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NANOEMULSIONS AS PROSPECTIVE DRUG DELIVERY SYSTEMS

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Key words: nanoemulsion; drug delivery; method of preparation; bioavailability

Nanoemulsions are promising for pharmaceutical industry due to a high bioavailability and increased shelf life of the pharmaceuticals. Nanoemulsions are transparent, thermodynamically stable, isotropic liquid mixtures of oil, water, surfactant and co-surfactant. They are emulsions with the average droplet size ranging from 5 nm to 100 nm. Studies have shown that the size of the droplets is conditioned by the surfactant nature. The particles can exist as oil-in-water and water-in-oil forms where the core of the particle is either oil or water, respectively. Nanoemulsions have widespread applications in different fields such as pharmaceuticals, food technology. Nanoemulsions are promising vehicle for increasing the aqueous solubility of poorly water-soluble drugs. The ability of nanoemulsions to dissolve large quantities of hydrophobics, along with their ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for the purpose of parenteral transport. 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. Nanoemulsions have many advantages; for instance, enhance drug solubility, perfect thermodynamic stability, ease of manufacturing and permeation over conventional formulations that convert them to important drug delivery systems. Additionally, the lack of flocculation, sedimentation and creaming combined with a large surface area offer obvious advantages over emulsions of the larger particle size. Nanoemulsions containing pharmaceutically active agents can be used for production of pharmaceuticals, in which the nanoemulsion being mixed as an active component with a solid or liquid vehicle suitable for therapeutic use. The mixture can be in the medicinal form required. For example, it can be produced in such medicinal forms as ampoules, especially sterile solutions for injections and infusions or for oral application; eye drops and nose drops containing various excipients; nondosing and dosing aerosols containing propellants and stabilizers; hydrophilic and hydrophobic gels and ointments; o/w or w/o creams; lotions and pastes.

Nanoemulsions are emulsions with mean droplet diameters ranging from 50 to 1000 nm. The particles can exist as oil-in-water and water-in-oil forms where the core of the particle is either oil or water, respectively [15].

Nanoemulsions are also referred to as miniemulsions, ultrafine emulsions and submicron emulsions. Studies have shown that the size of the droplets is conditioned by the surfactant nature.

The ability of nanoemulsions to dissolve large quantities of hydrophobics, along with their ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for the purpose of parenteral transport. 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 offer obvious advantages over emulsions of the larger particle size. Very large interfacial area positively influences on the drug transport and their delivery [1, 13].

Advantages of nanoemulsions

- Nanoemulsions are the way to improve water solubility and ultimate bioavailability of lipophilic drugs [8];
- Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible [5, 8];
- Fine oil droplets empty rapidly from the stomach and promote a wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation [12];
- Nanoemulsions have a higher solubilization ability than simple micelle solutions and their thermodynamic stability offers advantages over unstable dispersions such as emulsions and suspensions [14];
- They also provide ultra low interfacial tension and large o/w interfacial areas [14];
- Nanoemulsions may possess high kinetic stability and optical transparency resembling to microemulsions [21];
- The structures in the nanoemulsions are much smaller than the visible wavelength, so most nanoemulsions appear to be optically transparent, even at great loading [21];
- Nanoemulsions have a potential to deliver peptides that are prone to enzymatic hydrolysis in the GIT [16];
- Nanoemulsions have a higher surface area and higher free energy than macroemulsions that make them an effective transport system [11];

- Problems of inherent creaming, flocculation, coalescence, and sedimentation, which are commonly associated with macroemulsions, are not seen in nanoemulsions [2];
- They are non-toxic and non-irritant, so can be easily applied to the skin and mucous membranes [18];
- Nanoemulsions are formulated with surfactants approved for human consumption, so they can be taken by the enteric route [20];
- They do not damage healthy human and animal cells, so nanoemulsions are suitable for human and veterinary therapeutic purposes [9].

Disadvantages of nanoemulsions

- The formulation of nanoemulsions is an expensive process due to size reduction of droplets is very difficult as it required a special kind of instruments and process methods [4, 6].

Three types of Nanoemulsions are most likely to be formed depending on the composition:

- O/W Nanoemulsions, wherein oil droplets are dispersed in the aqueous phase;
- W/O Nanoemulsions, wherein water droplets are dispersed in the oil phase;
- Bi-continuous Nanoemulsions.

In all three types of nanoemulsions [17], the system is stabilized by an appropriate combination of surfactants and/or co-surfactants.

Components of Nanoemulsion

The main components of Nanoemulsions are as follows:

- oil;
- surfactants;
- co-surfactants.

Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy nanoemulsions are based on low interfacial tension. This is achieved by adding a co-surfactant, which leads to spontaneous formation of a thermodynamically stable nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the nanoemulsions transparent liquids [23]. In principle, nanoemulsions can be used to deliver drugs to the patients via several routes, but the transdermal application of nanoemulsions has gained increasing interest.

The surfactants used to stabilise such systems may be:

- non-ionic;
- zwitterionic;
- cationic;
- anionic.

A combination of ionic and non-ionic surfactants can be very effective in stabilization of nanoemulsions. Attempts have been made to rationalise the surfactant behaviour in terms of the hydrophilic-lipophilic balance (HLB) [3], as well as the critical packing parameter (CPP). [7, 10] The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3-6) surfactants are favoured for the formation

of w/o nanoemulsions, whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w nanoemulsion systems.

Methods of Preparation of Nanoemulsions

High Pressure Homogenization

This method makes use of high-pressure homogenizer/piston homogenizer to produce nanoemulsions of extremely low particle size (up to 1 nm). During this process, several forces, such as hydraulic shear, intense turbulence and cavitation, act together to yield nanoemulsions with extremely small droplet size. The resultant product can be re-subjected to high-pressure homogenization until a nanoemulsion with the desired droplet size and polydispersity index is obtained. The production of small droplets (submicron) requires application of high energy.

Microfluidization

Microfluidization is a patented mixing technology, which makes use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500-20,000 psi), which forces the product through the interaction chamber consisting of small channels called "microchannels". The product flows through the microchannels on to an impingement area resulting in very fine particles of the submicron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion [15]. The coarse emulsion is introduced into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber of the microfluidizer repeatedly until the desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion.

Phase Inversion Temperature Method

Phase inversion temperature (PIT) 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 owing to dehydration of polyoxyethylene groups. This phenomenon forms a basis of nanoemulsion fabrication using the PIT method. In the PIT method, oil, water and nonionic surfactants are mixed together at room temperature. This mixture typically comprises o/w microemulsions co-existing 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 the oily phase and the initial o/w emulsion undergoes phase inversion to w/o emulsion. The surfactant monolayer has a negative curvature at this stage. This method involves heating of the components and it may be difficult to incorporate thermolabile drugs, such as tretinoin and peptides, without affecting their stability. Although it may be possible to reduce the PIT of the dispersion using a mixture of components (surfactants) with suitable characteristics, in order to minimize degradation of thermolabile drugs.

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, the oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone. The organic phase is poured into the aqueous phase containing a surfactant to yield a spontaneous nanoemulsion by rapid diffusion of the organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation. Spontaneous nanoemulsification has also been reported when the solution of organic solvents containing a small percentage of oil is poured into the aqueous phase without any surfactant.

Phase Inversion Composition Method (Self-Nanoemulsification Method)

This method has drawn a great deal of attention from scientists in various fields (including pharmaceutical sciences) as it generates nanoemulsions at room temperature without use of any organic solvent and heat. Kinetically stable nanoemulsions with the small droplet size (~50 nm) can be generated by the stepwise addition of water into the solution of a surfactant in oil with gentle stirring and at constant temperature. The spontaneous nanoemulsification has been related to the phase transitions during the emulsification process and involves lamellar liquid crystalline phases or D-type bicontinuous microemulsion during the process. Nanoemulsions obtained from the spontaneous nanoemulsification process are not thermodynamically stable, although they might have high kinetic energy and long-term colloidal stability.

Application of nanoemulsions

Nanoemulsions containing pharmaceutically active agents can be used for production of pharmaceuticals, the nanoemulsion being mixed as the active component with a solid or liquid vehicle suitable for therapeutic administration. The mixture can be in the medicinal form required. For example, it can be produced in such medicinal forms as ampoules, especially sterile solutions for injections and infusions or for oral application; eye drops and nose drops containing various excipients; non-dosing and dosing aerosols containing propellants and stabilizers; hydrophilic and hydrophobic gels and ointments; o/w or w/o creams; lotions and pastes.

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 equivalently a better balance between ocular bioavailability improvement and the patient comfort following topical instillation into the eye e.g. Piroxicam, pilocarpine, indomethacin, cyclosporine A [22].

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 medicines and also provides water penetration, an excellent softener, to the skin e.g. Diazepam, α -tocopherol, antifungal drugs (econazole or miconazole nitrate), EMLA (eutectic mixtures of local anaesthetic) have proven to be useful medicines even for children. The mixture is an emulsion containing lidocaine and prilocaine. This cream gives an effective deep sedation [22].

Nasal Route

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by-passing the liver metabolism. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging the 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 the emulsion compared to the 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 [8].

Use of Nanoemulsions in Cosmetics

Due to their lipophilic interior, nanoemulsions 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 medicine to the skin. Furthermore, nanoemulsions gain increasing interest due to their own bioactive effects. This may reduce the trans-epidermal water loss (TEWL), indicating that the barrier function of the skin is strengthened. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence observed within macroemulsions. The incorporation of irritating surfactants can often be avoided by using high-energy equipment during manufacturing [19].

Antimicrobial Nanoemulsions

Antimicrobial nanoemulsions are oil-in-water droplets that range from 200-600 nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The nanoemulsion has a broad spectrum activity against bacteria (e.g., *E. coli*, *Salmonella*, *S. aureus*), enveloped viruses (e.g., *HIV*, *Herpes simplex*), fungi (e.g., *Candida*, *Dermatophytes*), and spores (e.g., *Anthrax*). The nanoemulsion particles are thermodynamically driven to fuse with lipid-containing organisms. This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge

on the pathogen. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death [22].

CONCLUSIONS

The importance of design and development of emulsion nanocarrier systems aimed at controlling and/or improving required bioavailability levels of therapeutic agents cannot be overemphasized. Nanoemulsions are promising as useful dispersions of deformable nanoscale

droplets that can have different flow properties and optical properties ranging from opaque to nearly transparent. Moreover, it is very likely that nanoemulsions will play an increasingly important role commercially. Nanoemulsions offer several advantages for the delivery of drugs and are thus receiving increasing attention as drug carriers for improving the delivery of active pharmaceutical ingredients. They are applicable for almost all routes of delivery, and therefore, are promising for different fields, for example, for cosmetics, pharmacy or biotechnology.

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НАНОЕМУЛЬСІЇ ЯК ПЕРСПЕКТИВНІ СИСТЕМИ ДОСТАВКИ ЛІКАРСЬКИХ ЗАСОБІВ

Ю.В.Соколов

Ключові слова: наноемульсії; доставка лікарських засобів; метод приготування; біодоступність

Наноемульсії є перспективними у фармацевтичній промисловості завдяки вищому значенню біодоступності та збільшенню строку придатності фармацевтичної продукції. Наноемульсії – прозорі, термодинамічно стійкі, ізотропічні рідкі суміші олій, води, сурфактанту і ко-сурфактанту. Вони є емульсіями з середнім розміром частинок від 5 нм до 100 нм. Розмір частинок залежить від складу емульсії. Частинки можуть існувати у формах «олія-в-воді» або «вода-в-олії», в яких ядром частинок є олія чи вода. Наноемульсії дуже поширені в різних галузях, наприклад, у виробництві ліків або харчовій технології. Наноемульсії – перспективний транспортний засіб для лікарських засобів, які є погано розчинними у воді. Здатність наноемульсій розчиняти у великих кількостях гідрофобні речовини, а також захищати речовини від гідролізу та ферментолізу робить їх ідеальними засобами для парентеральної доставки ЛР. Частота і дозування ін'єкцій можуть бути зменшені на протязі всього періоду терапії, т. я.

ці емульсії забезпечують поступове та кероване вивільнення лікарських засобів впродовж тривалого періоду часу. Наноемульсії мають багато переваг; наприклад, збільшення розчинності ліків, відмінна термодинамічна стабільність, легкість виробництва і проникнення в органи та/або тканини, що робить їх важливими системами доставки лікарських засобів. Крім того, відсутність флокуляції, седиментації та розшарування в поєднанні з великою площею поверхні є наявною перевагою у порівнянні з емульсіями з великим розміром частинок. Наноемульсії, що містять фармацевтично активні інгредієнти, можуть бути використані для отримання фармацевтичних препаратів, в яких наноемульсії змішуються в якості активного компонента з твердим або рідким носієм, придатним для терапевтичного застосування. Суміші можна надати необхідну лікарську форму: розчину, в т. ч. ін'єкційного, інфузійного і для перорального застосування; очних крапель і назальних крапель, що містять різноманітні допоміжні речовини; аерозолей – дозованих чи недозованих, які містять пропеленти і стабілізатори; гідрофільних і гідрофобних гелів і мазей; кремів «о/в» або «в/о»; лосьонів або паст.

НАНОЭМУЛЬСИИ КАК ПЕРСПЕКТИВНЫЕ СИСТЕМЫ ДОСТАВКИ ЛЕКАРСТВЕННЫХ СРЕДСТВ

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Ключевые слова: наноемульсия; доставка лекарственных средств; метод приготовления; биодоступность

Нанозэмульсии перспективны в фармацевтической промышленности благодаря высокой биодоступности и увеличению срока хранения фармацевтической продукции. Нанозэмульсии – прозрачные, термодинамически стойкие, изотропические жидкие смеси масла, воды, сурфактанта и ко-сурфактанта. Они являются эмульсиями со средним размером частиц от 5 нм до 100 нм. Размер частиц зависит от состава эмульсии. Частицы могут существовать в форме «масло-в-воде» и «вода-в-масле», в которых ядром частицы являются масло или вода. Нанозэмульсии широко распространены в разных отраслях, например, в производстве лекарств или пищевой технологии. Нанозэмульсии – перспективное средство для доставки липофильных активных фармацевтических ингредиентов. Способность нанозэмульсий растворять в больших количествах гидрофобные вещества, а также защищать вещества от гидролиза и ферментализации делают их идеальными средствами для парентеральной доставки ЛС. Частота и доза инъекций могут быть уменьшены на протяжении всего периода терапии, т. к. эти эмульсии обеспечивают постепенное и управляемое высвобождение лекарственных средств в течение длительного периода времени. Нанозэмульсии имеют ряд преимуществ: увеличение биодоступности препаратов, термодинамическая стабильность, легкость проникновения в органы и/или ткани. Кроме того, отсутствие флокуляции, седиментации и расслоения в сочетании с большой площадью поверхности являются очевидными преимуществами по сравнению с эмульсиями с большим размером частиц. Нанозэмульсии, содержащие фармацевтически активные ингредиенты, могут быть использованы для получения фармацевтических препаратов, в которых нанозэмульсии смешиваются в качестве активного компонента с твердым или жидким носителем, подходящим для терапевтического применения. Смеси можно придать необходимую лекарственную форму: раствора, в т. ч. инъекционного, инфузионного и для перорального применения; глазных капель и назальных капель, содержащих различные вспомогательные вещества; аэрозолей – дозируемых и недозируемых, содержащих пропелленты и стабилизаторы; гидрофильных и гидрофобных гелей и мазей; кремов «м/в» или «в/м»; лосьонов или паст.