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Updated Review on Submicron Emulsion and Their Applications

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ABSTRACT

An isotropic mixture of drugs, lipids, and surfactants known as a "submicron emulsion" is frequently combined with hydrophilic cosolvents and has droplet diameters between 10 and 500 nm. Due to their kinetic stability, high solubilizing capacity, and small globule size, submicron emulsions are becoming more and more popular in medicine. These qualities have led to their application in a number of industries, including agrochemicals, personal care, cosmetics, health care, and pharmaceuticals. The most cutting-edge nanoparticulate technologies for the systemic distribution of biologically active substances for targeted drug delivery are by far submicron emulsions. They are primarily made for pharmaceutical formulations suited for parenteral, ocular, transdermal, and oral delivery. Due to its multiple benefits, such as decreased first-pass metabolism, suppression of the P-glycoprotein efflux system, and improved absorption via intestinal lymphatic channel, this review paper discusses the significant potential of submicron emulsions for oral drug administration. Submicron emulsions can be created into solid dosage forms, such as solid self-emulsifying systems, to get around the drawbacks of liquid dosage forms. This article discusses several submicron emulsion types, including microemulsions, nanoemulsions, and self-emulsifying drug delivery systems (SEDDS), as well as their prospective pharmaceutical uses in oral delivery, with a focus on their benefits, drawbacks, and technological breakthroughs.

INTRODUCTION

The term bioavailability is defined as the rate and extent at which active drug moiety enters systemic circulation by crossing the intestinal barrier, thus accessing the site of action. It depends largely on the properties of a dosage form, physicochemical properties of the drug, restriction produced by intestinal barriers, several enzymes, metabolites and glycoproteins. The presence of intestinal barriers produces a major challenge for drug delivery. Various physiological factors that reduce the oral bioavailability of drugs include disease state, gastric emptying rate, circadian differences, interaction with food, intestinal motility and presence of intestinal microflora. Apart from these, many pharmaceutical barriers including poor solubility in gastrointestinal pH, and high molecular weight of drugs make oral delivery quite exigent one. (1,2)

Mechanisms of drug absorption through oral route

Various routes of entry of drugs through the oral route are mainly divided into four processes as: passive transcellular pathway, passive paracellular pathway, carrier mediated efflux transportation pathway and carrier-mediated active transportation pathway. These pathways generally operate at the brush border lining of intestinal epithelial cells and play a wider role in transport of many macromolecular drugs into systemic circulation. Passive transcellular pathway is found to operate at apical membrane of the intestinal epithelium and helps in transport of drugs from the apical side to basolateral side by diffusion mechanism.(3,4) The entry of drugs through this pathway largely depends upon the associated membrane structures like lipids and proteins which act as a barrier for entry of drugs. Low molecular weight drugs with moderate lipophilicity can be easily transported through this pathway. However, high lipophilicity drugs show poor permeation characteristics towards the basolateral side due to being trapped inside the epithelial-tight junctional cells. High molecular weight drugs with poor solubility show bioavailability problems as they cannot permeate through the barriers (5-8). The passive transcellular pathways are predominantly found in the upper part of the small intestine facilitating transport and migration of drugs from apical to the basolateral domain through aqueous water-filled pores. It is found to be highly permeable to cationic drugs compared to anionic and unionized drug molecules. Low molecular weight hydrophilic drugs with small to moderate size can easily migrate through this pathway (9-11). Carrier mediated active transport (transcytosis) and carrier-mediated efflux transport are the transportation pathways employ a series of transporters which helps in active migration of

drugs with expense of energy. Details on different types of transporters with their functions are given in the later section of this review. (12-13)

Major barriers to oral absorption of drugs

There are several barriers affecting oral absorption of drugs across intestinal routes into systemic circulation. Poor penetration and low oral bioavailability of drugs mainly depend on the obstruction created by major physiological barriers and several pharmaceutical barriers that restrict the brisk entry of drugs (Fig. 1.1).

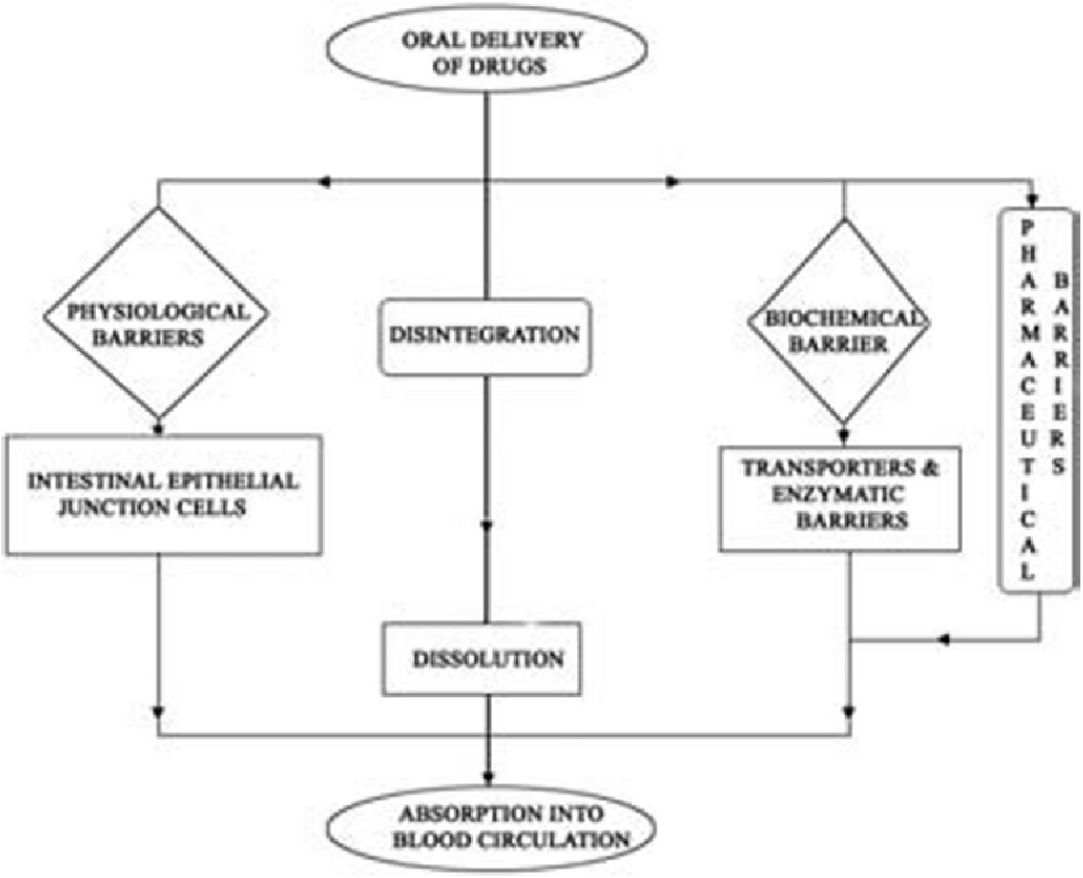

Figure 1.1. Schematic overview of different barriers to poor oral bioavailability of drugs.

Physiological Barriers

It comprises a physical barrier and a biochemical barrier. Intestinal paracellular tight junction acts as a physical barrier, while transporters and enzymes act as biochemical barriers.

The paracellular route is defined as the aqueous pathway along the intercellular space between adjacent epithelial cells, which is restricted by a tight junction. (Fig. 1.2) (14-15)

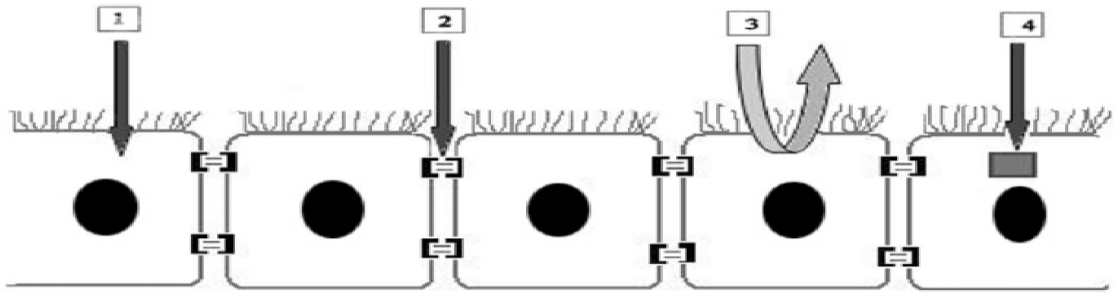

Figure 1.2: Routes of drug transport through intestinal epithelial cells. (1). Passive paracellular transport pathway, (2). Passive transcellular transport pathways, (3). Carrier-mediated efflux transport pathway, (4). Carrier-mediated active transport (transcytosis) pathways.

The presence of aqueous substances inside these pathways makes them susceptible to the transport of low molecular weight hydrophilic drugs by utilizing a passive diffusion mechanism. Investigation showed that tight junctions present on the gastrointestinal tract lining are identical with the Blood-Brain Barrier (BBB).

Basic morphology of tight junctions showed presence of microfibrils at the junctional cleft between two epithelial cells. Freeze fracture microscopy and transmission electron microscopy have revealed that intestinal cells have focal contact through plasma membranes to form a junctional complex. It appeared as a dense network of interdigitating strands (16). The microfibrils mainly contain two different types of tetraspanning transmembrane phosphoproteins such as occludin and claudin.(17-18) They are of varying molecular weight of 65 kDa and 20 kDa. Claudin appears as a structural component at the junctional cleft between two cells. It is due to intrinsic polymerization's ability to form linear fibrils and tight junctional strands.(19) Occludin forms short fragments of the fibrilar tight junction. Further tight junction has three major zones such as outer layer zona occludens attached with occludin while middle layer zonula adherens and inner layer macula adherens or desmosome are attached with claudin. Apart from these phosphoproteins, the epithelial tight junction also contains two skeletal proteins actin and myosin which provide additional tensile strength to the barrier. These proteins also act as a rate-controlling factor for the tight junction and selectively allow the entry of low molecular weight nutrient molecules only. (20)

Transporters are the chemically structural proteins found in the apical as well as basolateral membrane of the intestinal mucosa lining. They play a major role in limiting the intestinal permeability of drugs. Based upon the direction of mass transfer and solute movement, transporters are classified as Carrier-mediated transporters (CMT), Active efflux transporters (AET) and Receptor mediated transporters (RMT).(21-25) AET are found in the epithelial cells of intestinal brush border and transport drugs from basolateral to apical site.

They are classified into energy-dependent and energy-independent transporters. The ABC (ATP binding cassette) transporters are the energy-dependent transporters helps in the transportation of drugs from enteral villous cells with the aid of energy. They utilize efflux-P-glycoprotein (Pgp) as a major carrier for the transport of drugs. While organic anion transporter (OAT), glutamic amino acid transporter (GAAT) are the energy-independent transporters found in the apical and basolateral membrane of enteral epithelium. They are of higher impact in the field of drug delivery. The CMT and RMT includes a group of transporters that plays major role in the transportation of high molecular weight drugs like insulin, heparin, methionine, enkephalin, LHRH.

The role and functions of various types of transporters are determined using several assay models like Caco-2 cell line, the Madin-Darby Canine Kidney (MDCK) cell line. Thus by implication of necessary structural modifications in the transporter chemistry one can alter its barrier property for the absorption of drugs (26-29). In addition to transporters, several metabolic enzymes are found in intestinal enterocyte cells. They act as a major mediator for drug metabolism, inhibiting the transport of drugs and drug interaction. Cytochrome-P450 (CYP450) enzyme is predominantly distributed in the brush border of human small intestinal epithelial cells and tip of villous cells. CYP3A4/5 is a major isoform found in considerable quantities in the lower part of the intestine and responsible for the poor bioavailability of drugs like cyclosporine, tacrolimus, felodipine, midazolam, saquinavir due to extensive metabolic activity. (30-34)

Pharmaceutical Barriers

Poor solubility causes improper absorption of drugs. Solubility is an intrinsic property of the material that can be influenced by chemical modification such as salt formation, complexation to form prodrugs, by physical modification using solid dispersion with a suitable polymeric carrier. Solubility of a drug is related to dissolution tendency, which is a characteristic measure of oral bioavailability. Solubility depends on several factors like

composition of aqueous media, pH, temperature, crystal nature, ionic strength, presence of counter ions and polymorphism. New chemical entities (NCEs) synthesized by application of rapid drug discovery techniques like combinatorial chemistry and high throughput screening to speed-up the drug development process leads to poor aqueous solubility. Hence for resolving the bioavailability issues, solubility of drug substances are mandatory to improve for the desired pharmacological actions.(35)

The 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 the 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 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 drugs is frequently associated with low bioavailability (36-39). 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 solubilizer within a colloidal dispersion.

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.(40) 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. Submicron emulsion is an isotropic mixture of drugs, lipids and surfactants, usually with one or more hydrophilic cosolvents or cosurfactants.

Classification of submicron emulsions

The submicron emulsions are classified into the following

Three types:

- Oil in water submicron emulsion
- Water in oil submicron emulsion
- Bi-continuous submicron emulsion

Advantages of submicron emulsion

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

- These are thermodynamically stable and require minimum energy for formation.
- Ease of manufacturing and scale-up.
- Improved drug solubilization and bioavailability.
- This system is reckoned advantageous because of its wide application in colloidal drug delivery systems for the purpose of drug targeting and controlled release.(41-45)

Limitation of submicron emulsion

The main limitation of submicron emulsion is the use of high amounts of surfactant and cosurfactant that may be harmful to 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. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, sub-micron emulsion can offer an improvement in the rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, the 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.

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. 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 increases with increase in fatty acid chain lengths and decrease with increasing degree of instauration, which also increases the relative susceptibility to oxidation.(46-49)

Triglycerides are classified as short (<5 carbons), medium (6-12 carbons) or long chain(>12 carbon) and may be synthetically hydrogenated to decrease the degree of instauration to improve resistance to oxidation. Triglycerides are highly lipophilic and their solvent capacity for drugs is function of the effective concentration of ester groups therefore on weight basis medium chain triglycerides have more solvent capacity than long-chain triglycerides.(46-48)

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.

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 are used for the preparation of SEDDS without water-soluble components.(50-53)

Water-soluble Surfactants

These are the most commonly used surfactants for the 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.

- Ethanol has been used to enhance the dissolution of drug cyclosporin.
- Cosolvents are also used to increase solvent capacity of formulation in which drug is freely soluble.
- Third reason for the use of co-solvent 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 á-tocopherol, â-carotene, butylated hydroxytoluene (BHT) or propyl gallate are used to protect either unsaturated fatty acid chains or drug from oxidation.

Factors Affecting Choice of Excipients for Oral Submicron Emulsion

- **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.
- **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.
- **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.

- Morphology at room temperature.
- **Digestibility:** Fate of digested products.
- **Capsule compatibility:** Low molecular weight polar molecules present in capsule formulations are able to penetrate and plasticise 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.
- Purity, chemical stability.
- Cost of goods

Techniques of Submicron Emulsion Preparation

There are two methods of submicron emulsion preparation-

(a) High-energy Emulsification Methods

(b) Low-energy Emulsification Methods

High Energy Emulsification Methods

These methods include the use of devices that use very high mechanical energy to create nanoemulsion with high kinetic energy.

Methods are-

- High pressure homogenization
- Ultrasonic emulsification
- Microfluidization

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.(54-59)

During this process several forces such as hydraulic shear, intense turbulence and cavitations act together to produce submicron emulsion with extremely small size. In process of micro fluidization a positive pump is operated at a very high pressure of 20,000 psi. This pump forces macro emulsion droplets through an interaction chamber consisting of series of

microchannels. The macro emulsion passing through the micro channels colloids with high velocity on to an impingement area resulting in the 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 the interaction chamber.

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 the 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 the 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 the following limitations-

- Not suitable for thermo labile drugs such as retinoids and macromolecules, including proteins, enzymes and nucleic acids.
- High-energy methods require sophisticated instruments and extensive energy input, which increases the cost of submicron emulsion preparation.

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

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

These methods are mainly dependent on the modulation of the 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-

- Phase Inversion Temperature Method.
- Solvent Displacement Method.

- Phase Inversion Composition Method.

❖ **Evaluation parameters for Submicron emulsions**

Evaluation is a very important aspect of formulation development. The following parameters are used for the evaluation of submicron emulsions:

Droplet size analysis

Diffusion method by light scattering particle size analyzer Coulter LS 230 is used to measure the droplet size. Another method for the determination of particle size is the Dynamic Light scattering technique.

Viscosity Determination

Viscosity determination is an important parameter for the evaluation of submicron emulsion. It can be done with the help of a Brookfield viscometer or a rheometer. Viscosity determination confirms that the system is o/w or w/o emulsion.

Morphology and structure

Transmission electron microscopy (TEM) is used to study the morphology and structure of the submicron emulsion. Bright-field imaging at increasing magnification in combination with diffraction modes can also be used to disclose the size and form of submicron emulsion droplets.

Zeta potential

It is used to measure the charge on the surface as well as the stability of submicron emulsions. In this technique, Zetasizer is used for the determination of surface charge properties. The zeta potential between -30mV +30mV is desirable.

Percentage Transmittance

UV-Vis spectrophotometer is used to determine the percentage transmittance of prepared submicron emulsion. A clear transparent ultrafine emulsion will have a percentage transmittance value of approximately 100%.

Polydispersity

The uniformity of droplet size in submicron emulsion is measured as polydispersity. There exists non-uniformity in droplet size of submicron emulsions if the value of polydispersity is high. The polydispersity value which ranges from 0- 1, signifies monodisperse system and 1 signifies polydisperse system. Zetasizer is used to measure its value.

Dye Test

In this a water- soluble dye is used and when this dye is added to o/w submicron emulsion, the colour of the whole emulsion changes as the dispersion medium is water. On the other side, if the emulsion is w/o type, then the change in colour takes place only in dispersed phase i.e water and there is no change in colour of the whole emulsion. Microscopic examination of this can be done to see the changes that take place in emulsions.(60-63)

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 the skin. Another advantage is the small-sized droplet with its high surface area allowing effective transport of the active to the skin.

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 skincare 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.(64-65)

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 viruses, 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 the 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.(66)

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.

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.

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.

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 substances 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 nanaoemulsions in cell culture technology is 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 189mg/g wet tumor. This maximum Gd level was greater than the limit required for significantly suppressing tumor growth in neutron therapy.(67-68)

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