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Polymer-Based Nanoparticle Schemes for Drug delivery: A Comprehensive Review

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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 nanoemulsions 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 dosage 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. Nanoemulsions have wide applications in the field of medicine, skincare, agriculture, food and various other fields as they provide an effective and protective means or vehicle. In this review, we have discussed and compared the methods of nanoemulsion preparation and various methods of synthesis, along with few major applications in various fields of science and technology.

KEYWORDS: Nano-emulsion, delivery systems, nanotechnology, insulin, bioavailability, biodegradable platforms.

I. INTRODUCTION

Conventional delivery of antidiabetic 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 antidiabetic drugs. In recent years, the flaws of delivering anti-hypoglycaemic drugs have been overcome by choosing nanoemulsion drug technology. They are thermodynamically stable and also provide the therapeutic agent for a longer duration. Generally, nanoemulsions 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 nanoemulsions [1]. The blend of nanotechnology in the drug delivery system with the nanoemulsion (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. Nanoemulsions 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 nanoemulsions. The capacity of nanoemulsions 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 nanoemulsions 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 macrovascular



effects such as nephropathy, retinopathy, 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 hyperglycemic condition in DM are oral hypoglycemic 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, nanosize 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 [39]. H. Yuan et.al. 2008, Cholesterol modified siRNA has also been investigated for silencing 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 mesangial matrix expansion [38].

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].

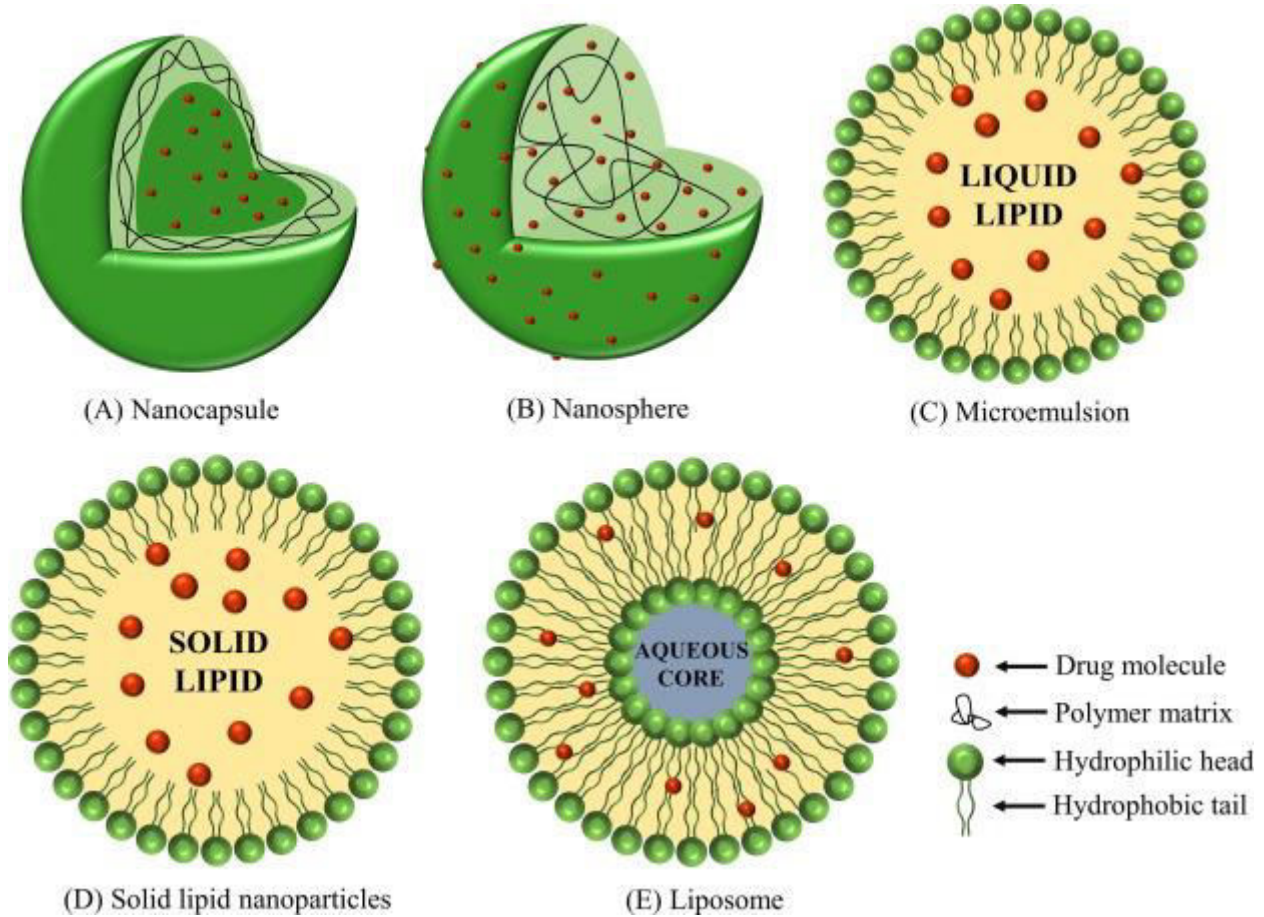


Figure:1 Nano drug delivery systems in diabetes.

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 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

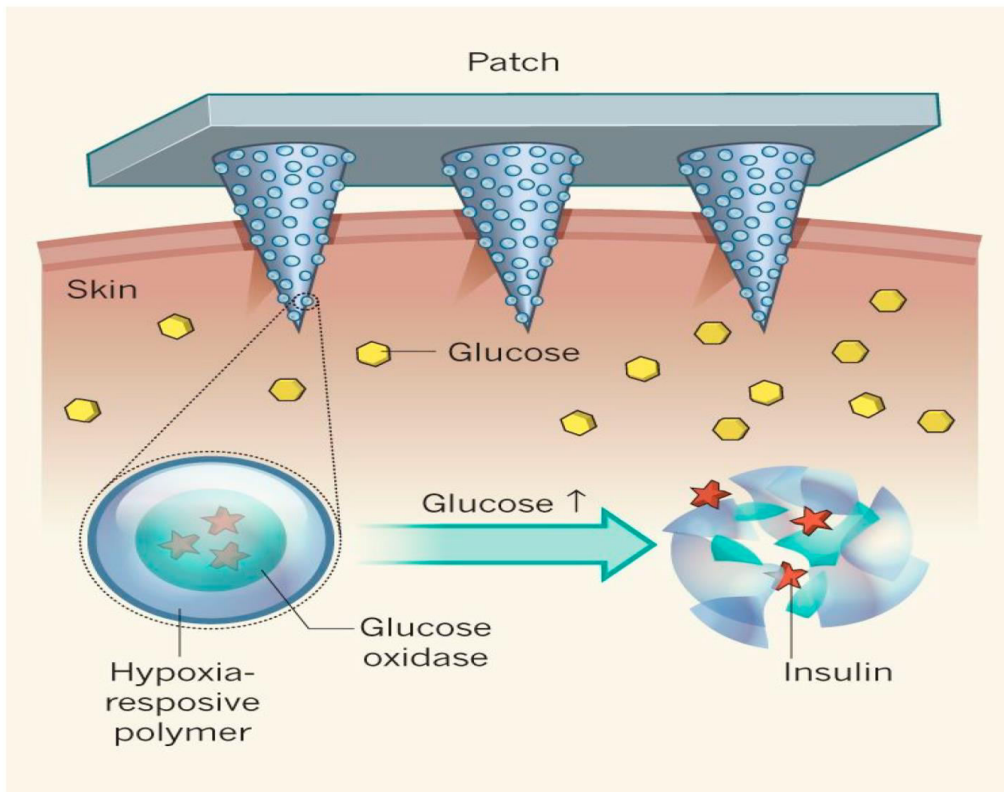


Figure: 2 Illustration of an insulin patch and stimuli-responsive mechanism for transdermal insulin delivery (reproduced with permission.(<https://doi.org/10.3390/polym11091380>)

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 Nanocapsules, or as a matrix system in which the drug is dispersed throughout the particles known as nanosphere [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, nonimmunogenic, biodegradable nature and controlled drug release into targeted cancer cells or tumor 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 photostability, and lower toxicity [19].

MICRO- AND NANO-EMULSIONS

Microemulsions/Nanoemulsions 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 microemulsions, nanoemulsions, 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 μ m. 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.

Nanoemulsions 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 nanoemulsions tend to be either transparent or only slightly turbid [26]. Juber Akhtar et.al.2016, Nanoemulsion of repaglinide 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 (SLNs) AND NANOSTRUCTURED LIPID CARRIERS (NLCs)

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 nanoemulsions 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 hydrolyze the triglycerides into di- and monoglycerides and free fatty acids. Further, solubilization 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, cosolvents 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-

lated nonionic 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 has 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/controlled release 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.
- Control of delivery profile
- Promotion of lymphatic drug transport.
- 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 predictive 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.
- In vitro model needs further development and validation.
- Different prototype lipid based formulations need 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 (SNEDDS):

Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water nanoemulsion when introduced into aqueous phases under gentle agitation. SEDDS typically produce emulsions with turbid appearance, and droplet size between 200 nm to 5 µm, while self micro-emulsifying drug delivery systems (SMEDDS) form translucent micro-emulsions with droplet size of less than 200

nm. However, self-nanoemulsifying 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 C_{max} 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].

Anti-cancer drugs were also formulated as SNEDDS. They include raloxifene hydrochloride, cyclosporine A, paclitaxel, flutamide. In raloxifene, the uptake of the drug by endocrine organs was assessed by administering the SNEDDS in alkalized and non-alkalized form to Wistar rats. Non-alkalized form showed good uptake by the endocrine organs than the alkalized form [57].

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 lipophilic 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 solubilization, 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.
- Nanoemulsions 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 microemulsions (which require a high surfactant concentration, usually in the region of 20 % and higher), nanoemulsions can be prepared using reasonable surfactant concentration. For a 20 % o/w nanoemulsion, a surfactant concentration in the region of 5 – 10 % may be sufficient.
- Nanoemulsions can be formulated in numerous dosage forms 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].

APPLICATIONS OF NANOEMULSIONS IN DRUG DELIVERY

Nanoemulsions containing pharmaceutically active agents can be utilized for the production of pharmaceutical preparations. If desired a special galenic form can be imparted to the mixture. Ampoules, especially sterile injection and infusion solutions; solutions, especially oral liquids, eye drops and nose drops which can contain various auxiliary substances can be formulated in the form of nanoemulsion; aerosols without metering feature and dosing aerosols, which can contain propellant gas and stabilizers besides the nanoemulsion; hydrophilic and hydrophobic gels and ointments containing the nanoemulsion; o/w or w/o creams containing the nanoemulsion; lotions and pastes containing the nanoemulsion are available in the market.

➤ **NASAL ROUTE**

The nasal route has received great attention due to number of advantages over parenteral and oral administration especially by bypassing the liver. Nanoemulsions increase absorption by solubilizing the drug in the inner phase of an emulsion and prolonging contact time between emulsion droplets and nasal mucosa [61].

➤ **PARENTERAL DELIVERY**

Nanoemulsions are advantageous for intravenous administration, due to the strict requirement of this route of administration, particularly the necessity for the formulation droplet size lower than 1 micrometer. Parenteral (or Injectable) administration of nanoemulsion is employed for a variety of purposes, namely nutrition eg. Fats, Carbohydrates, Vitamins etc [62]. Nanoemulsions of natural oils (soyabean, sesame and olive) with the non-toxic surfactant Pluronic F68 via ultrasound for parenteral feeding. Lipid nanoemulsion has been widely explored for parenteral delivery of drugs. Nanoemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle Nanoemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O Nanoemulsion can be used for parenteral delivery [63].

➤ **IN COSMETIC**

The aesthetic properties, i.e. low viscosity and transparent visual aspects of nanoemulsion with droplet sizes below 200nm, its high surface area allowing effective transport of the active ingredient to the skin make them especially attractive for their application in cosmetics [64]. Nanoemulsions are acceptable in cosmetics because there is no inherent creaming, sedimentation, flocculation or coalescence that are observed with macro emulsion. The incorporation of potentially irritating surfactants can be avoided by using high energy equipment during manufacturing. Nanogel technology to create miniemulsion from oil-in water concentrate suited to minimizing transepidermal water loss, enhanced skin protection and penetration of active ingredient. It would be useful for sun care products, moisturizing and antiageing creams. It helps to give skin care formulations a good skin feels [65].

➤ **TOPICAL DELIVERY**

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to affected area of the skin or eyes. The nanoemulsion can achieve a level of topical antimicrobial activity that has only been previously achieved by systemic antibiotics. The nanoemulsion has broad spectrum activity against bacteria (e.g. E.coli, S. aureus) fungi (e.g. Candida, Dermatophytes) [66].

➤ **DIABETES**

It is a consequence of defective or impaired insulin secretion and is treated by administering insulin and oral hypoglycemic [67]. Developing transdermal systems overwhelmed the shortcomings related with oral hypoglycemic like glibenclamide (GCL). Mohammed et al. 2013 have investigated GCL efficacy when it was emulsified in nano-carrier for transdermal delivery [68]. GCL transdermal nanoemulsion gel exhibited better control of hyperglycemia and more effectively reversed the diabetes mellitus complications than oral GCL administration in experimental animals. Better result of the gel is attributed

to the many factors such as larger amount of surfactant (labrafac) and cosurfactant (triacetin) carrying drug, high penetration into the skin, nanosized droplets, high solubilization of drug in nanoemulsion, high thermodynamic activity providing significant driving force for its release and permeation and lastly hydration of the stratum corneum due to external water phase of the nanoemulsion results in high diffusivity of lipophilic drug as droplet size approaches to molecular dispersion. Subsequently in 2015, Dina et al. [69] developed the nanoemulsion of essential oil of fennel which is highly recommended for diabetes owing to the presence of trans-anethole as one of the major constituent.

This nanoemulsion showed high potential in reducing plasma glucose levels of rats when delivered via transdermal route due to the presence of oleic acid and PG (propylene glycol; co-surfactant) as both of them acts as permeation enhancer for dermal delivery since they would increase the fluidity of the liquid portion of the stratum corneum. Moreover, Tween 20 (surfactant) enhanced the flux of the materials permeating through biological membranes resulted in better penetration of oil and hence improved activity [67].

➤ RHEUMATOID ARTHRITIS

It is characterized by a symmetric, peripheral polyarthritis that often results in severe joint damages. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs to reduce pain and inflammation of rheumatoid arthritis. NSAIDs commonly cause gastrointestinal ulcers, bleeding and adverse cardiovascular events after oral administration. Transdermal gel of etoricoxib nanoemulsion has been found to be active in maintaining the effective drug plasma concentration without portraying the adverse effects associated with its oral delivery. Unlike the etoricoxib conventional gel, nano-emulsified etoricoxib gel increased permeation and flux through the skin, transdermally. This transdermal gel was credited due to the smaller droplet size and fluidic nature that has improved the anti-inflammatory efficacy of etoricoxib [70]. Anti-inflammatory potential of piroxicam and ketoprofen are well exploited against rheumatism. Frequent oral intake of these drugs is not comfortable as they cause discomfort to the gastric mucosa. However, their transdermal nanoemulgel was prepared to improve their availability in to the systemic circulation. Oleic acid that is used in the development of nanoemulsion and constituted oil phase is thought to disrupt the cellular arrangement of the stratum corneum irreversibly and thereby allowed better penetration through the different skin layers. [71-72].

➤ CANCER

Despite remarkable progress in chemotherapy during last couple of decades, cancer still remains one of the most sickening diseases due to its almost inevitable fatality. It is the second leading cause of mortality all over the world [73]. Chemotherapeutics have been specifically targeted to the tumor site so as to avoid apoptosis of normal cell. This has been achieved by ligand mediated site specificity (in the influence of albumin, folate, glycyrrhetic acid receptors) following intravenous route of administration [74,75] however, transdermal route of administration is required for long-term management of cancer pain which have been extensively studied and very well documented [76]. Nanoemulsion technology has been proved as an important tool in chemotherapeutic applications. Properties like optical clarity, biocompatibility, non-immunogenic, ease of preparation and thermodynamic stability, place them to the new epoch. Caffeine o/w nanoemulsion (Surfactant Transcutol-HP and co-surfactant Isopropyl alcohol) offered significant increment in permeability as compared to its aqueous formulation which was attributed to small particle size (20.14 nm) and negative charge over the droplets to facilitate para-cellular transportation of caffeine [77]. Moreover, nanoemulsion of 5-fluorouracil was formulated to deliver by transdermal route owing to its very low oral bioavailability. Due to the presence of low HLB surfactant (Tanscutol-HP), flux of 5-fluorouracil was improved through skin barriers that portrayed the enhanced permeation of nanoemulsion through skin and finally higher apoptosis in SK-MEL-5 cancer cells [78]. Furthermore, transdermal application of an antioxidant synergy nanoemulsion formulation was found to be effective in reducing neuroblast growth rate in mouse model [79].

➤ PSORIASIS

The existing systemic therapies for psoriasis are both biological and non-biological which are commonly used as mono-therapies. Potential of methotrexate (MTX), cyclosporine and orally administrated retinoids have been explored extensively against psoriasis. Subsequently, the utility of topical MTX administration through nanoemulsion carrier in inhibiting epidermal cell proliferation and inflammation was firstly

reported by Pinto et al. in 2014. It avoided the chance of liver toxicity and gastrointestinal side effects usually observed after systemic administration of MTX. During transportation through skin, MTX loaded nanoemulsion improved the topical efficacy after modulating the cellular arrangement and interacting with the membrane components such as enzymes and transporters. The possible reason for enhanced biological activity of MTX is that the positively charged nanoemulsion facilitated enhanced penetration by ionic interactions with the skin cells and by forming hydrogen bonds. Polysorbate 60 (P60) and Polysorbate 80 (P80) affected the flux rate of MTX, where P60 based nano lipid carrier (NLC-P60) exhibited higher diffusion rate through the skin than that of P80 based NLC-P80 and pure MTX. Since it has been very clearly stated that the lipid and protein based carriers show better penetration through the severely altered stratum corneum of the psoriatic skin [80], the skin barrier integrity in the case of psoriasis was still unclear. In 2014, Somagoni et al. have highlighted penetration profile through the psoriatic skin. Their report reveals the low permeation of the drug through psoriatic skin because of the creation of a strong barrier for the penetration of nanoemulsion owing to the presence of plaque, scaling, epidermal alterations, epidermal thickening and elongation of epidermal ridges. This hypothesis was based on in vitro permeation and microdialysis experiments, where lesser permeation of the aceclofenac and capsaicin was observed into the receptor compartment through the inflamed skin (IMQ-induced skin inflammation) as compared to normal skin. Nano formulations NMG [a combination of nanoemulsion (NEM) and nanomicelles (NMI)] improved deposition of aceclofenac and capsaicin into the deeperskin layers (concentration was about 3-fold higher) compared to the marketed formulation due to the formation of drug deposits in the deep skin layers [81]. The role of TPGS based nanoemulsion was explored to localize paclitaxel (PCL) in to deeper skin layers for longer duration and to get its maximum enhanced efficacy as PCL is a poorly soluble and poorly permeable drug i.e. classified as class IV drug of Biopharmaceutics Classification System (BCS). Due to the lipophilic nature and high molecular weight, PCL was selected as the model candidate to localize in skin layers through nanoemulsion. Increasing concentration of drug locally at the therapeutic target and keeping the systemic drug concentrations at its minimum facilitate efficient treatment of psoriasis. TPGS based o/w nanoemulsion showed tremendous utility in accumulating PCL locally (improved dermal bioavailability) with minimum systemic availability. Distribution of PCL into stratum corneum, epidermis and dermis of skin showed regional pharmacokinetic advantage of nanoemulsion following topical administration. Upon dermal application, maximum local concentration in dermis layer reached to 10 $\mu\text{g}/\text{cm}^2$, whereas systemic concentration was about 100 ng/ml. However, after intravenous administration of the same formulation, maximum local concentration in dermis layer was reached to 1 $\mu\text{g}/\text{cm}^2$ [82].

➤ HYPERTENSION

It is a chronic medical condition in which the blood pressure in the arteries is persistently elevated. Several classes of medications viz. thiazide-diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been used in the treatment of hypertension. However, the drugs like carvedilol (α_1 and β -blocker), have several limitations like extensive first-pass metabolism and unpredictable or low bioavailability. Carvedilol nanoemulsion based nanogel formulation for transdermal delivery is an alternative to its low oral bioavailability [95]. The results revealed that nano size range of oil globules crossed the skin barriers and achieved effective drug concentration in blood. Numerous calcium channel antagonists i.e. nicardipine hydrochloride [96], amlodipine [97] and felodipine [98] have poor oral bioavailability, short elimination half-life and extensive hepatic first pass metabolism. Water in oil nanoemulsion of nicardipine hydrochloride and o/w nanoemulsion of amlodipine and felodipine have been developed for transdermal delivery and have been successfully assessed against the treatment of hypertension. The better penetration of these calcium channel antagonists through the skin was attributed to the higher flux (due to the presence of surfactant and co-surfactant) and small droplet size of nanoemulsion [99].

➤ NANOEMULSION VACCINE

Nanoemulsions adjuvant vaccine is known to be composed of surfactant (Cremophor), co-surfactant (propylene glycol), and MRSA (Methicillin-Resistant Staphylococcus aureus) recombination protein antigen. This nanoemulsion vaccine showed good protein stability, protein structure integrity and protein specificity. It also improved the immune responses of immunoglobulin such as IgA, IgG1, IgG2a, and IgG2b, in the C57 mice nasal immunization and in the serum after Balb/c mice intramuscular

immunization. It also improved cytokine cell immune response such as interleukin-17A and interferon- γ , increased the survival ratio and decreased bacterial growth [83].

Nanoemulsions are efficient carriers for vaccine delivery because they are able to stay in circulation for long duration and are mostly reserved by antigen-presenting cells. Formulated nanoemulsion for gastric cancer-specific antigen MG7 and immune stimulatory CpG to examine nano carriers as an efficient drug delivery tool and reported growth reduction in pre-immunized mice. Nanoemulsions protect drugs from degradation [84], region-specific delivery of drugs, provide stability during storage, drug-delivery tool via different routes of administration permissive routes as topical, intravenous, and oral drug delivery [85]. Nanoemulsion formulations are prepared by formulation scientists using generally recognized as safe components [86]. Nanoemulsions with betulinic acid inhibited angiogenesis and also increased delivery efficiency [85]. Nanoemulsions are applied against pathogenic microorganisms, for prevention of drug against oxidative degradation and UV light thereby improving stability of drug, for efficient bioavailability and absorption of drug [87].

➤ FOOD AND AGRICULTURE

Vitamins are encapsulated and distributed in the bloodstream via the digestive system with high efficiency. Foods and drinks are prepared with nanoparticles without affecting the characteristics or taste. Nanoemulsions have also been used in ice cream to improve uniformity and texture [88]. Nanoemulsions of a potent insecticide Norcantharidin, against *Plutellaxylostella* have been produced by spontaneous emulsification method. The Norcantharidin loaded nanoemulsions contained 20% of butanol, 20% of cremophor EL, and 80% of triacetin. This emulsion reported enhanced insecticidal activity than Norcantharidin acetone solution alone, thus demonstrating valuable applications in agriculture [89].

➤ NANOEMULSIONS IN MRI TECHNOLOGY

Perfluorocarbons (PFC) are biologically inert compounds with high vapor pressure and very high oxygen and carbon dioxide affinity. These properties along with a short T1 and a long T2 time combined with a simple NMR spectrum of ^{19}F make it an ideal tool for tracking in MRI scan [90]. The gyromagnetic ratio of this when compared to ^1H differs by 6% and the relative sensitivity is 0.83. Perfluorocarbon nanoemulsion is used as an ultrasound contrast agent, drug delivery system and ^{19}F MRI. Nanoemulsions of these PFC's are even more stable and inert and ideal to be used as trackers. Moreover, they are ideal for oxygen sensing. FDA has approved a ^{19}F loaded nanoemulsion designed for non-invasive clinical cell tracking and imaging [91]. Perfluorooctyl bromide nanoemulsions can be utilized as multimodal probes for the identification of tumor and cancerous cells. Nanoemulsions bound with ^{129}Xe are reported to be potential tools for detection of lung cancer [92]. Jelena and Janic [93] reported a method where nanoemulsion can be used as a tracker in MRI scan. In another study, PFPE, a synthetic linear perfluoropolyether polymer was introduced to meet all of the above characteristics for a ^{19}F MRI cell tracking reagent. Linear PFPEs, as well as PCE, are synthesized from analog hydrocarbons by direct fluorination. Recently, linear PFPE was first used for ^{19}F cell tracking and quantification in vivo in a mouse diabetes model [93]. Emulsions of PFC can be created using the Oswald ripening method. They generally do not require high amounts of surfactants and can be stabilized by steric effects. The main drawback of using this method is difficulty in synthesizing stable emulsions. Branched PFCs tend to give more stable nanoemulsions than that of unbranched ones, the stability is dependent on structure rather than the emulsifier [93]. The emulsifiers used were non-toxic, chemically stable and reduced the large interfacial tension of the PFC. Phospholipids and pluronic are most common emulsifiers [93]. Safflower oil is generally used as an emulsifier as this decreases the Oswald ripening rate. The resulting emulsions have a low droplet size and a high PDI and hence are more stable [94, 99].

II. CONCLUSION

Nanoemulsion systems have distinct and more advantages over the disadvantages. Problems in storage due to Ostwald ripening can also be addressed by optimizing the synthesis media and parameters to a great extent. Though fragile systems, there have been a wide range of applications ranging from disinfectants to drug delivery systems to providing food-grade system as well as cosmetics and, have proved to be more efficient than the traditional systems due to its entropy and increased surface area and reduced adverse effects. The most successful and widely used method on a commercial scale is the use of high-pressure homogenizer to create nanoemulsion systems. Various advantages of

nanoemulsion has lead to the patenting of various nanoemulsion based products for commercial use. Advantageously, the surface charge, nanometer size and liquid nature of nanoemulsion collectively play significant role in the efficient delivery of medicaments. Nanoemulsion systems are running short of industrial acceptability due to lesser understanding about mode of nanodroplets formation and stability issues in final semisolid dosage forms. Understanding the charge over the surface of nanoemulsion droplets and over the skin and interfacial characteristics may be helpful enough for better therapeutic effectiveness. Nano-emulgel usher a new generation nanoemulsion based dosage forms due to the long term stability of nanoemulsion inside the gel matrix. Double and triple layer coated nanoemulsions have shown a glimpse of future medication. Finally, nanoemulsions seem to be the profitable option to the currently available marketed dosage forms for topical and transdermal use and have bright future in potential delivery of eminent preexisting or newly developed therapeutics in a more adequate and effective manner with high commercial and societal applicability.

ABBREVIATIONS

NE: Nanoemulsion,
PEG: Polyethylene glycon,
DM: Diabetes Mellitus,
nm: Nanometer,
T1DM: Type-1 Diabetes Mellitus,
T2DM: Type-2 Diabetes Mellitus,
GLP-1: glucagon-like Peptide-1,
OHA: Oral Hypoglycemic Agents,
GLUT-4: Glucose transporter type-4,
siRNA: short interfering Ribonucleic Acid,
DR: Diabetic Retinopathy,
DN: Diabetic Neuropathy,
BGL: Blood Glucose Levels,
HLB: Hydrophillic-lipophillic Balance.

REFERENCES

1. V Manimaran, PM Sivakumar, J Narayanan. Nanoemulsions-A better Approach for Anti Diabeticdrugs Delivering.
2. Patra, J. K., Fraceto, L. F., Das, G., & Campos, E. V. R. (Eds.). (2020). *Green Nanoparticles. Nanotechnology in the Life Sciences.*
3. Chime, S. A., Kenechukwu, F. C., &Attama, A. A. (2014). *Nanoemulsions — Advances in Formulation, Characterization and Applications in Drug Delivery. Application of Nanotechnology in Drug Delivery.*
4. Kotta S, Khan AW, Pramod K, Ansari S H, Sharma R K, Ali J (2012) Exploring oral nanoemulsions for bioavailability enhancement of poorly water-soluble drugs. Ex- pert Opin. Drug Deliv. 9(5): 585-598.
5. Kesharwani, P., Gorain, B., Low, S. Y., Tan, S. A., Ling, E. C. S., Lim, Y. K., ... Pandey, M. (2018). *Nanotechnology based approaches for anti-diabetic drugs delivery. Diabetes Research and Clinical Practice: 136; 52–77.*
6. Veisheh O, Tang BC, Whitehead KA, Anderson DG, Langer R. Managing diabetes with nanomedicine: challenges and opportunities. Nat. Publ. Gr. 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;361:1339–48..
8. Nadkarni Prashant, Weinstock Ruth S. Carbohydrates – ClinicalKey. Henry’s clin diagnosis managed by lab methods; 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 Pharmacol2017; 8:74.
10. Sarah Wild, GojkaRoglic, Anders Green, Richard Sicree, Hilary K. Global prevalence of diabetes: estimates for the year 2000 and projection for 2030. Diabetes Care 2004; 27: 1047–53.
11. Garcí'a-Pe´rez L-E, Alvarez M, Dilla T, Gil-Guille´n V, OrozcoBeltra´n D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther2013;4: 175–94.

12. Costanzo Linda S. Endocrine physiology – ClinicalKey. Physiol Ed.; n.d. p. 383–446.
13. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Insulin Resistance and Prediabetes, (2014).
14. Veisoh O, Tang BC, Whitehead KA, Anderson DG, Langer R. Managing diabetes with nanomedicine: challenges and opportunities. Nat. Publ. Gr. 2014;14.
15. Uppal, S., Italiya, K. S., Chitkara, D., & Mittal, A. (2018). *Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: an emerging paradigm for effective therapy. Acta Biomaterialia.*
16. H. Shrestha, R. Bala, S. Arora, Lipid-based drug delivery systems, J. Pharm. 2014 (2014).
17. C.J.H. Porter, N.L. Trevaskis, W.N. Charman, Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs, Nat. Rev. Drug Discovery 6 (2007) 231.
18. Shrestha, H., Bala, R., & Arora, S. (2014). *Lipid-Based Drug Delivery Systems. Journal of Pharmaceutics, 2014; 1–10.*
19. Feng, X., Lv, F., Liu, L., Tang, H., Xing, C., Yang, Q., & Wang, S. (2010). *Conjugated Polymer Nanoparticles for Drug Delivery and Imaging. ACS Applied Materials & Interfaces, 2(8); 2429–2435.*
20. Ye, F.; Ke, T.; Jeong, E.-K.; Wang, X.; Sun, Y.; Johnson, M.; Lu, Z.-R. Mol. Pharm. 2006, 3, 507–515.
21. Godwin, A.; Bolina, K.; Clochard, M.; Dinand, E.; Rankin, S.; Simic, S.; Brocchini, S. J. Pharm. Pharmacol. 2001, 53, 1175–1184.
22. Bhatt, R.; Vries, P.; Tulinsky, J.; Bellamy, G.; Baker, B.; Singer, J. W.; Klein, P. J. Med. Chem. 2003, 46, 190–193.
23. Auzenne, E.; Donato, N. J.; Li, C.; Leroux, E.; Proce, R. E.; Farquhar, D.; Klostergaard, J. Clin. Cancer Res. 2002, 8, 573–581.
24. S.R. Mudshinge, A.B. Deore, S. Patil, C.M. Bhalgat, Nanoparticles: emerging carriers for drug delivery, Saudi Pharm. J. 19 (3) (2011) 129–141.
25. S. Bhatia, Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications, in: Natural Polymer Drug Delivery Systems, Springer International Publishing, 2016, pp. 33–93.
26. Rao, J., & McClements, D. J. (2011). *Formation of Flavor Oil Microemulsions, Nanoemulsions and Emulsions: Influence of Composition and Preparation Method. Journal of Agricultural and Food Chemistry, 59(9), 5026–5035.*
27. McClements, D., Edible nanoemulsions: fabrication, properties, and functional performance. Soft Matter 2010.
28. Qian, C.; McClements, D., Formation of Nanoemulsions stabilized by Model Food-Grade Emulsifiers using High Pressure Homogenization: Factors Affecting Particle Size. Food Hydrocolloids 20 .
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, D.; Decker, E.; Weiss, J. Emulsion Based Delivery Systems for Lipophilic Bioactive Components. J. Food Sci. 2007, 72 (8), R109–R124.
31. S. Dokania, A.K. Joshi, Self-microemulsifying drug delivery system (SMEDDS)– challenges and road ahead, Drug Delivery 22 (6) (2015) 675–690.
32. Akhtar, J., Siddiqui, H. H., Fareed, S., Badruddeen, Khalid, M., & Aqil, M. (2015). *Nanoemulsion: for improved oral delivery of repaglinide. Drug Delivery, 23(6), 2026–2034.*
33. Yoon, G., Park, J. W., & Yoon, I.-S. (2013). *Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. Journal of Pharmaceutical Investigation, 43(5), 353–362.*
34. Anton N, Benoit JP, Saulnier P (2008) Design and production of nanoparticles formulated from nano-emulsion templates—a review. J Control Release 128:185–199
35. Shidhaye SS, Vaidya R, Sutar S, Patwardhan A, Kadam VJ (2008) Solid lipid nanoparticles and nanostructured lipid carriers— innovative generations of solid lipid carriers. Curr Drug Deliv 5:324–331
36. Das S, Chaudhury A (2011) Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech 12:62–76
37. Chen CC, Tsai TH, Huang ZR, Fang JY (2010) Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. Eur J Pharm Biopharm 74:474–482
38. H. Yuan, L. Lanting, Z.-G. Xu, S.-L. Li, P. Swiderski, S. Putta, M. Jonnalagadda, M. Kato, R. Natarajan, 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. 295 (2) (2008) F605–F617

39. A. Reynolds, D. Leake, Q. Boese, S. Scaringe, W.S. Marshall, A. Khvorova, Rational siRNA design for RNA interference, *Nat. Biotechnol.* 22 (3) (2004) 326–330
40. Hamed AC, Vitthal VC, Pravin DC (2013) Self emulsifying drug delivery system: A review. *Int. J. Pharm. Chem. Sci.* 2(1): 34 – 44.
41. Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C. (2011) A novel lipid-based oral drug delivery system of nevirapine. *Int. J. Pharm. Tech. Res.* 3(2):1159-1168.
42. Jingling T, Jin S, Fude C, Zhonggui H (2006) Preparation of self-emulsifying drug delivery systems of Ginkgo biloba extracts and in vitro dissolution studies. *Asian J. Trad. Med.* 1: 3-4.
43. Chime SA, Onyishi VI (2013) Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. *Afr. J. Pharm. Pharmacol.* 7(8): 3034-3059.
44. Shobhit K, Satish KG, Pramod KS (2012) Self-emulsifying drug delivery systems (sedds) for oral delivery of lipid based formulations - A review. *Afr. J. Basic App. Sci.* 4 (1): 07-11.
45. Obitte NC, Chukwu A (2010) The excipient usefulness of Carbosil and Landolphiaowariensis in two oil-based self-emulsifying formulations. *Asian J. Pharmaceut.* 4(4): 213- 219
46. Sachan R, Khatri K, Kasture SB (2010) Self-emulsifying drug delivery system a novel approach for enhancement of bioavailability. *Int. J. Pharm. Tech. Res.* 2(3): 738-1745.
47. Newton M, Petersson J, Podczek F, Clarke A, Booth S (2001) The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. *J. Pharm. Sci.* 90(8): 987-95.
48. Kyatanwas AU, Gajdhiye ND, Jadhav KR, Kadam VJ. (2010) Solid self emulsifying drug delivery system: A review. *J. Pharm. Res.* 3(4): 877-882.
49. Wadhwa J, Nair A, Kumria R (2012) Emulsion forming drug delivery system for lipophilic drugs. *Acta Poloniae Pharmaceutica – Drug Res.* 69(2): 179-191.
50. Shaji J, Jadhav D (2010) Newer approaches to self-emulsifying drug delivery system. *Int. J. Pharm. Pharm. Sci.* 2(1): 37-42.
51. Mehta PP, Mankanikar V, Parekh PP (2011) Self emulsifying drug delivery system: A novel approach to enhance oral bioavailability of poorly soluble drugs. *J. Pharm. Res.* 4(7): 2191-2194.
52. Gajendra S, Khinchi MP, Gupta MK, Dilip A, Adil H, Natasha S (2012) Self emulsifying drug delivery systems (SEEDS): An approach for delivery of poorly water soluble drug. *Int. J. Pharm. Life Sci.* 3(9): 991-1996.
53. Sharma V, Saxena PS, Singh P (2011) Self emulsifying drug delivery system. *J. Pharm. Res.* 3: 500-504.
54. Balakumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S (2013) Self nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: Design, formulation, bioavailability and pharmacokinetic evaluation. *Colloids Surf. Biointer.* 112: 337-43.
55. Obitte NC, Ofokansi KC, Nzekwe IT, Esimone CO, Okoye IE (2011) Self-nanoemulsifying drug delivery systems based on melon oil and its admixture with a homolipid from *Bos indicus* for the delivery of indomethacin. *Trop. J. Pharm. Res.* 10(3): 299-307.
56. Thomas N, Holm R, Garmer M, Karlsson JJ, Müllertz A, Rades T (2013) Supersaturated self-nanoemulsifying drug delivery systems (Super-SNEDDS) enhance the bioavailability of the poorly water-soluble drug simvastatin in dogs. *AAPS PharmSciTech.* 15(1):219-227.
57. Elsheikh MA, Elnaggar YSR, Gohar EY, Abdallah OY (2012) Nanoemulsion liquid pre-concentrates for raloxifene hydrochloride: Optimization and in vivo appraisal. *Int. J. Nanomed.* 7: 3787-3802.
58. Hiral AM, Ami YB, Ramesh BP, Jalpa SP, Tank HM (2013) Self nano emulsifying drug delivery system (SNEDDS): Future aspects. *Asian J. Pharm. Res.* 2013; 3(1): 21-27.
59. Yashpal S, Tanuj H, Harsh K (2013) Nanoemulsions: A pharmaceutical review. *Int. J. Pharma. Prof. Res.* 4(2): 928-935.
60. Charles L, Attama AA (2011) Current state of nanoemulsions in drug delivery. *J. Biomat. Nanobiotech.* 2: 626-639.
61. Ashish D. Gadhave ; Nanoemulsions: Formation, Stability and Applications; International Journal for Research in Science & Advanced Technologies Issue-3, Volume-2, 038-043.
62. Ronak P. Patel and Jay R. Joshi; AN OVERVIEW ON NANOEMULSION: A NOVEL APPROACH; IJPSR (2012), Vol. 3, Issue 12; accepted 20 November, 2012.
63. Hadgraft J: Skin, the final frontier. *Int. J. Pharm.* 2001; 224:1–18.
64. Basphinar Y, Keck M.C, Borchert H.H: Development of a positively charged prednicarbate nanoemulsion *Int. J. Pharm.* 2010; 383:201-208.

65. Junyaprasert B.V, Muller H.R, Souto B.E et al.: Q10 loaded NLC versus nanoemulsions; stability, rheology and in vitro skin permeation. *Int. J Pharm.* 2009; 377:207-214.
66. Ruktanonchai U, Sakulku U, Nuchuchua o, et.al: Characterization and mosquito repellent activity of citronella oil nanoemulsion *Int. J Pharm.* 2009. 112: 256-282.
67. Rai, V. K., Mishra, N., Yadav, K. S., & Yadav, N. P. (2018). *Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. Journal of Controlled Release, 270, 203–225.*
68. A.S.M. Wais, I. Nazish, A. Khale, M. Aqil, M. Khan, Formulation development ex-vivo and in-vivo evaluation of nanoemulsion for transdermal delivery of glibenclamide, *Int. J. Pharm. Pharm. Sci.* 5 (2013) 747-754.
69. D.M. Mostafa, S.H. Abd El-Alim, M.H. Asfour, S.Y. Al-Okbi, D.A. Mohamed, G. Awad, Transdermal nanoemulsions of *Foeniculum vulgare* Mill. essential oil: Preparation, characterization and evaluation of antidiabetic potential, *J. Drug Deliv. Sci. Technol.* 29 (2015) 99-106.
70. R.R. Lala, N.G. Awari, Nanoemulsion-based gel formulations of COX-2 inhibitors for enhanced efficacy in inflammatory conditions, *Appl. Nanosci.* 4 (2014) 143-151.
71. A. Azeem, S. Talegaonkar, L.M. Negi, F.J. Ahmad, R.K. Khar, Z. Iqbal, Oil based nanocarrier system for transdermal delivery of ropinirole: a mechanistic, pharmacokinetic and biochemical investigation, *Int. J. Pharm.* 422 (2012) 436-444.
72. R. Arora, G. Aggarwal, S.L. Harikumar, K. Kaur, Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of Ketoprofen, *Adv. Pharmaceu.* 2014 (2014) 12.
73. Cancer, Fact sheet 2017., Media Centre, World Health Organization.
74. S. Ganta, M. Talekar, A. Singh, T.P. Coleman, M.M. Amiji, Nanoemulsions in Translational Research—Opportunities and Challenges in Targeted Cancer Therapy, *AAPS PharmSciTech*, 15 (2014) 694-708.
75. S. Ganta, A. Singh, N.R. Patel, J. Cacaccio, Y.H. Rawal, B.J. Davis, M.M. Amiji, T.P. Coleman, Development of EGFR Targeted Nanoemulsion for Imaging and Novel Platinum Therapy of Ovarian Cancer, *Pharm. Res.* 31 (2014) 2490-2502.
76. C. Peptu, R. Rotaru, L. Ignat, A.C. Humelnicu, V. Harabagiu, C.A. Peptu, M.M. Leon, F. Mitu, E. Cojocaru, A. Boca, B.I. Tamba, Nanotechnology approaches for pain therapy through transdermal drug delivery, *Curr. Pharm. Des.* 21 (2015) 6125-6139.
77. F. Shakeel, W. Ramadan, Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions, *Colloids Surf. B*, 75 (2010) 356-362.
78. F. Shakeel, N. Haq, A. Al-Dhfyhan, F.K. Alanazi, I.A. Alsarra, Chemoprevention of skin cancer using low HLB surfactant nanoemulsion of 5-fluorouracil: a preliminary study, *Drug Deliv.* 22 (2015) 573-580.
79. F. Kuo, T. Kotyla, T. Wilson, L. Kifle, T. Panagiotou, I. Gruverman, J.B. Tagne, T. Shea, R. Nicolosi, A nanoemulsion of an anti-oxidant synergy formulation reduces tumor growth rate in neuroblastoma-bearing nude mice, *J. Exp. Ther. Oncol.* 6 (2007) 129-135.
80. M.F. Pinto, C.C. Moura, C. Nunes, M.A. Segundo, S.A. Costa Lima, S. Reis, A new topical formulation for psoriasis: Development of methotrexate-loaded nanostructured lipid carriers, *Int. J. Pharm.* 477 (2014) 519-526.
81. J. Somagoni, C.H. Boakye, C. Godugu, A.R. Patel, H.A. Mendonca Faria, V. Zucolotto, M. Singh, Nanomiengel—a novel drug delivery system for topical application—in vitro and in vivo evaluation, *PloS one*, 9 (2014) e115952.
82. S. Khandavilli, R. Panchagnula, Nanoemulsions as versatile formulations for paclitaxel delivery: peroral and dermal delivery studies in rats, *J. Invest. Dermatol.* 127 (2007) 154- 162.
83. Naseema, A., Kovooru, L., Behera, A. K., Kumar, K. P. P., & Srivastava, P. (2020). *A critical review of synthesis procedures, applications and future potential of nanoemulsions. Advances in Colloid and Interface Science, 102318.* doi:10.1016/j.cis.2020.102318 .
84. Sánchez-López E, Guerra M, Dias-ferreira J, Lopez-machado A, Ettcheto M, Cano A, Espina M, Camins A Garcia ML, Souto EB. Current Applications of Nanoemulsions in Cancer Therapeutics. *Nanomaterials* 2019; 9: 1–29.
85. Choudhury H, Pandey M, Gorain B, Chatterjee B, Madheswaran T, Mak K, Tambuwala M, Chourasia MK, Kesharwani P. Nanoemulsions as Effective Carriers for the Treatment of Lung Cancer. Elsevier Inc.; 2019.
86. Chime SA, Kenechukwu FC, Attama AA. Nanoemulsions — Advances in Formulation, Characterization and Applications in Drug Delivery. 2014.



87. Gorain B, Choudhury H, Nair AB, Dubey SK, Kesharwani P. Theranostic application of nanoemulsions in chemotherapy. *Drug Discov Today* 2020; 00: 1–15.
88. Prasad R, Bhattacharyya A, Nguyen QD. Nanotechnology in Sustainable Agriculture : Recent Developments, Challenges, and Perspectives. *Front Microbiol* 2017; 8: 1–13
89. Zeng L, Liu Y, Pan J, Liu X. Formulation and evaluation of norcanthridin nanoemulsions against the *Plutellaxylostella* (Lepidoptera :Plutellidae). *BMC Biotechnol* 2019; 19: 1–11.
90. Lanza GM, Winter PM, Neubauer AM, Caruthers SD, Hockett FD WS. 1H/19 F magnetic resonance molecular imaging with perfluorocarbon nanoparticles. *Curr Top Dev Biol* 2005; 70: 58–78.
91. Elgqvist J. Nanoparticles as Theranostic Vehicles in Experimental and Clinical Applications — Focus on Prostate and Breast Cancer. *Int J Mol Sci* 2017; 18: 1–53.
92. Jayapaul J, Schroder L. Nanoparticle-Based Contrast Agents for 129 Xe HyperCEST NMR and MRI Applications. *Contrast Media Mol Imaging* 2019; 2019: 1–25.
93. Jelena MJ, Eric TA. Fluorine-containing nanoemulsions for MRI cell tracking. *Wiley Interdiscip Rev NanomedNanobiotechnol* 2009; 1: 492–501. Partlow KC, Chen J, Brant JA, Neubauer AM, Meyerrose TE, Creer MH, Nolta JA, Caruthers SD, Lanza GM, Wickline SA. 19F magnetic resonance imaging for stem/progenitor cell tracking with multiple unique perfluorocarbon nanobeacons. *FASEB J* 2007; 21: 1647–1654.
94. K.B. Singh Bhuwanesh Pratap, Jain S.K, ShafaatKausar, Development and Characterization of ANanoemulsion Gel formulation for Transdermal delivery of Carvedilol, *Int. J. Drug Dev. Res.* 4 (2012); 151-161.
95. P.C. Wu, Y.H. Lin, J.S. Chang, Y.B. Huang, Y.H. Tsai, The effect of component of microemulsion for transdermal delivery of nicardipine hydrochloride, *Drug Dev Ind. Pharm.* 36 (2010); 1398-1403
96. D. Kumar, M. Aqil, M. Rizwan, Y. Sultana, M. Ali, Investigation of a nanoemulsion as vehicle for transdermal delivery of amlodipine, *Die Pharmazie*, 64 (2009) 80-85.
97. M. Trotta, S. Morel, M.R. Gasco, Effect of oil phase composition on the skin permeation of felodipine from o/w microemulsions, *Die Pharmazie*, 52 (1997) 50-53.
98. Rai, V. K., Mishra, N., Yadav, K. S., & Yadav, N. P. (2018). *Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. Journal of Controlled Release*, 270, 203–225. Doi: 10.1016/j.jconrel.2017.11.049.
99. Naseema, A., Kovooru, L., Behera, A. K., Kumar, K. P. P., & Srivastava, P. (2020). *A critical review of synthesis procedures, applications and future potential of nanoemulsions. Advances in Colloid and Interface Science*, 102318.



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