Int J Pharm Bio Sci 2015 Oct ; 6(4): (P) 306 - 334

Review Article **Pharmaceutics**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

APPROACHES FOR OVERCOMING POOR ORAL BIOAVAILABILITY OF DRUGS: NANOARCHITECTURES IN FOCUS

RANJITH ANISHETTY, SHIVANI PURI, VARUN GARG, ANKIT KUMAR YADAV AND AMIT MITTAL*

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144411, Punjab, India

ABSTRACT

Poor solubility of new drugs and their low oral bioavailability have become a major challenge for the pharmaceutical industries and the agencies that regulate them. Moreover, enzymatic and metabolic instability of these drugs has overburdened the scientists working in these areas to think for a better approach to formulate these drugs using novel technologies. For the last fifteen years, the impact of nanotechnology has become more evident in the area of oral drug delivery. The present review discusses various nanoarchitectures like nanosuspensions, lipidic nanocarriers, self-emulsifying delivery systems, liquisolid compacts, polymeric micelles and inorganic nanoparticles respectively. It also illustrates the advantages and challenges associated with their efficient delivery. Nanosuspensions and self-emulsifying drug delivery systems have gained maximum interest in the pharmaceutical market because of their industrial feasibility during scale up, stability, ease of preparation and lesser toxicity.

KEYWORDS: **Oral bioavailability, Poor solubility, Nanoarchitectures, Nanosuspensions, SNEDDS, Stability**

AMIT MITTAL
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144411, Punjab, India

1. INTRODUCTION

Oral route is considered the commonest and oldest route of drug administration. It offers various advantages over other routes of drug administration that includes patient compliance, convenience, stability, safety and economy. Oral delivery is very efficient for drugs having high solubility and gastrointestinal permeability. But drugs with poor aqueous solubility are not sufficient to provide bioavailability and therapeutic efficacy of drugs. Solubility, quantitatively, is defined as concentration of solute in a saturated solution at a certain temperature, whereas qualitatively it, is the formation of homogenous molecular dispersion arising out of interaction of two or more than two substances.[1] As per biopharmaceutical classification system (BCS), based on intestinal permeability and solubility, poorly soluble drugs are classified under class II and class IV.[2] These drugs are not able to enter into the aqueous medium and thus it becomes difficult to formulate them. Moreover, the low solubility also hinders their pre-formulation studies. About 70% of drugs prepared synthetically are reported to have poor aqueous solubility and thus bioavailability.[3] Therefore, due to poor aqueous solubility, development of efficient dosage form becomes a great challenge for pharmaceutical industries and agencies which regulate them.

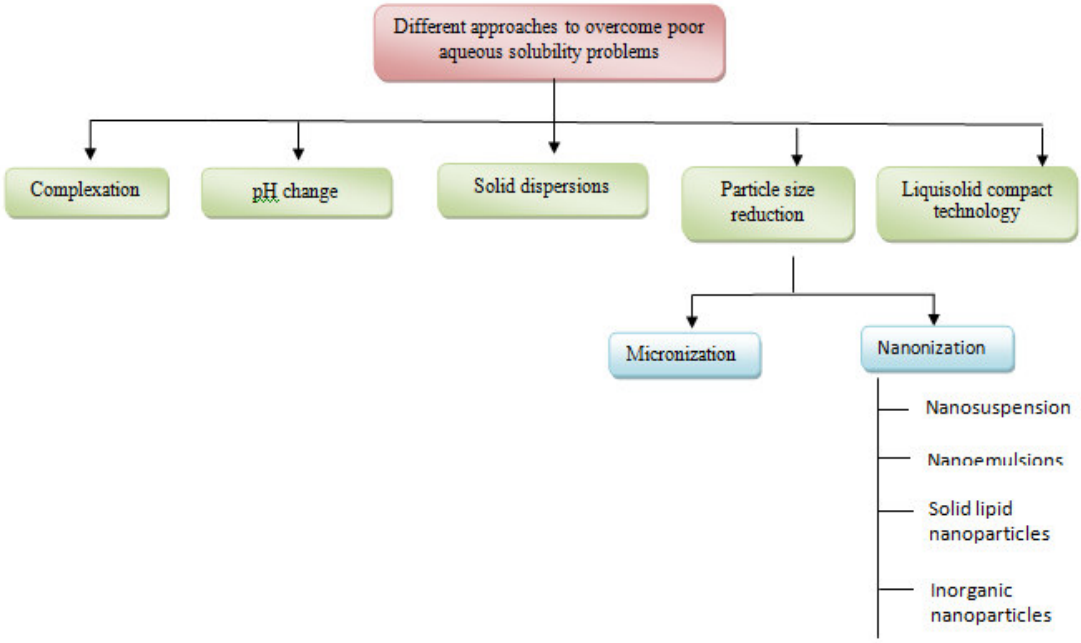
2.CHALLENGES /LIMITATIONS TO POORLY SOLUBLE DRUGS

1) *Poor aqueous solubility and intrinsic dissolution rate (mass of drug dissolved per unit time and area) of existing drugs.* Oral delivery of these drugs leads to low bioavailability, variability in absorption of drug, large variation in intra and inter subject pharmacokinetics and lack of dose proportionality.
2) *Reduced gastrointestinal permeability affects oral bioavailability of many drugs.* In these circumstances, higher drug doses are required to achieve plasma concentrations necessary for therapeutic effect e.g. Acyclovir.
3) *Presence of various chemical and enzymatic barriers in the gastrointestinal tract (GIT).* Enzymes like esterases, lipases cause degradation of many drugs, for example, antihyperlipidemic drugs like simvastatin, ezetimibe etc.
4) *Different pH at different location of GIT.* Stomach has an acidic pH of range 1.5-3.5 whereas intestine has basic pH of range 6.8 – 7.4. Different drugs undergo chemical degradation at different pH values. Ascandesartan, erythromycin, cilexetil etc. undergoes chemical degradation under acidic pH conditions while mercaptopurine, azathioprine etc. undergoes degradation under alkaline conditions.
5) *First pass metabolism.* High degree of first pass metabolism limit the oral bioavailability of many drugs such as antihypertensives, cardiovascular agents (beta-blockers, calcium channel blocker, ACE inhibitors) and antidiabetic agents (Repaglinide).
6) *Drug efflux transporters (p-glycoproteins).* These are responsible for efflux of various drugs like digoxin, paclitaxel which ultimately result in poor bioavailability.

3.VARIOUS APPROACHES TO OVERCOME THESE LIMITATIONS

These includes complexation, pH change, solid dispersions, particle size reduction (micronization and nanonization) and liquisolid compacts. The schematic diagram of various approaches to overcome poor aqueous solubility of drugs is shown in Figure 1.

Figure 1
Various approaches to overcome poor aqueous solubility of poorly soluble drugs.



3.1. Complexation

There are many examples where use of completion has helped in increasing the solubility of drugs. A typical example is Povidone Iodine. Complexation of poorly soluble drugs with cyclodextrins helps in enhancing the solubility and dissolution rate. Cyclodextrin is one of the versatile adjuvants which has gained good acceptance for enhancing solubility and dissolution rate. Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic cavity at the center which can accommodate a variety of hydrophobic drugs. These complexes are formed by adding nonpolar molecules (guests) into cavity of host molecule (Cyclodextrin). [4] The central hydrophobic cavity protects the poorly soluble molecule from the surrounding atmosphere. Consequently, lipophilic molecule is microencapsulated by the cyclodextrin (derivative) which results in favorable changes in chemical and physical properties of molecule. [5]

Limitations

I) Lipophilic compound should be able to form complex with the complexing agent or otherwise it may result in limited solubility enhancement.
II) Precipitation of complexes. This is also seen in combined techniques for solubility enhancement such as complexation with pH adjustment.
III) Toxicity due to complexing agents.
IV) Increased cost of production[4]

3.2. pH adjustment

Variability in pH within the GIT influences the bioavailability of pharmaceutical products. Drug absorption depends on diffusion rate which is largely affected by pH of GI fluid, pka of drug and permeability of plasma membrane to the drug. In case of drugs with poor water solubility, pH changes may cause protonation or, deprotonation of same chemical groups and thus affect the dissolution profile of the drugs. [4]

Limitations

I) Change in pH may result in hydrolysis of drug and can catalyze some degradative mechanism.

3.3. Solid dispersions

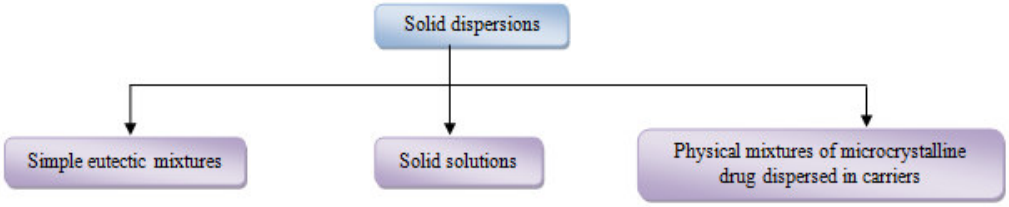
These are solid formulations, composed of carrier or matrix and drug. The carrier is inert and hydrophilic in nature, whereas the drug is hydrophobic. This method involves dispersion of one or more active ingredient in a highly

soluble solid hydrophilic inert carrier or matrix. [6,7] Carrier as well as drug dispersion can be either crystalline or amorphous in nature. [4] Most commonly used carriers are polyethylene glycols (PEGs), polyvinylpyrrolidone (PVP), labrasol, sugar, urea etc [8,9] Sulfathiazole, was the first drug whose rate and extent of absorption was enhanced using solid dispersion method. Improvement of solubility of poorly water soluble drugs is achieved by reduced particle size, improved wettability, increased porosity of particles and amorphous form of drug. [10, 11, 12, 13, 14] But commercial use of drugs prepared by using this technique is very limited. Solid dispersions are further sub-classified into simple eutectic mixtures, solid solutions and physical mixtures. The schematic diagram of classification of solid dispersions is shown in Figure 2.

Limitations

I) Lack of physical and chemical stability of drugs.
II) Method of preparation.
III) Formulation of solid dispersion into various dosage forms.
IV) Scale-up of manufacturing processes.
V) Lack of reproducibility of its physicochemical properties.

Figure 2
Classification of solid dispersions



3.4. Liquisolid compaction technology

This technique is considered as one of the efficient techniques to improve the dissolution and solubility. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medicament. Here the liquid medicament is the water insoluble drug. Suitable non-volatile solvent is used to carry the liquid medicament. By addition of various excipients, liquid medicament is converted into powdered form. [15] A non-sticky and easily compressible blend is formed by addition of proper concentrations of excipients such as carriers, disintegrants, coating material, lubricant and glidants. The process of formulation of liquisolid compacts is shown in Figure 3. This technique promotes dissolution by completely solubilising the drug in the solvent before its conversion into powdered mass. [16,17] The drug in solid dosage form may be present in a solution or in a solubilised form which leads to remarkable change in wetting properties and effective surface area. [15] Finally more drugs are available for dissolution which increase drug release characteristics and enhance oral bioavailability. A comparative study of dissolution rate of indomethacin by liquisolid compact technology (ILS-1), direct compressed tablet (DCT) and conventional capsule in different solution media is shown in Figure 4. Liquisolid compacts are comprised of non volatile liquid, carrier material, disintegrant, glidant, coating material, release retardant material and lubricant. List of various ingredients is shown in Table I.

Figure 3
Method of preparation of liquisolid compacts.

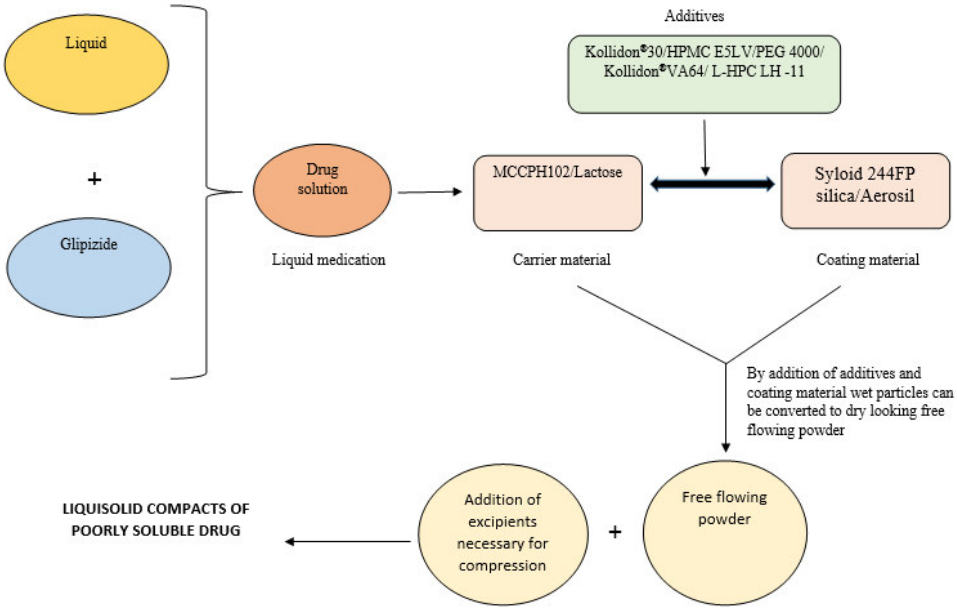


Figure 4
Comparision of 10-min dissolution rate of indomethacin shown by liquisolid compacts (ILS-1), directly compressed tablet (DCT) and conventional capsule in different dissolution media [18]

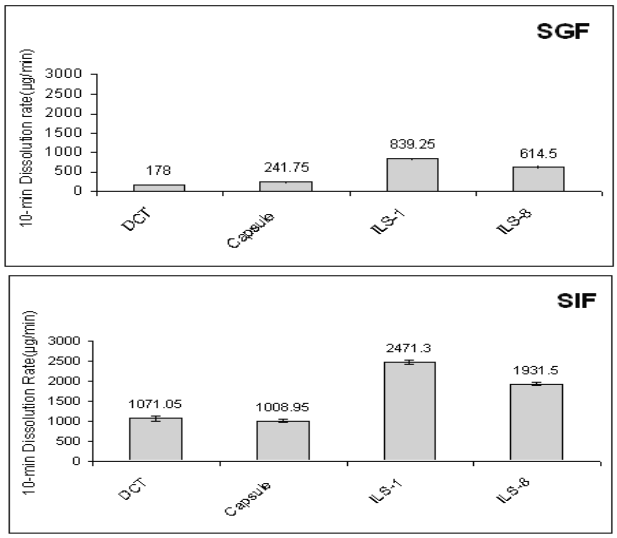


Table I
Components of Liquisolid Compact System. [19]

Components	Examples
Non Volatile Liquid	Polyethylene glycol (PEG) 200, PEG 300, PEG 400 Fixed oil, Glycerine, Propylene glycol.
Carrier Material	Microcrystalline cellulose (MCC) PH101, MCC PH200, Lactose, Methyl cellulose, Ethyl cellulose, Starch 1500, Hydroxy Propyl Methyl Cellulose, Guar Gum etc.
Disintegrant	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidone etc.
Glidant	Talc
Coating Material	Aerosil 200 (Cab-O-Sil M5), Syloid 244FP, Colloidal Silicon Dioxide.
Release Retardant Material	Eudragit RS, Eudragit RL, Hydroxyl Propyl Methyl Cellulose K100M, K15M, K4M.
Lubricant	Magnesium Stearate.

Limitations

I) Requirement of high solubility of drug in non-volatile solvent.
II) Higher specific surface area and absorption capability of non-volatile solvent.
III) High dose of insoluble drugs cannot be formulated as liquisolid compact (>100mg). In this technology the drug is first dissolved in a non-volatile liquid and followed by the adsorption of nonvolatile liquid on a solid carrier like aerosol of microcrystalline cellulose or, lactose. This is done to increase the flow property of powder and to avoid stickiness of the formulation to punches and dies during compaction process. Hence, if the dose of the poorly soluble drug is high, one has to increase the volume of non-volatile liquid to dissolve the drug. In order to make the drug solution freely flowable, the amount of solid carrier has to be increased. This would increase the total unit weight of tablet, even more than 1 gm. This lead to patient incompliance.
IV) Squeezing out of liquid drug at the time of compression result in inappropriate hardness.
V) Difficulty to load two or more poorly soluble drugs in a single non-volatile liquid for concomitant administration because it is not always possible that both the drugs used will be soluble to their required dose in a single non-volatile solvent will be soluble to their required dose in a single non-volatile liquid and within the same volume.

3.5. Particle size reduction

During last 20 years, a new strategy has been evolved to deal with reduction of drug particle size for overcoming poor oral bioavailability of various formulations.[20] Conventionally, the methods of comminution and spray drying are used for particle size reduction. These methods rely upon the principle of mechanical strength to break the active ingredient. Mechanical forces such as milling and grinding, often impart physical stress on drug particle due to which it undergoes degradation. Nowadays, particle size reduction is carried out by two ways

a) Micronization
b) Nanonization.

Micronization of drug particle (<10 µm) is done by milling techniques using jet mill, rotor stator colloid mill etc. This technique has applied to various drugs like spironolactone, progesterone, griseofulvin etc. It results in significant increase in absorption, oral bioavailability and efficacy of many pharmaceutical formulations. [21] Nanonization or nanotechnology has revolutionized the field of drug discovery. Nanosized drug particles increase the solution velocity and saturation solubility due to creation of high energy surfaces and vapor pressure effect. Various technologies under nanonization includes

I) Nanosuspension
II) Nanoemulsion
III) Self- Emulsifying Drug Delivery System (SEDDS)
  i. Self-Micro Emulsifying Drug Delivery System (SMEDDS)
  ii. Self-Nano Emulsifying Drug Delivery system (SNEDDS)
IV) Liposomes
V) Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC)
VI) Inorganic nanoparticles
VII) Polymeric micelles.

3.5.1. Nanosuspension

Nanosuspensions are defined as sub-micron colloidal dispersions of a drug particles in a continuous liquid phase. This formulation is preferred for ‘Brick Dust Compounds’ (which are not soluble in water as well as in lipid) due to high melting point, high crystal energy and a reluctance to dissolve in any solvent. Uniformity in particle size prevents the existence of varying saturation solubility and concentration gradient, ultimately preventing ‘Ostwald’s Ripening Effect’. This effect leads to growth of crystals and subsequently conversion of nanoparticles to microparticles. Varying particle size creates difference in dissolution pressure/saturation solubility. Molecules tends to diffuse from high concentration area (around small particles) having high saturation solubility to an area around larger particles. It leads to creation of supersaturated solution around larger particles which results in crystal growth. This preparation also lead to increase in crystal structure. Various processes used for preparation of nanosuspensions are

precipitation,[22,23] pearl milling,[24] high pressure homogenization. [25,26]

Advantages

I) Ease of manufacturing.
II) Ease of scale up in case of large scale production.
III) Prolonged stability due to stabilizers.
IV) Oral administration provides rapid onset of action and enhanced bioavailability.
V) IV administration of nanosuspension provides rapid dissolution and tissue targeting.
VI) In case of SC/IM administration, reduced tissue irritation.
VII) Ocular administration and inhalational delivery of nanosuspensions provides higher bioavailability.
VIII) Drugs with high logP valve can be formulated as nanosuspensions to enhance bioavailability.
IX) Enhanced biological response.
X) It can be formulated in the form of pellets, suppositories and hydrogels which make it suitable for various routes of administrations.

3.5.2. Nanoemulsions

These are dispersions of nanoscale droplet, consisting of emulsified oil and water system, with mean droplet diameter ranging from 50-1000 nm. These are formed with the use of pharmaceutical surfactants which are generally recognized as safe (GRAS). These emulsions can be readily manufactured in large quantity. A hydrophobic oily phase is intimately mixed with a hydrophilic phase by shear induced rupturing. This process yields uniform droplet particles that remain stable for many years even at elevated temperatures. The surfactants used provides good stability to the nanoemulsion by preventing coalescence. They possess capacity to dissolve large amount of less soluble drugs. They also prevent poorly soluble drugs from hydrolysis and enzymatic degradation. [27]

Advantages

I) Capacity to load large quantity of drug.
II) Enhanced drug solubility and bioavailability.
III) Controlled drug release.
IV) Reduction of variability in bioavailability patients.
V) Prevention of enzymatic degradation and hydrolysis.

3.5.3. Self-emulsifying drug delivery system (SEDDS)

These are the anhydrous isotropic mixtures oil, drug and one or, more surfactants resulting in the formation of nanoemulsion. Nanoemulsions are thermodynamically stable unlike the conversional emulsions. [28] SEDDS are constituted by lipids, surfactants and co-surfactants.

Advantages

I) Fast onset of action.
II) Reduced drug dose.
III)Ease of scale-up and manufacturing.
IV) Enhanced solubility and oral bioavailability.
V) Peptide delivery can also be done due to prevention of enzymatic hydrolysis in GIT.
VI) Increased drug loading capacity.

3.5.4. Liposomes

These are bilayer (double-layer), liquid filled bubbles made from phospholipids. These can be used to encapsulate both lipid soluble and water soluble drugs. These have proved to be very successful in delivery of antifungal drugs for systemic infection. A number of commercially available preparations have been successful in active as well passive targeting of drugs.

3.5.5. Solid Lipid Nanocarriers (SLN) and Nanostructured Lipid Carriers (NLC)

SLNs are formed of biodegradable lipids like monoglycerides, triglycerides, hard fats and waxes which are solid at physiological temperatures. On the other hand NLC comprise of both liquid lipids and solid lipids taken in an appropriate ratio.[29] Liquid lipid in NLC results in long-term colloidal stability, greater drug loading and drug encapsulation. [30,31] These both provide same advantages as that of SEDDS.

3.5.6. Inorganic Nanoparticles

These include particles composed of metals or metal oxides with dimensions in nanometer range. Most commonly used inorganic materials include gold, titanium, iron, silicon, mesoporous nanoparticles. Inorganic nanoparticles may have potential in oral drug

delivery system due to their immutability and lack of any biochemical alterations as reported in various studies. [32]

3.5.7. Polymeric Micelles

In this technology, lipophilic drug is encapsulated within core in dissolved state which is further stabilized by surfactant or polymeric shell to prevent rapid release of drug from core. Various surfactants used are poloxamers, lecithin and tween 80. In aqueous milieu, the polymers self-aggregate and form supramolecular structures, either with a solid core or a fluid structure. If solid core taken then nanospheres are formed and if fluid structure is taken polymeric micelles are formed. [33]

Advantages

I) Hydrophobic core serves as a solubilization depot for poorly aqueous soluble drugs.
II) Longer circulation time and improved accumulation at tissue site which ultimately prevents rapid clearance.

A detail study of different nanoarchitectures is described in subsequent sections.

4. NANOSUSPENSION

4.1. Choice of drug for nanosuspensions

I) Poorly water soluble /water insoluble but soluble in oil (high log P valve).
II) Brick dust compounds (insoluble in both water and oil).
III) For API (Active Pharmaceutical Ingredient) with large dose.
IV) Reduced ability of crystal to dissolve, regardless of solvent.

4.2. Methods of preparation of nanosuspension

Nanosuspensions are mostly prepared by two methods -

1) Bottom-up technology 2) Top-down technology

Various method of preparation of nanosuspensions are shown in Figure 5. Various excipients used in the formulation of nanosuspensions are enlisted below in Table II.

Figure 5
Various methods for preparation of nanosuspension

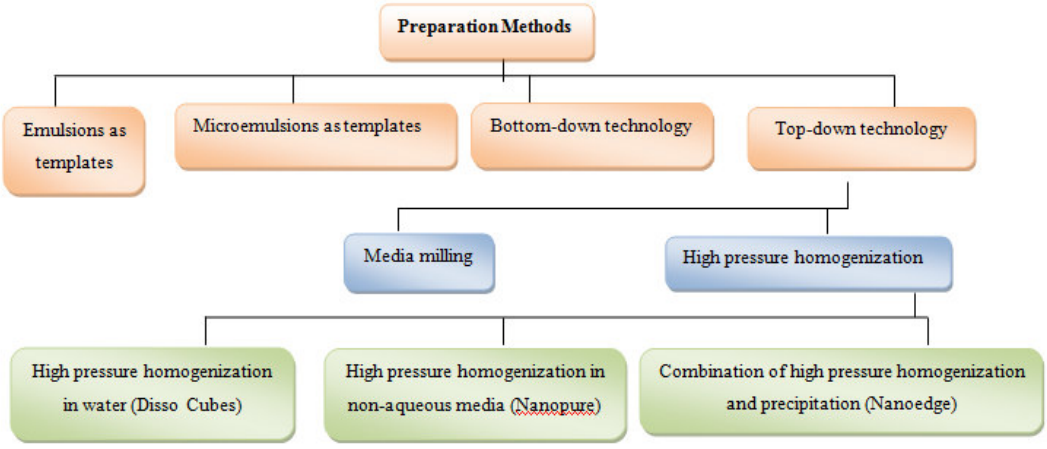


Table II
Excipients used in formulation of nanosuspension[4]

Sr.No.	Excipients	Functions	Examples
1	Stabilizers	For wetting of drug particles, Prevent agglomerate of particles and Ostwald's ripening effect also provide steric and ionic barrier.	Poloxamers, Polysorbate, Lecithin, Cellulosic, Povidones
2	Co-surfactants	Influence phase behavior	Dipotassium, Glycerrhizinate, Isopropanol, Bile salts, Transcutol, Glycofurol, Ethanol.
3	Organic solvents	Less hazardous solvents used for nanosuspension preparation.	Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol
4	Other additives	Based on the requirement of drug property and route of administration.	Buffers, Salts, Cryoprotectants etc.

4.2.1. Bottom-up technology

In this technology organic drug solution is admixed with miscible non solvent, this leads to formation of nanoparticles via precipitation. This is a traditional method known as Via Humid Paratum (V.H.P). Various strategies under bottom-up technology for nanoparticles preparation are

a) Solvent-antisolvent method
b) Supercritical fluid processes
c)High gravity controlled precipitation technology
d) Melt emulsification method
e) Confined liquid impinging jets
f) Sonoprecipitation
g) Multi-inlet vortex mixer
h) Spray drying
i) Freeze drying

Brief explanation of the different bottom-up technologies is shown in Table III. The major hurdle associated with this method is crystal growth after precipitation that leads to conversion of nanoparticle to microparticle. Presence of residual solvents is another problem. Various drug nanocrystals prepared by bottom-up technology are under clinical trials are shown in Table IV.

Table III

List of various bottom–up technologies for nanosuspension preparation

S. No.	Method of preparation	Principle	Advantages	Limitations	Compound loaded	References
1	Solvent-antisolvent method	Mixing the solution of poorly soluble drug and antisolvent using magnetic stirrer in a small beaker, when ingredients and conditions are appropriate.	Absence of Ostwald's ripening effect	Large amount of organic solvent required, problems in scale-up	Ezetimibe	34,35
2	Super critical fluid process	Supercritical fluid (SCF) is utilized. SCF have low density, viscosity and also high diffution rate to attain rapid micro-mixing for precipitation. e.g supercritical CO_2. Poorly soluble active ingredient when dissolved in low polarity CO_2 form a solution, it lead to loss of solvent power of SCF which results in precipitation of drug as fine particles.	Used for preparation of protein nanoparticle.	Difficulty in removal of residual solvent which act as an contaminant, use of hazardous solvents, usage of high proportions of stabilizers and surfactants in comparison to other techniques.	Triflusal	3, 36, 37
3	High gravity controlled precipitation technology (HGCPT)	Carried out using rotating packed bed and based on mass transfer principle. Micro-mixing of reaction phases is achieved under high gravity environment which facilitates generation of higher supersaturated concentration of the product in the precipitation process.	Cost effective scale up in case of large scale production, better control over various parameters like, particle size and distribution, particle shape, morphology and stability.	Key factors such as rotating speed (high-gravity level) and volume flow difficult to scale up.	Salbutamol sulphate	39,40,41
4	Melt emulsification	Formulation of hot emulsion with drug in dispersed phase, later homogenization with high pressure homogenizer and finally cooled to solidify the formed droplet.	Increase in mean particle size due to increase in drug concentration.	Formation of larger droplets and make particles unstable.	Ketoprofen,Naproxen	42
5	Confined liquid impinging jets (CLIJ)	Precipitation of drug is done by excess of turbulence and intense	It is a single pass process therefore precipitation	Crystal growth may occur.		43,44

		mixing generated by jet of drug solution impinging a jet of antisolvent entering through two opposite nozzles mounted inside a small chamber.	achieved sooner after mixing.			
6	Sonoprecipitation	Ultrasound boosts the mass transfer when it travels through liquid medium and initiate cavitation. It is followed by collapse releasing powerful shock waves due to high temperature and pressure for nucleation. Within seconds of ultrasound application to mixture, solvent and antisolvent mixed homogeneously. Ultrasound waves cause faster and more uniform nucleation through the sonicated volume, leading to more uniform crystals.	Amorphization, increased surface area, decreased diffusion layer thickness.	Lack of suitable equipment for commercial production.		45,46
7	Multi-inlet vortex mixer (MIVM)	It enables mixing of streams of unequal volumetric flows. MIVM has capability to control supersaturation as well as solvent quantity by changing individual stream velocity.	It depresses the rate of Ostwald's ripening effect, and final fluid phase is predominantly anti-solvent phase.	Optimization of flow rate is difficult in scale-up processes.		47,48
8	Spray drying	Liquid feedstock is atomized into spray of droplets and evaporates it in hot air chamber to form dry particles. It mainly involve four steps: 1) atomization of feed into spray, 2) spray-hot air contact, 3) drying of spray, 4) separation of dried product from hot air.	High percentage yield (>70%)	Chemical degradation due to hot drying air.	Mannitol, Trehalose	49,50
9	Freeze drying (lyophilization)	In this frozen solution is dried under vaccum, at which ice formed is eliminated by sublimation and a secondary drying to remove final traces of water which remains due to absorption.	Thermolabile compounds can also be processed.	Costly unit process.		51

Table IV
List of various nanosuspension prepared by bottom up technology which are in market and clinical trial [52]

Sr. No.	Brand Name, Active Ingredient, Company	Therapeutic Indication	Manufacturing process	Dosage form	Status
1	Gris-PEG®, Griseofulvin /Novartis	Antifungal	Bottom-up coprecipitation	Tablet	Marketed
2	Cesamel® Nabilone /Lilly	Antiemetic	Bottom-up coprecipitation	Capsule	Marketed
3	Itraconazole	Antifungal	Bottom-up precipitation	Nanosuspension	In-vivo (rat) in clinical trials

4.2.2. Top-down technology

This involves particle size reduction using various wet milling techniques such as: media milling and high pressure homogenization. In this, the micronized or nonmicronized drug particle is suspended in an aqueous or non-aqueous dispersion medium containing surfactants or polymeric stabilizers.[53] Then this suspension is passed through high pressure homogenizer or a ball mill and leads to break down of larger drug particles to nanosized particles.[54] Any drug which is poorly soluble in aqueous as well as non-aqueous media can be processed by using this technology. Top-down technology is more popular in comparison to bottom-up technology. Various processes under top-down technology are discussed below.

4.2.2.1. High pressure homogenization

This technique involves forcing of the suspension through a narrow gap of about 25 µm at a very high pressure of 1500 bars that lead to creation of cavitational forces. This force reduces drug particle size to nano range.[55] Reduction in particle size upto 25µm is accompanied by enhanced dynamic and reduced static pressure below the boiling point of water at room temperature. This leads to boiling of water at room temperature. Due to high pressure, gas bubbles are formed which cause cavitation. Then fluid leaves the homogenization gap. The particles size is also reduced due to high shear forces and collision of particles with each other. The size of the nanoparticles formed depends on various factors like number of homogenization cycles, homogenizer pressure, power density of homogenizer and temperature. [56] Drug in micron size range is preferred for this process so that less time is consumed in diminution process and also to prevent the clogging of the machine. Therefore, jet milled drug powders have to be used. [57]

Advantages

I) Very dilute as well as highly concentrated nanosuspensions can be prepared.
II) Does not cause erosion of processed material.
III) Can be used for drugs insoluble in both aqueous as well as non-aqueous media.
IV) Enables aseptic production of nanosuspensions for parenteral use.
V) Homogenization process has sterilizing effect.

Disadvantages

I) Micronization of drug is required.
II) Costly instruments are required, which increase cost of dosage form.

4.2.2.2. Media milling

Nanoparticles are formed by treating the drug to media milling. Media milling involves the shearing of milling media against the drug particles. This generates large amount of energy, which is sufficient to break microparticles into nanoparticles. The nanosuspensions are manufactured by using high shear media mills or pearl mills. The proper evaluation of type and concentration of stabilizer used is a key parameter to have a good nanosuspension using this technique. The procedure of operation includes addition of aqueous suspension of drug into the milling chamber containing small grinding balls/pearls. This is followed by addition of stabilizers in milling medium. The grinding balls rotate at a high shear speed resulting in the generation of friction and impact on drug particles, which ultimately causes reduction in

particle size. The milling media or balls are made of zirconium oxide, ceramic-sintered aluminum oxide or highly cross-linked polystyrene resins.[58] Typically, it requires 30-120 min to reduce the particle size to < 200nm. It is reported that zeta potential of nanosuspension is dependent upon drug and polymer ratio and the speed of milling, whereas particle size is dependent upon the time and speed of milling. The major disadvantage of wet media milling is crystal defects. These are due to unsymmetry in the crystal surface and generation of localized amorphous regions. There is restricted capacity of equipment due to heavy apparatus e.g. in ball mill, it is restricted to certain limited quantity of drug. Change on particles form of drug may also develop due to high shearing forces. Various FDA approved drugs prepared by top-down technology are shown in Table V.

Table V
Various marketed products manufactured by top-down technology which are taken by oral route. [59]

Sr. No.	Brand Name, Active Ingredient, Company	Therapeutic Category	Manufacturing process	Dosage form
1	Rapamune®, Sirolimus, Wyeth	Immunosuppressant	Top-down , Media milling	Tablet
2	Tricor®, Fenofibrate, Abbott	Hypercholesterolemia	Top-down , Media milling	Tablet
3	Megace®, ES, Megasterol acetate, Par pharmaceuticals	Appetite stimulant	Top-down , Media milling	Oral suspension
4	Emend®, Aprepitant, Merck	Antiemetic	Top-down , Media milling	Capsule
5	Triglide®,Fenofibrate, Skye pharma	Hypercholesterolemia	Top-down , high pressure homogenization	Tablet
6	Panzem®,NCD, 2-Methoxy estradiol, EnterMed Inc.	Anti-proliferative and anti-angiogenic effect	Nanosuspension	Nanosuspension

4.3. Other methods for preparation of nanosuspensions

4.3.1. Dry co-grinding

Dry milling technique can be used as an alternative to produce nanosuspensions. There are several successful reports wherein stable nanosuspensions of poorly soluble drugs have been prepared using dry-grinding technique using suitable polymers and co-polymers. [20,60,61] Itoh et al (2003) reported the colloidal particles formation of many poorly water soluble drugs like griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinyl pyrrolidone (PVP) and sodium dodecyl sulfate (SDS). Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxyl propyl methylcellulose (HPMC) and cyclo-dextrin derivatives have been used to prepare nanosuspensions by dry co-grinding. [62,63,64,65] The improvement in the surface polarity and transformation from a crystalline to an amorphous drug was the main cause for improvement of drug solubility, dissolution and other physicochemical properties of poorly water soluble drugs.[66,67] Dry cogrinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained.

4.3.2. Homogenization in Non Aqueous Media (Nanopure)

Nanopure is a unique technology in which suspension is homogenized in water-free media or water mixtures. [68] Dissocubes is the technology where cavitation is the determining factor for the production of nanosuspensions. But, in contrast to that technique where water is used, oils and oily fatty acids may be used as they have very low vapour pressure and a high boiling point. Thus, the drop of static pressure will not be sufficient enough to initiate cavitation. There are patents that cover disintegration of polymeric material by high-pressure homogenization at higher temperatures of about 80°C with promoted disintegration, which cannot be used for thermolabile compounds. "*The suspensions of drugs prepared in the non-aqueous media which are homogenized at 0°C or less. are called "deep-freeze" homogenization*". The results obtained were comparable to Dissocubes and hence they are found effective for production of nanosuspension of thermolabile substances at milder conditions.

4.3.3. Precipitation Method

Using precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent. In water-solvent mixture the solubility is low and the drug precipitates. Mixing processes in this method, vary considerably. Precipitation has also been coupled with high shear processing. The nanoedge process (registered trademark of Baxter International Inc. and its subsidiaries) relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy. [69] The major drawback of this technique is crystal growth/Ostwald ripening during long term stability.

4.3.4. Nanoedge

The basic principles of Nanoedge are the same as that of precipitation and homogenization. The combination of these two techniques results in smaller particle size and better stability of formulation in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology. Rapid addition of a drug solution to an anti-solvent leads to sudden super-saturation of the mixed solution, and generation of fine crystalline or, amorphous solids. Precipitation of an amorphous material may be favoured at high super-saturation when the solubility of the amorphous state is exceeded. The success of drug nanosuspensions prepared by precipitation techniques has been reported. [69,70,71,72] In this technique, the precipitated suspension is further homogenized, leading to reduction in particle size and avoiding crystal growth. Precipitation is carried out in water using water-miscible solvents such as methanol, ethanol and isopropanol. Although these solvents can be tolerated to a certain extent in the formulation but it is desirable to remove those solvents completely. For an effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be included to provide a solvent-free modified starting material followed by high-pressure homogenization.

4.3.4. Nanojet technology

Nanojet technology/ opposite stream uses a chamber where a stream of suspension is divided into two or more parts that collide with each other at high pressure. The high shear force produced during the process results in particle size reduction.The equipments used to prepare nano-suspensions by this technique include M110L and M110S micro fluidizers (Microfluidics). The major limitations of this technique include its high number of passes through the microfluidizer and the presence of a relatively larger fraction of microparticles in the product.

4.3.5. Emulsions as templates

Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The drugs that are soluble in either volatile organic solvent or partially water-miscible solvent, are suitable candidates to be formulated into nanosuspensions by using this technique. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drug nanosuspensions by using this emulsification method. In the first method, an organic solvent or mixture of solvents are loaded with the drug and then dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. It is important to note that since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion droplet. Optimization of the surfactant composition further increases the intake of organic phase and thereby ultimately affecting the drug loading in the emulsion. Organic solvents such as methylene chloride and chloroform are widely used to prepare nanosuspensions by this technique. [73]

4.3.6. Microemulsions as templates

Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant and co surfactant. [74]

4.4. Some examples of nanosuspensions prepared by top-down technology

Nevirapine

Nevirapine is used in treatment of AIDS. It is a BCS class 2, non-nucleoside reverse transcriptase inhibitor (NNRTIs). Its bioavailability is low and variable. Its bioavailability has been improved by formulating as nanosuspensions. Nevirapine nanosuspension was prepared using nanoedge method. Solubility studies were performed initially for selection of a suitable solvent. The solvents used were ethanol, methanol, dichloromethane, isopropanol, acetone and ethyl acetate. Nevirapine was dissolved with the help of a sonicator and cyclo mixture. Dichloromethane was found to be an optimum solvent and was used for the preparation of nanosuspension.

Two step process was used to prepare nanosuspension. Firstly the drug was solubilized in the selected solvent at room temperature. This drug solution was then added drop by drop, to two containers having different volumes of water, to which varying concentrations of surfactants have been added. The containers were stirred at room temperature on magnetic stirrer and volatile solvents were evaporated. After three hours of stirring, precipitation of nanosuspension was observed. By changing the surfactants and other excipients, a number of nanosuspensions with varying properties were prepared. [75]

Valsartan

Valsartan is an antihypertensive drug belonging to the class of angiotensin receptor blockers (ARBs). Initially the surfactants were dissolved in water in variable amounts. To this aqueous phase, the powdered drug was added and dispersed at high rpm in ultrasonic homogenizer for 30 minutes. [76]

Fenofibrate

Fenofibrate (Tricor) is used to reduce cholesterol level in blood and belongs to class fibrates. The drug is lipophilic in nature and to enhance its dissolution rate and bioavailability, its nanosuspension was prepared by the combination of melt emulsification method and high pressure homogenization. Polaxamer - 188 and PVP K-30 were used as surfactants. This method was found to be more energy efficient when compared to the conventional methods. The pharmacokinetic studies in rats revealed increased AUC (0-36h) and Cmax of the prepared nanosuspension as compared to the reference formulation. [77]

Itraconazole

Itraconazole is a triazole antifungal agent. Poor water solubility, insufficient bioavailability, fluctuating plasma level and high food dependency are the main problems with this drug. Its nanosuspension was prepared by media milling method, where zirconium oxide beads were used as milling media, glycerol as a wetting agent and poloxamer 407 as a stabilizer. The characterization of the prepared formulation was done by studying particle size distribution, drug loading, DSC, SEM and X-ray diffraction. Spherical particles with mean particle diameter of 294 nm were prepared in the optimized batch of nanosuspension. Drug was found to be chemically stable in the prepared nanosuspension and its dissolution profile was comparable to the marketed formulation and pure drug. [75]

4.5 Nanosuspensions prepared by bottom-up technology

Curcumin

It is obtained from rhizomes of *Curcuma longa,* It is mainly used as antioxidant, anti-inflammatory, chemopreventive and chemotherapeutic agent. In bottom up technology, the drug solution is first prepared in a non-polar solvent which is added to a polar solvent resulting in precipitation. Nanosuspension is prepared by this technology using saturation solubility with acetone as nonpolar solvent and water as polar solvent. About 200 mg of curcumin crystal was dissolved in 10 ml of acetone. This solution was added drop wise to 100 ml of distilled water which was previously kept on a magnetic stirrer for continuous stirring. The particle size of the prepared suspension showed the diameter of 436 ± 122.8 (1SD) nm. The density of the suspension was found to be 3.2g/cc at 27.6°C. [78]

Esomeprazole

Esomeprazole is a proton pump inhibitor. Its nanosuspension was prepared by evaporative precipitation ultrasonication method. The drug

was dissolved in methanol at room temperature to form solutions containing different strengths of the drug. Similarly antisolvents solutions containing varying concentration of non-ionic surfactants like pluronic F68 and pluronic F-127 were prepared. All solvents and antisolvent solutions were filtered to 0.2 µm syringe filter. The organic solutions were added drop by drop to antisolvent solutions, temperature of which was maintained at 40°C. These were subjected to with constant stirring for 2h for drug precipitation. The volatile solvent was evaporated and each sample was sonicated with an ultrasound probe. The samples were kept in ice water bath during sonication. [79]

4.5. Various patents on nanosuspensions formulation

There are various nanosuspension formulations which are patented and available present in the market. Some of these are listed below in Table VI.

Table VI
Patents on nanosuspension formulation

S.No.	Title/year	Patent number	References
1.	Nanosuspension of a poorly soluble drug via microfluidization process	US20110124702 A1	80
2.	Process for preparation of crystalline nanoparticle suspensions	WO2011102787 A1	81
3	Water-insoluble drug particle process	US20020012704 A1	82
4	Pharmaceutical formulation of nanonised fenofibrate	US20110311619 A1	83
5	Microprecipitation method for preparing submicron suspensions	US6951656 B2	84
6	Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution	US5858410 A	85
7	Method for producing ultrafine submicronic suspensions	US8034381 B2	86
8	Process for producing nanometer particles by fluid bed spray drying	WO2001045677 A1	87
9	Method of producing medicinal nanoparticle suspension	US7597278	88
10	Nanosusupension formulation comprising a polydimethyl siloxane hydrophobic phase	WO2011151418 A2	89

5. SELF-EMULSIFYING DRUG DELIVERY SYSTEM

Self-emulsifying drug delivery systems (SEDDS) are lipid based formulations which ensure significant increase in oral bioavailability of drugs. They help in reducing the slow and incomplete dissolution of a drug, enhance formation of its solubilized phase, increasing extent of drug transportation via intestinal lymphatic system and bypass p-glycoprotein efflux, thereby increase absorption from GIT. [90,91] SEDDS emulsify spontaneously to form fine o/w emulsion when put into aqueous phase under gentle agitation. [92] A list of recent approaches used in preparation of SEDDS is given in Table VII.

Table VII
List of recent approaches used to prepare SNEDDS

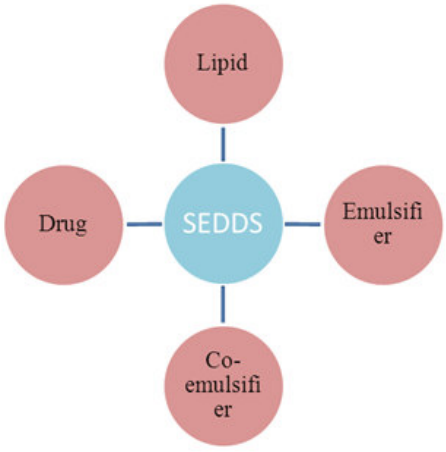
S.NO.	Research	Methodology	Outcomes of study	References
1	Study of cosurfactant effect on nanoemulsifying area and development of lercanidipine loaded (SNEDDS) self nanoemulsifying drug delivery system	Development and characterization of self-nanoemulsifying drug delivery system (SNEDDS) to improve the oral bioavailability of poorly soluble third generation calcium channel blocker lercanidipine (LER).	The in vitro dissolution profile of LER SNEDDS was found significant in comparison to the marketed LER (Zanidip) tablet and pure drug in pH 1.2, 4.5 and 6.8 buffers.	93
2	Design and optimization of a new self-nanoemulsifying drug delivery system	The influence of the constituent structure, concentration and the composition of SNEDDS formulations, and the emulsifier HLB value, on the properties of the resulting emulsions was systematically investigated	The optimal SNEDDS formulation had a mean nanoemulsion droplet diameters of 58 nm in phosphate buffer, pH 6.8 (simulated intestinal fluid), and released ibuprofen more than 95% within 30 min.	94
3	Nanoemulsions as self-emulsified drug delivery carriers for enhanced permeability of the poorly water-soluble selective β1-adrenoreceptor blocker Talinolol	In this study, a self-nanoemulsifying drug delivery system was utilized to enhance the bioavailability of the poorly water-soluble beta-blocker talinolol	Significant increase in drug release, permeability, and in vivo bioavailability were demonstrated as compared to standard drug suspension.	95
4	Self-double-emulsifying drug delivery system (SDEDDS): A new way for oral delivery of drugs with high solubility and low permeability	They developed a novel formulation, self-double-emulsifying drug delivery systems (SDEDDS) by formulating mixtures of hydrophilic surfactants and water-in-oil (w/o) emulsions, which were easier to be stable through formulations optimization	Plasma concentration–time profiles from pharmacokinetic studies in rats dosed with SDEDDS showed 2.56-fold ($p < 0.05$) increased absorption of pidotimod, compared to the pidotimod solution. These studies demonstrate that SDEDDS may be a promising strategy for peroral delivery of peptide and	96

			peptidomimetic drugs.	
5	Quality by design: Characterization of self-nano-emulsified drug delivery systems (SNEDDs) using ultrasonic resonator technology.	Ultrasonic resonator technology (URT) was utilized to measure sound velocity and absorption of self-nanoemulsified drug delivery systems (SNEDDs) consisting of various ratios of oil:surfactant :co-surfactant.	It can be envisioned from the results that the compressibility of the media increases with the addition of the oily component and thus reducing the sound velocity. Thus URT enabled direct and convenient analysis of the physical properties as well as influence of formulation factors of nano-emulsions which is an important indication of stability of these nano-emulsions.	97
6	Preparation and in vitro characterization of self-nanoemulsified drug delivery system (SNEDDS) of all-trans-retinol acetate	All-trans-retinol acetate SNEDDS was prepared using different concentrations of soybean oil (solvent) Cremophor EL (surfactant) and Capmul MCM-C8 (co-surfactant). Particle size and turbidity of the SNEDDS were determined after adding water to the oily solution.	The study revealed that the self-nanoemulsified drug delivery system of all-trans-retinol acetate increased its dissolution rate and has the potential to enhance its bioavailability without interaction or incompatibility between the ingredients.	98
7	Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil	Self-nanoemulsifying drug delivery systems (SNEDDS) were developed with the objective to overcome problems associated with the delivery of cefpodoxime proxetil (CFP), a poorly bioavailable high dose antibiotic having pH dependant solubility	The optimized CFP SNEDDS needed surfactant content less than 40% and yielded nanoemulsion of mean globule size 170 nm, which was not affected by the pH of dilution medium. The optimized SNEDDS released CFP completely within 20 min irrespective of the pH of dissolution medium.	99
8	Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs I. Formulation development	The specific aim of this study was to develop SNEDDS formulations. An experimental design was adopted to develop SNEDDS. Fluorescent labeled β-lactamase (FITC-BLM), a model protein, was loaded into SNEDDS through solid dispersion technique	A SNEDDS was developed to load FITC-BLM into the oil phase which can spontaneously form O/W nanoemulsion upon the addition of water.	100
9	Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs II. *In vitro* transport study	Fluorescently labeled BLM (FITC-BLM), a model protein, formulated into 16 SNEDDS preparations through a solid dispersion technique were studied for transport across MDCK monolayer.	It was found that the monolayer integrity was not compromised in the presence of SNEDDS NE-12-7 or its surfactant/ cosurfactant. The SNEDDS significantly increased the transport of FITC-BLM across MDCK monolayer *in vitro*. SNEDDS may be a potential effective delivery system for non-invasive protein drug delivery.	101
10	SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: An insight into its mechanism for neuroprotection	In this study they formulated and characterized self-nano emulsifying drug delivery system (SNEDDS) curcumin formulation to enhance its bioavailability and then evaluated its efficacy in experimental diabetic neuropathy.	Western blot analysis confirmed the greater neuroprotective action of SNEDDS curcumin. SNEDDS curcumin formulation due to higher bioavailability was found to afford enhanced protection in diabetic neuropathy.	102

5.1. Formulations aspects

SEDDS formulation should form a clear stable dispersion on dilution which remains stable.[103] Depending on globule size, it can be micro or nanoemulsion. It consists of lipid and emulsifying agent which help solubilizing the drug and it is shown in Figure 6. Various formulation considerations include nature of oil/emulsifier, emulsifier concentration, oil/emulsifier ratio, concentration and nature of co-emulsifier, emulsifier/co-emulsifier ratio and temperature at which self-micronization or nanonization occurs.

Figure 6
Constituents for formulation of SEDDS



5.1.1. Lipid

Large quantities of lipophilic drugs can be solubilized in lipids, which also aid in the transportation of drug through intestinal lymphatic system and hence drug absorption [104] Medium chain triglycerides like natural edible oils are not frequently used due to their poor ability to dissolve large amount of lipophilic drug. Various lipids used are triglyceride, hydrolyzed corn oil, dl-α-tocopherol, mixture of mono-and di-glycerides of caprylic/capric acid, corn oil, olive oil, oleic acid, sesame oil and hydrogenated soyabean oil. Lipidic constituents in all the SEDDS formulation having invariably been the mono-,di- or triglycerides derivatives with HLB values ranging from 1-6 and melting point ranging from -78°C-+78°C. Other than this, mixtures of mono-, di- and triglycerides with fatty acid esters of PEG having HLB values between 3 to18 have also been used [105]

5.1.2. Emulsifier

They are amphiphilic in nature and can dissolve high amounts of lipophilic drugs. Natural emulsifiers possess greater safety in comparison to synthetic but have less self-emulsification property. An emulsifier with high HLB value yields better o/w emulsions. [106,107,108,109] For proper absorption, the drug should remain solubilized for extended periods at the absorption site. To have effective absorption, precipitation of drug compound in the GI lumen should be prevented and drug should be kept solubilized for a prolonged period of time at the site of absorption. [110,111] Non-ionic surfactants with high HLB values are preferred emulsifiers e.g. solid or liquid ethoxylated polyglycolysed glycerides, polyoxyethylene oleate (TWEEN 80) and poly(ethylene oxide)-poly(propylene oxide) block copolymers like Pluronic F127 [112,113] Non-ionic surfactants are safer than ionic surfactants and a stable SEDDS formulation requires high concentration of surfactants i.e. in range between 30% and 60% w/w. Further increase in concentration may irritate GI mucosa. It is usually reported that there is an inverse relationship between droplet size and concentration of surfactant. [114,115] Due to this, there is improved stabilization of oil droplet as a consequence of the localization of surfactant at the oil water interface. But in some cases, there is an increase in size after reaching a critical concentration. [116,117,118] This is amenable to the interfacial disruption caused by water penetration into oil droplets, mediated by increased emulsifier concentration, thus leading to entry of oil droplet into the aqueous phase.

5.1.3 Cosolvents

These are used to enhance the dissolution of large amount of surfactant in SEDDS. Cosolvents have a serious limitation of getting evaporated from shells of sealed gelatin capsule leading to precipitation of the drug inside shell. Commonly used cosolvents are polyglyceryl-6 dioleate, sorbitan monooleate, propylene glycol monolaurate, PEG-60 hydrogenated castor oil, sodium lauryl sulfate etc. [119]

5.2. *Solidification of SEDDS*

Although liquid SEDDS filled capsules are a preferred dosage form, but problems like incompatibility of components with the capsule shell, precipitation of drugs during fabrication and storage at low temperature may limit their utility in certain cases. [120,121] Hence, development of solid oral formulations based SES has been attempted. As solid dosage forms are considered as efficient alternatives to conventional liquid dosage forms, recently SEDDS have also been transformed to solid dosage forms and termed as S-SEDDS. Adsorption of SEDDS onto porous tableting excipients like Aerosil 200 or Neusilin is the simplest way to obtain S-SEDDS. [120,122] Some of the techniques by which solidification can be achieved are (i) Capsule filling with liquid or semi-solid self-emulsifying systems (ii) Spray drying (iii) Adsorption to solid carriers (iv) Melt granulation (v) Melt extrusion / extrusion spheronization. [122] There are several marketed formulations of SEDDS which are encapsulated either in soft gelatin or hard gelatin capsules. These include Vesanoid (Roche) having Tretinoin as active drug with a dose of 10 mg in soft gelatin capsule. Other example include Gengraf (Abbott) having cyclosporine as active drug with dose of 25mg and 100mg in hard gelatin capsules. In the last 3 to 4 years, a number of efforts have been done by scientists to find out a suitable method for conversion of liquid SEDDS into

tablet dosage forms. This can be achieved by using liquisolid compaction technique. The liquisolid system is a powdered form of a liquid drug formed by blending the liquid drug formulation with selected carrier material and coating material to form dry looking, non-adherent, free-flowing and readily compressible powdered mixtures [123] Various grades of cellulose, starch, lactose etc., can be used as the carrier material, whereas very fine particle size silica powders and magnesium aluminum silicate powders may be used as the coating materials. Finally, the liquisolid powders are compressed to get tablet dosage form. Zhao et al. formulated self-micro emulsifying drug delivery system of Cyclosporine A and then converted into liquisolid compacts. In this study, oil system was prepared by mixing Maisine 35-1: Lauroglycol FCC (1:1, w/w) and PEG-35 Castor Oil with PEG-400. Cyclosporine A was then dissolved in the mixture, followed by gentle mixing and heating. Wet granules were prepared by mixing the above liquid solution with Avicel PH 101 as carrier material, 4% Ac-Di-Sol® added as an internal disintegrant and 0.5% magnesium stearate as a lubricant. The powder mixture was compressed into tablets on a Carver Press. The prepared liquisolid powders have given acceptable flowability and compressibility. The resultant compacts of Cyclosporine A gave a faster dissolution as compared to the conventional tablet of Cyclosporine A. [124]

5.3. Various patents on self-emulsifying drug delivery formulations

There are various self-emulsifying drug delivery formulations which are patented. Some of them are enlisted below in Table VIII.

Table VIII
Patents on self-emulsifying drug delivery formulations [119]

S. No.	Title/year	Patent number	References
1	Self-emulsifying pharmaceutical compositions of rhein or diacerein	WO2009040776 (A1)	125
2	Self-emulsifying formulations of CETP inhibitors	US/2009/0186926	126
3	Process for dosing self-emulsifying drug delivery systems	WO2008128960 (A1)	127
4	Butylphthalide self-emulsifying drug delivery system, its preparation method and application	HK1111299 (A2)	128
5	Delivery of tetrahydrocannabinol: A self-emulsifying drug delivery system to improve dissolution, stability, and bioavailability of drug compounds of dronabinol or other cannabinoids	US20070104741	129
6	Soft gelatin capsule and injection of Ibuprofen using SMEDDS as solubilization method	KR20020071037 (A)	130
7	Self-microemulsifying drug delivery systems of a HIV protease	US 2007/0104740 A1	131
8	Self-emulsifying formulations of cholesteryl ester transfer protein inhibitors CETP inhibitors have improved solubility and bioavailability in a lipophilic vehicle comprising a digestible oil, a lipophilic solvent, or a surfactant	US 2006/0014788 A1	132
9	Self-emulsifying formulations of fenofibrate and/or fenofibrate derivatives with improved oral bioavailability and/or reduced food effect	US 7022337	133
10	Self-nanoemulsifying oily formulation for the administration of poorly water-soluble drugs	US/2006/0292186	134

5.4. Various formulations prepared using SEDDS

Loratadine

Loratadine is an antihistaminic drug used to decrease the effect of histamine in the body. Its SEDDS formulation was prepared by using various types of Oils (Arachis Oil, Neobee M-5 Capmul PG 8, Miglyol 812, Oleic Acid, Soya bean Oil), Surfactant (Tween 80, Cremophor EL). [134]

Etoricoxib

Etoricoxib is a non-steroidal anti-inflammatory drug and selective cyclooxygenase-2 (COX-2) inhibitor. Etoricoxib self emulsifying tablets were prepared using different proportions of goat fat and Tween 60. The required amount of goat fat and Tween 60 were heated together in a crucible until completely homogenized. Etoricoxib (6 g) was added and stirred thoroughly. The mixture was poured in a plastic tablet mould and stored in a cool place. [135]

6. SOLID LIPID NANOPARTICLES (SLN) AND NANOSTRUCTURED LIPID CARRIERS (NLC)

"*SLNs are nano particles constituted by biodegradable lipids that are solid at body temperature. NLCs however contain an oil or*

mixture there of as well as lipids in varying proportions."[29] The presence of liquid lipid in the NLC results in long-term colloidal stability and greater drug encapsulation and loading unlike SLN. [30, 31, 136] SLN and NLC have similar merits as that of SNEDDS in case of oral drug delivery. However, because of the presence of solid lipids, SLN and NLC have the ability to sustain the therapeutic levels in drug in the plasma unlike SEDDS.[137] Employing a solid lipid carrier instead of liquid lipid is a strategy to achieve controlled release of drugs. This idea was generated first in 1980's by Speiser and coworkers who developed solid lipid nanoparticles in the form of pellets for oral administration which were termed as "Nanopellets". [138] Similar systems were developed by Domb as "Lipospheres". Later, these kinds of formulations were termed as "Solid Lipid Nanoparticles", which can be produced by high pressure homogenization, use of organic solvents, solvent evaporation, solvent emulsification, microemulsion based SLN preparation, spray drying and ultrasound. [139,140] The different types of lipids used for solid lipid nanoparticles are triglycerides, partial glycerides, steroids and waxes. Since these are prepared from physiological lipids there is very less chance of toxicity. The basic difference between the uses of high pressure homogenizer for production of SLN over nanosuspension prepared by homogenization is, we can use hot homogenization and cold homogenization for the production of SLN. The parameters which are to be considered during production are emulsification time, stirring rate, cooling conditions on particle size and zeta potential. The composition of ingredients (lipids and emulsifiers) used in production of solid lipid nanoparticles possesses great influence on product quality. Different lipids used in formulation have different impact on quality, for example velocity of lipid crystallization, lipid hydrophilicity that influences self-emulsifying properties [141] and shape of lipid crystals. On the other hand, concentration of emulsifiers used has great impact on product quality. [142] Zur-Muhlen (1996) has investigated the influence of emulsifier concentration on particle size using Compritolo SLN dispersions and found best results with 5% sodium cholate or poloxamer 188. Low concentration of emulsifier was found to have more number of microparticles because higher concentrations of emulsifier reduces the surface tension and facilitate the particle partitioning during homogenization. [139] Recent researches on Solid Lipid Nanoparticles are listed in Table IX. Key factors which influence the stability and release kinetics of solid lipid nanoparticles are particle size, zeta potential, degree of crystallinity, lipid modification and coexistence of micelles, liposomes etc.

Table IX
List of recent researches on Solid Lipid Nanoparticles

S.No.	Research Topic	Methodology	Outcomes of study	References
1.	Preparation of solid lipid nanoparticles using a membrane contactor	The present study investigates a new process for the preparation of SLN using a membrane contactor. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets.	It is shown that the membrane contactor allows the preparation of SLN with a lipid phase flux between 0.15 and 0.35 m^3/h m^2, and a mean SLN size between 70 and 215 nm. The advantages of this new process are its facility of use, the control of the SLN size by an appropriate choice of process parameters, and its scaling-up abilities.	143
2	Preparation of solid lipid nanoparticles with clobetasol propionate by a novel solvent diffusion method in aqueous system and physicochemical characterization	Monostearin SLN were prepared by a novel solvent diffusion method in an acidic aqueous system in order to improve the recovery of the method. The drug and monostearin were dissolved in acetone and ethanol at 50 °C in water bath, the resultant organic solution was poured into an acidic aqueous (pH 1.10) containing 1% polyvinyl alcohol (PVA) under mechanical agitate at room temperature.	The recovery of nanoparticles was markedly increased compared to using a usual aqueous (pH 5.73) containing the same concentration of PVA. After burst drug release at the first 3 h, a distinctly prolonged release over a monitored period of 4 days was observed and nearly 6% drug was released in each day	144
3	Preparation of solid lipid nanoparticles by a solvent emulsification–diffusion technique	A preparation method for nanoparticles based on the emulsification of a butyl lactate or benzyl alcohol solution of a solid lipid in an aqueous solution of different emulsifiers, followed by dilution of the emulsion with water, was used to prepare glyceryl monostearate nanodispersions with narrow size distribution	By using lecithin and taurodeoxycholic acid sodium salt, on increasing the GMS percentage from 2.5 to 10% an increase of the mean diameter from 205 to 695 nm and from 320 to 368 nm was observed for the SLN prepared using benzyl alcohol and butyl lactate, respectively	145
4	Solid lipid nanoparticles: Formulation factors affecting cell transfection capacity	In this, work different formulations based on SLN–DNA complexes were formulated in order to evaluate the influence of the formulation components on the “in vitro” transfection capacity. SLNs composed by the solid lipid Precirol® ATO 5, the cationic lipid DOTAP and the surfactant Tween 80, and SLN–DNA complexes prepared at different DOTAP/DNA ratios were characterized by studying their size, surface charge, DNA protection capacity, transfection and cell viability in HEK293 cultured cells.	The formulations prepared at DOTAP/DNA ratios 7/1, 5/1 and 4/1 provided almost the same transfection levels (around 15% transfected cells), without significant differences between them ($p > 0.05$). DNA condensation is a crucial factor which conditions the transfection capacity of SLNs, because it influences DNA delivery from nanoparticles, gene protection from external agents and DNA topology.	146
5	Solid lipid nanoparticles as potential tools for gene therapy: In vivo protein expression after intravenous administration	Naked plasmid DNA is a powerful tool for gene therapy, but it is rapidly eliminated from the circulation after intravenous administration. They aimed to evaluate the capacity of SLN–DNA vectors to transfect in vivo after intravenous administration to mice. The SLNs, composed of Precirol® ATO 5, DOTAP and Tween 80 were complexed with the plasmid pCMS-EGFP which encodes the enhanced green fluorescent protein (EGFP).	The intravenous administration in mice led to transfection in hepatic tissue and spleen. Protein expression was detected from the third day after administration, and it was maintained for at least 1 week. This work shows for the first time the capacity of SLN–DNA vectors to induce the expression of a foreign protein after intravenous administration, supporting the potential of SLNs for gene therapy.	147
6	Lipid nanoparticles for brain targeting I. Formulation optimization	The aim of this study was to optimize the formulation of lipid nanoparticles (NPs), intended for brain targeting, with the aid of a computer generated experimental design. The high pressure homogenization technique, selected for this purpose, was suitable to formulate the 3 investigated lipids (i.e., Softisan®	Even though all the 3 optimized formulations were suitable for intravenous infusion, CP NPs showed the smallest particle size and the appropriate thermal behaviour to be used as carriers in brain targeting applications.	148

		142, SOFT; Compritol® 888 ATO, COMP; cetyl palmitate, CP) into nanometre-length particles		
7	Solid lipid nanoparticles (SLN) - based hydrogels as potential carriers for oral transmucosal delivery of Risperidone: Preparation and characterization studies	Two different solid lipid nanoparticles (SLN)-based hydrogels (HGs) formulations were developed as potential mucoadhesive systems for risperidone (RISP) oral transmucosal delivery. The suitability of the prepared semi-solid formulations for application on oral mucosa was assessed by means of rheological and textural analysis, during 30 days.	In vitro drug release studies revealed a more pronounced RISP release after SLN hydrogel entrapment, when compared to the dispersions alone. In addition, a pH-dependent release was observed as well. The predicted in vivo RISP release mechanism was Fickian diffusion alone or combined with erosion.	149
8	Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin	Solid lipid nanoparticles (SLN) loaded with doxorubicin were prepared by solvent emulsification-diffusion method. Glyceryl caprate (Capmul®MCM C10) was used as lipid core, and curdlan as the shell material. Dimethyl sulfoxide (DMSO) was used to dissolve both lipid and drug. Polyethylene glycol 660 hydroxystearate (Solutol®HS15) was employed as surfactant. Major formulation parameters were optimized to obtain high quality nanoparticles.	The drug release behavior was studied by *in vitro* method. Cell viability assay showed that properties of SLN remain unchanged during the process of freeze-drying. Stability study revealed that lyophilized SLN were equally effective ($p < 0.05$) after 1 year of storage at 4 ◦C. In conclusion, SLN with small particle size, high EE, and relatively high DL for doxorubicin can be obtained by this method.	150
9	DNA delivery via cationic solid lipid nanoparticles (SLNs)	The use of cationic SLNs developed by the technique of microemulsion, which are complexed with DNA in order to study their application as non-viral vectors in gene therapy, is reported.	The nanoparticles obtained presented a particle size of 340 nm with a positive surface charge of 44 mV and the capability of forming lipoplexes with DNA plasmids was stated.	151
10	Baclofen-loaded solid lipid nanoparticles: Preparation, electrophysiological assessment of efficacy, pharmacokinetic and tissue distribution in rats after intraperitoneal administration	Intrathecal baclofen administration is the reference treatment for spasticity of spinal or cerebral origin, but the risk of infection or catheter dysfunctions are important limits. To explore the possibility of alternative administration routes, we studied a new preparation comprising solid lipid nanoparticles (SLN) incorporating baclofen (baclofen-SLN). We used SLN because they are able to give a sustained release and to target the CNS	demonstrated the efficacy of a novel formulation of baclofen, which exploits the advantages of SLN preparations. However, for clinical purposes, high baclofen concentrations in brain tissue and sedation may be unwanted effects, requiring further studies and optimization of dosages.	152

7. INORGANIC NANOPARTICLES

These can be defined as particles of metal oxide or metallic composition possessing at least one length scale in the nanometer range. Mostly used inorganic materials include gold, titanium, mesoporous nanoparticles of calcium. Out of these, gold has been used since ancient times as a therapeutic agent in traditional indian system of medicine as well as Chinese medicine. [153] In one of the studies, the nanoparticles of silicon dioxide have shown several advantageous features in the form of diagnostics and targeting of specific cell types in the context of drug delivery. [154] It was found that casein coated calcium phosphate-polyethylene glycol nanoparticles which contain insulin can be used as oral delivery system for insulin. [28]

8. POLYMERIC MICELLES

This is a kind of nano platform in which lipophilic drugs are encapsulated within core in dissolved state, which is stabilized by surfactants or polymeric shell to prevent rapid diffusion of drug from core. Generally used reservoirs for lipophilic drugs are oil droplets which include saturated and unsaturated fatty acids, fatty acid esters and soybean oils. [33] Stability of these formulations can be achieved by various surfactants like poloxamers, lecithin and Tween 80. Formulations available in market include Estrasorb® (estradiol, Novavax/ Graceway), Flexogan® (camphor, menthol and methyl salicylate, AlphaRX, Canada) and Restasis® (cyclosporine, Allergan). [33] The basic mechanism behind this formulation is that the polymers self-aggregate in aqueous environment to form

supramolecular core–shell structures,either with a solid core or a more fluid structure. In the former case, nanospheres are formed and in the latter structures polymeric micelles are formed. Major advantages include formation of hydrophobic core that serves as a solubilization depot for drugs with poor aqueous solubility. Also, a small size of polymeric micelles contributes towards longer blood circulation time by evading scavenging by mononuclear phagocytic system in the liver and thus by passing the filtration of inter-endothelial cells in the spleen. As a result longer circulation time leads to improved accumulation at tissue sites. In oral delivery polymeric micelles help in protection against rapid clearance from circulation, which can lead to a reduced amount of drug available for absorption. [33]

9. CONCLUSION AND FUTURE PERSPECTIVES

The oral bioavailability and therapeutic efficacy of poorly soluble drugs can be improved using nanotechnology. In the last 10 years various nano-architectures and nano carriers have been developed for achieving successful oral delivery of synthetic as well as peptide and nucleic acid based drugs. In the scale up of nanoparticles from lab to pharmaceutical market several challenges and barriers are involved. This is because commercialization of nanotechnology is determined by various factors like cost to benefit ratio, regulatory status, market potential of the drug, ease of fabrication and reproducibility of method, respectively. To date, the most industrially feasible techniques to overcome the poor bioavailability of drugs are nanosuspensions and SEDDS which have gained their market potentials. It is important to note that no matter what new, innovative and judicious formulation strategies will be developed to deal with poorly soluble compounds, they will be affected by one or more of the challenges discussed above in a way to get translated from lab to commercial scale.

REFERENCES

1. Martin A, Swarbrick J, Cammarata A, Physical pharmacy, Varghese publishing house: Mumbai, (1991).
2. Brahmanker DM, Jaiswal S. Ed. Biopharmaceutics and Pharmacokinetics-A Treatise, 3rd Edn, Vallabh Prakashan: Delhi, (2009).
3. Lipinski CA. Poor aqueous solubility - an industry wide problem in drug discovery. Am Pharm Rev, 5:82-85, (2004).
4. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res, 2:32-67, (2012).
5. Saravana KK, Sushma M, Prasanna RY. Dissolution enhancement of poorly soluble drugs by using complexation technique – A review. J Pharm Sci & Res,5:120-124, (2013).
6. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci, 60:1281-1302, (1971).
7. Ford JL. The current status of solid dispersions. Pharm Acta Helv, 61:69-88, (1986).
8. Habib MJ. Ed. Pharmaceutical Solid Dispersion Technology. Washington: CRC (2000).
9. Mooter GVD, Augustijns P, Blaton N, Kinget R. Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm, 64:67-80, (1998).
10. Ghaderi R, Artursson P, Carlfors J. Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS). Pharm Res, 16:676-681, (1999).
11. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinyl pyrrolidone. Eur J Pharm Biopharm, 63:103-114, (2006).

12. Leunner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 50:47-60, (2000).
13. Prabhu S, Ortegra M, Ma C. Novel lipid based formulations enhancing the in-vitro and permeability characteristics of poorly water soluble model drug, piroxicam. Int J Pharm, 301:209-221 (2005).
14. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today, 12:1068-1075, (2007).
15. Gowree MP, VedhaHari BN, Ramya DD. Emerging Liquisolid Compact Technology for Solubility Enhancement of BCS Class-II Drug. J Pharm Sci Res, 3:1604-11, (2011).
16. Babatunde A, Elkordoy AA, Esse, EA, Elhagar S. Liquisolid Systems to Improve the Dissolution of Furosemide Scientia Pharmaceutica, 78: 325-44 (2010).
17. Yadav AV, Shete AS, Dabke AP. Formulation and evaluation of orodispersible liquisolid compacts of aceclofenac. Indian J Pharm Educ Res, 44:227-35 (2010).
18. Nokhodchi A. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharmaceut Sci, 8:18-25, (2005).
19. Chandel P, Raj K, Kapoor A. A liquisolid technique: an approach for enhancement of solubility. J Drug Deliv Therap, 3:131-137 (2013).
20. Paun JS, Tank HM. Nanosuspension: An Emerging Trend for Bioavailability Enhancement of Poorly Soluble Drugs. Asian J Pharm Tech, 2:157-68, (2012).
21. Chaumeil JC. Micronisation: A method of improving the bioavailability of poorly soluble drugs. Exp Clin Pharmacol, 20:211-215, (1998).
22. Trotta M, Gallarete M, Pattarino F, Morel S. Emulsions containing partially water-miscible solvents for the preparation of drug nanosuspension. J Control Release, 76:119 –28, (2011).
23. Debuigne F, Cuisenaire J, Jeunieau L, Masereel B, Nagy JB. Synthesis of nimesulide nanoparticles in the microemulsion epikuron/isopropyl myristate/water/*n*-butanol (or isopropanol). J Colloid Interf Sci, 243:90–101, (2001).
24. Liversidge GG, Conzentino P. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm, 125:309-313, (1995).
25. Moschwitzer J, Achleitner G, Pomper H, Muller RH. Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. Eur J Pharm Biopharm, 58:615–619, (2004).
26. Peter K, Leitzke S, Diederichs JE, Borner K, Hahn H, Muller RH, Ehlers S. Preparation of clofazamine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in *Mycobacterium avium* infection. J Antimicrob Chemother, 45:77–83, (2000).
27. Chime SA, Kenechukwu FC, Attama AA. Ed. Nanoemulsions advances in formulation, characterization and applications in drug delivery. In: Sezer AD, editor. Nanotechnology and Nanomaterials: Application of Nanotechnology in Drug Delivery, 1st ed. Croaita: Intech, 77-126, (2014).
28. Pallavi M, Nigade, Patil SL, Tiwari SS. Self-emulsifying drug delivery system (SEDDS): A Review. Int J Pharm Biol Sci, 2:42-52, (2012).
29. Patravale VB, Abhijit AD, Desai PP. Overcoming poor oral bioavailability using nanoparticles formulations – opportunities and limitations. Drug Discov Today, 9:e87- e99, (2012).
30. Muchow M, Maincent P, Muller RH. Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev Ind Pharm, 34:1394– 1405, (2008).
31. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomed, 2:289–300, (2007).
32. Pokharkar, V, Dhar, S, Bhumkar, D, Mali, V, Bodhankar, S, Prasad, BL. Acute and

subacute toxicity studies of chitosan reduced gold nanoparticles: a novel carrier for therapeutic agents. J Biomed Nanotechnol, 5:233-239 (2009).
33. Lu Y, Park K. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. Int J Pharm, 453:198-214, (2013).
34. Chan HK, Kwok PCL. Production methods for nano drug particles using bottom-up approach. Adv Drug Deliver Rev, 63:406–16, (2011).
35. Suker H, Gassmann P. Improvements in pharmaceutical compositions. GB Patent 2269536A, (1994).
36. Bustmani RT, Chan HT, Dehghani F, Foster NR. Generation of micro-particles of proteins for aerosol delivery using high pressure modified carbon dioxide. Pharm Res, 1:1360–1366, (2000).
37. Byrappa k, Ohara S, Adschiri T. Nanoparticles synthesis using supercritical fluid technology-towards biomedical applications. Adv Drug Deliv Rev, 60:299-327, (2008).
38. Reverchon E, De Marco I, Torino E. Nanoparticles production by supercritical antisolvent precipitation: a general interpretation. J Supercrit Fluids, 43:126-138, (2007).
39. Chen JF, Wang YH, Guo F, Wang XM, Zheng C. Synthesis of nanoparticles with novel technology: high gravity reactive precipitation. Ind Eng Chem Res, 39:948–954, (2000).
40. Fowler R. Higee- a status report. Chem Eng Sci, 456:35–37, (1989).
41. Hu TT, Wang JX, Shen ZG, Chen JF. Engineering of drug nanoparticles by HGCP for pharmaceutical applications. Particuology, 6:239–251, (2008).
42. Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drug. Int J Pharm, 312:179–186, (2006).
43. Benet N, Muhr H, Plasari E, Rousseaux JM. New technologies for the precipitation of solid particles with controlled properties. Powder Technol, 128:93–98, (2002).
44. Johnson BK, Prudhomme RK. Engineering the direct precipitation of stabilized organic and block copolymer nanoparticles as unique composites, Polymeric materials. Sci Eng, 89:744–745, (2003).
45. Dhumal RS, Biradar SV, Yamamura S, Paradkar AR, Peter Y. Preparation of amorphous cefuroxime axetil nanoparticles sonoprecipitation for enhancement of bioavailability. Eur J Pharm Biopharm, 70:109-115, 2008.
46. Luque CMD, Priego-Capote F. Ultrasound-assisted crystallization (sonocry stallization). Ultrason Sonochem, 14:717–24, (2007).
47. Liu Y, Cheng C, Prudhomme RK, Fox RO. Mixing in a multi-inlet vortex mixer (MIVM) for flash nano-precipitation. Chem Eng Sci, 63:2829-2842, (2008).
48. Zhu B, Kwok PC, Prudhomme RK, Traini D, Chan HK, Young PM. The use of quad-impinging jet technology for the production of pharmaceutical nanoparticles, Formula VI Abstracts, PDP10, (2010).
49. Cal K, Sollohub K. Spray drying technique I: hardware and process parameters. J Pharm Sci, 99:575–586, (2010).
50. Schmid K, Arpagaus C, Friess W. Evaluation of the Nano Spray Dryer B-90 for pharmaceutical applications. Pharm Dev Technol, 16:287-94, (2010).
51. Teagarden DL, Baker DS. Practical aspects of lyophilization using non-aqueous co-solvent systems. Eur J Pharm Sci, 15:115–133, (2002).
52. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. Asian J Pharm, 10:13-23, (2015).
53. Palla BJ, Shah DO. Stabilization of high ionic strength slurries using surfactant mixtures: molecular factors that determine optimal stability. J Colloid Interface Sci, 256:143–152, (2001).
54. Bernoulli P, Sucker S, Fuchs H, Speiser P. Ed. Pharmazeutische Technologie Stuttgart: Georg Thieme; (1978).
55. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. Adv Drug Deliver Rev, 47:3–19, (2001).

56. Nagaraju P, Krishnachaithanya K, Srinivas VDN, Padma SVN. Nanosusoension: A promising drug delivery. Int J Pharm Sci and Nanotech, 2:679-683, (2010).
57. Moschwitzer J, Müller RH. New method for the effective production of ultrafine drug nanocrystals. J Nanosci Nanotechnol, 6: 3145–3153, (2006).
58. Date AA, Patravale VB, Current Strategies for engineering drug nanoparticles. Curr Opin Colloid Interface Sci, 9:222–235, (2004).
59. Singh SK, Srinivasan KK, Gowthamarajan K, Dhananjay S, Prakash D, Gaikwad NB. Investigation of preparation parameters of nanosuspension by top-down media milling to improve dissolution of poorly water soluble glyburide. Eur J Pharm Biopharm, 78:441-446, (2011).
60. Wongmekiat A, Tozuka Y, Oguchi T, Yamamoto K. Formation of fine drug particles by cogrinding with cyclodextrin. I. the use of β-cyclodextrin anhydrate and hydrate. Pharm Res, 19:1867-1872, (2002).
61. Itoh K, Pongpeerapat A, Tozuka Y, Oguchi T, Yamamoto K. Nanoparticle formation of poorly water soluble drugs from ternary ground mixtures with PVP and SDS. Chem Pharm Bull, 51:171-174, (2003).
62. Mura P, Faucci MT, Bettinetti GP. The influence of polyvinylpyrrolidone on naproxen complexation with hydroxyl propyl- β-cyclodextrin. Eur J Pharm Sci, 13: 187-194, (2001).
63. Mura P, Cirri M, Faucci MT, Ginès-Dorado JM, Bettinetti GP. Investigation of the effects of grinding and cogrinding on physicochemical properties of glisentide. J Pharm Biomed Anal, 30:227-237, (2002).
64. Otsuka M, Matsuda Y. Effect of co-grinding with various kinds of surfactants on the dissolution behaviour of phenytoin. J Pharm Sci, 84:1434-1437, (1995).
65. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water soluble polymer. Int J Pharm, 160:11-19, (1998).
66. Yonemochi E, Kitahara S, Maeda S, Yamamura S, Oguchi T, Yamamoto K. Physicochemical properties of amorphous clarithromycin obtained by grinding and spray drying. Eur J Pharm Sci, 7:331-338, (1999).
67. Watanabe T, Ohno I, Wakiyama N, Kusai A, Senna M. Stabilization of amorphous indomethacin by co-grinding in a ternary mixture. Int J Pharm, 241:103-111, (2002).
68. Venkatesh T, Reddy AK, Maheswari JU, Dalith MD, Ashok KCK. Nanosuspensions: Ideal approach for the drug delivery of poorly water soluble drugs. Der Pharmacia Lettre, 3:203-213, (2011).
69. Kipp JE, Wong JCTW, Doty MJ, Christine LR. Microprecipitation method for preparing submicron suspensions. US Patent 7037528, B2, (2006).
70. Zili Z, Sfar S, Fessi H. Preparation and characterization of poly-β-carprolactone nanoparticles containing griseofulvin. Int J Pharm, 294:261-267, (2005).
71. Trotta M, Gallarate M, Pattarino F, Morel S. Emulsions containing partially water-miscible solvents for the preparation of dry nanosuspensions. J Control Release, 76:119-128, (2001).
72. Zhang X, Xia Q, Gu N. Preparation of all-trans retinoic acid nanosuspensions using a modified precipitation method. Drug Dev Ind Pharm, 32:857-863, (2006).
73. Bodmeier R, McGinity JM. Solvent selection in the preparation of poly (DL-lactide) microspheres prepared by solvent evaporation method. Int J Pharm, 43:179–186, (1998).
74. Eccleston GM, Ed. Microemulsions. In: Swarbrick S, Boylan CJ, editors Encyclopedia of pharmaceutical technology, Marcel Dekker: New York, , 375–421 (1992).
75. Raju A, Reddy AJ, Satheesh J, Jithan AV. Preparation and Characterisation of Nevirapine Oral Nanosuspensions.Indian J Pharm Sci, 76:62–71, (2014).
76. Rajalakshmi R, Thanda V, Kumar RA, Sree KD, Kiranmayi MD. Design and characterization of valsartan

nanosuspension. Int J Pharmacother, 2:70-81, (2012).
77. Li X, Gu L, Xu Y, Wang Y. Preparation of fenofibrate nanosuspension and study of its pharmacokinetic behavior in rats. Drug Dev Ind Pharm, 35:827-833, (2009).
78. Srinivasan M., Steffi PF. Preparation, Characterization and Stabilization of Curcumin. Nanosuspension. Int J PharmTech Res, 6:842-849, (2014).
79. Agarwal V, Bajpai M. Preparation and optimization of esomeprazole nanosuspension using evaporative precipitation–ultrasonication. Trop J Pharm Res, 13:497-503, (2014).
80. Ming JC, Ho-Wah H, Thomas LPK, Sekhar S, Nanosuspension of a Poorly Soluble Drug via Microfluidization Process. US20110124702 A1, (2011).
81. Lindfors L, Skantze U, Ohgren, C. Process for preparation of crystalline nano-particle suspensions. WO2011102787 A1, (2011).
82. Pace G, Mishra A. Water-insoluble drug particle process. US20020012704 A1, (2002).
83. Herry C, Oury P, Pharmaceutical formulation of nanonised fenofibrate. US20110311619 A1, (2011).
84. Kipp JE, Wong TJC, Doty MJ. Rebbeck CL, Brynjelsen S, Microprecipitation method for preparing submicron suspensions. US6951656 B2, (2005).
85. Muller RH, Becker R, Kruss B, Peters K, Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution. US5858410 A, (1999).
86. Moschwitzer J, Method for producing ultrafine submicronic suspensions. US8034381 B2, (2011).
87. Nicholas JK, Process for producing nanometer particles by fluid bed spray-drying. WO2001045677 A1, (2001).
88. Asahi T, Masuhara H, Sugiyama T, Oh I, Ryo S, Kato H, Umeda I, Method of producing medicinal nanoparticle suspension. US7597278, (2009).
89. Breitenbach J, Didier R, Lefebvre, Lipari JM. Nanosusupension formulation comprising a polydimethylsiloxane hydrophobic phase. WO2011151418 A2.(2011).
90. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drug. Adv Drug Deliver Rev, 25:103-128, (1997).
91. Porter CJ, Charman WN. Intestinal lymphatic drug transport: An update. Adv Drug Deliv Rev, 50:61-80, (2001).
92. http://www.slideshare.net/mayurmayurpatilpatil/self-emulsifying-drug-delivery-systems Slide share.net [Internet] [cited 2014 November 26].
93. Parmar N, Singla N, Amina S, Kohli K. Study of cosurfactant effect on nanoemulsifying area and development of lercanidipine loaded (SNEDDS) self nanoemulsifying drug delivery system. Colloids and Surfaces B, 86:327–338, (2011).
94. Wang JD, Chen J, Eastoe J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid and Interf Sci, 330:443–448, (2009).
95. Ghai D, Sinha VR. Nanoemulsions as self-emulsified drug delivery carriers for enhanced permeability of the poorly water-soluble selective β1-adrenoreceptor blocker Talinolol. Nanomedicine: NBM, 8:618–626, (2012).
96. Qi X, Wang L, Zhu J, Hu Z, Zhang J. Self-double-emulsifying drug delivery system (SDEDDS): A new way for oral delivery of drugs with high solubility and low permeability. Int J Pharm, 409: 245–251, (2011).
97. Shah RB, Zidan AS, Funck T, Tawakkul MA, Nguyenphoa A, Khan MA. Quality by design: Characterization of self-nano-emulsified drug delivery systems (SNEDDs) using ultrasonic resonator technology. Int J of Pharm, 341:189–194, (2007).
98. Taha EI, Al-Saidan S, Samy AM, Khana MA. Preparation and in vitro characterization of self-nanoemulsified drug delivery system (SNEDDS) of all-trans-retinol acetate. Int J Pharm, 285:109–119, (2004).
99. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm, 329:166–172, (2007).

100. Rao SVR, Shao J. Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs I. Formulation development, Int J Pharm, 362:2–9, (2008).
101. Rao SVR, Shao J. Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs II. In vitro transport study, Int J Pharm, 362:10-15, (2008).
102. Joshi RP, Negi G, Kumar A, Pawar YB, Munjal B, Bansal AK, Sharma SS. SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: An insight into its mechanism for neuroprotection. Nanomedicine, 9:776-785, (2013).
103. Spernath A and Aserin A. Microemulsions as carriers for drugs and nutraceuticals. Adv Colloid Interface Sci, 128-130:47-64, (2006).
104. Gershanik T, Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. Eur J Pharm Biopharm, 50:179-188, (2000).
105. Chambin O, Jannin V. Interest of multifunctional lipid excipients: case of Gelucire 44/14. Drug Dev Ind Pharm, 31:527-534, (2005).
106. Devani M, Ashford M, Craig DQ. The emulsification and solubilisation properties of polyglycolysed oils in self-emulsifying formulations. J Pharm Pharmacol, 56:307-316, (2004).
107. Pouton CW. A study of self-emulsifying oil/surfactant mixtures. Ph.D. thesis, University of London. (1982).
108. Pouton CW. Self-emulsifying drug delivery systems: Assessment of the efficiency of emulsification. Int J Pharm, 27:335-348, (1985).
109. Pouton CW. Formulation of self-emulsifying drug delivery systems. Adv Drug Deliver Rev, 25:47-58, (1997).
110. Serajuddin AT, Sheen PC, Mufson D, Bernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. J Pharm Sci, 77:414-417, (1988).
111. Shah NH, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int J Pharm, 106:15-23, (1994).
112. Ofokansi KC, Chukwu KI, Ugwuanyi SI. The use of liquid self-microemulsifying drug delivery systems based on peanut oil/tween 80 in the delivery of griseofulvin. Drug Dev Ind Pharm, 35:185-191, (2009).
113. Fernandez-Tarrio M, Yanez F, Immesoete K, Alvarez-Lorenzo C, Concheiro A. Pluronic and tetronic copolymers with polyglycolyzed oils as self-emulsifying drug delivery systems. AAPS Pharm.SciTech, 9:471-479, (2008).
114. Gershanik T, Benzeno S, Benita S. Interaction of a self-emulsifying lipid drug delivery system with the everted rat intestinal mucosa as a function of droplet size and surface charge. Pharm Res, 15:863-869, (1998).
115. Nielsen FS, Petersen KB, Mullertz A. Bioavailability of probucol from lipid and surfactant based formulations in minipigs: Influence of droplet size and dietary state. Eur J Pharm Biopharm, 69:553-562, (2008).
116. Wakerly MG, Pouton CW, Meakin BJ and Morton FS. Self-emulsification of vegetable oil-non-ionic surfactant mixtures. ACS Symp Series, 311:242–255, (1986).
117. Craig DQM, Barker SA, Banning D and Booth SW. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int J Pharm, 114:103-110, (1995).
118. Kommuru TR, Gurley B, Khan MA and Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int J Pharm, 212:233-246, (2001).
119. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare OP. Self-emulsifying drug delivery system (SEDDS): Formulation Development, Characterization, and Applications. Ther Drug Carrier Syst, 26:427-521, (2009).
120. Date AA, Desai N, Dixit R, Nagarsenker M. Self-nanoemulsifying drug delivery

systems: formulation insights, applications and advances. Nanomedicine, 5:1595 –1616, (2010).
121. Cole ET, Cade D, Benameur H, Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration, Adv Drug Deliv Rev, 60:747–756, (2008).
122. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discov Today, 13:606–612, (2008).
123. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A, Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm, 341:26–34, (2007).
124. Zhao Y, Wang C, Chow A.H, Ren K, Gong T, Zhang Z, Zheng Y. Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: formulation and bioavailability studies. Int J Pharm, 383:170–177, (2010).
125. Premchand N, Prashant M. Self-emulsifying pharmaceutical compositions of rhein or diacerein. WO2009040776 (A1), (2009).
126. Sheth AR, Rege B, Ghosh S, Alani LL, Cruanes MT, Mckelvey CA,. Self-emulsifying formulations of CETP inhibitors. US/2009/0186926, (2009).
127. Schwarz, Franz, Xaver. Process for dosing self-emulsifying drug delivery systems. WO2008128960 (A1), (2008).
128. Liu Z, Yang L. Butylphthalide self-emulsifying drug delivery system, its preparation method and application. HK1111299 (A2), (2008).
129. Murty RB, Lexington KY, Murty SB, Delivery of tetrahydro cannabinol: A self-emulsifying drug delivery system to improve dissolution, stability, and bioavailability of drug compounds of dronabinol or other cannabinoids. US20070104741, (2007).
130. Seok BK, Wook CY. Soft Gelatin Capsule and Injection of Ibuprofen Using SMEDDS as solubilization Method. KR20020071037 (A). (2011).
131. Voorspoels JFM, Self-micro emulsifying drug delivery systems of a HIV protease. US 2007/0104740 A1, (2007).
132. Gumkowski MJ, Franco L, Murdande SB, Perlman ME. Self-emulsifying formulations of cholesteryl ester transfer protein inhibitors CETP inhibitors have improved solubility and bioavailability in a lipophilic vehicle comprising a digestible oil, a lipophilic solvent, or a surfactant. US 2006/0014788 A1, (2006).
133. Liang L, Shojaei AH, Ibrahim SA, Burnside BA. Self-emulsifying formulations of fenofibrate and/or fenofibrate derivatives with improved oral bioavailability and/or reduced food effect. US 7022337, (2006).
134. Garrigue JS, Lambert G, Razafindratsita A, Benita S, Yang S, Gursoy N. Self-nanoemulsifying oily formulation for the administration of poorly water-soluble drugs. US/2006/0292186, (2006).
135. Nayak AK, Jana S. A Solid Self-Emulsifying System for Dissolution Enhancement of Etoricoxib. Journal of Pharm Sci Tech, 2:87-90, 2013.
136. Almeida A, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv Drug Deliv Rev, 59:478–490, (2007).
137. Muller RH, Runge SA, Ravelli V, Thunemann AF, Mehnert W, Souto EB. Cyclosporine-loaded solid lipid nanoparticles (SLN): drug–lipid physicochemical interactions and characterization of drug incorporation. Eur J Pharm Biopharm, 68:535–544, (2008).
138. Eldem T, Speiser P, Hincal A. Optimization of spray-dried and congealed lipid micropellets and characterization of their surface morphology by scanning electron microscopy. Pharm Res, 8: 47–54, (1991).
139. Mehnert W, Ma¨der K. Solid lipid nanoparticles Production, characterization and applications. Adv Drug Deliv Rev, 47: 165–196, (2001).
140. Sjostrom B, Bergenstahl B. Preparation of submicron drug particles in lecithin-stabilized o/w emulsions. I. Model studies of the precipitation of cholesteryl acetate. Int J Pharm, 88:53–62, (1992).

141. Siekmann B, Westesen K. Submicron-sized parenteral carrier systems based on solid lipids. Pharm Pharmacol Lett, 1:123–126, (1992).
142. Muller RH, Mehnert W, Lucks JS, Schwarz C, Zur Muhlen A, Weyhers H, Freitas C, Ruhl D. Solid lipid nanoparticles (SLN)-an alternative colloidal drug carrier system for controlled drug delivery. Eur J Pharm Biopharm, 41:62-69, (1995).
143. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release, 108:112–120, (2005).
144. Hu FQ, Yuan H, Zhang HH, Fang M. Preparation of solid lipid nanoparticles with clobetasol propionate by a novel solvent diffusion method in aqueous system and physicochemical characterization. Int J Pharm, 239:121–128, (2002).
145. Trotta M, Debernardi F, Caputo O. Preparation of solid lipid nanoparticles by a solvent emulsification–diffusion technique. Int J Pharm, 257:153–160, (2003).
146. Pozo-Rodríguez AD, Delgado D, Solinís MA, Gascón AR, Pedraz JL. Solid lipid nanoparticles: formulation factors affecting cell transfection capacity. Int J Pharm, 339:261-268, (2007).
147. Pozo-Rodríguez AD, Delgadoa D, Solinis MA, Pedraza JL, Echevarri E, Rodriguezc JM, Gascon AR. Solid lipid nanoparticles as potential tools for gene therapy: In vivo protein expression after intravenous administration. Int J Pharm, 385:157–162, (2010).
148. Blasi P, Giovagnoli S, Schoubbena A, Puglia C, Bonina F, Rossia C, Ricci M, Lipid nanoparticles for brain targeting: Formulation optimization. Int J Pharm, 419:287– 295, (2011).
149. Silva AC, Amarala MH, Gonzalez-Mirac E, Santosa D, Ferreiraa D. Solid lipid nanoparticles (SLN) - based hydrogels as potential carriers for oral transmucosal delivery of Risperidone: Preparation and characterization studies. Colloids Surfaces B Biointerfaces, 93:241–248, (2012).
150. Subedi RK, Kanga K, Choi H. Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin, Eur J Pharm Sci, 37:508–513, (2008).
151. Carrillo C, Sánchez-Hernández N, García-Montoya E, Pérez-Lozano P, Suñé-Negr JM, Ticó JR, Suñé C, Miñarro M. DNA delivery via cationic solid lipid nanoparticles (SLNs). Eur J Pharm Sci, 13:928-987, (2013).
152. Priano L, Zara GP, El-Assawy N, Cattaldo S, Muntoni E, Milano E, Serpe L, Musicanti C, Pérot C, Gasco MR, Miscio G, Mauro A. Baclofen-loaded solid lipid nanoparticles: Preparation, electrophysiological assessment of efficacy, pharmacokinetic and tissue distribution in rats after intraperitoneal administration, Eur J Pharm Biopharm, 79:135–141, (2011).
153. Bhattacharya R, Mukherjee P. Biological properties of “naked” metal nanoparticles. Adv Drug Deliver Rev, 60:1289–1306, (2008).
154. Vallet-Regí M, Balas F, Arcos D. Mesoporous materials for drug delivery. Angew Chem Int. Ed Engl, 46:7548–7558, (2007).