, 2009; Shakeel and Ramadan, 2010). They are non equilibrium systems and hence their preparation involves the input of a large

amount of either energy or surfactants and in some cases a combination of both. Consequently, high energy or low energy methods may direct their syntheses (Tadros *et al,* 2004; Anton and Vandamme, 2009).

The high energy approach utilizes mechanical devices to create intensely disruptive forces which break up the oil and water phases to form nanosized oil droplets. This can be achieved with microfluidisers, high pressure homogenisers and ultrasonicators (Graves *et al,* 2005; Mason *et al*, 2006; Jafari *et al,* 2007, Gupta *et al.,* 2010). Particle size here will depend on the types of instruments employed and their operating conditions like time and temperature along with sample properties and composition (Qian and Mc Clement, 2011). This method allows for a greater control of particle size and a large choice of composition, which in turn controls the stability, rheology and color of the emulsion.

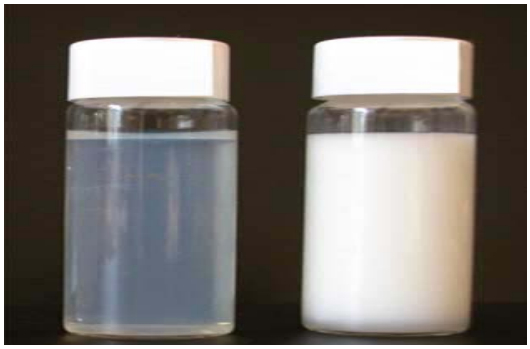

Fig.1. Nano-emulsion (left) with dia 35nm and a macro-emulsion (right) with dia 1μm

The low energy synthesis method is interesting because it utilizes the stored energy of the system to form small droplets. This emulsification can be brought about by changing the parameters which would affect the hydrophilic lipophilic balance of the system like temperature, composition, etc (Sole *et al,* 2006; Kelmann *et al.,* 2007; Ee *et al.,* 2008; Yang *et al,* 2009; Freon *et al,* 2010; Sole *et al,* 2010). Further, a careful selection of surfactant - co surfactant combination and mixing ratio may also be important (Izquierdo *et al,* 2005).

One of the versatile applications of nanoemulsions prepared by either of these methods is in the area of drug delivery where they act as efficient carriers for bioactives, facilitating administration by various routes. Their parenteral delivery has been adopted for supplying nutritional requirements, controlled drug release, vaccine delivery and for drug targeting to specific sites (Tamilvanan, 2004). Intravenous administration of nanoemulsions is shown to be very advantageous, particularly due to their less than 1 μm droplet size (Tamilvanan *et al,* 2005). The advantages and applications of oral drug delivery through these vehicles are numerous where the droplet size is related to their absorption in the gastrointestinal tract (Nicoloas *et al*, 2003). Nanoemulsions have also been studied for their use in ocular delivery where pharmacological drugs are more sustained compared to their respective solutions (Tamilvanan, 2004; Rabinovich-Guilatt *et al,* 2004). Pulmonary route is another way of administering nanoemulsified drugs (Bivas-Benita *et al,* 2004). Transdermal delivery system is a successful channel wherein drug loaded nanoparticles are delivered through the skin (Fang *et al,* 2004; Huailiang *et al,* 2001).

This review elaborates on the possible routes by which bioactives and active pharmaceutical ingredients can be delivered using nanoemulsions as vehicles. They can subsequently be directed to specific tissue and cell targets by the process of passive and /or active targeting to prevent and regress various pathological conditions (Koo *et al*, 2005).

ORAL ADMINISTRATION OF DRUG LOADED NANOEMULSIONS

The most convenient, easiest and cost effective way for non invasive drug administration is by the oral route which dominates the drug delivery market (Pinto, 2010). It is also regarded as the optimal means for achieving therapeutic targets due to increased patient compliance and efforts are on to use this route for personalized medicine (Wening and Breitkreutz, 2011) However, this route of delivery has its limitations with respect to geriatric, pediatric and possibly trauma / epileptic patients where patient cooperation is a constraint. Alternatively, physiochemical properties of certain drugs may not be conducive to pathway of administration. Oral delivery of drugs with poor aqueous solubility poses some serious problems with respect to drug stability in the gastrointestinal tract. Peptide drugs are known to undergo hydrolysis and enzymatic degradation which inturn limits their intestinal absorption. Their limited ability to permeate the membrane and hygroscopic nature may present additional drawbacks. Many approaches have been put forth to increase their bioavailability, which include micronization, solid dispersion, complexation with cyclodextrins and use of particulate delivery systems which are soluble or dispersable in aqueous environment (Francis *et al,* 2004; Brusewitz, *et al.,* 2007; Sachan *et al,* 2010). These strategies aim to protect the drugs from degradation in the gastrointestinal tract, prolong the drug transit time, and target them to specific sites to assist specific absorption pathways.

Niwa *et al* (2011) have developed wet milling techniques to prepare oral nano suspensions for poorly soluble drugs. The milling techniques, based on stirring, oscillating and turbulent motions break drugs into miniature particles for incorporation into nano suspensions for subsequent delivery. The smaller particles may be able to penetrate the GIT membrane to a better extent which could not have been feasible by the conventional delivery. In this case however, extensive optimization of formulations and process variables needs to be carried out especially from the industrial perspective (Singare *et al,* 2010). The targeting of nanoparticulate drug carriers, which have been used for HIV/AIDS therapy, to viral reservoir sites with subsequent lowering of the viral loads below the detection limit, has been reviewed (Vyas *et al*, 2006). O/W nanoemulsions made with polyunsaturated fatty acids and loaded with Saquinivir may also be promising for HIV-AIDS therapy by enhancing oral bioavailability and brain disposition (Vyas *et al,* 2008).

Paclitaxel (PTX), a diterpenoid pseudoalkaloid, is an antineoplastic drug with proven activity against a number of tumors. O/W nanoemulsions prepared with this drug, containing pine nut oil as the lipophilic phase and egg lecithin as emulsifier and prepared by sonication showed improved bioavailability as detected in the systemic circulation when compared to administration of control aqueous solution. The absorbed drug was found to be distributed in the liver, kidneys, and lungs showing promising targeting effects (Tiwari and Amiji, 2006). Further, the association between PTX-2 hydroxypropyl beta cyclodextrin and polyanhydride nano particles induces a positive effect over the intestinal permeability of the drug (Agueros *et al*, 2009). The *in vitro* transport of beta lactamase, by self nano emulsifying drug delivery system (SNEDDS), was studied by Rao *et al* (2008). All the SNEDDS showed higher transport rate than free solutions, with transport rate depending on their composition. Hence it was reported to be a very effective non invasive delivery system for proteins. The absorption of ramiprilat from ramipril with nanoemulsions was reported to be 2.94 times compared to

conventional capsules and 5.4 times compared to drug suspensions. Hence its use for geriatric and pediatric patients was recommended (Shafiq *et al,* 2007).

In the gastrointestinal tract, the oils are effectively absorbed through various lipid absorption mechanisms. Thus, one of the best ways to increase the absorption of drugs, specially the protein drugs, is to load them inside the oils, such that there would be a significant increase in the level of absorption of drugs along with the oils. An innovative strategy is to use oils as components of nanoemulsions to load the drugs, ultimately leading to increased absorption of drugs in gastro intestinal tract. Use of nanoemulsions in the oral drug delivery systems is known to bring about promising results in increasing the effectiveness of the drug to the target site. This system of delivery can bring about the enhancement of the drug bioavailability, enhanced permeability, cell and tissue targeting, imaging, and therapeutic functions (Ganta *et al,* 2010).

NANOEMULSION BASED PARENTERAL DRUG DELIVERY SYSTEMS

This is one of the most common and effective routes for the drug administration usually adopted for actives with low bioavailability and narrow therapeutic index. The stability of nanoemulsions used here mainly depends upon the composition, preparation techniques and storage conditions. Their capacity to dissolve large quantities of hydrophobics, along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation makes them ideal vehicles for the purpose of parenteral transport.

Further, the frequency and dosage of injections can be reduced throughout the drug therapy period as these emulsions guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites. Major clinical and preclinical trials have hence been carried out with parenteral nanoemulsion based carriers. The advances in these novel drug delivery systems have been reviewed by Patel and Patel (2010).

Parenteral administration of drugs had a major breakthrough after the successful use of fat emulsions in 1960s. Since then, there had been a development in nano based products which indicated the interest of pharmaceutical industry in such vehicles for delivery by this route. The use of lipid nanoparticles for the parenteral delivery of actives has been reviewed (Joshi and Muller, 2009). The utility of these, as adjuvants, confers an additional advantage in spite of some toxicity being caused by them. A similar review discusses the parameters which influence encapsulation of drugs along with their release and biodistribution with *in vivo/in vitro* toxicity and efficacy case studies (Constantinides *et al*., 2008).

Tocol nanoemulsions offer an appealing alternative for drug delivery by this route. The utility of tocol based emulsions are numerous (Constantinides *et al.,* 2004). Nanoemulsions loaded with thalidomide have been synthesized where a dose as low as 25mg leads to plasma concentrations which can be therapeutic (Araujo et al., 2011). However, a significant decrease in the drug content of the nanoemulsion was observed at 0.01% drug formulation after two months storage which could be overcome by the addition of

polysorbate 80. Nanostructured lipid carriers (NLC) have also been used for carrying Silybin, a poorly water soluble antihepatopathy agent, by the intravenous route in rabbits and mice. The results showed higher AUC (Area under tissue concentration curve) values with NLC linked silybin circulating in the blood for a longer period than silybin solution. The drug uptake was also found to be higher in the tissues, suggesting the potential role for NLC in sustained drug release and efficient uptake by cells (Jia *et al,* 2010).

Chlorambucil, a lipophilic anticancer agent has been used against breast and ovarian cancer. Its pharmacokinetics and anticancer activity has been studied by loading it in parenteral emulsions prepared by high energy ultrasonication method. Treatment of colon adenocarcinoma in the mouse with this nanoemulsion leads to higher tumor suppression rate compared to plain drug solution treatment concluding that the drug loaded emulsion could be an effective carrier for its delivery in cancer treatment (Ganta *et al,* 2008). Carbamazipine, a widely used anticonvulsant drug had no parenteral treatment available for patients due to its poor water solubility. Kelmann *et al* (2007) have developed a nanoemulsion for its intravenous delivery which showed favorable *in vitro* release kinetics.

The nano interventions for neurodegenerative disorders have been reviewed by Fernandes *et al* (2010). The use of nanoparticles to deliver drugs to the brain infiltrating the blood brain barrier may open up new strategies to overcome the challenges posed by the anatomical barriers of the brain. Further, the ability of these nanoparticles to cross the barrier without altering the original characteristics of the therapeutic drug molecule offer additional advantages.

EFFICACY OF NANOEMULSIONS IN TRANSDERMAL DELIVERY OF DRUGS

Drug delivery through the skin to the systemic circulation is convenient for a number of clinical conditions due to which there has been a considerable interest in this area (Muller - Goymann, 2004; Gaur *et al.,* 2009). It offers the advantage of steady state controlled drug delivery over extended periods of time, with self administration also being possible, which may not be the case with parenteral route. The drug input can be eliminated at any time by the patient just by removing the transdermal patch. An extra advantage is the total absence of gastrointestinal side effects like irritation and bowel ulcers which are invariably associated with oral delivery. Transdermal drug products have been developed for a number of diseases and disorders including cardiovascular conditions, Parkinsons' and Alzheimer diseases, anxiety, depression, etc.

However, the fundamental disadvantage which limits the use of this mode of administration is the barrier imposed by the skin for effective penetration of the bioactives. The three routes by which drugs can primarily penetrate the skin are through the hair follicles, sweat ducts or directly across stratum corneum which restricts their absorption to a large extent and limits their bioavailability. For improved drug pharmacokinetics and targeting, the primary skin barriers need to be overcome. Also the locally applied drug redistribution through cutaneous blood and lymph vessel system needs to be controlled.

Nanotechnology with the use of nano sized particles has largely succeeded in overcoming this barrier and have proved to be much better than microemulsions (Kotyla *et al,* 2008; Cevc and Vierl, 2010). Nano sized emulsions are able to easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for

effective delivery. There are different ways by which the skin penetration of drugs can be enhanced. This includes optimization of drug and vehicle properties, for e.g., maximum penetration is observed when the drug is at its maximum thermodynamic activity like in the case of supersaturated solution (Benson, 2005; Yilmaz and Borchert, 2006; Klang *et al,* 2010).

Caffeine has been used for treatment of different types of cancer by oral delivery. Water in oil nanoemulsion formulations of caffeine has been developed for transdermal drug delivery. Comparison of *in vitro* skin permeation profile between these and aqueous caffeine solutions showed significant increase in permeability parameters for the nanoemulsion loaded drugs (Shakeel and Ramadan, 2010).

The development of magnetic nanoemulsions is an innovative approach for cancer therapy. These can deliver photosensitizers like Foscan to deep tissue layers across the skin thereby inducing hyperthermia for subsequent free radical generation. This methodology can be used for the treatment of cancer in the form of photodynamic therapy (Primo *et al.,* 2007). Shakeel *et al.* (2008) have reported the comparative pharmacokinetic profile of aceclofenac obtained from oral delivery and transdermal application inferring that the absorption of this drug in the latter case resulted in 2.95 fold increase in bioavailability.

Use of nanoemulsions in transdermal drug delivery represents an important area of research in drug delivery, which enhances the therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. It is also regarded as a promising technique with many advantages including, high storage stability, low preparation cost, thermodynamic stability, absence of organic solvents, and good production feasibility. They have also made the plasma concentration profiles and bioavailability of drugs reproducible. These systems are being used currently to provide dermal and surface effects, for deeper skin penetration, etc.

NANOEMULSIONS FOR INTRANASAL ROUTE OF DRUG DELIVERY

Intranasal drug delivery system has now been recognized as a reliable route for the administration of drugs next to parenteral and oral routes. Nasal mucosa has emerged as a therapeutically viable channel for the administration of systemic drugs and also appears to be a favorable way to overcome the obstacles for the direct entry of drugs to the target site (Pires *et al.,* 2009). This system has been accepted in the Ayurvedic system of Indian medicine and in the recent times, this is mostly preferred over the oral administration due to their better systemic bioavailability, as the gastrointestinal metabolism of the drug is avoided (Rahisuddin *et al.,* 2011). This route is also painless, non invasive and tolerated favorably.

There are several problems associated with targeting drugs to brain, especially the hydrophilic ones and those of high molecular weight. This is because of the impervious nature of the endothelium which divides the systemic circulation and barrier between the blood and brain (Pardridge, 1999). The olfactory region of the nasal mucosa provides a direct connection between the nose and brain, and by the use of nanoemulsions loaded with drugs, conditions such as Alzheimer's disease, migraine, depression, schizophrenia, Parkinson's diseases, meningitis, etc. can be treated (Kumar *et al.,* 2008; Mistry *et al.,* 2009).

It is particularly more useful compared to oral and parenteral routes

among pediatric patients as the former routes may increase the anxiety among them (Goldman, 2006). Mistry *et al.* (2009) have reviewed the use of nanoparticles for the direct delivery of drugs from nose to brain. They also emphasize for the need for evaluating the toxicity of the nanoparticle delivery system through the nasal route. Preparation of nanoemulsions containing risperidone for its delivery to the brain via nose has been reported (Kumar *et al.,* 2008). It is inferred that this emulsion is more effective through the nasal rather than intravenous route. These types of emulsions can also be used as a non toxic mucosal adjuvant for influenza vaccine virus (Myc *et al.,* 2003).

Another application of intranasal drug delivery system in therapeutics is their use in development of vaccines. Immunity is achieved by the administration of mucosal antigen. Currently, the first intranasal vaccine has been marketed (Csaba, 2009). The nasal cavity is one of the most efficient sites because of its reduced enzymatic activity, high availability of immuno active sites and its moderately permeable epithelium (Ugwoke, 2005). Among the possible delivery systems, the use of nano based carriers hold a great promise to protect the biomolecules, promote nanocarrier interaction with mucosae and to direct antigen to the lymphoid tissues. Therefore the use of nanoemulsions in intranasal drug delivery system is set to bring about significant results in targeting drugs to the brain in treatment of diseases related to the central nervous system (Clark et al, 2001).

Limitations in intra nasal delivery systems include interaction of drug with nasal mucosa thereby influencing the nasal drug absorption and also its therapeutic efficacy (Illum, 2002). Moreover, only restricted amounts of drug formulations can be administrated due to the low volume of the nasal cavity (Costantino, 2007).

OTHER ROUTES OF DRUG DELIVERY WITH NANOEMULSIONS

Alternative routes used for nano emulsion based drug delivery is through the ocular channel. In the last decade, oil-in-water emulsions have been exploited for the development and improvement of ocular bioavailability (Tamilvanan and Benita, 2004). Ocular drug delivery is one of the most challenging routes due to the critical and pharmacokinetically specific environment that exist in the eyes (Koevary, 2003; Behar-Cohen, 2004). Kumaran *et al.* (2010) have reviewed the conventional and advanced ocular delivery formulations with respect to their applicability, acceptance, characteristics and utility. Hydrocortisone nanosuspensions showed sustained effects with significant improvement in ocular bioavailability. This was in comparison to the drug solution, and provides an opportunity to decrease the administration frequency and also improve patient compliance for drug delivery by this route (Ali *et al.*,2011).

The cytosolic drug delivery system using nanoemulsions is also promising, which is an efficient route for the administering drugs that undergo a large cell efflux through the transporters like multi drug resistant proteins (Panyam and Labhasetwar, 2004). Research associated with the use of nanoparticles for cytosolic drug delivery is under progress. These nanoparticles are being developed in such a way that along with targeting the drug to the action site, their concentrations can also be maintained at required levels for a longer time period (Vasir and Labhasetwar, 2007).

CONCLUSION

Nanoemulsions have been intensively exploited for their significant applications in therapeutics and pharmaceutics. Their versatile properties include enhanced drug loading capabilities along with offering the drugs sufficient protection in the biological

environment. Some multifunctional nanocarriers also direct the drugs to specific targets with attached homing molecules guiding them to the required site of action. This has lead to the development of smart nanoemulsions with tremendous potential for the focused treatment of various pathological conditions like cancer and atherosclerosis. The major routes for the administration of drugs using these vehicles, *viz.,* oral, parenteral, transdermal and intranasal channels, have been reviewed here.

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