10.37021/ijper.v8i1.01

REVIEW ARTICLE

The Evolving Landscape of Nano-Emulsion Drug Systems in diabetes: Updated Review

Aslam[1], Arabind Kumar[2], Anuj[3], Rohit[4*], Vivek kushwaha[5], Deepak Kumar[6], Abhimanyu Kumar[7], Triloki Prasad[8]

ABSTRACT

The use of Nano emulsion in augmenting dermal and transdermal effectiveness of drugs has now well established. The development of Nano emulsion based semisolid dosage forms is an active area of present research. The thickening or liquid-to-semisolid conversion of the nano-emulsions provides opportunities to the formulation scientist to explore novel means of solving instability issues during transformation. Conventional dosage forms of the anti-diabetic drugs exhibit variable/less bioavailability and short half-life, demanding frequent dosing and causing increased side-effects resulting in ineffectiveness of therapy and non-compliance with the patients. Considering the chronic nature of diabetes, nanotechnology-based approaches are more promising in terms of providing site-specific delivery of drugs with higher bioavailability and reduced regimen. Many studies have hinted at the possibility of administering peptide drugs like glucagon like peptides orally by encapsulation into nanoparticles. Nanoparticles also allow further modifications including their encapsulation into micro-particles, polyethylene glycol (PEG)-PEGylation- or functionalization with ligands for active targeting.

Keywords: Nano-emulsion, Delivery systems, Nanotechnology, Bioavailability

How to cite this article: Aslam, Kumar A, Anuj, Rohit, Vivek kushwaha V, Kumar D, Kumar A, Prasad T. The Evolving Landscape of Nano-Emulsion Drug Systems in diabetes: Updated Review. Int. J. Pharm. Edu. Res. 2026;8(1):1-8.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Conventional delivery of anti-diabetic drugs faces many problems like poor absorption, low bioavailability, and drug degradation. Nano emulsion is a unique drug technology, which is very suitable for the delivery of anti-diabetic drugs. In recent years, the flaws of delivering anti-hypoglycaemic drugs have been overcome by choosing Nano emulsion drug technology. They are thermodynamically stable and also provide the therapeutic agent for a longer duration. Generally, Nano emulsions are made up of either oil-in-water or water-in-oil and the size of the droplets is from 50-1000 nm. Surfactants are critical substances that are added in the manufacturing of Nano emulsions.[1] The blend of nanotechnology in the drug delivery system with the Nano emulsion (NE) formulations is widely noted as safe on account of its greater advantages such as good stability, bioavailability of drugs, and preventing the hydrolysis of drugs, which in turn acts as a good transporter of the drug particle.[2]

An ideal drug delivery system fulfils the objective of maximizing therapeutic effect while minimizing toxicity. With the progress in time and advances in science and technology, dosage forms have evolved from simple mixtures and pills, to highly sophisticated systems, which are known as novel drug delivery systems. Nano emulsions are novel drug delivery systems consisting of emulsified oil and water systems with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm and can exist as oil-in-water (o/w) or water-in-oil (w/o) form, where the core of the particle is either oil or water, respectively.[3] Several types of oils-natural semi-synthetic and synthetic are used in the formulation of nan emulsions. The capacity of Nano emulsions to dissolve large quantities of low soluble drugs along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal drug delivery vectors. The major advantages of Nano emulsions as drug delivery carriers include increased drug loading, enhanced drug solubility and bioavailability, and reduced patient variability, controlled drug release, and protection from enzymatic degradation.[4] Diabetes mellitus (DM) is a chronic lifelong metabolic disorder that alters the life of billions of people throughout the world .[5,6] It can be classified into two major forms, namely Type-1 DM (T1DM) and Type-2 DM (T2DM). In DM, constant hyperglycemia may result in chronic micro- and macro vascular effects such as nephropathy, retinopathy,

[1,8]Assistant Professor, Kalka Institute for research and advanced studies, Partapur bypass, Meerut, U.P.-250103

[2]Associate Professor, Ram-Eesh Institute of vocational & Technical Education, Greater Noida, Uttar Pradesh, Uttar Pradesh, India, 201310

[3]Lecturer, MIIT college of Pharmacy, Ghat road Meerut, UP. 250103

[4]Research scholar, Rama university faculty of pharmaceutical sciences Kanpur, UP., India.

[5, 6,7]Research scholar, Swami sahajanand college of pharmacy harraiya, Azamgarh, UP.

Corresponding Author: Rohit, Ram Research scholar, Rama university faculty of pharmaceutical sciences Kanpur, UP., India., E-mail: rohitkumar705441@gmail.com

neuropathy, stroke and cardiovascular disease.[7-8] The number of diabetic patients is increasing tremendously worldwide, where a recent report has indicated the increase of 422 million patients in 2014 from 171 million in 2000, showing the sharp increase in the sufferers.[9]

Adaptation of sedentary lifestyle and increasing in demographics with the age of >65 years suggesting this increased incidence of diabetes may be doubled, approximately 366 million in 2030.[10] Therefore, management is needed to control diabetes conditions and consequence complications. Monitoring programmes make people aware for effective management diabetic through adaptation of proper low carbohydrate diet, regular physical exercise, and adherence to medication therapy.[11] The conventional medications used now-a-days to control hyperglycaemic condition in DM are oral hypoglycaemic agents (OHA) and parenteral preparations of insulin and glucagon-like Peptide-1 (GLP-1) receptor agonists.The coordinated responses which stimulate glucose oxidation and inhibit gluconeogenesis simultaneously led to the hypoglycaemic action of insulin. The plasma glucose concentration decreases when insulin directs the glucose transporters (GLUT 4) into the cell membranes and increases glucose transport into target cells.[12] The aim of insulin therapy is to provide insulin replacement as close as possible in all patients. However, insulin resistance sometimes may happen during insulin therapy for the management of diabetic conditions.[13] Therefore, nano-size particles have comes out as for a more convenient, safe and non-invasive route for insulin delivery in order to overcome such limitations in diabetes management.[14]

Latest Advancements In Diabetes Therapy

The most popular is the treatment via short interfering ribonucleic acid (siRNA) and clustered regularly interspaced short palindromic repeats (CRISPR)/ CRISPR associated protein (Cas9) system. siRNA unlike a traditional RNA molecule is double stranded and is used for knocking down the expression of a particular gene by binding to the complementary base pairs in the messenger RNA (mRNA). It can thus be used for silencing of genes responsible for progression of diabetes. RNA induced silencing complex (RISC) is responsible for converting it into single stranded siRNA, which then binds to the complementary mRNA and cleaves it thus preventing its further translation into the desired protein. This strategy is being widely studied to treat complications like DN, diabetic retinopathy (DR), delay the onset of diabetes and even to treat diabetes induced delayed wound healing. H. Yuan et.al. 2008, Cholesterol modified siRNA has also been investigated for silencing

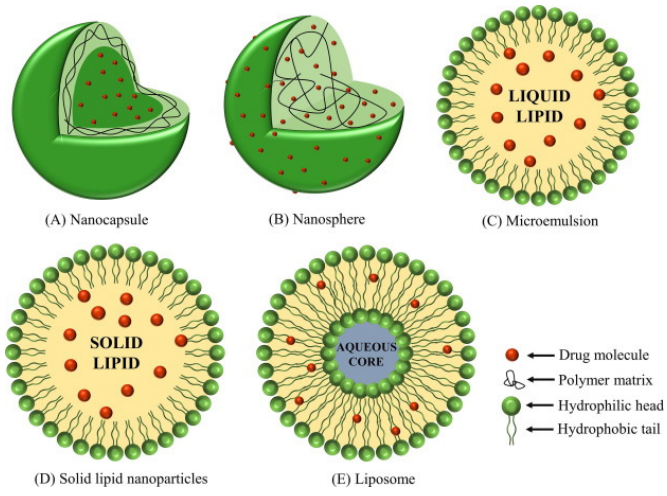

Figure: 1 Nano drug delivery systems in diabetes.

12/15-lipoxygenase (12/15-LO) which is known to be involved in the pathogenesis of DN. It has been reported that cholesterol can improve cellular uptake as well as in vivo pharmacological activities of siRNA without the use of any transfection agent. Inhibition of 12/15 LO resulted in reduction in renal structure damage, albuminuria, proteinuria, macrophage infiltration and glomerular meningeal matrix expansion.

Nano Drug Delivery Systems In Diabetes

Nano drug delivery systems intended for administration through oral route

Oral route for drug administration is the most preferred route, especially for chronic diseases, requiring repeated dosing. Better patient compliance, no pain and reduced risk of cross infection as well as needle stick injuries are some of the advantages offered by oral administration of the therapeutic agents.[15]

Lipid Based Drug Delivery Systems

Lipid based drug delivery systems (LBDDS) have been investigated in anti-diabetic therapy to enhance the solubility of hydrophobic drugs along with offering high degree of biocompatibility and versatility.[16] Lipids are also known to improve the drug absorption by alternating the composition as well as the character of the intestinal milieu. They can also alter the drug uptake, disposition, uptake and formation of metabolites by interacting with the enterocyte-based transport process. Further, recruitment of the intestinal lymphatic drug transport system can bypass the first pass metabolism and directly transport the drug into the systemic circulation.[17] These systems are commercially viable to formulate pharmaceuticals for topical, oral, pulmonary, or parenteral delivery. Lipid formulations can be modified in various ways to meet a wide range of product requirements as per the disease condition, route

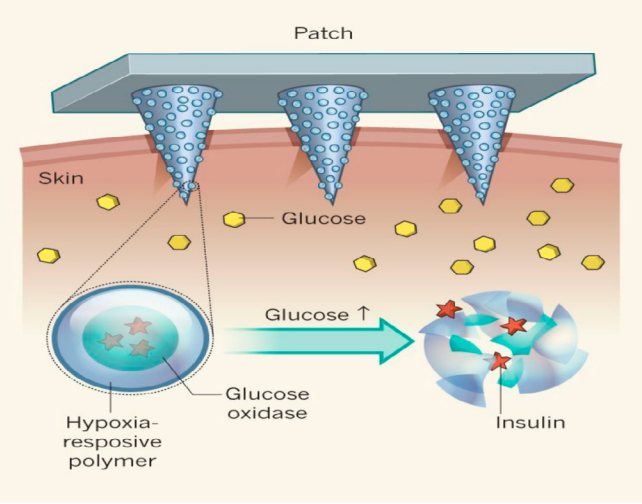

Figure: 2 Illustration of an insulin patch and stimuli-responsive mechanism for transdermal insulin delivery (reproduced with permission.

of administration, and also cost product stability, toxicity, and efficacy. General Routes of LBDDS, Routes like oral, parenteral, ocular, intranasal, dermal/transdermal, and vaginal can be for the administration of the lipid-based drug delivery systems (LBDDS).[18]

Polymeric Nanoparticles-Based Drug Delivery System

NPs are colloidal drug delivery systems that encompass particles in the size range of 10–1000 nm in diameter. They can be in the form of a reservoir system in which the drug is confined in a cavity surrounded by a polymeric membrane known as Nano capsules, or as a matrix system in which the drug is dispersed throughout the particles known as Nano sphere.[24-25] The polymer-based delivery systems where anticancer drugs are chemically encapsulated by covalent linking to polymers have attracted much attention because of their biocompatible, no immunogenic, biodegradable nature and controlled drug release into targeted cancer cells or tumour tissues. Furthermore, polymer-drug conjugates can facilitate higher drug payloads, lower systemic toxicity, prolong drug circulation time, and improve drug solubility and targeting.[22-23] In this respect, negatively charged poly (L-glutamic acid) is an ideal drug carrier, and several poly (L-glutamic acid)-drug conjugates have been developed and used in various stages of clinical trials.[20-21] The simultaneous imaging and therapeutic capabilities of these systems is advantageous over conventional chemotherapy in improving the therapeutic outcome of drug therapy. Very recently, several conjugated polymers have been prepared for live-cell imaging because of their high fluorescence brightness, good photo stability, and lower toxicity.[19]

Micro- And Nano-Emulsions

Micro emulsions/Nano emulsions are isotropic mixtures composed of surfactant, oil, water and co-surfactant or co-solvent.[31] A number of different colloid-based delivery systems have been shown to be particularly suitable for this purpose, including micro emulsions, Nano emulsions, and emulsions. These colloidal systems differ in their compositions, physicochemical properties, and thermodynamic stabilities, which lead to differences in their functional performances.Colloidal delivery systems can be fabricated entirely from food-grade ingredients using simple processing operations.[27-28] Each type of colloidal delivery system has specific physicochemical properties that may give it advantages or disadvantages for particular applications. Emulsions contain droplets with mean radii between about 100 nm and 100 μm. They are thermodynamically unstable systems because the contact between oil and water molecules is unfavorable, and so they will always break down over time.[29-30] Emulsions tend to be optically turbid or opaque because the droplets have a similar size to the wavelength of light and so strongly scatter light. Nano emulsions can be considered to be emulsions that have relatively small droplet sizes, i.e., mean radii<100 nm.The relatively small size of the droplets compared with the wavelength of light means that Nano emulsions tend to be either transparent or only slightly turbid.[26] Juber Akhtar et.al.2016, Nano emulsion of repaginate reported a quicker drug release in 24 h, with maximum cumulative drug release of 98.22%, when compared with the commercially available tablet (REGAN). In vivo studies in diabetic rats reported a 38%, 67% and 68% decrease in BGL upon administration of 0.5 mg/kg, 1 mg/kg and 2 mg/kg of the formulation, as compared to 64% decrease in BGL by marketed preparation (2 mg/kg). Optimized formulation reported plasma concentration for 12 h. Authors concluded that the decrease in BGL by 1 mg/kg of the formulation was similar to that by 2 mg/kg of commercial preparation. Small globule size coupled with low viscosity and low polydispersity contributed to the faster drug release and better absorption.[32]

Solid Lipid Nanoparticles (SIns) And Nanostructured Lipid Carriers (NIcs)

Among numerous types of nanoparticles, solid lipid-based nanoparticles (SLBNs) showed many advantages such as biocompatibility, production scalability, organic solvent-free preparation process, and wide application spectrum. Moreover, one fundamental advantage of SLBNs over other lipid based colloidal drug delivery systems such as liposomes and nano-emulsions are their rigid morphology. Therefore, SLBNs have been

intensively explored for drug delivery in the last decade. [33-34] SLBNs provide a lipophilic matrix in which drugs can be incorporated. Their particle sizes are mainly between 150 and 300 nm, and small sizes less than 100 nm or larger sizes up to 1,000 nm can be obtained as well. Two generations of SLBNs are distinguished: the first generation is solid lipid nanoparticles (SLNs); the second generation is nanostructured lipid carriers (NLCs). SLNs are prepared from lipids which are solid at room temperature as well as at body temperature. There are several advantages of SLNs formulations such as the protection of photosensitive, moisture sensitive and chemically labile drugs, biocompatibility and versatility of lipids used in SLNs, and cost-effective scale-up process. [35] SLNs prepared from one highly purified lipid can crystallize in a perfect crystalline lattice that allows smaller space for the incorporation of drugs, which may lead to a limited drug-loading capacity and stability problems including drug expulsion, particle growth and gelation. NLCs, spatially different lipid molecules are mixed to create a lipid particle matrix as imperfect as possible.[36] Generally, solid and liquid (oil) lipids are mixed to produce NLCs that are still solid at room temperature as well as at body temperature.[37]

Nano Emulsion-Based Delivery System: Types And Properties

Self-Emulsifying Formulations (Sefs)

Self-emulsifying formulations (SEFs) are mixtures of oil, surfactant, co-surfactant, and cosolvents (absence of external phase water) and forms a transparent isotropic solution, which emulsify under gentle agitation similar to those which would be encountered in gastro intestinal tract (GIT). It has been recognized that this formulation when administered orally undergo spontaneous emulsification in aqueous GI fluids.[40] This emulsified oil (triglycerides) stimulates bile secretion and drug containing oil droplets are further emulsified by bile salts. Lipid droplets are then metabolized by lipases and co lipases, secreted from the salivary gland, gastric mucosa and pancreas, which also hydrolyse the triglycerides into di-and monoglycerides and free fatty acids. Further, solubilisation of these molecules occurs during the passage through the GI tract and eventually forms a range of emulsion droplets, vesicular structures and mixed micelles containing bile salts, phospholipids and cholesterol.[40] Upon mixing with water the system SEFs have an ability to form fine colloidal droplets with very high surface area. In many cases, this accelerates the digestion of the lipid formulation, improves absorption, and reduces food effect and inter-subject variability.[41] Self emulsifying formulations distribute readily in the GI tract, the digestive motility of the stomach and the intestines provides sufficient agitation enough for the spontaneous formation of emulsions.[42,43] SEFs prepared using surfactants of HLB < 12 possess high stability and improved dissolution (for poorly soluble drugs) due to enhancement in surface area on dispersion.[40]

Self-Emulsifying Drug Delivery Systems (Sedds):

Self-emulsifying drug delivery system (SEDDS) is a strategy that has drawn wide research interest, basically due to its distinct capacity to solubilize and improve the bioavailability of hydrophobic drugs. This it does by ensuring aqueous solubility of the lipophilic drug.[44] The presence of oil makes SEDDS unique and distinguishes them from ordinary surfactant dispersions of drugs .[45] SEDDS are isotropic combination of drug, lipid/oil, solvents and surfactants.[44] On dilution by an aqueous phase they form fine stable oil-in-water (o/w) emulsions or fine lipid droplets which is the characteristic feature of these systems. When such a formulation is released into the lumen of the GIT, it disperses to form a fine emulsion generally o/w emulsion. SEDDS are generally formulated with triglyceride oils and ethoxy- latednonionic surfactants. In general, the concentration of surfactant is greater than 25% in the formulation. The size of droplets ranges approximately less than 100 nm.[44]

Advantages of SEDDS include more consistent drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, protection of drug(s) from the gut environment, control of delivery profiles, reduced variability including food effects, enhanced oral bioavailability enabling reduction in dose and high drug loading efficiency.[46] These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. SEDDS are prepared in two forms: Liquid and solid SEDDS (S-SEDDS). S-SEDDS are prepared by solidification of liquid self-emulsifying components into powder. This powder is then used to produce various solid dosage forms, for example self-emulsifying pellets, self-emulsifying tablets etc.[44] S-SEDDS do not suffer with the problems like liquid SEDDS (L-SEDDS).the advantages like low manufacturing cost, more stability and is more patient compliance, because they are available as solid dosage form in tablets or pellet form. In many studies it have been reported that SEDDS are used for delivering and targeting hydrophobic drugs such as coenzyme Q10, halofantrine, vitamin E and cyclosporine-A.[44] The solid SEDDS focus on the incorporation of liquid/semisolid ingredients into powders employing diverse solidification techniques like spray drying, melt granulation, moulding, melt extrusion, and nanoparticle technology.The idea of blending the potential SEDDS with that of the pellets

through the inclusion of a self-emulsifying mixture into microcrystalline cellulose, and the production of pellets using extrusion-spheronization was first introduced by Newton et al.[47] Different dosage forms of S-SEDDS include the dry emulsions, self-emulsifying capsules, self-emulsifying sustained/controlled-release tablets, self-emulsifying sustained/controlledrelease pellets, self-emulsifying solid dispersions, self-emulsifying beads, self-emulsifying sustained-release microspheres, self-emulsifying nanoparticles, self-emulsifying suppositories and self-emulsifying implant.[48-51]

ADVANTAGES OF SEDDS

- Improvement and reduction in the variability of GI absorption of poorly water soluble, lipophilic drugs. Food does not interfere with the absorption of drug by use of such systems.
- Relative ease of manufacture using readily available equipment.
- The dose ranging from less than 25 mg to greater than 2000 mg can be administered by using these systems.
- These systems enhance oral bioavailability due to bypass of hepatic metabolism and delivers drug directly into systemic circulation.
- Inhibition of p-glycoprotein mediated drug efflux and pre-absorptive metabolism by gut membrane bound cytochrome enzyme.
- Protection of sensitive drug substances High drug payloads. Liquid or solid dosage forms. Reduced energy requirement for emulsion formation.
- They enhance absorption of lipophilic drugs by stimulating pancreatic and biliary secretions and by prolongation of gastric residence time.[52]

Disadvantages Of Sedds

- Lack of good predicative in vitro models for assessment of the formulations.
- Traditional dissolution methods do not work, because formulations are independent on digestion prior to release of the drug.
- Different prototype lipid based formulations needs to be developed and tested in vivo. • Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) may irritate GIT.
- Volatile co solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.[52-53]

Self-Nano Emulsifying Drug Delivery Systems (Sneddss)

Self-Nano emulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water Nano emulsion when introduced into aqueous phases under gentle agitation. SEDDSs typically produce emulsions with turbid appearance, and droplet size between 200 nm to 5 μm, while self micro-emulsifying drug delivery systems (SMEDDSs) form translucent micro-emulsions with droplet size of less than 200 nm. However, self-Nano emulsifying drug delivery systems (SNEDDS) produce clear or transparent emulsion with droplets size less than 100 nm.[54] Successful formulation of SNEDDS depends on the thorough understanding of the spontaneous nano-emulsification process and also on the physicochemical and biological properties of the components used for the fabrication of SNEDDS.SNEDDS offer a reduction in bioavailability and can offer reproducibility in plasma profiles of drugs. The ability of the SNEDDS in improving Cmax and oral bioavailability or therapeutic effect has been established for various hydrophobic drugs. The improvement in bioavailability can be translated into reduction in the drug dose and dose-related side effects of many hydrophobic drugs, such as antihypertensive and antidiabetic drugs. SNEDDS are used for enhancing the solubility of anti-inflammatory drugs such as indomethacin.[55] Fibrinolytic drugs such as simvastatin, atorvastatin, valsartan, gemfibrozil were also formulated as SNEDDS for improved bioavailability. Super-SNEDDS of simvastatin show increased bioavailability compared to the conventional SNEDDS due to the increased drug loading.[56]

Advantages Of Snedds

- Protection of sensitive drug substances.

Selective targeting of drug(s) toward specific absorption window in GIT.Enhanced oral bioavailability enabling reduction in dose.

- High drug payloads.
- It can be easily stored since it belongs to a thermodynamics stable system.
- Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GIT, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.[58]

Disadvantages Of Snedds

- Lack of good predicative in vitro models for assessment of the formulations because traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an in vitro model simulating the digestive processes of the duodenum has been developed.
- Need of different prototype lipid-based formulations

to be developed and tested in vivo in a suitable animal model.[58]

Factors Affecting Snedds

- Drugs which are administered at very high dose are not suitable for SNEDDS, unless they exhibit extremely good solubility in at least one of the components of SNEDDS, preferably lipophillic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SNEDDS.
- The ability of SNEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilisation, then there could be a risk of precipitation, as dilution of SNEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant.[58]

Advantages, Disadvantages Nanoemulsions As Drug Delivery Systems

- The small size of the droplets allows them to deposit uniformly on substrates.
- The very small droplet size causes a large reduction in the gravity force and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.
- The small droplet size also prevents any flocculation of the droplets. Weak flocculation is prevented and this enables the system to remain dispersed with no separation.
- Nano emulsions are suitable for efficient delivery of active ingredients through the skin. The large surface area of the emulsion system allows rapid penetration of actives.
- Unlike micro emulsions (which require a high surfactant concentration, usually in the region of 20 % and higher), Nano emulsions can be prepared using reasonable surfactant concentration. For a 20 % o/w Nano emulsion, a surfactant concentration in the region of 5 – 10 %may be sufficient.
- Nano emulsions can be formulated in numerous dosage foam such as creams, liquids, sprays and foams.
- Various routes like topical, oral and intravenous can be used to deliver the product.
- Possibilities of controlled drug release and drug targeting, and the incorporation of a great variety of therapeutic actives.[59-60]

CONCLUSION& SUMMARY

Nano-emulsion systems offer several distinct advantages that outweigh their limitations. Although they are prone to storage-related problems such as Ostwald ripening, these issues can be effectively minimized by optimizing formulation components and processing parameters. Despite being relatively fragile, nano-emulsions have demonstrated wide applicability—ranging from disinfectants and drug-delivery systems to food-grade formulations and cosmetics—and have proven more efficient than traditional systems due to their higher entropy, increased surface area, and reduced adverse effects. Among various preparation techniques, high-pressure homogenization remains the most successful and commercially viable method for producing nano-emulsions. However, limited industrial acceptability persists because of an incomplete understanding of nano-droplet formation mechanisms and stability challenges in final semisolid dosage forms. A deeper insight into droplet surface charge, skin interaction, and interfacial behaviour could significantly enhance therapeutic performance. Overall, nano-emulsions represent a highly promising alternative to conventional topical and transdermal delivery systems and possess strong potential for future application in delivering existing and novel therapeutics more effectively, with considerable commercial and societal value.

REFERENCES

1. Mc Clements DJ, Jafari SM. General aspects of nanoemulsions and their formulation. In Nanoemulsions. Academic Press; 2018. p. 3–20.
2. Patra JK, Fraceto LF, Das G, Campos EVR, editors. Green Nanoparticles. Cham: Springer; 2020.
3. Chime SA, Kenechukwu FC, Attama AA. Nanoemulsions — Advances in formulation, characterization and applications in drug delivery. In: Sezer AD, editor. Application of Nanotechnology in Drug Delivery. London: IntechOpen; 2014.
4. Kotta S, Khan AW, Pramod K, Ansari SH, Sharma RK, Ali J. Exploring oral nanoemulsions for bioavailability enhancement of poorly water-soluble drugs. Expert Opin Drug Deliv. 2012;9(5):585-598.
5. Kesharwani P, Gorain B, Low SY, Tan SA, Ling ECS, Lim YK, et al. Nanotechnology based approaches for anti-diabetic drugs delivery. Diabetes Res ClinPract. 2018;136:52–77.
6. Veiseh O, Tang BC, Whitehead KA, Anderson DG, Langer R. Managing diabetes with nanomedicine: challenges and opportunities. Nat Rev Drug Discov. 2014;14.
7. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361(14):1339–1348.
8. Nadkarni P, Weinstock RS. Carbohydrates. In: McPherson RA, Pincus MR, editors. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. St. Louis: Elsevier; 2017. p. 205–220.e2. (Chapter 16).
9. Li W, Yuan G, Pan Y, Wang C, Chen H. Network pharmacology studies on the bioactive compounds and action mechanisms

of natural products for the treatment of diabetes mellitus: a review. Front Pharmacol. 2017; 8:74.
10. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projection for 2030. Diabetes Care. 2004; 27(5):1047–1053.
11. García-Pérez LE, Alvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther. 2013;4(2):175–194.
12. Costanzo LS. Endocrine physiology. In: Costanzo LS. Physiology. 6th ed. Philadelphia: Elsevier; 2018. p. 383–446.
13. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Insulin Resistance and Prediabetes. Bethesda: U.S. Department of Health and Human Services; 2014.
14. Veiseh O, Tang BC, Whitehead KA, Anderson DG, Langer R. Managing diabetes with nanomedicine: challenges and opportunities. Nat Rev Drug Discov. 2014; 14.
15. Uppal S, Italiya KS, Chitkara A, Mittal A. Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: an emerging paradigm for effective therapy. Acta Biomater. 2018; 81:20-42.
16. Shrestha H, Bala R, Arora S. Lipid-based drug delivery systems. J Pharm. 2014; 2014:1–10. [Note: Duplicate of Reference 18].
17. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007; 6(3):231-248.
18. Shrestha H, Bala R, Arora S. Lipid-based drug delivery systems. J Pharm. 2014; 2014:1–10. [Note: Duplicate of Reference 16].
19. Feng X, Lv F, Liu L, Tang H, Xing C, Yang Q, et al. Conjugated polymer nanoparticles for drug delivery and imaging. ACS Appl Mater Interfaces. 2010;2(8):2429–2435.
20. Ye F, Ke T, Jeong EK, Wang X, Sun Y, Johnson M, et al. Noninvasive MRI evaluation of biodegradable polymeric macromolecular MRI contrast agents for Gd-DTPA delivery into prostate cancer. Mol Pharm. 2006; 3(5):507–515.
21. Godwin A, Bolina K, Clochard M, Dinand E, Rankin S, Simic S, et al. New polymers for drug delivery. J Pharm Pharmacol. 2001;53(9):1175–1184.
22. Bhatt R, de Vries P, Tulinsky J, Bellamy G, Baker B, Singer JW, et al. Synthesis and in vivo antitumor activity of poly(L-glutamic acid)-camptothecin conjugates. J Med Chem. 2003;46(2):190–193.
23. Auzenne E, Donato NJ, Li C, Leroux E, Price RE, Farquhar D, et al. Evaluation of poly(L-glutamic acid)-paclitaxel conjugate in an orthotopictumors model of human ovarian cancer. Clin Cancer Res. 2002;8(2):573–581.
24. Mudshinge SR, Deore AB, Patil S, Bhalgat CM. Nanoparticles: emerging carriers for drug delivery. Saudi Pharm J. 2011;19(3):129–141.
25. Bhatia S. Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. In: Natural Polymer Drug Delivery Systems. Cham: Springer; 2016. p. 33–93.
26. Rao J, McClements DJ. Formation of flavor oil microemulsions, nanoemulsions and emulsions: influence of composition and preparation method. J Agric Food Chem. 2011;59(9):5026–5035.
27. McClements DJ. Edible nanoemulsions: fabrication, properties, and functional performance. Soft Matter. 2010;6(16):3731-3747.
28. Qian C, McClements DJ. Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: factors affecting particle size. Food Hydrocolloid. 2011;25(5):1000-1008.
29. Garti N, Yaghmur A, Leser M, Clement V, Watzke H. Improved oil solubilization in oil/water food grade microemulsions in the presence of polyols and ethanol. J Agric Food Chem. 2001;49(5):2552–2562.
30. McClements DJ, Decker E, Weiss J. Emulsion-based delivery systems for lipophilic bioactive components. J Food Sci. 2007;72(8):R109–R124.
31. Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS)—challenges and road ahead. Drug Deliv. 2015; 22(6):675–690.
32. Akhtar J, Siddiqui HH, Fareed S, Badruddeen, Khalid M, Aqil M. Nanoemulsion: for improved oral delivery of repaglinide. Drug Deliv. 2015; 23(6):2026–2034.
33. Yoon G, Park JW, Yoon IS. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. J Pharm Investig. 2013; 43(5):353–362.
34. Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates—a review. J Control Release. 2008; 128(3):185–199.
35. Shidhaye SS, Vaidya R, Sutar S, Patwardhan A, Kadam VJ. Solid lipid nanoparticles and nanostructured lipid carriers—innovative generations of solid lipid carriers. Curr Drug Deliv. 2008;5(4):324–331.
36. Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech. 2011; 12(1):62–76.
37. Chen CC, Tsai TH, Huang ZR, Fang JY. Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. Eur J Pharm Biopharm. 2010; 74(3):474–482.
38. Yuan H, Lanting L, Xu ZG, Li SL, Swiderski P, Putta S, et al. Effects of cholesterol-tagged small interfering RNAs targeting 12/15-lipoxygenase on parameters of diabetic nephropathy in a mouse model of type 1 diabetes. Am J Physiol Renal Physiol. 2008; 295(2):F605–F617.
39. Reynolds A, Leake D, Boese Q, Scaringe S, Marshall WS, Khvorova A. Rational siRNA design for RNA interference. Nat Biotechnol. 2004; 22(3):326–330.
40. Hamed AC, Vitthal VC, Pravin DC. Self emulsifying drug delivery system: a review. Int J Pharm Chem Sci. 2013;2(1):34–44.
41. Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C. A novel lipid-based oral drug delivery system of nevirapine. Int J PharmTech Res. 2011; 3(2):1159-1168.
42. Tang J, Sun J, He Z. Preparation of self-emulsifying drug delivery systems of Ginkgo biloba extracts and in vitro dissolution studies. Asian J Tradit Med. 2006;1(3-4):116-120.
43. Chime SA, Onyishi VI. Lipid-based drug delivery systems (LDDS): recent advances and applications of lipids in drug delivery. Afr J Pharm Pharmacol. 2013;7(48):3034-3059.
44. Kumar S, Gupta SK, Singh PS. Self-emulsifying drug delivery systems (SEDDS) for oral delivery of lipid based formulations - a review. Afr J Basic Appl Sci. 2012;4(1):7-11.
45. Obitte NC, Chukwu A. The excipient usefulness of Carbosil and Landolphiaowariensis in two oil-based self-emulsifying formulations. Asian J Pharm. 2010;4(4):213-219.
46. Sachan R, Khatri K, Kasture SB. Self-emulsifying drug delivery system: a novel approach for enhancement of bioavailability. Int J PharmTech Res. 2010;2(3):1738-1745.
47. Newton M, Petersson J, Podczeck F, Clarke A, Booth S. The influence of formulation variables on the properties of

pellets containing a self-emulsifying mixture. J Pharm Sci. 2001;90(8):987-995.
48. Kyatanwar AU, Gajdhiye ND, Jadhav KR, Kadam VJ. Solid self emulsifying drug delivery system: a review. J Pharm Res. 2010;3(4):877-882.
49. Wadhwa J, Nair A, Kumria R. Emulsion forming drug delivery system for lipophilic drugs. Acta Pol Pharm. 2012;69(2):179-191.
50. Shaji J, Jadhav D. Newer approaches to self-emulsifying drug delivery system. Int J Pharm Pharm Sci. 2010;2(1):37-42.
51. Mehta PP, Makanikar V, Parekh PP. Self emulsifying drug delivery system: a novel approach to enhance oral bioavailability of poorly soluble drugs. J Pharm Res. 2011;4(7):2191-2194.
52. Singh G, Khinchi MP, Gupta MK, Dilip A, Adil H, Natasha S. Self emulsifying drug delivery systems (SEDDS): an approach for delivery of poorly water soluble drug. Int J Pharm Life Sci. 2012;3(9):1991-1996.
53. Sharma V, Saxena PS, Singh P. Self emulsifying drug delivery system. J Pharm Res. 2011;3:500-504.
54. Balakumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S. Self nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf B Biointerfaces. 2013; 112:337-343.
55. Obitte NC, Ofokansi KC, Nzekwe IT, Esimone CO, Okoye IE. Self-nanoemulsifying drug delivery systems based on melon oil and its admixture with a homolipid from Bosindicus for the delivery of indomethacin. Trop J Pharm Res. 2011; 10(3):299-307.
56. Thomas N, Holm R, Garmer M, Karlsson JJ, Müllertz A, Rades T. Supersaturated self-nanoemulsifying drug delivery systems (Super-SNEDDS) enhance the bioavailability of the poorly water-soluble drug simvastatin in dogs. AAPS PharmSciTech. 2014; 15(1):219-227.
57. Elsheikh MA, Elnaggar YSR, Gohar EY, Abdallah OY. Nanoemulsion liquid preconcentrates for raloxifene hydrochloride: optimization and in vivo appraisal. Int J Nanomedicine. 2012; 7:3787-3802.
58. Shah HA, Patel AY, Patel RP, Patel JP, Tank HM. Self nano emulsifying drug delivery system (SNEDDS): future aspects. Asian J Pharm Res. 2013;3(1):21-27.