Introducing Self-Nanoemulsifying Drug Delivery System to Increase the Bioavailability of Oral Medications

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Article Type:
Review Article

Article History:
Received: 22 Apr. 2018
Revised: 18 Aug. 2018
Accepted: 18 Sep. 2018

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Abstract

The oral route is the most convenient route of administration of drugs because of low cost, ease of administration, patient compliance and flexibility in design of dosage form. Regardless of the advantages of this method, the main challenge in the bioavailability of oral drugs is gastrointestinal instability. Nanotechnology is used to improve the solubility and bioavailability of poorly water-soluble drugs. The self-nanoemulsifying drug delivery system is an ideal method for improving the solubility and bioavailability of poorly water-soluble drugs. This system is stable mixture of oil, surfactant and cosurfactant. The combination of these components creates an oil-in-water nanoemulsion, with droplet in the nanometer size range and ultimately increases the bioavailability and oral absorption of poorly water-soluble drugs. This system not only increases the medication's effectiveness, but it also reduces undesirable side effects.

Keywords: Nanoemulsion, Drug Delivery, Bioavailability, Self-nanoemulsifying
Introduction

According to the biopharmaceutics classification system, drugs are divided into four groups based on their solubility and intestinal permeability. In this classification, drugs belonging to groups two-four have solubility problems, low permeability, or both, which lead to a reduction in bioavailability and oral absorption (1). The solubility of this group of drugs determines their bioavailability and therapeutic effects (2). The oral route is the most convenient and accessible pathway to administer medications (3). However, the main challenge is the bioavailability of oral medications, the physiological barrier of the body, gastrointestinal instability, and systemic drug metabolism (4).

One of the goals of nanotechnology is increasing the rate of drug delivery. Nanoscale materials are widely used due to their unique physical and chemical properties (5-7). Over the past two decades, drug carriers such as liposomes, nanoemulsions, organogels, and nanocapsules have been introduced as effective drug delivery systems and have improved the therapeutic index of poorly water-soluble drugs by increasing solubility and modifying the pharmacokinetics of drugs. The essential criteria for the efficient use of these systems are tolerance towards additives, stability over a wide temperature range, low viscosity, small size, biodegradability, and easy elimination from the body. Among these carriers, nanoemulsions have been selected as particularly convenient carriers for numerous drugs due to having most of the mentioned criteria (8, 9).

Emulsion is a mixture of two immiscible liquids, such as water and oil (10). When shaken vigorously, an emulsion is formed temporarily. However, the emulsate separates into two layers in a relatively short time (11). A stable emulsion is made by adding a third substance to the mixture called surfactant, which causes the thermodynamic stability of the mixture (12). The type and concentration of the surfactant should be selected carefully so that surfactant molecules can stabilize the nanoparticles with a very low surface tension created on the common surface of water and oil. The physicochemical properties of the drug and its polarity contribute to the formation of nanoemulsions, in which the size of droplets is in the range of less than 100 nm (13). The term mini-emulsion is also used as a synonym for nanoemulsion. Due to the small size of the droplets, the nanoemulsions have adequate stability against sediment and the Ostwald ripening phenomenon, which is the main mechanism of increasing the size of the droplets (14).

Self-nanoemulsifying Drug Delivery System (SNEDDS)

The SNEDDS is a sustainable combination of oil, surfactant, and cosurfactants (15). The schematic illustration of this system is shown in Figure 1 (16).

Figure 1. Nanoemulsion Droplets (16)

The combination of these components, for example in the stomach and intestines, creates a transparent nanoemulsion of oil in water...
slowly with droplets in the range of nm (17), which ultimately increases bioavailability and oral absorption of drugs (18). The SNEDDS can be easily spread in the visceral pathway (19), and the gastrointestinal movements provide the necessary motor energy for their self-emulsifying (20). Three-level systems are referred to systems that are free of cosurfactant, whereas those containing cosurfactants are known as quasi-three-level systems, in which surfactants and cosurfactants are one phase together.

**Nanoemulsion Components**

**Oil**

Oil is one of the most important nanoemulsion components due to its ability to dissolve poorly water-soluble drugs. In addition, oil increases the transmission of these drugs through the intestinal lymph system and, as a result, improves their absorption through the gastrointestinal system (21). In general, the oil used in the SNEDDS formulation is based on some criteria such as solubility, the degree of sterility, and some physical properties (13).

**Surfactants**

With their dual properties, surfactants help eliminating the problem of dissolving poorly water-soluble drugs. Non-ionic surfactants are preferred to ionic surfactants due to lower toxicity, lower critical micelle concentration (CMC), faster formation of oil droplets in water, and better self-emulsifying performance (22). By adding the surfactants to two immiscible liquids, they reduce the surface tension between two phases and prevent the dual-phase of the liquids (23). Surfactants are selected based on hydrophilic-

**Cosurfactants**

Creating the ideal SNEDDS requires a relatively high concentration of surfactants (more than 30% of weight). Increasing the amount of surfactant decreases the droplet size but increases the time required to form an emulsion (24). Therefore, the concentration of surfactant can be reduced with cosurfactant. In addition, sustainable surface tension is rarely obtained with the use of surfactants and there is often a need for adding a cosurfactant to the environment (21).

**Aqueous Phase**

The droplet size and the stability and performance of the emulsion formed by the SNEDDS formulation are also controlled by the nature of the aqueous phase formation. Therefore, in the design of SNEDDS, ionic content and pH of the aqueous phase should be considered. The pH range of the physiological environment of the body is from 1.2 (pH in the stomach) to 7.4 and higher (pH in blood and intestines). Moreover, the presence of various ions significantly affects the nanoemulsion properties produced from SNEDDS.

**Nanoemulsion Preparation Methods**

Various methods have been proposed for the preparation of nanoemulsions, which can be divided into high-energy (relying on mechanical devices) and low-energy (relying on phase changes) methods (25).
**High-energy Methods**

Creation of nanoemulsions in high-energy methods is carried out by using equipment such as high-pressure homogenizers, microfluidizers, and ultrasonic homogenizers. Some of the features of high-energy methods include better control of the distribution of droplets’ size and a need for a low concentration of surfactants (26). Nevertheless, the technique has some limitations, including low thermodynamic efficiency that leads to increased energy use. Creating a significant temperature during the creation of a product is another limitation of this method (27). Some of the high-energy methods are presented, as follows:

**Sonication**

Sonication is the best method for nanoemulsion preparation. In this technique, the input energy is provided by a probe sonicator, and the size of emulsion droplets is reduced with the sonication mechanism. Nevertheless, this method is not suitable for creating a large number of nanoemulsions and can only prepare low amounts of nanoemulsions (28, 29).

**Microfluidizers**

With this technique, we can produce emulsions at pressures above 700 MPa. The initial emulsion solution flows through two microchannels and collides in a chamber, which ultimately leads to the reduced size of droplets. Therefore, an emulsion with small-size droplets is produced by this method (30).

**Low-energy Methods**

The phase change from oil to water or water to oil occurs in low-energy methods, which include phase inversion method and spontaneous emulsification method. Some of the limitations of low-energy methods are the need for a precise selection of surfactant and oil types, the need for high amounts of synthetic surfactants, and low industrial production capacity (31, 32).

**Phase Inversion Method**

In this method, the dispersion of droplets during the emulsification time is obtained by the chemical energy produced by the phase transfer, which is created by a change in composition at a constant temperature or with constant temperature change (31). The temperature of the inversion phase is the temperature at which the water-in-oil nanoemulsion becomes the oil-in-water nanoemulsion. At lower temperatures, the solubility of the surfactant is higher in water and the oil nanoemulsion is formed in water. In other words, if a system that is at a higher temperature than the phase inversion temperature is suddenly diluted with water, its temperature comes below the phase inversion temperature and a sudden change occurs in the phase. Therefore, the nanoemulsion is changed from the water-in-oil state into the oil-in-water state (33).

**Solvent Displacement Method**

In this method, the oil phase is entered into water-soluble organic solvents (e.g., acetone or ethanol) containing the surfactant so that the nanoemulsion is created simultaneously. Afterwards, the organic solvent is removed by a suitable method such as vacuum evaporation. By this method, nanoemulsion can be created at room temperature and by a simple stirring. Therefore, researchers use this technique to produce nanoemulsions. However, the major drawback of this method is the need to remove organic solvents. Additionally, a high proportion of solvent to
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System Characterization

Droplet size is a determinant of self-emulsifying performance since the stability of the emulsion determines the rate and extent of drug release. Dynamic light scattering, photon correlation spectroscopy, laser diffraction, and other microscopic techniques are mainly applied to determine the size of formulation droplets.

Dynamic Light Scattering

This method is exploited to determine the average diameter of nanoemulsion droplets and the distribution of droplet size and zeta potential. In addition, polydispersity shows the quality and homogeneity of droplet size and is determined based on two factors, namely uniformity the (distribution symmetry around the middle point) and the width of the interval. In a fluid, the collision of moving particles with solvent molecules leads to random movement of molecules, known as the Brownian motion.

When a laser beam hits these moving particles at a given frequency, light is scattered at a different frequency, and oscillation is generated in scattered light phase. The level of change in the frequency of scattered light is correlated with the droplet size and is used to determine their sizes. In addition, the dispersion intensity of the scattered light can be measured using a suitable detector and depends on the solvent penetration rate.

Zeta Potential

Zeta potential ($\zeta$) is a measure of the charge near the surface of a particle or emulsion droplet. In addition, zeta potential shows the amount of repulsion between adjacent charged droplets in solution, and is recognized as an important tool for understanding the surface state of nano-droplets, predicting and controlling the long-term sustainability of nanoparticle-containing solutions. In general, the instability/stability boundary of solutions can be determined by zeta potential. The particles with zeta potentials above +30 mV or -30 mV are more sustainable. When the zeta potential is within the range of -30 to +30, the gravity forces may overcome the repulsion forces between droplets, which leads to the breaking and aggregation of the emulsion. In the self-emulsifying drug delivery system, the zeta potential shows the load of oil droplets.

SNEDDS Advantages

- The extremely small size of fluid droplets reduces the gravity force and the Brownian motions. When there is a decrease in the gravity force, the formation of sediment in long-term is prevented, and droplets will remain dispersed without any phase separation.

- In contrast to microemulsions that require a large number of surfactants, nanoemulsions can be prepared with a small concentration of surfactants, which is confirmed for human use. This amount of surfactant is eliminated in the intestinal pathway.

- In the self-emulsifying system, the drug is dispersed in a long duration.

- Application of SNEDDS is associated with the improved bioavailability of oral drugs due to increased solubility and effective drug transfer. In addition, the increase of

bioavailability results in a lower drug dose (36).

- Compared to various lipid drugs, nanoemulsions are created by a simpler technique (37).

Other advantages of this system include high bioavailability and solubility of drugs due to high surface to volume ratio of droplets (24), high physical and kinetic stability and spontaneous and simple formation (38), decreased drug side effects (39), reduced first pass effect of the liver (40), decreased gastric stimulation (2), less need for organic solvents (41), controlled (42) and constant (43) drug delivery, protecting both hydrophilic and poorly water-soluble drugs (44), diversity in the use of oils and surfactants in one formulation, and several other applications (45).

However, the use of nanoemulsion-based systems is associated with some limitations, including:

- Effect of environmental factors (e.g., temperature and pH) on system stability
- Surfactant toxicity for drug use. Therefore, a low amount of non-toxic surfactants must be applied.
- Phase separation in some cases after the synthesis of the nanoemulsion

**Effect of Nanoemulsions on Delivery of Oral Drugs**

Heparin is an effective anticoagulant for the prevention of deep vein thrombosis and pulmonary embolism. However, it is only prescribed as an injection for patients due to low oral bioavailability. Meanwhile, the bioavailability of oral heparin increases by 1.5% in mice when it is attached to deoxycholic acid and is formulated in the emulsion system (46). In a research by Wu et al., which was conducted to improve the solubility and bioavailability of curcumin, chromophore, ethanol, and isopropyl myristate were selected as emulsion components. Compared to its suspension, the bioavailability and area under the time-concentration curve (AUC) of this type of drug increased by 1213% and 12 times, respectively. After 10 minutes, the drug’s solubility was 100%, and the drug content was reported more than 98% after eight hours (47).

In another research, the self-emulsifying drug delivery system was used to increase the bioavailability of curcumin. In the mentioned study, maximum drug concentration in the blood and its bioavailability increased by 3.95 and 1.94 times, respectively (48). A research was conducted to improve the solubility of tadalafil in a self-emulsifying drug delivery system. According to the results of the aforementioned study, drug delivery was reported 96.6% and 12.4% after 24 hours in the nanoemulsion form and suspension state, respectively. Moreover, the solubility of this drug successfully increased, compared to its solubility in aqueous environments (49). In a previous study, Khani et al. designed a self-emulsifying drug delivery system for a calcium channel blocker (mebudipine), which has a low bioavailability due to low water solubility and first pass effect of the liver. According to the results, the area under the curve and plasma drug concentration significantly increased with the new formulation (50). Using the drug formulation in the emulsion, an increase was observed in the dissolution of a mixture of anesthetic drugs (lidocaine and prilocaine) (51).
Moreover, progesterone and indomethacin solubility increased by 3300 and 500 times, respectively (52). Integration of ibuprofen, ketoprofen, tamoxifen, testosterone and tolbutamide in oil-in-water microemulsion increased their solubility by 60-20000 times (52).

In addition, the new formulation of the antiepileptic drug of clonazepam showed the fast delivery of the drug to the brain in animal studies (54). The low solubility of amphotericin B. (an antibiotic with strong antifungal activity, the drug of choice for AIDS, transplantation, and chemotherapy) led to a reduction in the bioavailability of the drug in the oral route. The intravenous administration of this drug in the body shows the acute toxicity of this drug. According to the results, encapsulation of this drug in a nanosystem decreased the toxicity, improved the pharmacokinetic behavior (absorption, distribution, metabolism, and excretion) and increased the solubility of the drug (55).

**Effect of Nanoemulsions in Various Drug Delivery Routes**

The encapsulation of drugs in nanoemulsion protects them from the macrophages of the reticuloendothelial system. In this regard, Gupta et al. encapsulated quercetin with antiparasitic properties on the subcutaneous route, reporting a significant improvement in its efficiency in the hamster model (56). In another study, glimepiride transdermal patches were designed based on the self-emulsifying system to reduce blood glucose. According to the results, the permeability, bioavailability, and duration of drug action through the skin improved by this form (57). The absorption of diazepam from the nasal route in the emulsion system is relatively rapid, and the maximum plasma concentration of the drug is generated within minutes. Therefore, this formulation can be an effective method for fast delivery of diazepam in the emergency treatment of epilepsy (58). To date, only a few studies have been conducted on the use of nanoemulsion for intravenous use, which might be due to the potential toxicity of surfactants in the formulation. As such, the surfactants applied must be safe.
Table 1. Examples of Bioavailability of Drugs Following the Administration of the SNEDDS Formulation

<table>
<thead>
<tr>
<th>No</th>
<th>Drug</th>
<th>Formulation</th>
<th>Study design</th>
<th>Level of increase</th>
<th>Comparison with</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cilostazol</td>
<td>SNEDDS</td>
<td>in rabbit</td>
<td>1.12 fold</td>
<td>Marketed tablets</td>
<td>(59)</td>
</tr>
<tr>
<td>2</td>
<td>Ibuprofen</td>
<td>SNEDDS</td>
<td>in vitro</td>
<td>2 fold</td>
<td>Ibuprofen suspension</td>
<td>(60)</td>
</tr>
<tr>
<td>3</td>
<td>Cefpodoxime Proxetil</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>4 fold</td>
<td>Plain drug</td>
<td>(61)</td>
</tr>
<tr>
<td>4</td>
<td>Rosuvastatin calcium</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.45 fold</td>
<td>Suspension</td>
<td>(62)</td>
</tr>
<tr>
<td>5</td>
<td>Irbesartan</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>1.78 fold</td>
<td>Marketed tablets</td>
<td>(63)</td>
</tr>
<tr>
<td>6</td>
<td>Telmisartan</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>4.34 fold</td>
<td>Tablet</td>
<td>(64)</td>
</tr>
<tr>
<td>7</td>
<td>Paclitaxel</td>
<td>SNEDDS</td>
<td>in vitro</td>
<td>99%</td>
<td>Suspension</td>
<td>(65)</td>
</tr>
<tr>
<td>8</td>
<td>Coenzyme Q10</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>4 fold</td>
<td>Powder Formulation</td>
<td>(66)</td>
</tr>
<tr>
<td>9</td>
<td>Simvastatin</td>
<td>Super-SNEDDS</td>
<td>in dog</td>
<td>180±53.3%</td>
<td>Capsules</td>
<td>(67)</td>
</tr>
<tr>
<td>10</td>
<td>Cyclosporine</td>
<td>SNEDDS</td>
<td>in dog</td>
<td>1.10 fold</td>
<td>Tablet</td>
<td>(68)</td>
</tr>
<tr>
<td>11</td>
<td>Oleanolic acid</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.4 fold</td>
<td>Tablet</td>
<td>(69)</td>
</tr>
<tr>
<td>12</td>
<td>Tacrolimus</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2 fold</td>
<td>commercial product</td>
<td>(70)</td>
</tr>
<tr>
<td>13</td>
<td>Glipizide</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.7 fold</td>
<td>Pure drug</td>
<td>(71)</td>
</tr>
<tr>
<td>14</td>
<td>Arteether</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.57 fold</td>
<td>Conventional drug</td>
<td>(72)</td>
</tr>
<tr>
<td>15</td>
<td>Ezetimibe</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>1.77 fold</td>
<td>Drug powder</td>
<td>(73)</td>
</tr>
<tr>
<td>16</td>
<td>Efavirenz</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.63 fold</td>
<td>Neat Efavirenz</td>
<td>(74)</td>
</tr>
<tr>
<td>17</td>
<td>Lacidipine</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>2.5 fold</td>
<td>Marketed tablets</td>
<td>(75)</td>
</tr>
<tr>
<td>18</td>
<td>Valsartan</td>
<td>SNEDDS</td>
<td>in rat</td>
<td>196.87%</td>
<td>Suspension</td>
<td>(76)</td>
</tr>
</tbody>
</table>
Discussion

The potential benefits of nanotechnology in improving the quality of drug delivery systems have been determined for more than 20 years now. Improving drug delivery techniques, which increases the efficiency of drugs, is associated with many benefits for patients. A large number of new drugs are poorly soluble in aqueous solvents. These types of compounds have low bioavailability, which is a considerable challenge in the use of these drugs. Considering the benefits of nanoemulsions, including higher drug loading, specific aggregation in the lesion site, reduced treatment costs and decreased side effects of drugs, special attention has been paid to these systems in the design of drugs, delivery of bioactive and drug compounds, and drug delivery in a controlled and purposeful manner. Therefore, not only is this system able to increase the therapeutic effect of drugs but also it can reduce the unfavorable side effects of drugs.

Acknowledgements

We would like to thank the Research Council of Shiraz University of Medical Sciences (11451) for supporting this research.

Declarations

Funding source(s)

Research Council of Shiraz University of Medical Sciences (11451)

Conflict of interest

None

Authors' contributions

All authors contributed equally to this work.

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How to cite: