# A review on recent updates on solid lipid nanoparticles as a vehicle for enhanced oral delivery

**Rada Santosh KumarAnd Vasudeva Reddy Matta**

Department of Pharmaceutics, GITAM School of Pharmacy, GITAM (Deemed to be University), Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India

**CorrespondencetoAuthor:**

R.Santosh Kumar, Assistant Professor, Department of Pharmaceutics, GITAM School of Pharmacy, GITAM (Deemed to be University), Visakhapatnam-530045, Andhra Pradesh, India.

ABSTRACT

Drugs that are poorly soluble in water typically have difficulties developing conventional dosage forms due to the issues like poor oral bioavailability, slow onset of action, lack of dose proportionality, inability to reach study state plasma concentrations, and adverse effects. To improve the penetration or absorption through oral administration, new strategies are being developed and published. Lipid nanoparticles gained much attention for the oral absorption of medications to improve therapeutic effectiveness following oral delivery. The pharmacological and therapeutic effects of a substance on a biological system are primarily described by its pharmacokinetic and pharmacodynamics activities. The lymphatic transit is facilitated by lipid nanoparticles, specifically solid lipid nanoparticles consisting of physiologically inert lipid molecules. There is a wealth of literature on the impact of lipid nanoparticles and other colloidal carrier systems on the pharmacokinetic characteristics of medications with poor oral bioavailability, as well as on the corresponding processes for the improvement of oral bioavailability.The history of solid lipid nanoparticles, from their inception to the present, is described in this paper. Additionally, various methods for creating stable solid lipid nanoparticles are addressed. The study also provides information on the state of pharmacokinetic and pharmacodynamics research on SLNs. The prospective application of solid lipid nanoparticles on commercially available preparations was briefly reviewed in the conclusion.

**Key words:** Solid lipid nanoparticles,pharmacodynamics, pharmacokinetics, evaluation, future perspective.

## INTRODUCTION:

The most widely used drug delivery method is still oral administration, largely because it is the simplest. Despite the oral route's acceptance and adaptability, the significant issues are still persisting. Not all drug molecules have the physical, chemical, or biological properties required for effective oral delivery. Potential medication candidates are frequently rejected as usable products due to issues like low /very low solubility or chemically instable in the GIT, low permeability through biological membranes, or susceptibility to metabolism. In order to get beyond some of the most difficult chemical or physical obstacles connected to poorly absorbed medications, lipid-based drug delivery systems have been developed[4].

The more traditional emulsions and microemulsions, as well as more contemporary liposomes, microspheres, solid lipid nanoparticles (SLN), and nanostructured lipid carriers, are all examples of potential drug delivery methods (NLC). The solid lipid nanoparticles used as carriers are the main topic of the current review.Similar to lipid emulsions, polymeric nanoparticles and liposomes, solid lipid nanoparticles (SLN) have become a viable alternative for colloidal drug delivery. SLN is better to conventional colloidal carriers in terms of cellular absorption, longer drug release, huge surface area, increased stability, and minimal toxicity[36]. In-depth research has also been done on colloidal systems that use biodegradable polymers, and these systems have proven to be excellent candidates for drug delivery.

However, the primary issue with colloidal particle delivery is their opsonized clearance by the reticuloendothelial system (RES). The phagocytic cells of the RES efficiently and quickly remove the opsonized foreign particles from the blood stream.The opsonization by serum proteins and the reduction in reticuloendothelial clearance are obstacles that the lipid nanoparticles are designed to avoid. The helper lipids in the lipid nanoparticles aid in cell binding, cholesterol fills in spaces between lipids, and polyethylene glycol slows down reticuloendothelial system clearance. Depending on the use and distribution method, the ratios of the constituents—helper lipids, cholesterol, and PEG—should be tuned. The kind of lipid, size, and surface charge all affect the lipid nanoparticles' in-vivo behaviour.Due to their biocompatibility and simplicity of cellular uptake, lipid-based nanoparticles like liposomes and SLN have grown in popularity. Cellular uptake is influenced by the outer lipid layer. Additionally, metabolising lipid-based colloidal carriers into harmless by products is simple. Although similar in design, the content and function of liposomes and SLN are different. Unlike solid lipid nanoparticles, which are constructed of a lipid monolayer encasing a solid lipid core, liposomes are composed of a lipid bilayer enclosing an aqueous core. These two lipid-based nanoparticles are more effective drug delivery systems.

By encasing various genetic payloads, including as siRNA, mRNA, and saRNA, lipid nanoparticles have proven to be a helpful tool for the transport of genes. The BNT162b2 COVID-19 m-RNA and mRNA-1273 vaccines from Pfizer/ BioNTech and Moderna respectively, were created using the Lipid nanoparticle technique. These most recent vaccine advancements highlight how this technology may be used to overcome numerous treatment difficulties.

**HISTORY:**

First, oil-in-water emulsions, microparticles, liposomes and nanoparticles based on synthetic polymers or natural macromolecules have all been explored as particulate drug carriers for many years. In the 1950s, the oil in water (O/W) emulsions were effectively introduced to the clinic for parenteral nourishment. On the basis of these emulsions for parenteral nourishment, emulsion formulations comprising substances like diazepam and etomidate have been created. Diazepam-Lipuro, Etomidate-Lipuro, and Diazemuls are commercial products. These emulsions' sole purpose was to lessen adverse medication reactions including injection pain and swelling (from drugs like diazepam), which were common side effects[38].

Despite these O/W emulsions' outstanding tolerability, there aren't many of them on the market, which suggests that they haven't been very successful. The physical instability that the integrated medication may create is one of the key factors hindering a wider introduction of emulsions as a drug delivery system. Additionally, approved oils such soybean oil, MCT, LCT, and mixes thereof exhibit inadequate solubility for the incorporation of potentially interesting medicines into emulsions. Although the emulsion is a really intriguing delivery technology, it seems that pharmaceutical corporations are hesitant to continue to research this delivery system.The need to find novel oils with enhanced solubility capabilities, which of course also necessitates a costly toxicological investigation, could be one explanation for this[50].

Later, in 1986, Bangham's 1965 rediscovered phospholipid vesicles—now known as "liposomes"—found their way to the cosmetics industry. Pharmaceutical treatments based on liposomes were made possible by the anti-aging product Capture (Dior). Dior was the first liposome item available for purchase. The first pharmaceutical product was introduced in late 1980's or early 1990's namely Alveofact® (Dr Karl GmbH- Germany) the lung surfactant (synthetic) for pulmonary instillation. Still the marketed liposome products are very less. The lack of a "affordable" pharmaceutical liposome is one of the causes of this, in addition to potential technological issues[50]. There aren't many products based on polymeric microparticles available now. Only a small number of microparticulate products were introduced after the first set of products (such as Depot®, Parlodel LA®, Decapeptyl Depot®, and Enantone Parlodel LAR®) were released. After more than 30 years of research, now it is considerably worse for nanoparticles (made up of polymer) because there is essentially no delivery method for them. One exception is that "Abdoscan" which was manufactured by the Nycomed, however it still functions as a diagnostic tool rather than a formulation for chronic care[50].

This is due to a number of well-known factors, including the cytotoxicity of polymers and the absence of an efficient method for producing them on a big scale. Nanoparticles made of polymers approved for use as implants may not always be well tolerated. The polymer can be absorbed by cells (like macrophages) when it is a few nanometers or smaller, and its cellular breakdown can have negative effects, as has been seen for polyester polymers, for instance[70 &74].

Since last couple of decades, there has been a lot of interest in creating effective medication delivery systems using nanoparticles. Nanoparticles typically have diameters between 10nano meter (nm) to 1000nano meter (nm). The first nanoparticles were created during 1970's. Actually, they were developed as delivery systems for vaccinations and anticancer medications. The first step in this manner was to concentrate on creating strategies to target

tumours while simultaneously minimising the reticuloendothelial system's uptake of nanoparticles[74].

Both synthetic and natural polymers have been employed. Polymer nanospheres, polymer nanocapusles and water soluble polymer drug conjugates,are examples of polymer-based systems in the submicron range. These systems' extensive variety of chemical changes is a benefit. However, the fundamental issue with these systems is the polymer's cytotoxicity and potential organic leftovers throughout the synthesis process. It is important to consider polymer hydrolysis during storage, and lyophilization is frequently necessary to stop polymer deterioration[38].

**Table 1: Benefits and drawbacks of various colloidal drug delivery methods[69]**

| | Systemic toxicity | Organic solvents (Residue) | Cytotoxicity | Commercial Viability | Feasibility for Autoclave | RES avoidance | Release modification (SR) |
|---|---|---|---|---|---|---|---|
| Solid Lipid nanoparticles | Low | No | Low | Yes | Yes | Size dependent | Yes |
| Polymer Nanoparticles | > or = to SLN | Yes | > = to SLN | No | No | No | Yes |
| Lipid Emulsions | Low | No | Low | Yes | Yes | Yes | Yes |
| Liposomes | Low | May or may not | Low | Yes | No | Yes | < or = to SLN |

Diverse research teams have been concentrating on solid lipid nanoparticles since the 1990s as a replacement for polymeric nanoparticles (SLN). Lipid pellets for oral medication administration (such as Mucosolvan® retard capsules) are a well-known example of how solid lipids can be used as a matrix compound for drug delivery. Basically, lipids that the body tolerates well can be employed (e.g., the parenteral nutrition emulsions contain glycerides constituted of fatty acids). High pressure homogenization that produces SLN can be used to produce large quantities of goods in a relatively straightforward and cost-effective manner[50].

Because SLNs' lipid matrix is made up of physiological lipids, there is less chance for damge during shelf life of the product. Some of these systems' key benefits include the ability to sterilise and the option of controlling medication release and targeting with a higher drug payload.

## SOLID LIPID NANOPARTICLES (SLNS)

Better physical stability and a lack of coalescence when warming up at room temperature (after preparation or storage) are further benefits. The particles wouldn't show any observable drug leaking because the solid lipid nanoparticles' severely reduced mobility of the integrated drug molecule. Recently, there has been a lot of interest in the development of SLNs as carriers for chemotherapeutic drugs, cosmetics, peptides, genetic material etc[26&87].

The solid lipid nanoparticles (SLNs), which are made of lipids that are solid at both room temperature and body temperature, are stabilised by a surfactant (s). By definition, the lipids can be waxes, complicated glyceride mixes, or highly purified triglycerides. The SLN carrier system has undergone extensive characterization thanks to the efforts of numerous research

teams. The US patent, issued in 1993, included claims regarding various SLN production processes.

The use of drug delivery technologies, such as solid lipid nanoparticles, has led to significant advancements for the treatment of many diseases (SLN). Colloidal carriers known as SLNs were created during the last decade as an alternative to conventional carriers now in use (polymeric nanoparticles emulsions and liposomes). The main difference between SLN and nanoemulsions as colloidal drug carrier systems is the type of lipid they include. The liquid lipid used in emulsions is substituted out for a lipid that is solid at room temperature in SLN, such as high-melting point glycerides or waxes). Controlled drug delivery, improved tissue distribution and drug targeting[21], and augmentation of bioavailability of entrapped pharmaceuticals via modulation of dissolution rate have all been described utilising SLN.

***Structure of solid lipid nanoparticles:***

SLNs have a solid lipid core with a bioactive component that is a part of the lipid matrix (as shown in figure 1). A layer of surfactants stabilises the particle; this layer may be made up of a single surfactant, but it usually consists of a combination of surfactants. It has typically been demonstrated that using crystalline lipids rather than liquid lipids increases control over the release and stability of integrated bio-actives. This is done in order to alter the lipid matrix's physical state, which impacts the mobility of the bioactive.

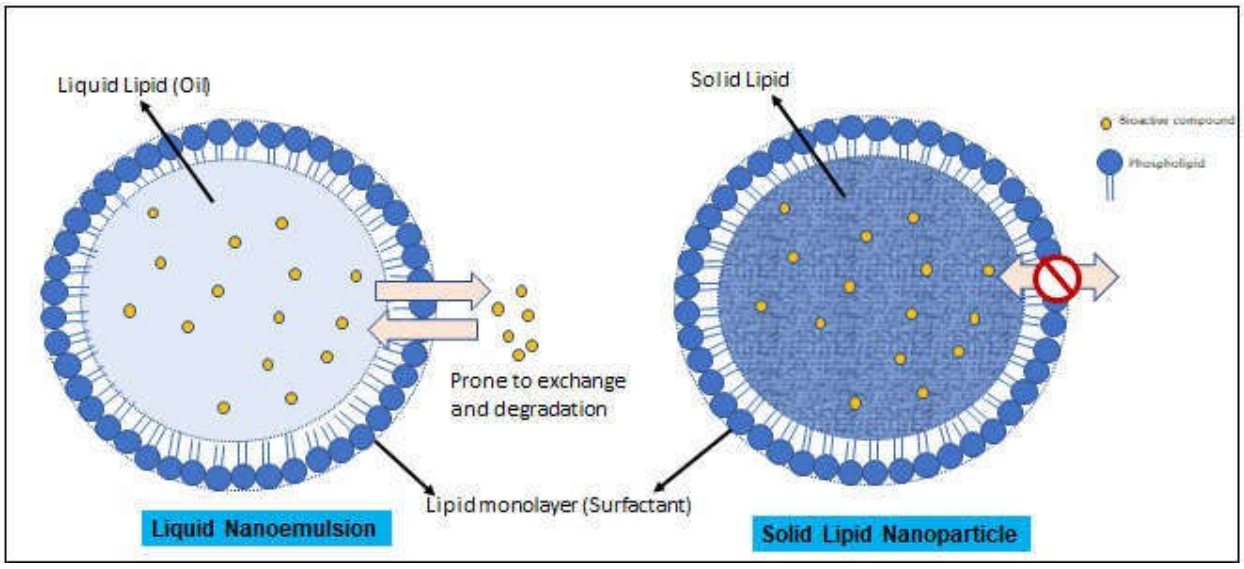


**Fig. 1. A lipid monolayer stabilises a liquid Nano emulsion (L) and solid lipid nanoparticles (R). The bioactive is enclosed and dispersed in the liquid lipid (liquid nanoemulsion) or solid lipid (SLN).**

***ADVANTAGES (SLN)***

The advantages of Solid Lipid Nanoparticles are as follows:

1. The RES (Reticulo Endothelial System) cells do not readily take up the nanoparticles and SLNs, especially those are present in the range of 120-200 nm, and as a result, they skip liver and spleen filtration[50].
2. It is possible to obtain controlled drug release for up to a few weeks[42&43] . Furthermore, the potential for drug targeting is expanded by coating SLNs with ligands or attaching them to them[1&15]
3. Three-year stable SLN formulations have been created. Regarding the other colloidal carrier systems, this is of utmost importance[14&7].

4. High pressure homogenization approach found to be cost effective with excellent repeatability[20] .
5. The viability of combining medicines that are both hydrophilic and hydrophobic[66] .
6. The carrier lipids degrade naturally and are hence secure [89].
7. Refrain from using organic solvents[41].
8. Various application routes[79].
9. In recent years, the coating of SLN to offer receptor-mediated drug and gene delivery has also received more attention. It has been shown that coating colloidal carriers improves the stability of the particles and increases transmucosal transport of the related drugs after administration by nasal, oral or ocular routes[84].
10. Topical therapy for skin conditions offers the advantage of achieving high medication levels at the site of disease and reducing systemic side effects when compared to oral or parenteral drug delivery. NSAIDs, COX-II inhibitors, Glucocorticoids, antimycotics and retinoids, are some of the medications now being researched for cutaneous delivery utilising lipid nanoparticles[69].
11. In cases where SLNs were made using natural lipids and not aseptically manufactured, the stability of the SLNs can be improved against microorganisms by adding preservatives.
12. The availability of large-scale production facilities is another obvious benefit of SLNs over polymeric nanoparticles. To sum up, SLNs have the potential to be used as delivery systems in commercial items, particularly in regards to industrial production features.

***Limitations of SLN:***

1. The payload for many medicines is too low.
2. Drug ejection while being stored.
3. The SLN dispersions have a lot of water in them.

***Factors to take into account for SLN fabrication:***

Water, emulsifiers, co-emulsifiers, and lipids (matrix materials) are often utilised elements in the creation of SLN. To address the demands of stability and targeting elements, homing devices, stealthing agents, and charge modifiers are also utilised. Lipid matrices (Solid lipid), emulsifiers, co-emulsifiers, charge modifiers, cryoprotectants and agents to enhancing circulation time are some of the excipients utilised during the SLN formulation.

*Selection of lipids*

Recently, the justification for the selection of lipid materials for oral medicinal dosage forms had been examined. The following appropriate qualities should be present in lipid matrices used to create SLNs for intravenous delivery. The lipids should be biodegradable, should be in the nanometer size range, should have enough loading capacity with lipophic and hydrophilic medicaments, should also have good stability along with less or no toxic degradants.

*Selection of emulsifier*

Emulsifiers must to be non-toxic, agreeable with other excipients, able to produce desirable sizes with a minimum amount used, and also capable of providing adequate stability to the SLN by coating nanoparticle surfaces. It is clear from the literature that the kind and quantity of emulsifier used, as well as the preparation technique, affect the size of the particles and their stability. The ideal amount of emulsifier to cover the nanoparticles' surface should be used. Lower emulsifier concentrations result in particle aggregation and an increase in particle size. However, excessive emulsifier use should be avoided to avoid harmful effects related to surfactants, burst release as seen in SLN release experiments, and reduction in

entrapment efficiency [50]. At the interface, it appears that using two or more emulsifying agents together results in mixed surfactant films.

*Selection of co-emulsifier:*
The phospholipids employed to create SLNs are neither highly dynamic micelles nor are they soluble in continuous phase. During the homogenization process, extra phospholipid molecules create tiny, primarily unilamellar vesicles. However, the mobility of phospholipid molecules linked to vesicles is somewhat restricted. As a result, when they recrystallize, they are unable to instantly cover the newly formed interfaces. Due to the phospholipid molecules' poor mobility, a sudden loss of emulsifier on a particle's surface causes particle aggregation and an increase in the particle size of SLN. Co-emulsifiers are used to prevent this.They prevent triglycerides from recrystallizing in their colloidally dispersed state. These emulsifiers that are water soluble can create micelles. Compared to vesicles, polymer molecules can diffuse to the particle surface in a lot less time. However, because of their harmful effects, it is not advised to employ rapidly dispersing surfactants such sodium lauryl sulphate[37].

## SOLID LIPID NANOPARTICLES PREPARATION METHODS

In addition to the materials used to make SLNs, the preparation process has a significant impact on factors including particle size, drug loading capacity, drug stability, etc. Solid Lipid Nanoparticles shall be produced by solvent emulsification technique, hot homogenization, High pressure homogenization, cold homogenization (for thermo labile pharmaceuticals), microemulsion technique, , and solvent emulsification-diffusion technique. Using a double emulsion approach to encapsulate hydrophilic medicines, solvent injection as a newly disclosed method for producing SLN, homogenization is followed by ultrasonication and membrane contactor.

## CHARACTERIZATION OF SOLID LIPID NANOPARTICLES:

The following are a few factors that must be taken into account during characterization of SLNs;PSD (particle size distribution), measurement of morphology and shape, Photon Correlation Spectroscopy (PCS), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), Measurement of zeta potential and entrapment efficiency (EE %) measurement.

## IMPORTANCE OF SLN IN VARIOUS ADMINISTRATION ROUTES

The most popular method for administering medication is orally. Utilizing SLNs as oral drug delivery vehicles can be enticing because of their significant potential to enhance oral BA of medicines, concurrently reduce drug toxicity, and increase drug stability in both plasma and Gastro Intestine Track (Table 2).

***Oral administration:***
Aqueous dispersion of SLN is an option for oral administration, as is transformation into a conventional dosage form, such as tablets, capsules, pellets, or powders in sachets. The aqueous SLN dispersion can replace a granulation fluid during the process of granulation to produce tablets. Alternately, SLN can be dried using a spray gun to turn it into a powder, then mixed with the other excipients (blend used for tablets). The SLN dispersion shall be employed as a wetting agent in the extrusion process to produce pellets. Hard gelatin capsules can be filled with SLN powders. Powders that have been lyophilized or spray-dried can also be made into sachets. Spray drying might be the best technique for turning SLN dispersions into powders due to cost considerations.

There is a great deal of pharmaceutical interest in the utilisation of specific submicron-size delivery systems for oral medication delivery, particularly for peptide medicines. According to Damgé et al. (1990), these systems' controlled release characteristic allows the bypassing of stomach and intestinal degradation of the encapsulated medication as well as their potential uptake and transport across the intestinal mucosa. To determine if colloidal carriers are suitable for oral delivery, it is necessary to evaluate the stability of the carriers in GI fluids. According to reports, nanoparticles' sticky characteristics boost bioavailability and lessen or eliminate irregular absorption. Nanoparticles can be absorbed through the mucosa of the gut in various different ways, including through paracellular pathways, Peyer's patches and intracellular uptake. For oral drug delivery, solid lipid nanotechnology has caught the attention of numerous businesses. A cyclosporine Solid Lipid Nanoparticle formulation for oral administration was created by Pharmatec (Italy) [46]. In this instance, reduced variability in the plasma profile and avoidance of a strong plasma peak were offered. Rifampicin-loaded SLN is also being tested in preclinical stages by AlphaRx (RifamsolinTM). Since rifampicin has a weak cellular antibiotic penetration, it is mostly used to treat tuberculosis, which necessitates long-term treatment. In order to boost this medication's effectiveness and, consequently, patient compliance, AlphaRx seeks to deliver it inside the human cell.

***Parenteral administration:***

SLN is essentially suited for all parenteral applications involving polymeric nanoparticles. This can be administered intra-articularily or intravenously. Several groups have conducted studies utilising SLN given intravenously. Higher and longer-lasting plasma levels of Paclitaxel were produced by the intravenously injected SLN .

SLNs are small enough to circulate through the microvascular system when given intravenously and, in the case of hydrophilic coating, prevent macrophage absorption. Thus, SLNs have been suggested for the transport of both viral and non-viral gene delivery. As a result of electrostatic interactions, it has been demonstrated that cationic SLN directly binds genes and may be helpful in the development of targeted gene therapies for the treatment of cancer.

Effective treatment of disorders of the central nervous system, such as brain tumours, AIDS, neurological and psychiatric issues, is commonly hampered by the blood brain barrier (BBB), which is made up of the basal membrane, the endothelium of the brain veins, and neurological cells. Colloids' hydrophilic surface promotes BBB passage and tissue dispersion (Kreuter, 2001). Doxorubicin was only found in the brain at a detectable dosage following the administration of stealth SLN, according to Fundaro et al2000.'s study. Formulations of nanoparticulate technology, such as solid lipid nanoparticles and nanosuspensions, are being developed by SkyePharma in the UK.

***Topical application:***

SLN and NLC are very desirable colloidal carrier systems for skin applications in addition to possessing the characteristics of a colloidal carrier system. They are perfect for use on damaged or irritated skin because they are based on non-irritating and non-toxic lipids. The use of SLNs has been the subject of extensive study. A nonsteroidal antiandrogen for topical application, RU 58841, as well as vitamin E tocopherol acetate, retinol, ascorbyl palmitate, clotrimazole, and triptolide have all been evaluated with SLN and NLC recently.

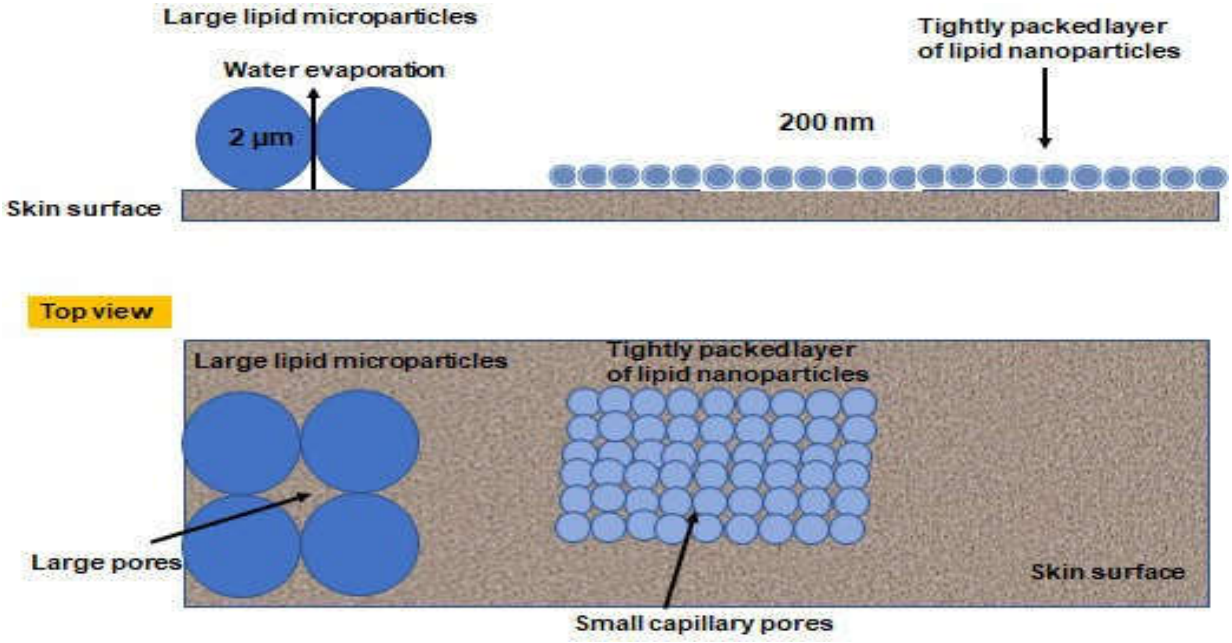


**Fig. 2. Schematic representation of Occlusion Effect by film formation on the skin**

The development of a film on the skin by SLNs resulted in occlusive qualities that lessen transdermal water loss. Atopic eczema symptoms are lessened and the appearance of healthy human skin is also improved by an increase in skin's water content. Additionally, occlusion facilitates medication absorption through the skin[37]. A brand-new, presently under investigation application for SLN is in sunblock products. UV-blocking molecular sunscreens can penetrate the skin and cause discomfort as a result[87]. It was also discovered that sunscreens with titanium dioxide particles may enter the skin. This can be avoided or minimized by entrapping molecular and particle sunscreens within the SLN matrix. Unexpectedly, it was discovered that the SLN itself also have sun protection properties. This is because of the scattering of Ultra Violet light; their particle nature makes them protective (same as that of TiO2 titanium dioxide). Additionally, it was also discovered that using SLN and molecular sunscreens together has a synergistic effect.

***Ocular administration:***

Technologies for colloidal drug administration are believed to increase the bioavailability of drugs in aqueous humour (drug bioavailability in the eye)[51&52]. Medication is typically delivered to the tear film using eye drops, which are widely available and, for the majority of patients, easy to administer. Obtaining the ideal dosage of a drug at the site of action,however, is a substantial problem. Poor bioavailability of drugs from ocular dosage forms is caused by pre-corneal loss factors include tear dynamics, nonproductive absorption, temporary residency in the cul-de-sac, and relative impermeability of the corneal epithelial membrane[53]. A significant problem is creating an alternative to solution-type eye drops that would deliver drugs over time i.e., Sustain Release[12].

The ingredients used in SLN formulations are generally regarded as safe (GRAS)and SLN formulations are sticky, which may boost bioavailability and prolong the dosage form's residence time in the eye. The GRAS status of the components used in the formulation of SLN makes it exceedingly biocompatible, in contrast to some polymeric systems that have been proven to damage the corneal epithelium by rupturing the cell membrane and may release dangerous compounds upon breakdown. A gentamicin-loaded SLN product called

OcusolinTM from AlphaRx is still in the preclinical stages of research. When SLNs loaded with tobramycin were applied topically on rabbits instead of regular commercial eye drops, they greatly increased the drug's aqueous humour bioavailability.

***Nasal administration:***

Nasal administration is a promising alternative noninvasive way of drug delivery due to fast absorption and rapid initiation of impact, rapid drug activity, avoiding GI tract degradation of labile pharmaceuticals (such as peptides and proteins), and insufficient transport across epithelial cell layers. To improve drug absorption through the nasal mucosa, formulation development and prodrug derivatization have both been used. SLN has been suggested by many research groups as an alternate transmucosal delivery route for macromolecular medicinal and diagnostic substances. As nasal medication carriers, SLN's hydrophilic coating will also enable interaction with and passage through the nasal mucosa, which will result in significant advantages and improved compliance.

**Application of SLNs in Pharmacodynamic studies:**

Numerous research teams have found that solid lipid nanoparticles can enhance the oral bioavailability; nevertheless, their contribution to pharmacodynamic action has not yet been documented. In this context, candesartan cilexetil (CC) and nisoldipine, two hypertension medications, were used to assess the pharmacodynamic impact of SLNs. In a pharmacodynamic research, CC-SLNs reduced systolic blood pressure in fructose-induced hypertensive rats for 48 hours, whereas suspension only reduced systolic blood pressure for 2 hours. When CC-SLN was administered, the medication was released continuously for at least 24 hours. As a result, the SLNs that were created were successful to regulate the hypertension for an about 48-hour period.The produced SLN formulation was clearly able to overcome the drawbacks of oral administration of CC, such as low bioavailability and high first-pass metabolism. By creating the medications in SLN formulation, Additionally, it becomes clinically advantageous to treat hypertension consistently, gradually, and for an extended period of time.

Similarly, nisoldipine SLN pharamcodynamic study reveals that, when using customised ND-SLNs in comparison to a controlled solution, a substantial decrease in blood pressure (BP--Systolic) was seen that persisted for 36 hours. The SLN technique also improved the pharmacodynamic impact of isradipine.

Lipid lowering tests employing a Triton-induced hyperlipidemia model were used to compare the anti-hyperlipidemic activity of rosuvastatin calcium loaded solid lipid nanoparticles (RC-SLN) to a control dispersion. According to the findings, the pharmacodynamic action of RC-SLN caused a considerable drop in total cholesterol, LDL, VLDL, and TG levels as well as a rise in HDL levels over the course of 36 hours, but the effects of RC suspension persisted for only 24 hours[52].

**Future perspective:**

A weakly water soluble medicine's oral formulation should, in general, increase drug solubility and maximise bioavailability, permit dosage proportionality, and provide repeatable plasma concentration-time profiles. Significant academic and commercial interest has been shown in the use of lipid-based drug delivery systems, such as solid lipid nanoparticles and niosomes, as a potential formulation strategy for improving the oral bioavailability of drugs that are poorly water soluble and resolving hepatic first-pass

metabolism. With these nanocarriers, pharmacodynamic activity was further improved. The drug impact was shown to be prolonged using SLN delivery methods, which helped with dose reduction and, in turn, side effects reduction. Additionally, the frequency of administration could be lowered. This might help with high levels of patient compliance. Additionally, these SLN delivery systems can be dried utilising freeze drying or spray drying techniques to become powder. The preparation of oral solid drug delivery forms can then be produced by adding material into capsules or by producing the pellets and compressing them as tablets. In addition to being tricky to scale up, complex formulations can also be expensive and even complicated from a regulatory standpoint. Industry groups might focus on ways to speed up the development of SLNs for medications that aren't very water soluble. Then, instead of using the standard dosage form, the doctor will have the option of prescribing the designed SLN delivery method for the patient's benefit. The biological stability, specificity, and safety of the SLN delivery methods, which can be easily transferred from bench to bedside, should continue to be emphasised.

**Table 2: Different SLN formulations were investigated by various researchers to increase the oral bioavailability of medications.**

| Molecule investigated | Issues Associated | Adopted Methods | Lipid | Inference | Reference |
|---|---|---|---|---|---|
| Adefovir dipivoxil | Low Bioavailability | solvent injection | - | Bioavailability was increased | 72 |
| Baicalin | Poor Bioavailability | coacervation | Stearic acid | Enhanced bioavailability | 23 |
| Camptothecin | Poor solubility and acid liability | HPH (Hot) | Stearic acid | Stability was improved along with Sustain release | 89 |
| Capecitabine | Low BA and stability issues | HH-US | 114-Dynasan | Achieved the tumor target along with enhanced BA | 54 |
| Cyclosporine A | Low solubility, firstpass metabolism | Hot HPH | Inwitor 900 | BA was improved along with constant plasma conc. | 48 |
| Cryptotanshinone | Poorly water soluble | Ultrasonic and highpressure homogenization | GMS Compritol 888 ATO | Solubility was enhanced along with improved BA | 27 |
| Fenofibrate | Poor solubility and less BA | Hot HPH | Vitamin (E TPGS and E 6100) | BA was improved | 22 |
| Lovastatin | Due to First pass metabolism BA was low | HH-US | Triglycerides | BA enhanced | 76 |
| Nimodipine | BA was poor | HPH | Palmitic acid | Bioavailability was improved | 9 |
| Nisoldipine | Low solubility and Bioavailability | HH-US | Tripalmitate | BA was improved | 56 |
| Ofloxacin | Improve the pharmacological activity | HH-US | Palmitic acid | Enhanced the pharmacological activity | 88 |
| Olanzapine | poorlysolubility, high firstpass metabolism | microemulsion technique | GMS and Stearic acid | Relative bioavailability was enhanced | 75 |
| Peptides/proteins | Low Permeability and Instability in GIT | Cold homogenization | cetyl alcohol Witepsol E85 | Permeability was enhanced along with Stability | 2 |
| Puerarin | Poor solubility, short half life | Solvent injection method | Monostearin | BA was improved | 33 |
| Quercetine | Poor Absorption capability | Emulsification-solidification | GMS | Absorption was enhanced by using SLN | 25 |

| | | | | | |
|---|---|---|---|---|---|
| Quetiapine fumarate | Low BA due to first-pass metabolism | HH-US | Dynasan (114, 118), Inwitor 900 | Bioavailability was increased | 5 |
| Rifampicin, Isoniazid and Pyrazinamide | Low BA and degradation issues in Acid | Emulsion and solvent diffusion | Stearic acid | BA was improved | 60 |
| Rosuvastatin calcium | Low BA | HH-US | Dynasan 112 | Improved BA | 52 |
| Raloxifene hydrochloride | Low solubility along with first-pass metabolism | solvent emulsification/evaporation | Compritol 888 ATO | Bioavailability enhanced | 3 |
| Raloxifene hydrochloride | Low solubility along with first-pass metabolism | hot homogenization | Tristearin, Trimyristin, Tripalmitin | Bioavailability enhanced | 83 |
| Simvastatin | Low BA due to First-pass metabolism | Solvent injection | GMS | BA was improved | 65 |
| Triptolide | Low solubility and hepatotoxicity (drug induced) | Probe soniation | Tristearin glyceride | Increase BA,With less toxicity | 40 |
| Vinpocetine | Low Solubility and poor BA | Ultrasonic-solvent emulsification | GMS | BA was improved | 34 |
| Zaleplone | Bioavailability was low | HH-US | Dyansan 114 | Bioavailability was improved | 51 |

Bioavailability (BA), Glyceryl monostearate (GMS), High Pressure Homogenization (HPH) and Hot Homogenization followed by Ultra-Sonication (HH-US) .

**References:**


1) Allen DD, Lockman PR, Oyewumi MO, Koziara JM, Roder KE, Mumper RJ Brain uptake of thiamine-coated nanoparticles: Journal of Controlled Release (2003), pp. 271–282
2) Almeida AJ, Runge S, Muller RH Peptide-loaded solid lipid nanoparticles (SLN) influence of production parameters: International Journal of Pharmaceutics 149 (1997), pp 255-65
3) Anand Kumar Kushwaha, Parameswara Rao Vuddanda, Priyanka Karunanidhi, Sanjay Kumar Singh, and Sanjay Singh Development and Evaluation of Solid Lipid Nanoparticles of Raloxifene Hydrochloride for Enhanced Bioavailability: BioMed ResearchInternational., 584549, (2013) pp. 1-9
4) Andrew J. Humberstone, William N. Charman Lipid-based vehicles for the oral delivery of poorly water soluble drugs: Advanced Drug Delivery Reviews 25 (1997) pp. 103- 128
5) Arjun, N., Kishan, V Preparation, characterization and evaluation of quetiapine fumarate solid lipid nanoparticles to improve the oral bioavailability: Journal of Pharmaceutics 265741(2013), pp. 1-7 http://dx.doi.org/10.1155/2013/265741
6) Arun Butreddy, Narendar Dudhipala and KishanVeerabrahma Development of olmesartan medoxomil lipid based nanoparticles and nanosuspension: Preparation, characterization and comparative pharmacokinetic evaluation. Artificial cells: Nanomed and biotech, 46(1) (2018), pp126-137
7) C. Freitas C, Müller RH Effect of light and temperature on zeta potential and physical stability in solid lipid nanoparticles (SLN) dispersions: International Journal of Pharmaceutics 168 (1998), pp.221–229
8) Cavalli R, Bargoni A, Podio V, et al. Duodenal administration of solid lipid nanoparticles loaded with different percentages of tobramycin: Journal of Pharmaceutical Sciences 92 (2003), pp.1085-95
9) Chalikwar SS1, Belgamwar VS, Talele VR, Surana SJ, Patil MU Formulation and evaluation of Nimodipine-loaded solid lipid nanoparticles delivered via lymphatic transport system: Colloids Surf B Biointerfaces 97 (2012), pp. 109-16
10) Damgé C., Michel C., Aprahamian M. Nanocapsules as carriers for oral peptide delivery: Journal of Controlled Release, 13 (1990), pp. 233–239.
11) De Campos A, Sanchez A, Alonso MJ Chitosan nanoparticles: a new vehicle for the improvement of the ocular retention of drugs. Application to cyclosporin A: International Journal of Pharmaceutics, 224 (2001), pp. 159–68
12) De Campos AM, Sanchez A, Gref R, et al. The effect of a PEG versus a chitosan coating on the interaction of drug colloidal carriers with the ocular mucosa: European Journal of Pharmaceutical Sciences, 20 (2003), pp.73–81
13) Demirel M, Yazan Y, Muller RH, et al. Formulation and in vitro-in vivo evaluation of piribedil solid lipid micro- and nanoparticles: Journal of Microencapsulation, 18 (2001), pp. 359-71
14) Diederichs JE, Müller RH Liposomes in cosmetics and pharmaceutical products: Pharm. Ind. 56 (3), (1994), pp. 267–275
15) Dingler A, Blum RP, Niehus H, et al. Solid lipid nanoparticles (SLN™/Lipopearls™) – a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products Journal of Microencapsulation, 16 (1999), pp.751–67
16) Dudhipala N Ocular iontophoresis for anterior and posterior segment drug delivery: Saudi Journal of Medical and Pharmaceutical Sciences, 3(8A) (2017), pp. 853-857.
17) Fundaro A, Cavalli R, Bargoni A, et al. Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetics and tissue distribution after iv administration to rats: Pharmaceutical Research, 42 (2000), pp. 337–43.
18) G. Suvarna, D. Narender and V. Kishan Preparation, Characterization and In vivo Evaluation of Rosuvastatin Calcium Loaded Solid Lipid Nanoparticles: International Journal of Pharmaceutical Sciences and Nanotechnology, 8(1) (2015), pp. 2779-2785
19) Garcia-Garcia E, Andrieux K, Gil S, et al. A methodology to studyintracellular distribution of nanoparticles in brain endothelial cells: International Journal of Pharmaceutics, 298 (2005), pp. 310–314.
20) Gohla SH, Dingler A. Scaling up feasibility of the production of solid lipid nanoparticles (SLN™): Pharmazie, 56 (2001), pp.61–63.
21) Goppert TM, Muller RH. 2005 Adsorption kinetics of plasma proteins on solid lipid nanoparticles for drug targeting: International Journal of Pharmaceutics, 302 (2005), pp. 172–186

22) Hanafy A, Spahn-Langguth H, Vergnault G, et al. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions ofmicronized drug: Advanced Drug Delivery Reviews Rev, 59 (2007), pp.419-426
23) Hao, J., Wang, F., Wang, X., Zhang, D., YBi, Y., Gao, Y., Zhao, X., & Zhang, Q. Development and optimization of baicalin-loaded solid lipid nanoparticles prepared by coacervation method using central composite design: European Journal of Pharmaceutical Sciences, 47 (2012), pp.497-505
24) Ho Lun Wong, Reina Bendayan, Andrew M. Rauth, Yongqiang Li, Xiao Yu W u. Chemotherapy with anticancer drugs encapsulated in solidlipid nanoparticles: Advanced Drug Delivery Reviews, 59 (2007), pp. 491–504
25) HouLi Li, XiaoBin Zhao, YuKun Ma, GuangXi Zhai, LingBing Li, HongXiang Lou Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles: Journal of Controlled Release, 133 (3) (2009), pp. 238–244
26) Hu F.Q., Hong Y., Yuan H. Preparation and characterization of solid lipid nanoparticles containing peptide: International Journal of Pharmaceutics, 273(1–2) (2004), pp.29-35
27) Hu LD, Xing Q, Meng J, et al. Preparation and enhanced oral bioavailability of cryptotanshinone-loaded solid lipid nanoparticles: AAPS PharmSciTech 11 (2010), pp. 1-6
28) Jani PU, Halbert GW, Langridge J, et al. Nanoparticle uptake by therat gastrointestinal mucosa: quantitation and particle size dependency: Journal of Pharmacy and Pharmacology, 42 (1990), pp. 821–826
29) Jenning V, Gysler A, Schafer-Korting M, et al. Vitamin A-loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. European Journal of Pharmaceutics and Biopharmaceutics, 49 (2000), pp.211–219
30) Kakizawa Y, Kataoka K. 2002. Block copolymer micelles for delivery of gene and related compounds. Advanced Drug Delivery Reviews, 54 (2002), pp.203–205
31) Kreuter J. 2001. Nanoparticulate systems for brain delivery of drugs: Advanced Drug Delivery Reviews, 47 (2001), pp.65–81
32) Liu et al., Solid lipid nanopartiles for pulmonary delivery of insulin: International Journal of Pharmaceutics, 356 (2008), pp.333-344
33) Luo CF, Yuan M, Chen MS, et al. Pharmacokinetics, tissue distribution and relative bioavailability of puerarin solid lipid nanoparticles following oral administration: International Journal of Pharmaceutics, 410 (2011), pp.138-44
34) Luo Y, Chen D, Ren L, et al. Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability: J Control Release, 114 (2006), pp. 53-59
35) M.R. Aji Alex, A.J. Chacko, S. Jose, E.B. Souto. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting: European Journal of Pharmaceutical Sciences, 42 (2011), pp.11–18
36) Manjunath K, Venkateswarlu V. Pharmacokinetics, tissue distribution and bioavailability of nitrendipine solid lipid nanoparticles after intravenous andintraduodenal administration: Journal of Drug Targeting, 14 (2006), pp.632-645
37) Manjunath, K., Venkateswarlu, V. Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nanoparticles after intravenous and intraduodenal administration: Journal of Controlled Release, 107 (2005), pp.215-228
38) Mehnert, W., Mäder, K. Solid lipid nanoparticles production, characterization and applications: Advanced Drug Delivery Reviews,47(2001), pp. 165-196
39) Mehnert, W., Mäder, K.Solid lipid nanoparticles production, characterization and applications: Advanced Drug Delivery Reviews, 64 (2012), pp. 83-101
40) Mei Z, Li X, Wu Q, et al. The research on the anti-inflammatory activity and hepatotoxicity of triptolide-loaded solid lipid nanoparticle: Pharmaceutical Research , 51 (2005), pp.345-351.
41) Mohammad M. Mojahediana,, Saeid Daneshamouz, Soliman Mohammadi Samani, Arman Zargaran. A novel method to produce solid lipid nanoparticles using n-butanol as an additional co-surfactant according to the o/w microemulsion quenching technique: Chemistry and Physics of Lipids, 174 (2013), pp.32–38
42) Mühlen, A.Z., Schwarz, C., Mehnert, W. Solid lipid nanoparticles (SLN) for controlled release drug delivery-drug release and release mechanism: European Journal of Pharmaceutics and Biopharmaceutics, 45 (1998), pp.149-155

43) Müller R.H., Mehnert W., Lucks J.S., Schwarz .C, Zur Mühlen A., Weyhers H., Freitas C., Ruhl D. Solid lipid nanoparticles (SLN)—An alternative colloidal carrier system for controlled drug delivery: European Journal of Pharmaceutics and Biopharmaceutics, 41 (1995), pp.62–69
44) Müller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles: Journal of Biotechnology, 113 (2004), pp. 151–70
45) Müller RH, Mehnert W, Lucks JS, et al. Solid lipid nanoparticles (SLN) – An alternative colloidal carrier system for controlled drug delivery: European Journal of Pharmaceutics and Biopharmaceutics, 41 (1995), pp.62–69
46) Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations: Advanced Drug Delivery Reviews, 54 (2002), pp. S131–155.
47) Müller RH, Runge S, Ravelli V, et al. Oral bioavailability of cyclosporine: Solid lipid nanoparticles (SLN) versus drug nanocrystals: International Journal of Pharmaceutics, 317 (2006), pp.82-9
48) Müller RH, Runge SA, Ravelli V, et al. Cyclosporine-loaded solid lipid nanoparticles (SLN): Drug-lipid physicochemical interactions and characterization of drug incorporation: European Journal of Pharmaceutics and Biopharmaceutics 68 (2008), pp. 535-544
49) Müller RH, Schwarz C, Zur Muhlen A, et al. Incorporation of lipophilic drugs and drug release profiles of solid lipid nanoparticles (SLN): Proc Int Symp Control Rel Bioact Mater, 21 (1994), pp.146–147
50) Müller, R.H., Mäder, K., Gohla, S. Solid lipid nanoparticles (SLN) for controlled drug delivery a review of the state of the art: European Journal of Pharmaceutics and Biopharmaceutics, 50 (2000), pp.161-177
51) Narendar D and Karthikyadav J. Lipid nanoparticles of zaleplon for improved oral delivery by Box-Behnken design: Optimization, in vitro and in vivo evaluation: Drug Development and Industrial Pharmacy, 43(7) (2017), pp.1205-1214
52) Narendar D and Kishan V. Improved anti-hyperlipidemic activity of Rosuvastatin Calcium via lipid nanoparticles: pharmacokinetic and pharmacodynamic evaluation: European Journal of Pharmaceutics and Biopharmaceutics, 110 (1) (2017), pp. 47-57
53) Narendar D. Polymeric matrices at micro and nanoscale for ocular drug delivery: Saudi Journal of Biomedical Research, 2 (1)(2017), pp. 96-100
54) Narendar D, Govardhan K. Capecitabine lipid nanoparticles for anti-colon cancer activity in 1, 2-dimethylhydrazine induced colon cancer: Preparation, cytotoxic, pharmacokinetic and pathological evaluation: Drug Development and Industrial Pharmacy, Eraly online, (2018), pp. 1572-1582 https://doi.org/10.1080/03639045.2018.1445264
55) Narendar D, Karthik Yadav J, Thirupathi G. Comparative study of nisoldipine-loaded nanostructured lipid carriers and solid lipid nanoparticles for oral delivery: preparation, characterization, permeation and pharmacokinetic evaluation: Artificial cells, nanomed and biotech. Early online, (2018),pp.616-625 doi.org/10.1080/21691401.2018.1465068
56) Narendar Dudhipala and Kishan Veerabrahma. Pharmacokinetic and pharmacodynamic studies of nisoldipine loaded solid lipid nanoparticles by central composite design: Drug Development and Industrial Pharmacy, (2015), pp.1968-1977 https://doi.org/10.3109/03639045.2015.1024685
57) Narendar, D., & Kishan V.Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation: Drug Delivery., Early Online,1-10 (2014), pp. 395-404 https://doi.org/10.3109/10717544.2014.914986
58) Olbrich C, Bakowski U, Lehr CM, et al. Cationic solid-lipid nanoparticles can effi ciently bind and transfect plasmid DNA: J Control Release, 77 (2001), pp. 345–55
59) Paliwal R, Rai S, Vaidya B, et al. Effect of lipid core material on characteristics of solid lipid nanoparticles designed for oral lymphatic delivery: Nanomedicine: NBM, 5 (2009), pp. 184-191
60) Pandey R, Sharma S, Khuller GK. Oral solid lipid nanoparticle-based antitubercular chemotherapy: Tuberculosis, 85 (5-6) (2005), pp. 415-420
61) Pankaj Dwivedi, Renuka Khatik, Kiran Khandelwal, Isha Taneja, Kanumuri Siva Rama Raju, Wahajuddin, Sarvesh Kumar Paliwal, Anil Kumar Dwivedi, Prabhat Ranjan Mishra. Pharmacokinetics study of arteether loaded solid lipid nanoparticles: An improved oral bioavailability in rats: International Journal of Pharmaceutics, 466 (2014), pp. 321–327
62) Ponchel G, Montisci MJ, Dembri A, et al. Mucoadhesion of colloidal particulate systems in the gastro-intestinal tract: European Journal of Pharmaceutics and Biopharmaceutics, 44 (1997), pp. 25–31

63) R.H. Müller, S. Maaûen, H. Weyhers, F. Specht, J.S. Lucks, Cytotoxicity of magnetite loaded polylactide, polylactide/glycolide particles and solid lipid nanoparticles (SLN): International Journal of Pharmaceutics, 138 (1996), pp.85- 94
64) Rabea Parveen, F. J. Ahmad Z. Iqbal, M. Samim & Sayeed Ahmad Solid lipid nanoparticles of anticancer drug andrographolide: formulation, in vitro and in vivostudies: Drug Development and Industrial Pharmacy, 40(9)(2014), pp.1206-1212
65) Radheshyam Tiwari, Kamla Pathak. Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: Comparative analysis of characteristics, pharmacokinetics and tissue uptake: International Journal of Pharmaceutics,415 (1-2) (2011), pp. 232-243
66) Rohit Bhandari, Indu Pal Kaur. Pharmacokinetics, tissue distribution and relative bioavailability of isoniazid-solid lipid nanoparticles: International Journal of Pharmaceutics, 441 (2013), pp. 202–212
67) Sandeep V, Narendar D, Arjun N and Kishan V. Lacidipine loaded solid lipid nanoparticles for oral delivery: Preparation, characterization and In vivo evaluation: International Journal of Pharmaceutics , 9(6)(2016), pp. 3524-30
68) Sanjula B. Effect of poloxamer 188 on lymphatic uptake of carvedilol-loaded solid lipid nanoparticles for bioavailability enhancement: Journal of Drug Targeting, 17 (2009), pp. 249-256
69) Sanket N., Palak K., Bharadia P.D, Modi D.A. Novel drug delivery system for lipophilic Agents: Solid lipid nanoparticles: IJPI's Journal of Pharmaceutics and Cosmetology, 1(4) (2011), pp.77-89
70) Scheffel U., B.A. Rhodes, T.K. Natajaran, H.N. Wagner Jr., Albumin microspheres for study of the reticuloendothelial system: journal of nuclear medicine, 13(1970), pp. 498–503.
71) Schwarz, C. Solid lipid nanoparticles (SLN) for controlled drug delivery II. Drug incorporation and physicochemical characterization: Journal of Microencapsulation. 16(2)(1999), pp. 205-213
72) Shamsunder, Dodiya., Sandip, Chavhan., Aruna, Korde., &Krutika, K. Sawant. Solid lipid nanoparticles and nanosuspension of adefovir dipivoxil for bioavailability improvement: formulation, characterization, pharmacokinetic and biodistribution studies: Drug Development and Industrial Pharmacy, 39 (5) (2013), pp. 733-743
73) Siekmann B, Westesen K. Submicron-sized parenteral carrier systems based on solid lipids: Pharm Pharmacol Lett ,1 (1992), pp. 123–6
74) Smith A., Hunneyball I.M. Evaluation of poly (lactic acid) as a biodegradable drug delivery system for parenteral administration: International Journal of Pharmaceutics, 30 (1986): 215-220
75) Sumeet Sooda, Natarajan Jawahara, Kunal Jain, Kuppusamy Gowthamarajan, Subramania Nainar Meyyanathan. Olanzapine Loaded Cationic Solid Lipid Nanoparticles for Improved Oral Bioavailability: Current Nanoscience, 9 (2013), pp. 26-34
76) Suresh G, Manjunath K, Venkateswarlu V, et al. Preparation, characterization, and in vitro and in vivo evaluation of lovastatin solid lipid nanoparticles: AAPS PharmSciTech 8 (2007), pp 162-70
77) Tao Yang, Huan-Huan Sheng, Nian-Ping Feng, Hai Wei, Zheng-tao Wang, Chang-Hong Wang. Preparation of Andrographolide-Loaded Solid Lipid Nanoparticlesand Their In Vitro and In Vivo Evaluations: Characteristics, Release,Absorption, Transports, Pharmacokinetics, and AntihyperlipidemicActivity: Journal of Pharmaceutical Sciences 102 (2013), pp. 4414–4425
78) Thirupathi G, Swetha E and Narendar D. Role of isradipine loaded solid lipid nanoparticles in the pharmacodynamic effect of isradipine in rats: Drug Research, 67 (03) (2017), pp. 163-169
79) Üner, M., Yener, G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives: International journal of Nanomedicine. 2(3)(2007), pp.289-300
80) Usha Kiranmai Gondrala, Narendar Dudhipala and Veerabrahma Kishan. Preparation, characterization and in vivo evaluation of felodipine solid lipid nanoparticles to improve the oral bioavailability: International Journal of Pharmaceutical Sciences and Nanotechnology. 8 (4) (2015), pp. 1-8
81) Vandita Kakkar, Sukhjit Singh, Dinesh Singla, Indu Pal Kaur. Exploring solid lipid nanoparticles to enhance the oral bioavailability of Curcumin: Molecular Nutrition food research, 55 (2011), pp. 495–503
82) Venkateswarlu V, Manjunath K. Preparation, characterization and in vitro release kinetics of clozapine solid lipid nanoparticles: Journal of Control Release, 95 (2004), pp. 627–638
83) Vijaykumar Nekkanti, Vobalaboina Venkateshwarlu and Raviraj Pillai. Preparation, Characterization and in vivo Evaluation of Raloxifene Hydrochloride Solid Lipid Nanoparticles; Pharmaceutical Nanotechnology, 1(1) (2012), 68-77.

84) Vila A, Gill H, McCallion O, Alonso MJ. Transport of PLA-PEG particles across the nasal mucosa: effect of particle size and PEG coating density: Journal of Control Release, 98(2004), pp. 231–44
85) Vinay Kumar, V., Chandrasekhar, D., Ramakrishna, S., Kishan, V.B., Madhusudan Rao, Y., Prakash, V.D. Development and evaluation of nitrendipine loaded solid lipid nanoparticles: Influence of wax and glyceride lipids on plasma pharmacokinetics: International Journal of Pharmaceutics, 335 (2007), pp. 167-175
86) Vinay Kumar, V., Raghavendra, C., Rojarani, K., Laxminarayana, A., Ramakrishna, S., & Prakash, V. D. Design and evaluation of polymer coated carvedilol loaded solid lipid nanoparticles to improve the oral bioavailability: A novel strategy to avoid intraduodenal administration: Colloids and Surfaces B: Biointerfaces, 95 (2012), pp. 1–9
87) Wissing SA, Muller RH. Cosmetic applications for solid lipid nanoparticles (SLN): International Journal of Pharmaceutics, 254 (2003), pp. 65-68
88) XIE S, ZHU L, DONG Z, WANG Y, WANG X, ZHOU W. Preparation and evaluation of ofloxacin-loaded palmitic acid solid lipid nanoparticles: INT J NANOMEDICINE. (2011), pp.547-555.
89) Yang S, Zhu J, Lu Y, et al. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharmaceutical Research, 16 (1999), pp. 751–757
90) Zara GP, Bargoni A, Cavalli R, et al. Pharmacokinetics and tissue distribution of idarubicin loaded solid lipid nanoparticles after duodenal administration to rats: Journal of Pharmaceutical Science, 91 (2002), pp. 1324-33
91) Zhang N, Ping Q, Huanga G, et al. Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin: International Journal of Pharmaceutics 327 (2006), pp. 153-159