ORAL SUBMICRON EMULSION- A BATTER APPROACH FOR ORAL DELIVERY OF BCS CLASS-II DRUGS

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Abstract

Sub-micron emulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Sub-micron emulsion is a vital tool in solving low bioavailability issues of poorly soluble drugs. In sub-micron emulsion hydrophobic drugs can be dissolved which makes them able to be administered as a unit dosage form for per-oral administration. When such a system is released in lumen of the gastrointestinal tract, it disperses to form a fine emulsion (micro/nano) with the aid of GI fluid. This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathway, bypassing the first-pass effect. The basic structure of submicron emulsion is a natural lipid core (i.e.-triglyceride) stabilized by a monolayer of amphiphilic lipid (i.e. - phospholipids). Such emulsion can stabilize considerable amounts of lipophilic drugs in core or/amphiphilic ones in the surface monolayer.

Keywords: Submicron emulsion, Solubility, BCS Class-II.

Introduction

Submicron emulsion can be defined as emulsions with mean droplet diameters ranging from 50 to1000 nm. Usually, the average droplet size is between 100 and 500 nm. The globules can exist as water-in-oil and oil-in-water forms, where the core of particle is either water or oil, respectively. Submicron emulsions are made from surfactants approved for human consumption and common food substances that are “Generally Recognized as Safe” (GRAS) by the FDA. These emulsions are easily produced in large quantities by mixing a water-immiscible oil phase into an aqueous phase with a high stress, a mechanical extrusion process that is available worldwide.

Nearly half of the new drug candidates that reach formulation scientists have poor water solubility and oral delivery of such drug is frequently associated with low bioavailability [1]. To overcome these problems various formulation strategies have been exploited, such as the use of surfactants, lipids, permeation enhancers, micronization salt formation, cyclodextrines, nanoparticles and solid dispersions. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion [2].

Much attention has been focused on lipid solutions, emulsions and emulsion preconcentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems [3].

Submicron emulsion is isotropic mixture of drug, lipids and surfactants, usually with one or more hydrophilic cosolvents or cosurfactants [4].

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Advantages of submicron emulsion

Submicron emulsions are potential drug carrier systems for various routes of administration. These are having advantages when compared to the other dosage forms.

i. These are thermodynamically stable and require minimum energy for formation.
ii. Ease of manufacturing and scale-up.
iii. Improved drug solubilization and bioavailability.
iv. This system is reckoned advantageous because of its wide application in colloidal drug delivery systems for the purpose of drug targeting and controlled release.

Limitation of submicron emulsion:

The main limitation of submicron emulsion is the use of high amounts of surfactant and cosurfactant that may be harmful for human consumption.

Drug candidate identification for Sub-micron Emulsion

One of the primary challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of gut [Driscoll, C.M. and Griffin et al. 2008-36]. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, sub-micron emulsion can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of sub-micron emulsion can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs.

These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs.

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Drug name</th>
<th>Route</th>
<th>Objective</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Clotrimazole</td>
<td>Oral Submicron emulsion</td>
<td>Improvement of stability</td>
<td>[9]</td>
</tr>
</tbody>
</table>

Table 1: Research work carried out on submicron emulsion
Drug candidate identification for Sub-micron Emulsion

One of the primary challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of gut [16]. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, sub-micron emulsion can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of sub-micron emulsion can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs.

These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs.

### Application of Sub-micron emulsion in various BCS category drugs

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class- I</td>
<td>Enzymatic degradation, gut wall efflux</td>
</tr>
<tr>
<td>Class- II</td>
<td>Solubilization and bioavailability</td>
</tr>
<tr>
<td>Class- III</td>
<td>Enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
<tr>
<td>Class- IV</td>
<td>Solubilization, enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
</tbody>
</table>

### Table 3: List of BCS class-II drugs according to World Health Organization

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Dose</th>
<th>BCS Class</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid antibacterial agent</td>
<td>Low</td>
<td>High</td>
<td>250; 500</td>
<td>II</td>
<td>[17, 18, 19, 20, 21, 22]</td>
</tr>
<tr>
<td>Nevirapine antiviral</td>
<td>Low</td>
<td>High</td>
<td>200</td>
<td>II</td>
<td>[23, 24]</td>
</tr>
<tr>
<td>Praziquental antihelmintic</td>
<td>Low</td>
<td>High</td>
<td>150; 600</td>
<td>II</td>
<td>[17, 25, 23]</td>
</tr>
<tr>
<td>Rifampicin antituberculotic</td>
<td>Low</td>
<td>High</td>
<td>150; 300</td>
<td>II</td>
<td>[17, 26, 27, 28]</td>
</tr>
<tr>
<td>Albendazole antiparasitic</td>
<td>Low</td>
<td>Low/High</td>
<td>400</td>
<td>II/IV</td>
<td>[29, 30, 31, 32, 33]</td>
</tr>
<tr>
<td>Amiutripine antidepressive</td>
<td>Low/High</td>
<td>High</td>
<td>25 (hydrochloride)</td>
<td>I/II</td>
<td>[17, 25, 34, 23, 35]</td>
</tr>
<tr>
<td>Artemether+Lumefantrine antimalarial agents</td>
<td>Low Low/High</td>
<td>High</td>
<td>20 + 120</td>
<td>II/IV</td>
<td>[17, 23, 36, 37, 38, 39]</td>
</tr>
<tr>
<td>Chlorpromazine antidepressive</td>
<td>Low</td>
<td>Low/High</td>
<td>100 (hydrochloride)</td>
<td>II/IV</td>
<td>[17, 25, 34]</td>
</tr>
<tr>
<td>Ciprofloxacin antibiotic</td>
<td>Low</td>
<td>Low/High</td>
<td>250 (hydrochloride)</td>
<td>II/IV</td>
<td>[17, 43, 34, 40, 41, 42, 43]</td>
</tr>
<tr>
<td>Clifazime antibiotic</td>
<td>Low</td>
<td>Low/High</td>
<td>50; 100</td>
<td>II</td>
<td>[44, 45, 46]</td>
</tr>
<tr>
<td>Dilexandine antiprotozoal agent</td>
<td>Low</td>
<td>Low/High</td>
<td>500 (furoate)</td>
<td>II/IV</td>
<td>[17, 25, 47]</td>
</tr>
<tr>
<td>Efavirenz antiviral</td>
<td>Low</td>
<td>Low/High</td>
<td>50; 100; 200</td>
<td>II/IV</td>
<td>[48, 49]</td>
</tr>
<tr>
<td>Ethyl estradiol hormone</td>
<td>High</td>
<td>Low/High</td>
<td>0.03 (+0.15 Levonorgestrel) 0.05 (+0.25 Levonorgestrel)</td>
<td>II/IV</td>
<td>[17, 25, 50]</td>
</tr>
<tr>
<td>Felic acid</td>
<td>Low</td>
<td>Low/High</td>
<td>1; 5</td>
<td>II/IV</td>
<td>[17, 51, 52]</td>
</tr>
<tr>
<td>Glibencemide antidiabetic</td>
<td>Low</td>
<td>Low/High</td>
<td>2.5; 5</td>
<td>II/IV</td>
<td>[17, 53]</td>
</tr>
<tr>
<td>Haloperidol neuroleptic</td>
<td>Low</td>
<td>Low/High</td>
<td>2; 5</td>
<td>II/IV</td>
<td>[17, 25, 24, 54, 55, 56, 57]</td>
</tr>
<tr>
<td>Iver</td>
<td>Low</td>
<td>Low/High</td>
<td>3; 6</td>
<td>II/IV</td>
<td>[17, 25]</td>
</tr>
<tr>
<td>Limavair antiviral</td>
<td>Low</td>
<td>Low/High</td>
<td>133.3 (+33.3 Ritonavir)</td>
<td>II/IV</td>
<td>[21]</td>
</tr>
<tr>
<td>Mebendazole antihelmintic</td>
<td>Low</td>
<td>Low/High</td>
<td>100; 500</td>
<td>II/IV</td>
<td>[58]</td>
</tr>
<tr>
<td>Mefloquine antimalarial</td>
<td>Low</td>
<td>Low/High</td>
<td>250 (hydrochloride)</td>
<td>II/IV</td>
<td>[25, 59]</td>
</tr>
<tr>
<td>Niclosamide antihelmintic</td>
<td>Low</td>
<td>Low/High</td>
<td>500</td>
<td>II/IV</td>
<td>[17]</td>
</tr>
<tr>
<td>Pyrantel anthelmintic</td>
<td>Low</td>
<td>Low/High</td>
<td>250 (embonate)</td>
<td>II/IV</td>
<td>[17]</td>
</tr>
<tr>
<td>Pyrimethamine Toxoplasmosis</td>
<td>Low</td>
<td>Low/High</td>
<td>25</td>
<td>II/IV</td>
<td>[17, 60]</td>
</tr>
</tbody>
</table>
Excipients for Submicron Emulsion

Triglycerides

Triglycerides are used for oral lipid based submicron emulsion. These have advantages that they are commonly ingested in food, fully digested and absorbed and therefore do not present any safety issue [2]. Naturally occurring oils and fats are comprised of mixtures of triglycerides which contain fatty acids of varying chain lengths and degree of saturation. The melting point of an oil increase with increase in fatty acid chain lengths and decrease with increasing degree of instauration, which also increases the relative susceptibility to oxidation.

Triglycerides are classified as short (<5 carbons), medium (6-12 carbons) or long chain (>12 carbon) and may be synthetically hydrogenated to decrease degree of instauration to improve resistance to oxidation [82].

Triglycerides are highly lipophilic and their solvent capacity for drugs is function of effective concentration of ester groups therefore on weight basis medium chain triglycerides have more solvent capacity than long chain triglycerides [2].

Mixed Triglycerides

Partial hydrolysis of triglycerides is used to produce a wide range of mixed glyceride excipients in which different proportions of monoglyceride, diglyceride and triglyceride are present. Mixed long chain glycerides are better solvent for lipophilic drugs than triglycerides. They are useful for preparation of SEDDS (self-emulsifying drug delivery system) with and without water-insoluble components [2].

Water-insoluble Surfactants

For preparation of oral lipid based formulations excipients with HLB value 8 to 12 are used, which adsorb strongly at oil-water interfaces, as water-insoluble surfactants. These surfactants are not sufficiently water-soluble but to dissolve in water but sufficiently hydrophilic to promote self-emulsification. Examples of such surfactants are polyoxyethylene sorbitan trioleate (tween-85) and polyoxyethylene glyceryl trioleate. These two examples have HLB values between 11 and 11.5 and used for preparation of SEDDS without water-soluble components.

Water-soluble Surfactants

These are the most commonly used surfactants for formation of SEDDS or SMEDDS.

Cosolvents

Several marketed lipid-based products contain water-soluble cosolvents. The most popular cosolvents have been PEG-400, propylene glycol, ethanol and glycerol. There are three reasons for using cosolvents:

i. Ethanol has been used to enhance dissolution of drug cyclosporin.

ii. Cosolvents are also used to increase solvent capacity of formulation in which drug is freely soluble.
iii. Third reason for use of cosolvent is to aid dispersion system which contain high proportion of water soluble surfactants.

**Cosolvents have following practical limits**-
(a) Immiscibility with oil components.
(b) Incompatibility of low molecular weight cosolvents with capsule shell.

**Additives**
Lipid-soluble antioxidants such as \( \alpha \)-tocopherol, \( \beta \)-carotene, butylated hydroxy toluene (BHT) or propyl gallate are used to protect either unsaturated fatty acid chains or drug from oxidation [2].

### 1.3 Factors Affecting Choice of Excipients for Oral Submicron emulsion

I. **Regulatory issues**- irritancy, toxicity, knowledge and experience. All surfactants are potentially irritant or poorly tolerated as a result of these non-specific effects. In general terms cationic surfactants are more toxic than anionic surfactants which in turn are more toxic than non-ionic surfactants.

II. **Solvent capacity**- Triglycerides are poor solvents for all but highly lipophilic compounds, so most submicron emulsions contain polar oils, surfactant and/or cosurfactant to improve the solvent capacity of anhydrous formulation.

III. **Miscibility**- Mutual miscibility of excipients is necessary to produce a clear, stable, submicron emulsion. Long chain triglyceride oils are not usually miscible with hydrophilic surfactants or cosolvents so in practice it is often necessary to blend these materials with a polar oil (or cosurfactant) to promote mutual solubility.

IV. **Morphology at room temperature**.

V. **Digestibility**- fate of digested products.

VI. **Capsule compatibility**- Low molecular weight polar molecules present in capsule formulations are able to penetrate and plastisize gelatin capsule shells, which restricts the concentration of cosurfactants that can be used in capsule fills. Surfactants can also destabilize capsule shells but there are differences between soft and hard gelatin capsules [83].

VII. **Purity, chemical stability**.

VIII. **Cost of goods**. [84]

**Techniques of Submicron emulsion preparation**
There are two methods of submicron emulsion preparation-
(a) High-energy Emulsification Methods
(b) Low-energy Emulsification Methods

I. **High Energy Emulsification Methods**- These methods include use of devices that use very high mechanical energy to create nanoemulsion with high kinetic energy.

Methods are-
(a) High pressure homogenization
(b) Ultrasonic emulsification

(a) High-pressure homogenization- this is the most common method used for submicron emulsion preparation. In this method during homogenization the coarse macro emulsion is passed through a small orifice at an operating pressure in range of 500 to 5000 psi.
During this process several forces such as hydraulic shear, intense turbulence and cavitations act together to produce submicron emulsion with extremely small size [84]. In process of micro fluidization a positive pump is operated at very high pressure of 20,000 psi. This pump forces macro emulsion droplets through an interaction chamber consisting of series of micro channels.

The macro emulsion passing through the micro channels colloids with high velocity on to an impingement area resulting in very fine submicron emulsion. The submicron emulsion with desired size range and dispersity can be obtained by varying the operating pressure and the number of passes through interaction chamber.

(b) Ultrasonic emulsification- in this method a probe is used that emits ultrasonic waves to disintegrate the macroemulsion by means of cavitation force.

By varying the ultrasonic energy input and time the submicron emulsion with desired size can be obtained. High-pressure homogenization can be employed for preparation of both o/w and w/o submicron emulsion.

High-pressure homogenization and microfluidization can be used for preparation of submicron emulsion at both laboratory and industrial scale. Ultrasonic emulsification is mainly used at laboratory scale.

High-energy method of submicron emulsion preparation methods have following limitations:
1. Not suitable for thermo labile drugs such as retinoid and macromolecules, including proteins, enzymes and nucleic acids.
2. High-energy methods require sophisticated instruments and extensive energy input, which increases the cost of submicron emulsion preparation.

These limitations resulted in development of low-energy methods for submicron emulsion preparation.

I. Low-energy emulsification methods- these methods require low energy for preparation of submicron emulsion preparation.

These methods are mainly dependent on modulation of interfacial phenomenon/phase transition and intrinsic physicochemical properties of surfactants, cosurfactants and oil to yield submicron emulsion droplets.

There are three types of low-energy emulsification methods-
(a) Phase Inversion Temperature Method.
(b) Solvent Displacement Method.
(c) Phase Inversion Composition Method.

(a) Phase Inversion Temperature Method- The phase inversion temperature (PIT) method was first described by Shinoda and Saito as an alternative to high shear emulsification methods [86, 87]. The method employs temperature-dependent solubility of nonionic surfactants such as polyethoxylated surfactants, to modify their affinities for water and oil as a function of the temperature. It has been observed that polyethoxylated surfactants, tend to become lipophilic on heating due to dehydration of polyoxyethylene groups. This phenomenon forms a basis of nanoemulsion fabrication using PIT method.

In the PIT method oil, water and nonionic surfactants are mixed together at room temperature. This mixture typically comprises O/W microemulsions coexisting with excess oil, and the surfactant monolayer exhibits positive curvature. When this macroemulsion is heated gradually, the polyethoxylated surfactant becomes lipophilic and at higher temperatures, the surfactant gets completely solubilized in oily phase and the initial O/W emulsion undergoes phase inversion to W/O emulsion. The surfactant monolayer has negative curvature at this stage [88, 89, 90, 16, 91]. At an intermediate temperature (also termed hydrophilic-lipophilic balance [HLB] temperature), the nonionic surfactant similar affinity for aqueous and oily phase and this ternary system has extremely low interfacial tension (in the order of 10^{-2}-10^{-5} mNm^{-1}) and spontaneous curvature typically reaches zero. The ternary system at this stage typically consists of a D-phase bicontinuous microemulsions [88, 91] or a mixture of a D-phase bicontinuous microemulsion and lamellar liquid crystalline phase [87]. It has been observed that nanoemulsions with very small droplet size and polydispersity index can be generated by rapid cooling of the single-phase or multiple bicontinuous microemulsions maintained at either PIT or a temperature above PIT (transitional-phase inversion) [87].
It should be noted that the step of rapid cooling or dilution of the single-phase or multiphase bicontinuous microemulsion is important as poly disperse emulsions with greater propensity to coalescence have been obtained when rapid cooling was not performed [85, 91].

(b) Solvent Displacement Method- The solvent displacement method for spontaneous fabrication of nanoemulsion has been adopted from the nanoprecipitation method used for polymeric nanoparticles. In this method, oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone [92, 93]. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous nanoemulsion by rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation [92]. Interestingly, spontaneous nanoemulsification has also been reported when solution of organic solvents containing a small percentage of oil is poured into aqueous phase without any surfactant. This phenomenon is known as ‘Ouzo effect’ [93]. This phenomenon has mainly been used for fabricating polymeric nanocapsules using nanoemulsion as a template [91, 93]

(c) Phase Inversion Composition Method (Self-nanoemulsification Method)- This method has drawn a great deal of attention from scientists in various fields (including pharmaceutical science) as it generates nanoemulsion at room temperature without use of any organic solvent and heat. In this method kinetically stable nanoemulsions with small droplet size (~50nm) can be generated by stepwise addition of water into solution of water into solution of surfactant in oil, with gentle stirring and at constant temperature [94]. The spontaneous nanoemulsification has been related to the phase transitions during the emulsification process and involves lamellar liquid crystalline phase or D-type bicontinuous microemulsion during the process [95, 91]. It is important to know the phase behavior of the system in order to identify the conditions suitable for generating nanoemulsions by this process. It has also been established that physicochemical properties of the components and ratio of the surfactant to oil are major determinants of the properties of the nanoemulsions obtained by this method [91, 95]. It should be noted that the nanoemulsions obtained from the spontaneous nanoemulsification process are not thermodynamically stable, although they might have high kinetic energy and long-term colloidal stability [95].

1.5 Application of submicron emulsion

Cosmetics- Submicron emulsion has recently become increasingly important as potential vehicles for the controlled delivery of cosmetics and for the optimized dispersion of active ingredients in particular skin layers. Due to their lipophilic interior they are more suitable for the transport of lipophilic compounds than liposomes. Similar to liposomes they support the skin penetration of active ingredients and thus increase their concentration in skin. Another advantage is the small sized droplet with its high surface area allowing effective transport of the active to skin [96].

New Jersey-based TRI-K Industries and its parent company Kemira have launched a new nano-based gel aimed at enhancing the efficacy of a wide range of skin care prosucts. Kemira NanoGel is said to be a unique submicron emulsion Carrier system that has been designed around easy formulation, combined with the added benefits brought about by its nanotechnology properties.

Antimicrobial- Antimicrobial submicron emulsions are oil-in-water droplets that range from 200 to 600nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The submicron emulsion has a broad-spectrum activity against bacteria, enveloped virus, fungi and spores. The submicron particles are thermodynamically driven to fuse with lipid containing organism. The fusion is enhanced by the electrostatic attraction b/w the cationic charge of emulsion and anionic charge on pathogen. When enough nanoparticles fuse with pathogens, they release part of energy trapped within emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lyses and death [97].

Bio-terrorism attack- Based on their antimicrobial activity, research has begun on use of submicron emulsion as a prophylactic medication, a human protective treatment, to protect people exposed to bio-attack pathogens such as anthrax and ebola [98].
**Mucosal vaccines**- Submicron emulsions are being used to deliver either recombinant proteins or organisms to a mucosal surface to produce an immune response. The first application, an influenza vaccine and an HIV vaccine, can proceed to clinical trials. The submicron emulsion causes proteins applied to the mucosal surface to be adjuvanted and it facilitates uptake by antigen-presenting cells [99].

**Non-toxic disinfectant cleaner**- A breakthrough nontoxic disinfectant cleaner for use in commercial markets that include healthcare, hospitality, travel, food processing, and military applications has been developed by EnviroSystems, Inc. that kills tuberculosis and a wide spectrum of viruses, bacteria and fungi in 5-10 min without any of the hazards posed by other categories of disinfectants. The product needs no warning labels. It does not irritate eyes and can be absorbed through the skin, inhaled, or swallowed without harmful effects [100].

**Cell culture technology**- Cell cultures are used for in vitro assays or to produce biological compounds, such as antibiotic or recombinant proteins. To optimize cell growth, the culture medium can be supplemented with a number of defined molecules or with blood serum. Up to now, it has been very difficult to supplement the media with oil-soluble substance that are available to the cells, and only small amounts of these lipophilic compounds could be absorbed by the cells. Submicron emulsions are a new method for the delivery of oil-soluble substances to mammalian cell cultures. The delivery system is based on a nanoemulsion which is stabilized by phospholipids. These nanoemulsions are transparent and can be passed through 0.1 mm filters for sterilization. Nanoemulsion droplets are easily taken up by the cells. The encapsulated oil-soluble substances therefore have a high bioavailability to cells in culture. The advantage of using nanoemulsions in cell culture technology are better uptake of oil-soluble supplements in cell culture; improve growth and vitality of cultures cells, and allowance of toxicity studies of oil-soluble drugs in cell cultures.

**Cancer therapy**- The effects of the formulation and particle composition of gadolinium (Gd)-containing lipid NE (Gd-nanoLE) on the biodistribution of Gd after its intravenous (IV) injection in D1-179 melanoma-bearing hamsters were evaluated for its application in cancer neutron-capture therapy. Biodistribution data revealed that Brij 700 and HCO-60 prolonged the retention of Gd in the blood and enhanced its accumulation in tumors. Among the core components employed soybean oil yielded the highest Gd concentration in the blood and tumor, and the lowest in the liver and spleen. When each Gd-nanoLE was IV injected once or twice at a 24-h interval, the Gd concentration in the tumor correlated well with the total dose of Gd, and it reached the maximum of a 189mg/g wet tumor. This maximum Gd levels was greater than the limit required for significantly suppressing tumor growth in neutron therapy.

**Conclusion**- Submicron emulsions have potential to incorporate high amount of drugs with poor water solubility due to presence of lipids in their structure. Submicron emulsions provide improvement and reduction in the variability of GI absorption of poorly water soluble drugs. Due to these reasons it can be effectively used for oral administration of poorly waters-soulble drugs. There are several methods of preparation of submicron emulsion including high and low energy methods. Now these days low energy method is more in common due to less bioavailability and spontaneous formation of suvmicron emulsion. Submicron emulsion plays multidimensional role and it is used in fields of cosmetics, biotechnology and cancer therapy in oral route. Therefore submicron emulsion can be considerd as one of effective oral drug delivery system.

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