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NANOEMULSION A NOVEL APPROACH FOR LIPOPHILIC DRUGS - A REVIEW

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ABSTRACT

Formulation of highly lipophilic drugs has been the major challenge because of the poor oral bioavailability. One of the most promising technologies are the nanoemulsion drug delivery system, which is being applied to enhance the solubility and bioavailability of lipophilic drugs. As the drug is lipophilic in nature it can be easily soluble into the oil phase that is used in the formulation of the nanoemulsions and also reduced particle size to the nanometer range favors the formulation to achieve more surface area there by solubility of the lipophilic drug can be achieved. As the solubility always relates to bioavailability as directly proportional therefore finally it results in the enhanced bioavailability of the drug. As it is the two phase system the stability of the formulation can be maintained by a surfactant and co-surfactant. Nanoemulsions have many advantages, including clarity, high stability, and ease of preparation. Hence it has proved the best alternative for the formulation of highly lipophilic drugs.

Key words: Nanoemulsion, surfactant, oil, co-surfactant.

INTRODUCTION

In the present scenario, oral drug delivery is continuously looking into newer avenues due to the realization of the factors like poor drug solubility and/ or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability due to food effect which are playing major role in disappointing *in vivo* results leading to the failure of the conventional delivery systems. Since the last decade, the oral drug delivery has taken a new dimension with the increasing application of lipid as a carrier for the delivery of poorly water soluble lipophilic drugs [1].

In drug discovery, about 40% of exciting new molecular entities (NMEs) display low solubility in water leading to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity. Therefore, producing suitable formulations is very important to improve the solubility and bioavailability of such drugs [2]. Formulation and development of poorly water soluble drugs (PWSD) candidates continue to be a challenge to formulation scientists mainly because of the emerging new drug discovery programs. The various options available to overcome the hurdle include micronisation, salt formation, use of microspheres, solid dispersions, co-grinding, complexation, lipid-surfactant based formulations and many others. The lipid based formulation approach has attracted wide attention in order to enhance drug solubilization in the gastrointestinal tract (GIT) and to improve the oral bioavailability of BCS (Biopharmaceutical drug classification system) Class II and IV drugs (Fig. 1) [3]. Examples of few lipid based products which have been commercialized are Neoral® (Cyclosporine), Norvir® (Ritonavir), Fortovase® (Saquinavir) and Agenerase® (Amprenavir) [4].

Use of lipid based drug delivery systems has led to effective development of many such compounds with acceptable oral bioavailability. The ability to efficiently deliver lipophilic drug molecules, especially in combination with lipid based delivery systems has led to renewed interest in intestinal lymphatic drug transport. After absorption into the enterocytes, the vast majority of orally administered drugs rapidly diffuse across the cell, are absorbed into the capillaries of portal vein and are thereby processed via liver to systemic circulation. Highly lipophilic drug molecules, however, may associate with

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Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

lymph lipoprotein in the enterocytes and gain access to the mesenteric (intestinal) lymphatics, effectively bypassing the liver and gaining access to the systemic circulation via the thoracic lymph duct. The extremely high drug concentration attainable in lymph (up to 1000 times higher than the plasma concentration) often drug delivery advantages in addition to reduced first-pass metabolism for lymphatically transported drugs, including specific delivery to lymph resident B and T lymphocytes and opportunity to target the principle pathway of tumour metastasis [5].

CLASSIFICATION OF LIPID BASED FORMULATIONS

The lipid based formulations are exemplified by self nano or microemulsifying formulations, self-emulsifying pellets, liposomes, solid lipid nanoparticles (SLNs), nanoemulsions etc. Lipid formulations are a diverse group of formulations consisting of a mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants and co-solvents.

Approaches in the design of lipid based oral formulations

Self-emulsifying formulations comprise isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvent(s) which spontaneously emulsify under mild agitation when exposed to the fluids of GIT to form o/w emulsions or microemulsions. They also generate a high surface area of interaction between the formulation and the GI fluids and is thought of improvement to offer an improvement in the rate and the extent of absorption and to result in more reproducible blood-time profiles. Due to the large number of possible excipient combinations that may be used to assemble lipid-based formulations and self-emulsifying systems in particular, a classification system (Lipid Formulation Classification System, LFCS) has been proposed by Pouton. The main purpose of the LFCS is to enable *in vivo* studies to be interpreted more readily and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, i.e. with reference to their physicochemical properties [6].

Type I Systems: consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an o/w emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) Polysorbate 60 and 1.2 % (w/v) Lecithin. Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/colipase in the GIT to generate more amphiphillic lipid digestion products and promote drug transfer into the colloidal aqueous phase. However, for readily digestible formulations this process is typically efficient. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).

Type II Systems: Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of lipids and lipophilic surfactants (HLB< 12) that self emulsify to form fine o/w emulsions when introduced in aqueous media. Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (> 50-60% w/w) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. PWSD can be dissolved in SEDDS and encapsulated in soft or hard gelatin capsules to produce convenient single unit dosage forms. This system provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.

Type III Systems: Commonly referred to as Self-microemulsifying drug delivery systems (SMEDDS) are defined as an isotropic mixture of lipid, hydrophilic surfactants (HLB > 12), co-surfactant, co-solvents and the drug substance. Many of the marketed products are Type III systems. But, this group is particularly diverse as a result of the wide variation in the proportions of oily and water soluble materials used. This group has been further divided into Type III A and Type III B formulations in order to identify more hydrophilic systems (Type III B) where the content of the hydrophilic surfactants and the co-solvents increases and the lipid content reduce. Type III B formulations typically achieve greater dispersion rates when compared with Type III A although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content, which will affect the rate of absorption of the drug.

The distinction between SEDDS (Type II) and SMEDDS (Type III) formulations is also commonly made on the particle size and optical clarity of the resultant dispersion.
SEDDS- opaque dispersions (particle size > 100 nm).
SMEDDS- optically clear or slightly opalescent dispersions (particle size <100nm).

Type IV systems: These do not contain natural lipids and represent the most hydrophilic formulations comprising drug solution in a single surfactant. These formulations commonly offer increased drug payloads (due to higher drug solubility in the surfactants and the co-solvents) when compared to formulations containing simple glycerides lipids and also produce very fine dispersions when introduced in aqueous media. This in turn lead to

Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

rapid drug release and increased drug absorption e.g. capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase®).

Characteristic features, advantages and disadvantages of the various types of lipid formulations [7]

LFCS Type	Characteristics	Advantages	Disadvantages
Type I	Non dispersing; requires digestion	GRAS status; simple; excellent capsule compatibility	Poor solvent capacity; unless drug is highly lipophilic
Type II	SEDDS without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersions, Particle size 0.25-2µm.
Type III A	SEDDS/SMEDDS with water soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type III B	SMEDDS with water soluble components & low oil content	Clear dispersion; drug absorption without digestion	Likely loss of solvent capacity on dispersion
Type IV	Oil-free formulation based on surfactants and co-solvents	Good solvent capacity for many drugs; disperses to micellar solutions	Loss of solvent capacity on dispersion; may not be digestible

NANOEMULSIONS

Nanoemulsions are defined as isotropic, thermodynamically stable, transparent or translucent; dispersions of oil and water stabilized by an interfacial film of surfactant molecules having the droplet size 20-500nm [7]. Ease of preparation and scale-up, stability and increased bioavailability are features of these formulations which have attracted the attention of researchers [8].

Its basic principle lies in its ability to spontaneously generate fine o/w microemulsion under mild agitation following dilution with aqueous phases. These conditions mimic the digestive motility in the GIT necessary to provide the agitation required for *in vivo* self emulsification. Unlike emulsions, self-nanoemulsified drug delivery systems (SNEDDS) generates microemulsion with a narrow droplet size distribution of less than 50 nm due to which these systems have also been addressed as nanoemulsions. The fine droplets of this dosage form have the advantage of presenting the drug in a dissolved form with a large interfacial surface area for drug absorption which results in more uniform and reproducible bioavailability. Moreover, the drug is maintained in the dissolved state throughout the GIT which helps in enhancing the bioavailability of PWSD. In addition, the fine droplets offer large surface area for pancreatic lipase to hydrolyze the lipids and therefore enhance the rate of drug release. The adequate solubility of the drug in the lipid/surfactants blend, nature of the lipid/surfactant pair, the ratio between the lipid and the surfactant, the surfactant concentration and the uniform droplet size distribution following self-emulsification are necessary components to be monitored during the development of SMEDDS [9].

ADVANTAGES OF NANOEMULSION

1. Nanoemulsion is the approach to improve water solubility and ultimate bioavailability of lipophilic drugs. The nano-sized droplets leading to enormous interfacial areas associated with nanoemulsions would influence the transport properties of the drug, an important factor in sustained and targeted drug delivery [10].
2. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible [11].
3. Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of the drug and gut wall [12].
4. Nanoemulsions have a higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions such as emulsions and suspensions because they can be manufactured with little energy input (heat or mixing) and have a long shelf life [13].
5. They also provide ultra low interfacial tension and large o/w interfacial areas [14].
6. They also offer an advantage over existing self-emulsifying system in terms of rapid onset of action (no extra time for dispersion) and reduced intersubject variability in terms of GIT fluid volume.
7. Nanoemulsions may possess high kinetic stability and optical transparency resembling to microemulsions[15].
8. The structures in the nanoemulsions are much smaller than the visible wavelength, so most nanoemulsions appear optically transparent, even at large loading [16].
9. Nanoemulsions have potential to deliver peptides that are prone to enzymatic hydrolysis in GIT [17].

Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

MAJOR COMPONENTS OF NANOEMULSION

Oils: Selection of an appropriate oily phase is very important as it influences the selection of other ingredients of nanoemulsions, mainly in case of O/W nanoemulsions. Usually, the oil which has maximum solubilising potential for selected drug candidate is selected as an oily phase for the formulation of nanoemulsions. This helps to achieve maximum drug loading in the nanoemulsions [18].Naturally occurring oils and fats are comprised of mixtures of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation. Triglycerides are classified as short (<5 carbons), medium (6-12 carbons), or long chain (>12 carbons) and may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. The choice of oily phase is often a compromise between its ability to solubilize the drugs and its ability to facilitate formation of nanoemulsion of desired characteristics. Thus mixture of oils can be used to meet both the requirements. For example, a mixture of fixed oil and medium chain triglycerides is used to have good balance between drug loading and emulsification[19].Both long chain and medium chain triglyceride oils with different degrees of saturation have been used in design of SMEDDS [20]. Triglycerides are highly lipophilic and their solvent capacity for drugs is commonly a function of the effective concentration of ester groups, thus on weight basic medium chain triglycerides (MCT) have higher solvent capacity and resistance to oxidation compare to long chain triglycerides [21]. Recently, MCT have been replaced by novel semi-synthetic MCT containing compounds such as gelucire. Other suitable oil phases are modified vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, hydrogenated soybean oil, peanut oil and beeswax [22].

Surfactants: The surfactant should favour microemulsification of the oily phase and should also possess good solubilising potential for the hydrophobic drug compounds. The choice of the surfactant is critical for the nanoemulsion formulation. Surfactants with an HLB value <10 are hydrophobic (such as sorbitan monoesters) and form w/o nanoemulsion where as high HLB (>10) surfactants such as polysorbate 80 are hydrophilic and form o/w nanoemulsion. In many cases, mixture of lipophilic (low HLB) and hydrophilic surfactants (high HLB) may be required to obtain nanoemulsion [23]. Surfactants in solution below their critical micellar concentration (CMC) improve drug solubility by providing regions for hydrophobic drug interactions in solution. Above the CMC, surfactants self-aggregate in defined orientation to form micelles with the hydrophobic core and a hydrophilic surface. The hydrophobic core enhances the entrapment of drug, thus increasing its solubility. When the oil content is high, surfactant concentrate on the oil/water interface forming emulsions, where in the drug is solubilized in the internal oil phase. On the other hand when the oil content is low, minute oil-entrapped surfactant globules are produced, which are known as nanoemulsions [24]. The surfactant used in nanoemulsion formation could be ionic or non-ionic but ionic surfactants are not preferred due to toxicological concerns. Non-ionic water soluble surfactants are commonly used for SMEDDS formulation. Among various surfactants that are available, lecithins, poloxamers and polysorbate 80 are most preferred. The usual surfactant concentration in SMEDDS formation and maintaining emulsion stage ranges from 30-60% w/w of the formulation. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to smaller droplets such as in the case of a mixture of saturated C_8-C_{10} polyglycolized glycerides (Labrafac). This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase [25].

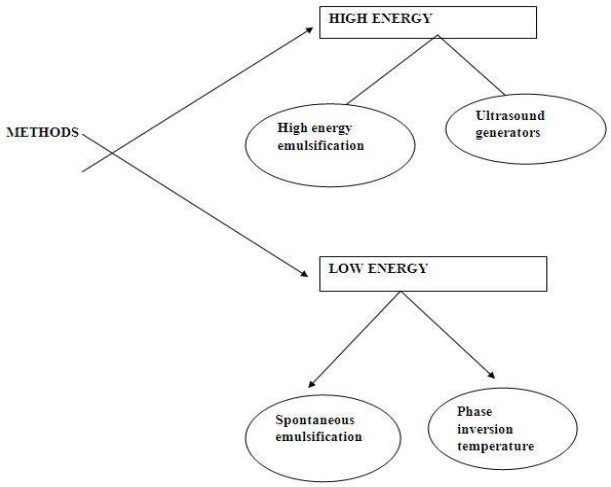
Cosurfactants: Most of the times, surfactant alone cannot lower the oil-water interfacial tension sufficiently to yield a nanoemulsion which necessitates the addition of an amphiphillic short chain molecule or cosurfactant to bring about the surface tension close to zero. Cosurfactants penetrate into the surfactant monolayer providing additional fluidity to interfacial film and thus disrupting the liquid crystalline phases which are formed when surfactant film is too rigid [26]. Usually a very low HLB cosurfactant is used with a high HLB surfactant to modify the overall HLB of the system. Unlike surfactant, the cosurfactant may not be capable of forming self-associated structures like micelles on its own. Hydrophilic cosurfactants preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol, which are known to reduce the oil/water interface and allow the spontaneous formation of nanoemulsion [27].

Cosolvents: The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as ethanol, glycerol, propylene glycol (PG), polyethylene glycol(PEG) are suitable for oral delivery, and they enable dissolution of large quantity of either the hydrophilic surfactant or the drug in the lipid base by co-solvency and

Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

by making the environment more hydrophobic by reducing the dielectric constant of water. Alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin or hard gelatin capsules in conventional SMEDDS leading to drug precipitation. Thus, alcohol free formulations have been designed [28].

METHODS OF PREPARATION OF NANOEMULSION



MECHANISM FOR BIOAVAILABILITY ENHANCEMENT OF DRUGS FROM SMEDDS

The fate of SMEDDS following oral administration and mechanism for improved bioavailability are shown in Figure 6. Most of the dietary lipids are triglycerides which are fatty acid esters of glycerol. On ingestion of triglycerides initial lipid emulsification takes place in the stomach leading to formation of crude emulsion (lipid droplets of 1-100µ in size). This is facilitated by combination of gastric agitation and gastric emptying and promoted by presence of dietary phospholipids, proteins and polysaccharides which act together to stabilize the oil - water interface. Around 10-30% of the overall hydrolysis of ingested triglycerides takes place in stomach. The crude emulsion passes to the upper section of large intestine where particle size reduction of the droplets takes place due to the presence of range of emulsifying agents including bile salts, cholesterol, phosphatidylcholine, lecithin and lysolecithin resulting in formation of small oil droplets of approximately 0.5µm in size. Subsequently the process of lipid digestion is completed under action of the pancreatic lipase-colipase complex. There are several reports indicating enhanced drug absorption from SMEDDS and various mechanisms have been proposed.

A combination of raised levels of endogenous bile salts, phospholipids and cholesterol and the presence of exogenous lipid and surfactants forms lipidic microenvironments into which poorly water soluble drugs may partition. Thus it forms a reservoir of solubilised drug at the absorption site and generates the concentration gradient require to drive improved absorption. Bile salts may also enhance the solubilisation of poorly water soluble drugs by improving wetting at concentration below the CMC. The presence of additional solubilising excipients (such as surfactants, cosurfactants and cosolvents) also play a major role in increasing the absorption of drug. Drug may be absorbed through the lymphatics via chylomicron synthesis of the fatty components of the oil phase of emulsion. A lipophilic drug, which preferably remains in the oil droplet, mayinfact be ~absorbed via bile salts micelles (Fig. 4). Increased mucosal permeability via incorporation of lipids from mixed micelles and enhanced mesenteric lymph flow may be responsible for the enhanced drug absorption.

Absorbed drug molecules entering the cell can be secreted back into the gastrointestinal lumen by P-glycoprotein (P-gp) efflux pumps' which is an ATP dependent transport protein located at the apical membrane of epithelial cells. Common pharmaceutical excipients like polyethylene glycol, Tween 80 and Cremophor EL have been shown to inhibit P-gp activity. Their inclusion in the formulation, therefore can be expected to increase the bioavailability for drugs which are known substrates of P-gp efflux pumps [29].

CHARACTERIZATION OF NANOEMULSIONS

Characterization of SMEDDS involves the physical and chemical tests related to oral liquid dosage forms which includes assay, uniformity of content, appearance, pH, viscosity, density, conductivity, surface tension, size and zeta potential of the dispersed phase etc. with respect to the effect of the composition on physical parameters

1. ***Differential scanning calorimetry (DSC)*** provides information on the interactions of different components and polarization microscopy using crossed polarizers is employed to confirm isotropicity of the formulation.
2. The process of self-emulsification can be evaluated by ***visual assessment***. Its efficiency would be estimated by determining the rate of emulsification and droplet size distribution.
3. ***Turbidity measurements*** are carried out to determine the rapid equilibrium reached by the dispersion and reproducibility of this process**.**
4. The ***droplet size*** of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. Photon correlation spectroscopy (PCS) and light scattering techniques like static light scattering (SLS), dynamic light scattering (DLS) are a useful method for determination of emulsion droplet size**.**

Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

5. ***Viscosity, conductivity and dielectric methods*** provide useful information at the macroscopic level. Viscosity measurements for example can indicate the presence of rod-like or worm-like reverse micelles and conductivity measurements provide the means of determining whether a nanoemulsion is oil-continuous or water-continuous, as well as providing a means of monitoring phase inversion phenomena. Dielectric measurements are a powerful means of probing both the structural and dynamic features of microemulsion system.

6. Structural features of microemulsions have been studied using ***self-diffusion nuclear magnetic resonance (SD NMR)*** and ***small angle x-ray scattering (SAXS)***. Freeze fracture electron microscopy has also been used to study microemulsion structure, however extremely rapid cooling of the sample is required in order to maintain the structure and minimize the possibility of artifacts**.**

7. ***Emulsion droplet polarity*** is also a very important factor in characterizing emulsification efficiency. The HLB, chain length and degree of unsaturation of fatty acids, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/ or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by the polarity**.**

8. The ***charge of the oil droplets*** of SMEDDS is another property that should be assessed. Usually it is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1-3%, will yield cationic SMEDDS. Thus, each systems have a positive zeta potential value of about 35-45 mV. This positive zeta potential value is preserved following the incorporation of the drug compounds [30-34].

APPLICATIONS OF NANOEMULSIONS

Nanoemulsions containing pharmaceutically active agents can be utilized for the production of pharmaceutical preparations, the nanoemulsion being mixed, as the active component, with a solid or liquid vehicle suitable for therapeutic administration. If desired, a special galenic form can be imparted to the mixture. The following galenic forms of administration can be considered, in this connection: Ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances in addition to the nanoemulsion; aerosols without metering feature, and dosing aerosols, which can contain propellant gas and stabilizers besides the nanoemulsion; hydrophilic and hydrophobic gels and ointments containing the nanoemulsion; o/w or w/o creams containing the nanoemulsion; lotions and pastes containing the nanoemulsion.

- **Ocular delivery:** Oil in water emulsions are being explored for improved topical lipophilic drug delivery to the eye. Lipophilic drug loaded o/w ocular emulsions provide equivocally a better balance between ocular bioavailability improvement and patient comfort following topical instillation into the eye e.g. Piroxicam, pilocarpine, indomethacin, cyclosporine A**.**
- **Percutaneous route:** Many drugs exhibit low skin penetration, which results in poor efficacy. As opposed to common chemical skin penetration enhancers, organic solvents, which are generally associated to some degree with skin irritation, toxicity and sensitization, a solvent free topical vehicle based on drug entrapment in the o/w emulsion droplets of submicron size is more efficacious in terms of percutaneous absorption with possibly devoid of adverse effects. In addition, the uniqueness of the large internal hydrophobic core of o/w submicronized emulsion droplets allows high solubilization capacity for water insoluble topically active medicaments and also aids in carrying water, an excellent softener, to the skin e.g. NSAIDs, diazepam, α-tocopherol, antifungal drugs (econazole or miconazole nitrate), EMLA (Eutectic mixtures of local anaesthetic) has proven to be a useful medication for children. It is an emulsion containing a mixture of lidocaine and prilocaine. This cream gives an effective deep sedation**.**
- **Nasal route:** The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by-passing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa e.g. a lipid soluble rennin-inhibitor was incorporated into an o/w emulsion. Enhanced and prolonged *in vivo* nasal absorption was observed in emulsion compared to aqueous suspension. Other drugs which have been formulated for nasal delivery are insulin and testosterone**.**
- **Pulmonary delivery:** A novel pressurized aerosol system has been devised for the pulmonary delivery of salbutamol using lecithin-stabilized microemulsions formulated in trichlorotrifluoroethane**.**
- Oil in water nanoemulsion has been used to solubilize steroidal drugs such as prednisolone, hydrocortisone and betamethasone, testosterone and its esters and progesterones**.**
- Azelaic acid, a drug used in the treatment of pigmentary disorders has also been investigated as a topical o/w microemulsion formulation**.**
- Nanoemulsions can also be utilized for the preparation of nutrient solutions for cell cultures by adding to the nanoemulsions, for example, natural amino acids, antibiotics, small amounts of transferrin and optionally glucose. In such nutrient solutions, the nanoemulsions serve as energy deliverers and can at least in part replace

Asian J. Pharm. Res. Vol 3, Issue 2, 84-92, 2013.

the proteins used in conventional nutrient solutions, e.g. those made from calf serum [35-41].

Fig 1. Biopharmaceutical classification system

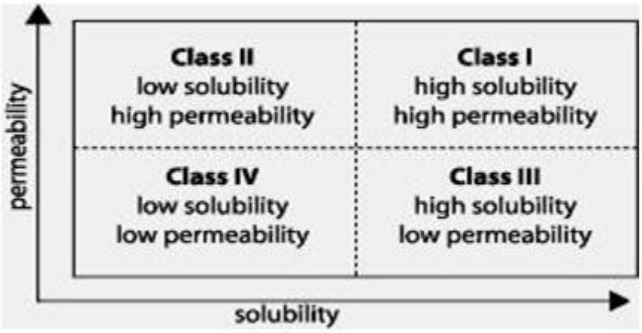


Fig 2. A diagrammatic representation of uptake of lipids intestinal lymphatics

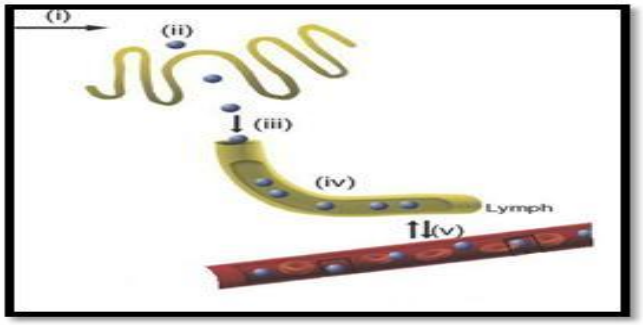


Fig 3. Structure of Nanoemulsion droplet

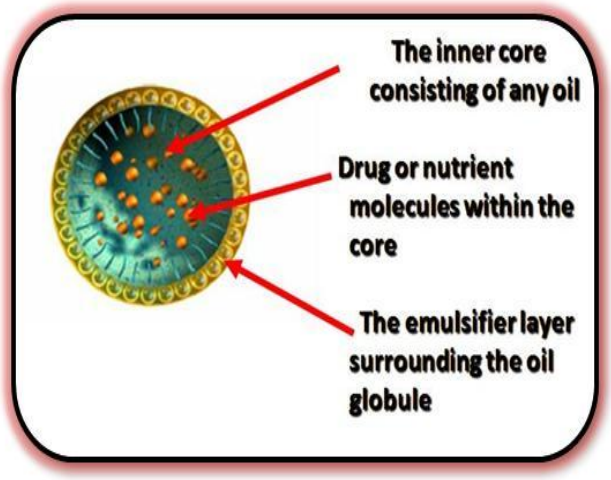
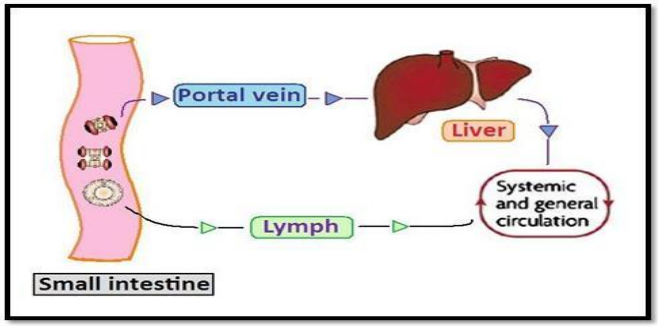
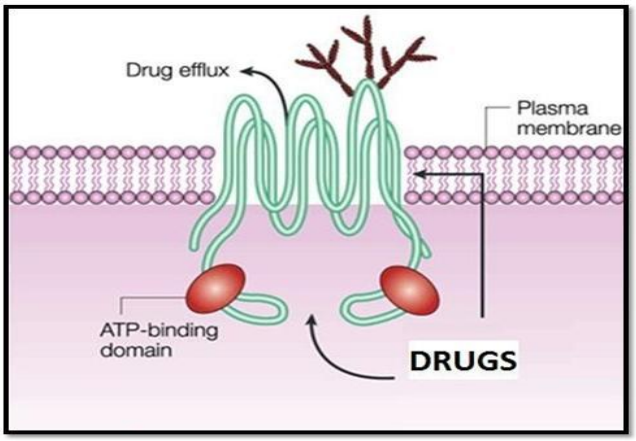


Fig 4. Various mechanisms of enhancement of drug bioavailability in the presence of lipids:



solubilization of drug in the intestinal fluid by formation of colloidal species viz., vesicles, mixed micelles and micelles; followed by selective lymphatic uptake which reduces first-pass drug metabolism as intestinal lymph travels directly to the systemic circulation.

Fig 5.P-glycoprotein (P-gp) as transmembrane drug efflux pump



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