



CODEN [USA]: IAJPB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Review Article

**REVIEW OF OF APIGENIN LOADED ANTI-INFLAMMATORY
NANO GEL**¹Miss. Kiran Dinesh Nagote, ¹Dr. Kiran D. Baviskar¹Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda - 425107**Article Received:** May 2023**Accepted:** June 2023**Published:** July 2023**Abstract:**

Transdermal drug delivery systems provide an easy, reliable mechanism of administering drugs when rapid onset is not important. Transdermal drug delivery bypasses the enterohepatic circulation, thereby providing a more reliable clinical action. Nanogels are commonly used in sensing, diagnostics, and bioengineering, but they are also often used in drug delivery. Nanogels have benefits over conventional and macro-sized delivery systems because of their higher drug loading capacity, high stability, and improved contact time with the skin surface, which makes it more convenient as a transdermal drug delivery system. Nanogels composed of nanosize particles formed by physically or chemically cross linked polymer networks that swells in a good solvent. The nanogel systems have proven their potential to deliver drugs in controlled, constant and targetable mode. With the promising field of polymer sciences it has now become predestinated to prepare smart nano-system which can establish effectual for treatment, diagnosing as well as clinical trials progress.

Keywords: Anti-inflammatory, Nanogel, Apigenin.**Corresponding author:****Kiran Dinesh Nagote,**

Smt. Sharadchandrika Suresh Patil College of Pharmacy,

Chopda – 425107.

QR code



Please cite this article in press **Kiran Dinesh Nagote et al, Review Of Of Apigenin Loaded Anti-Inflammatory Nanogel, Indo Am. J. P. Sci, 2023; 10 (07).**

INTRODUCTION:

The Skin:

The human skin is the outer covering of the body and the largest organ of the integumentary system. The skin constitutes one of the largest interfaces between the body and environment. The skin has up to seven layers of ectodermal tissue and guards the underlying muscles, bones, ligaments and internal organs. The skin of an average adult body covers a surface area of approximately 2 m² and receives about one-third of blood circulating through the body. There are two general types of skin; hairy and glabrous skin (hairless). Skin plays an important role in protecting the body against pathogens, excessive water loss, insulation, temperature regulation, sensation, synthesis of vitamin D and the protection of vitamin B folates (Rousso et al., 2015).(1,2)

Skin Origin:

The skin arises by the juxtaposition of two major embryological elements: the prospective epidermis, which originates from a surface area of the early gastrula, and the prospective mesoderm, which is brought into contact with the inner surface of the epidermis during gastrulation. The mesoderm not only provides the dermis but is essential for inducing differentiation of the epidermal structures, such as the hair follicle in mammals. The neural crest also makes an important contribution to the skin, namely the

pigment cells, although their bulk is small (Saladin & Miller, 1998).

Skin Organization:

The skin is the largest organ in the human body. For the average adult human, the skin has a surface area of between 1.5-2.0 square meters (16.1-21.5 sq. ft.). The thickness of the skin varies considerably over all parts of the body, and between gender and age. The skin on the forearm which is on average 1.3 mm in the male and 1.26 mm in the female (Luck et al., 1964). The average square inch (6.5 cm²) of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes, and more than 1,000 nerve endings. The average human skin cell is about 30 micrometers in diameter, but there are variants.

A skin cell usually ranges from 25-40 micrometers (squared) and composed of three primary layers: the epidermis, the dermis and the hypodermis (Gladcova et al., 2000). It has a complex structure with multiple layers, the uppermost layer refers as stratum corneum, followed by the viable epidermis and hypodermis and it contains appendages, sweat glands, sebaceous glands and hair follicles (Figure 1.). Even with all these, it has a thickness of only a few millimeters (2.97 ± 0.28 mm) and separates the underlying blood circulation network and viable organs from the outside environment (Jacques et al., 2002).

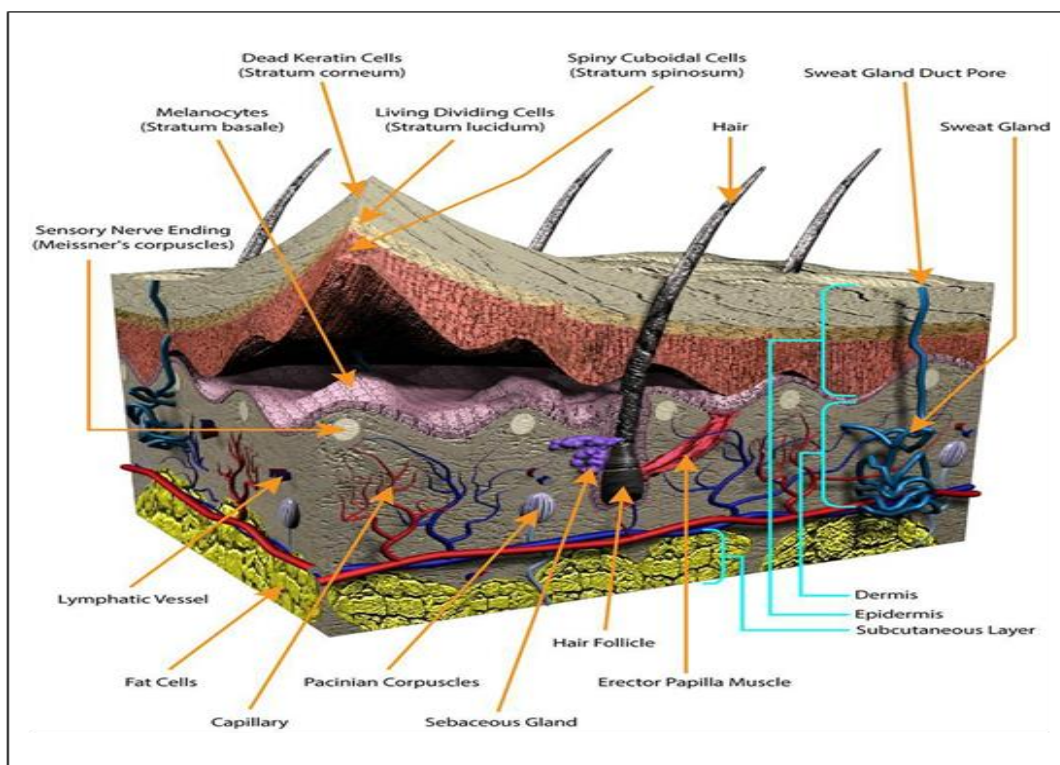


Fig.No 1: Structure of Human Skin.

Epidermis:

Epidermis is the outermost layer of the skin and forms the waterproof, protective wrap over the body's surface which also serves as a barrier to infection and is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis chiefly consist Merkel cells, keratinocytes with melanocytes, Langerhans cells and lacks blood vessels (Grimbaldeston et al., 2007). The epidermis can be again divided into two.

Stratum Corneum (SC):

It is the uppermost desquamating horny layer comprises of 15-20 layers of flat, separated, nonviable, cornified, almost non-permeable coenocytes embedded into a continuous lipid bilayer made of various classes of lipids. Structurally, this layer is best referred as "brick and mortar model system". The thickness of this layer ranges from 10-25 μm depending upon the region of the body and is the thickest in the palms of the hand and sole of the feet. This SC is remarkably more formidable barrier to drug transport in comparison to the epithelial

barriers of gastrointestinal, nasal, buccal, vaginal or rectal drug delivery routes (Biggs et al., 2010). These horny cells have lost their nuclei and physiologically rather inactive. Epidermis is divided into the main five sub layers or strata. They are as follows Stratum corneum, Stratum lucidum, Stratum granulosum, Stratum spinosum and Stratum germinativum ("stratum basale") (Figure 2).

In normal SC, the cells have a water content of only 20% compared to the normal physiological level of 70% in the physiologically active stratum germinativum (Jasaitiene et al., 2011). The SC requires a minimum moisture content of 10% (w/w) to maintain flexibility and softness. In the thicker parts of the skin, the transition from the living cells of the germinativum to the dead cornified cells of the SC is made prominent by three layers, the stratum spinosum (prickly layer), stratum granulosum (granular layer) and stratum lucidum (clear layer). Like SC, the stratum granulosum and stratum lucidum are also physiologically important (Kusuma et al., 2010).

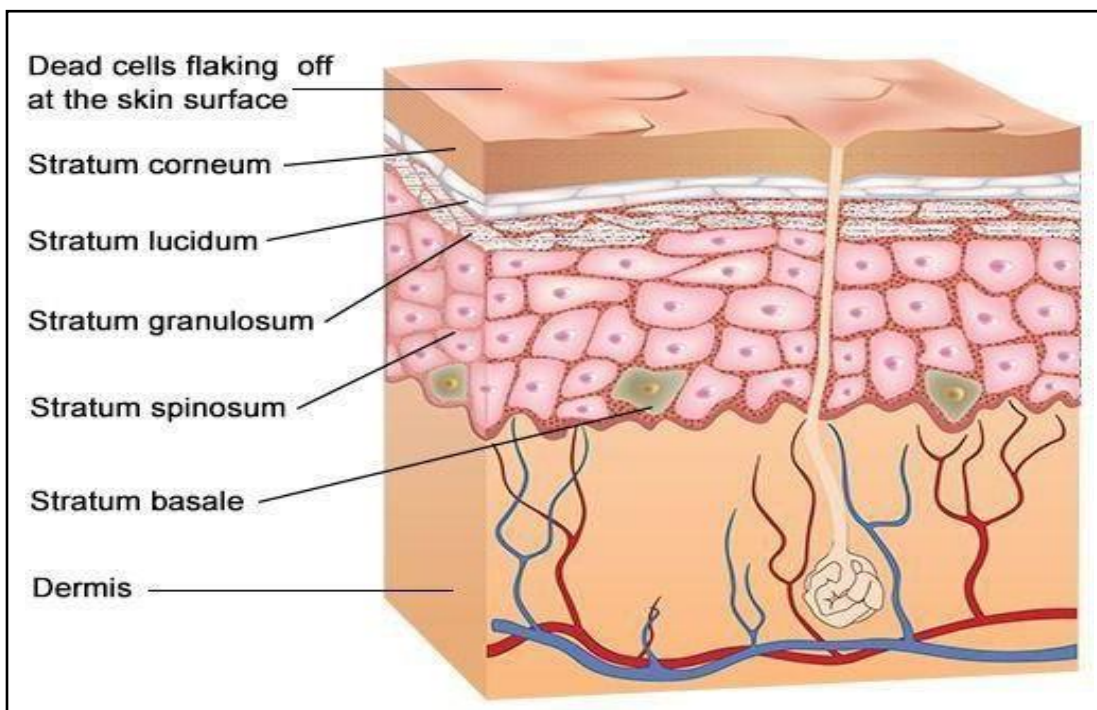


Fig. No 2: Demonstration of various sub-layers of epidermis.

Viable Epidermis:

The thickness of the viable epidermis is about 150 μm and comprises of many layers below the SC as mentioned above. Furthermore, the melanocytes, producing melanin for light protection and the langerhans cells responsible for the immune response

of the skin are localized in the viable epidermis (Brash et al., 1991). There is no vascularization in this layer.

Dermis:

The thickness of dermis ranges from 3-5 mm. This consists of a matrix of connective tissue composed of collagen, elastin and reticulin and is inter-dispersed by skin appendages. The network of connective tissue is actually a gel containing oriented tropocollagen (polypeptide) macromolecules. This network or gel structure is responsible for the elastic properties of the

skin (Brownstein et al., 1981). Furthermore, the nerves, blood and lymphatic vessels are located in this layer. The dermis is structurally divided into two areas: a superficial area adjacent to the epidermis, called the papillary region, and a deep thicker area known as the reticular region (Figure 3).

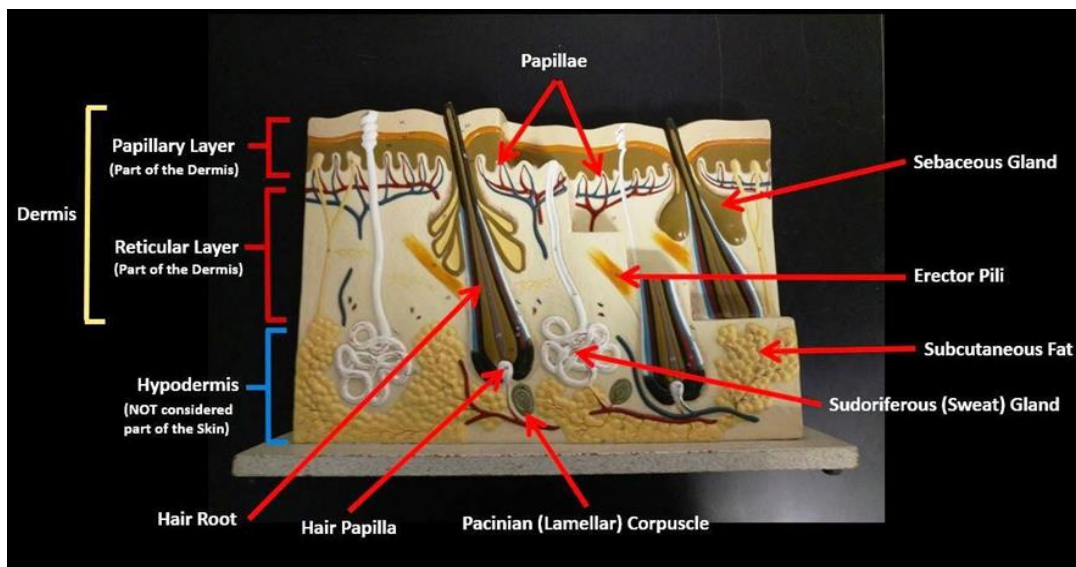


Fig. No 3: Demonstration of dermis layer.

Papillary Region:

The papillary region is composed of loose areolar connective tissue. It is named for its fingerlike projections called papillae that extend toward the epidermis. The papillae provide the dermis with a "bumpy" surface that inter-digitates with the epidermis, strengthening the connection between the two layers of skin (Enterline et al., 1960).

Reticular Region:

The reticular region lies deep in the papillary region and is usually much thicker. It is composed of dense irregular connective tissue, and receives its name from the dense concentration of collagenous, elastic, and reticular fibers that weave throughout it. These protein fibers give the dermis its properties of strength, extensibility, and elasticity. Also located within the reticular region are the roots of the hairs, sebaceous glands, sweat glands, receptors, nails and blood vessels (Friedman et al., 1985).

Subcutaneous Tissue:

The subcutaneous tissue (also hypodermis and subcutis) is not part of the skin and lies below the dermis of the cutis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves (Gallagher et al., 1990). It consists of loose connective tissue, adipose tissue

and elastin. The main cell types are fibroblasts, macrophages and adipocytes (subcutaneous tissue contains 50% of body fat). Fat serves as padding and insulation for the body. It mainly acts as a heat insulator and stores readily available high energy chemicals (Johnson & Helwig, 1966).

Functions of Skin:

The skin performs the following functions:

- ❖ **Protection:** The skin is an anatomical barrier from pathogens and damage between the internal and external environment in bodily defense.
- ❖ **Sensation:** It contains a variety of nerve endings that react to heat and cold, touch, pressure, vibration and tissue injury.
- ❖ **Heat regulation:** The skin contains a blood supply which allows precise control of energy loss by radiation, convection and conduction. Dilated blood vessels increase perfusion and heat loss, while constricted vessels greatly reduce cutaneous blood flow and conserve heat.
- ❖ **Control of evaporation:** The skin provides a relatively dry and semi-impermeable barrier to fluid loss.
- ❖ **Storage and synthesis:** It acts as a storage center for lipids and water, as well as a

means of synthesis of vitamin D by action of UV on certain parts of the skin.

- ❖ **Excretion:** The sweat contains urea; however its concentration is 1/130th that of urine, hence excretion by sweating is at most a secondary function to temperature regulation.
- ❖ **Absorption:** In addition, medicine can be administered through the skin, by ointments or by means of adhesive patch. The skin is an important site of transport and absorption in many other organisms.
- ❖ **Water resistance:** The skin acts as a water-resistant barrier so essential nutrients are not washed out of the body (Jones et al., 1997, Rousso et al., 2015 & Brash et al., 1991).

Novel Drug Delivery System (NDDS):

Novel drug delivery system or targeted drug delivery system is a method of delivering medication to a patient in a manner that increases the concentration of the medication in desired parts and reducing the relative concentration of the medication in the remaining tissues. The novel ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition and efficacy of drugs were provoked (Barbe et al., 2004). These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio-conjugate chemistry and molecular biology. The drug's therapeutic index, as measured by its pharmacological response and safety, relies in the access and specific introduction of the drug with its candidate receptor, whilst minimizing its introduction with non –target tissue. The desired differential distribution of drug its targeted delivery would spare the rest of the body and thus significantly reduce the overall toxicity while maintaining its therapeutic benefits (Illum et al., 1994).

Advantage of Novel Drug Delivery System:

The therapeutic benefits of these new systems include:

- ❖ Increased efficacy of the drug
- ❖ Site specific delivery
- ❖ Decreased toxicity/side effects
- ❖ Increased convenience
- ❖ Viable treatments for previously incurable diseases
- ❖ Potential for prophylactic applications
- ❖ Better patient compliance (Langer, 1990 & Lawrence et al., 2000)

Novel Drug Delivery Carriers

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter developed by optimizing drug/polymer concentration and release properties, long shelf-life and low toxicity (Barry, 2001).

The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties (Tacar et al., 2013).

Types of Novel Drug Delivery Systems

The most common types of novel drug delivery carriers (Figure 4) are as follows;

- ❖ Liposomes
- ❖ Nanoparticles
- ❖ Microspheres
- ❖ Nanogels
- ❖ Dendrimers
- ❖ Niosomes
- ❖ Micelles
- ❖ Carbon Nanotubes (Drummond & Fong, 1999 & Barry, 2001)

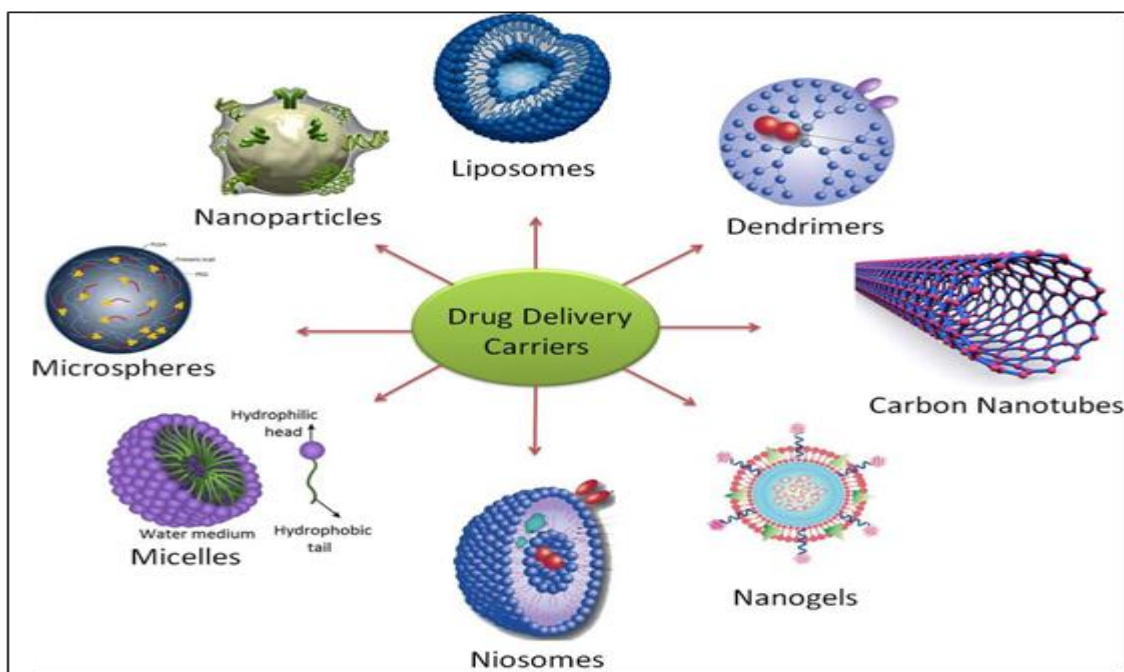


Fig. No 4: Different carriers of novel drug delivery system.

Nanogel:

The term “Nanogel” (Nano-Gel) was first introduced to define cross- linked dual- functional networks of a poly-ions and a non-ionic polymer for delivery of polynucleotide. Nanogels composed of nanosize particles formed by physically or chemically cross linked polymer networks that swells in a good solvent

(Du et al., 2010)(Figure 5). The nanogel systems have proven their potential to deliver drugs in controlled, constant and targetable mode. With the promising field of polymer sciences it has now become predestinated to prepare smart nano-system which can establish effectual for treatment, diagnosing as well as clinical trials progress (Gota et al., 2009).

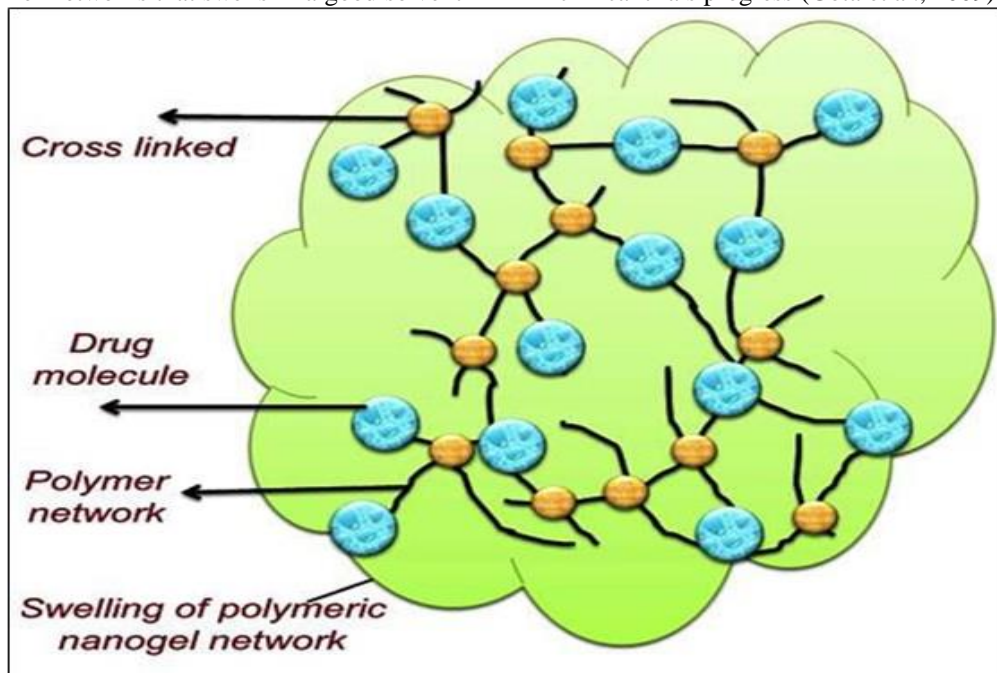


Fig. No 5: Nanogel carrier system

Nanogel basically falls in two major categories (Figure 6) i.e., Responsive type (Non-responsive nanogels and Stimuli responsive nanogel) and Linkage type. The linkage type nanogel further sub classified into following subtypes i.e., physical cross-linked, liposomes modified, micellar type, hybrid type and chemically cross-linked nanogel (Hasegawa et al., 2005).

Applications of Nanogel:

Nanogels is been proving as a promising drug delivery system and offers variety of characteristics like on site drug delivery system, sustained release formulation, high drug entrapment properties, water solubility, biodegradability, low toxicity etc. Due to these multi functionality properties and features nanogel utilized extensively in many drug deliver fields (Paciotti et al., 2004). Composite with polymers, metals and other active molecules nanogel turned out as excellent drug delivery system. The nanogel system broadly employed in many streams like medicine, diagnosing tool, food processing etc. With diverse properties and potential applications the nanogel comprehensively employed in following fields

Transdermal Drug Delivery (TDD):

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. TDD has many advantages over other conventional routes of drug delivery. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allows many placement options on the skin for transdermal absorption. Furthermore, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects. It can improve patient compliance due to the reduction of dosing frequencies and is also suitable for patients who are unconscious or vomiting, or those who rely on self-administration [13]. TDD avoids pre-systemic metabolism, thus improving bioavailability. With reference to the use of the skin as a novel site for vaccination strategies, this organ is known to be replete with dendritic cells in both the epidermal and dermal layers which play a central role in immune responses making TDD an attractive vaccination route for therapeutic proteins and peptides [14]. The requirement for an inexpensive and non-invasive means of vaccination, especially in the

developing world [3, 14,15], has given rise to substantial research focused on the development of simple, needle-free systems such as TDD for vaccination purposes.

Advantages of Transdermal Drug Delivery System (TDDS):

- Longer duration of action resulting in a reduction in dosing frequency
- Increased convenience to administer drugs which would otherwise require frequent dosing
- Improved bioavailability
- More uniform plasma levels
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval
- Flexibility of terminating the drug administration by simply removing the patch from the skin
- Improved patient compliance and comfort via non-invasive, painless and simple application

Limitations of Transdermal Drug Delivery System:

- Possibility that a local irritation at the site of application
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation

Topical drug delivery can be defined as application of medication containing formulation to the skin to directly treat the cutaneous or subcutaneous disorders and diseases like acne or fungal infections by providing the drug to the surface of the skin or within the skin. In spite of many advantages of transdermal and dermal drug delivery over other drug delivery system, relatively few topical drug formulations are commercially available in market. The main challenging step in the topical delivery is the crossing of most impermeable epithelia of human body that is stratum corneum. Stratum corneum becomes a barrier for the exogenous substances. Hence this fact is to be considered at the time of formulating a new formulation for the topical administration of drug so that maximum penetration of the drug into the skin without irreversibly disturbing the skin barrier function can be achieved.

Mechanism of TDDS

Following are the major routes by which the nanotechnology based nanogel provoked its desired effect on transdermal administration (Sugawara et al., 2006).

Transport across the Intact Stratum Corneum:

SC is the major rate limiting barrier in transdermal permeation. It comprises of multi layered "Brick &

Mortar” like organization of keratin rich corneocytes (bricks) in an intercellular matrix (mortar) consist of primarily of long chain ceramides, free acids, triglycerides, cholesterol, cholesterol sulphates etc (Yan et al., 2006) (Figure 1.13). The Nanogel

transported across intact stratum corneum which passes:

- ❖ Through intercellular space- intercellular route.
- ❖ Through the interior of cells- the transcellular (intracellular) route

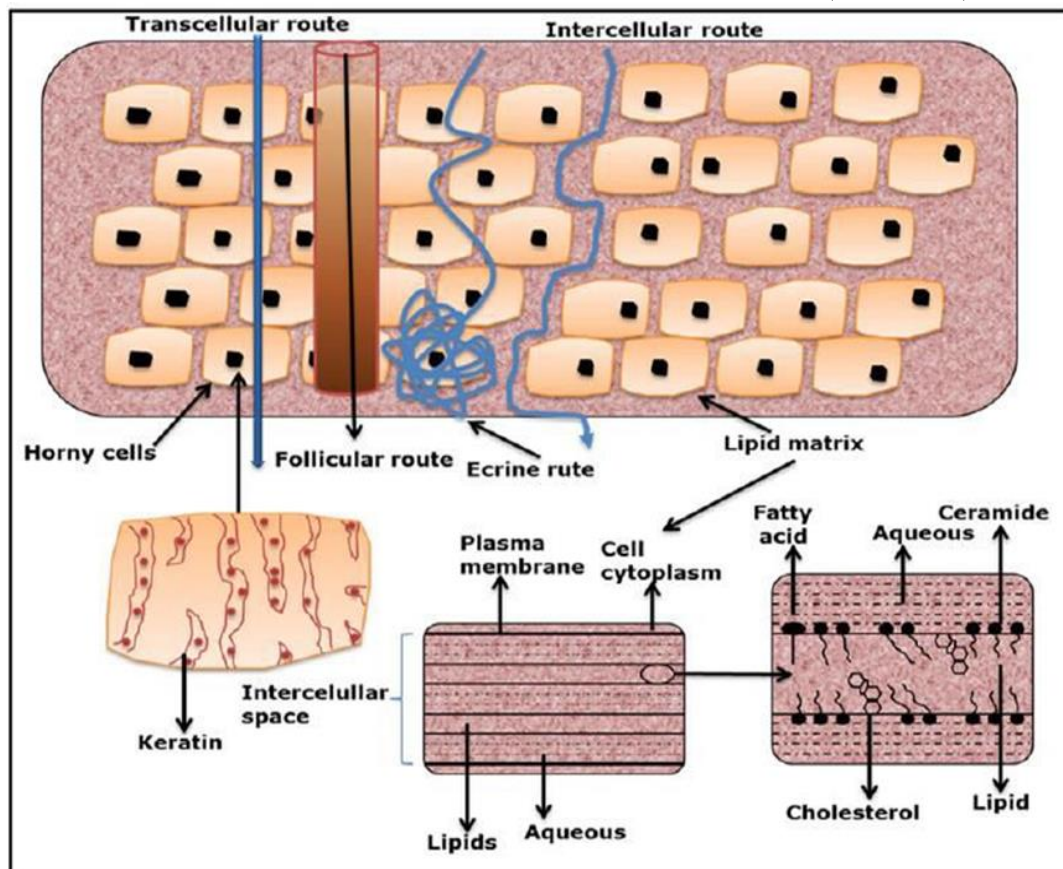


Fig. No 6 Drug transportation mechanism via intact stratum corneum pathway.

Solid lipid nanoparticles:

Solid lipid nanoparticles (SLN) were developed as a colloidal carrier at the beginning of the 1990s as an alternative system to the existing traditional carriers like emulsions, liposomes, niosomes and polymeric nanoparticles. Nanoparticles made up of solid lipid have more advantages than any other carrier system. SLN have more entrapment of drug in solid lipid. Solid lipid nanoparticles are composed of lipid in solid form at room temperature along with surfactant (emulsifier) for stabilizing of SLN dispersion. The reasons for the increasing interest in lipid-based system are many – fold and include.

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
 2. Better characterization of lipid excipients.
 3. An improved ability to address the key issues of technology transfer and manufacture scale-up.
- Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig. 2. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.

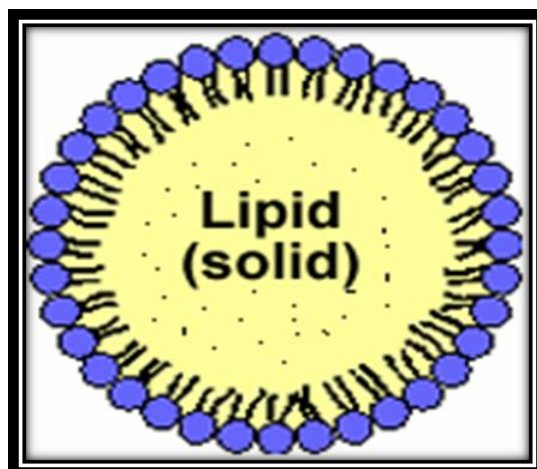


Fig. No.7 .Structure of solid lipid nanoparticle (SLN)

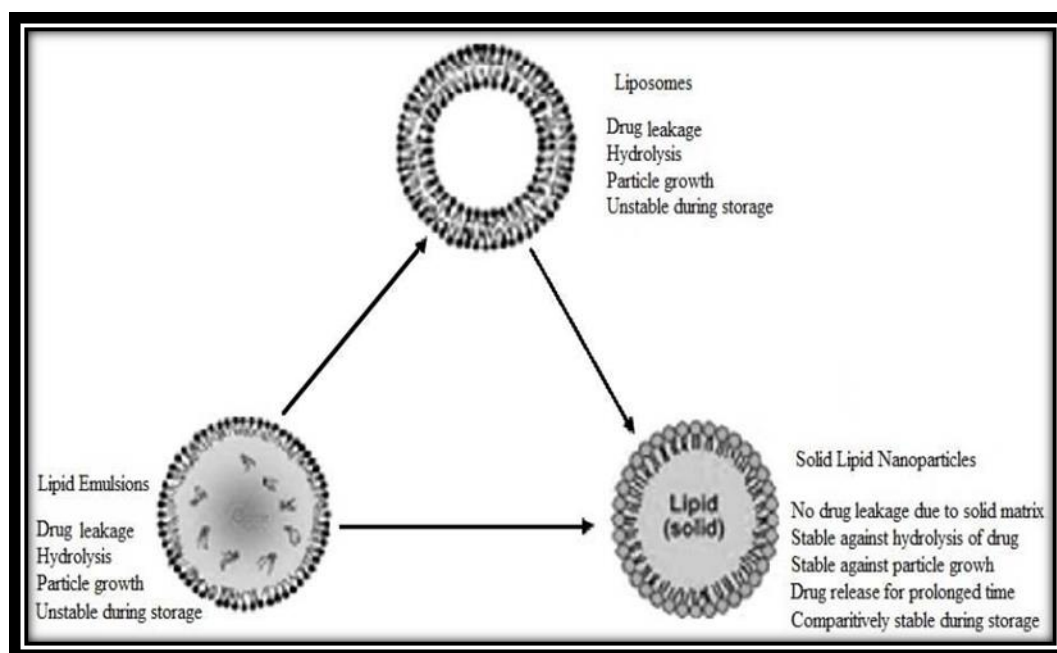


Fig. No. 8 A diagrammatic representation on SLN over emulsions and liposomes

Different types of lipids and surfactants reported in the formulation of solid lipid nanoparticles are given in table 1.

Table 1: Lipids and Surfactants used

Lipids	Surfactant
Triacylglycerols	Phospholipids
Tricarpin	Soy lecithin
Trilaurin	Egg lecithin
Tripalmitin	Phosphatidylcholine
Tristearin	Ethylene oxide/propylene oxide copolymer
Acylglycerol	Poloxamer 188
Glycerol Monostearate	Poloxamer 182
Glycerol behenate	Poloxamer 407
Glycerol palmitostearate	Poloxamer 908
Fatty acids	Sorbitan ethylene oxide
Stearic acid	Polysorbate 20

Palmitic acid	Polysorbate 60
Decanoic acid	Polysorbate 80
Behenic acid	Alkylaryl polyether alcohol polymers
Waxes	Tyloxapol
Cetyl palmitate	Bile salts
Cyclic complexes	Sodium cholate
Cyclodextrin	Sodium glycocholate
Para-acyl-calix-arenes	Sodium taurocholate Sodium taurodeoxycholate Alcohols Ethanol Butanol

Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature. The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in Figure 3. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

Advantages of SLN:

- Control and / or target drug release.
- Excellent biocompatibility
- Improve stability of pharmaceuticals
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

Disadvantages of SLN:

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions.

Preparation of solid lipid nanoparticles

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

Methods of preparation of solid lipid nanoparticles

1. High pressure homogenization
 - A. Hot homogenization
 - B. Cold homogenization
2. Ultrasonication/high speed homogenization
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

High pressure homogenization (HPH)

It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

Two general approaches of HPH are hot homogenization and cold homogenization, work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization: Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid.

In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the

homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

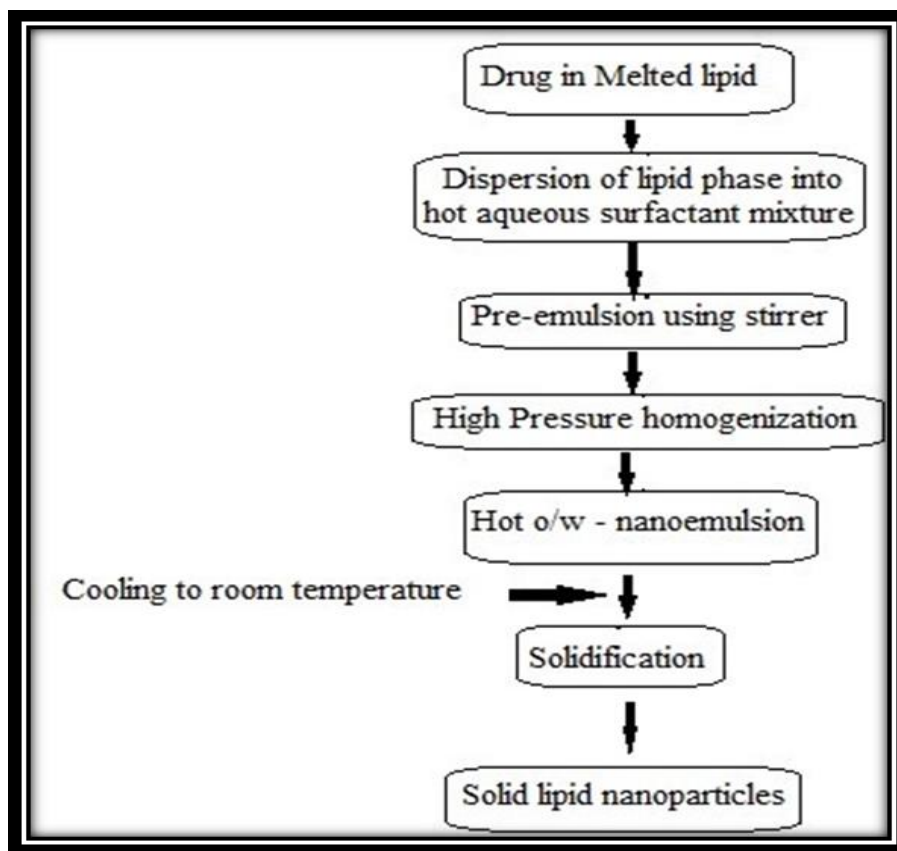


Fig. No.9. Solid lipid nanoparticles preparation by hot homogenization process

Cold homogenization: Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

➤ **Advantages**

1. Low capital cost.
2. Demonstrated at lab scale.

➤ **Disadvantages**

1. Energy intensive process.
2. Demonstrated at lab scale Biomolecule damage.
3. Polydisperse distributions.
4. Unproven scalability.

Ultrasonication/high speed homogenization:

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required.

➤ **Advantages**

1. Reduced shear stress.

➤ **Disadvantages**

2. Potential metal contamination.
3. Physical instability like particle growth upon storage.

Solvent evaporation:

SLNs can also be prepared by solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).

➤ **Advantages**

1. Scalable.

2. Mature technology.
3. Continuous process.
4. Commercially demonstrated.

➤ **Disadvantages**

1. Extremely energy intensive process.
2. Polydisperse distributions.
3. Biomolecule damage.

Solvent emulsification-diffusion method:

The particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique.

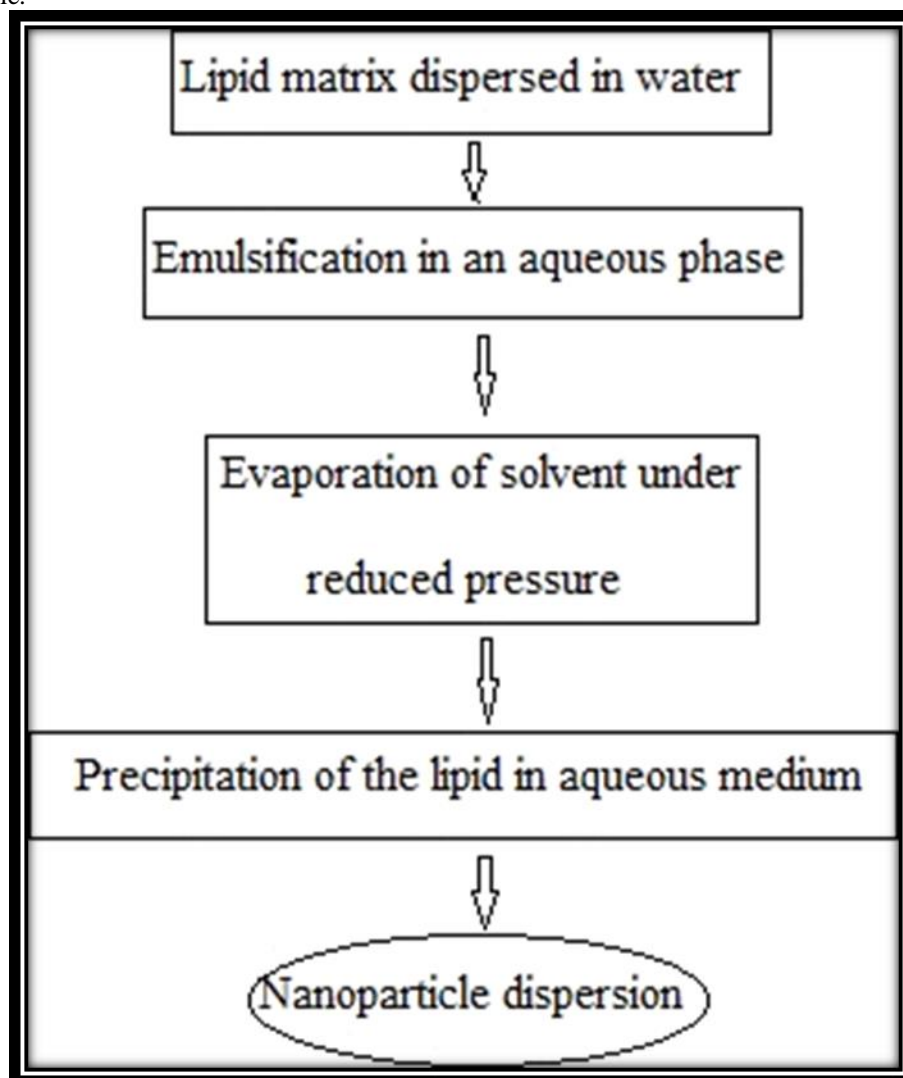


Fig. No.10.Systematic representation for emulsification-diffusion method

Supercritical fluid method:

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS)

➤ **Advantages**

1. Avoid the use of solvents.

2. Particles are obtained as a dry powder, instead of suspensions.
3. Mild pressure and temperature conditions.
4. Carbon dioxide solution is the good choice as a solvent for this method.

Microemulsion based method:

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g.

stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.

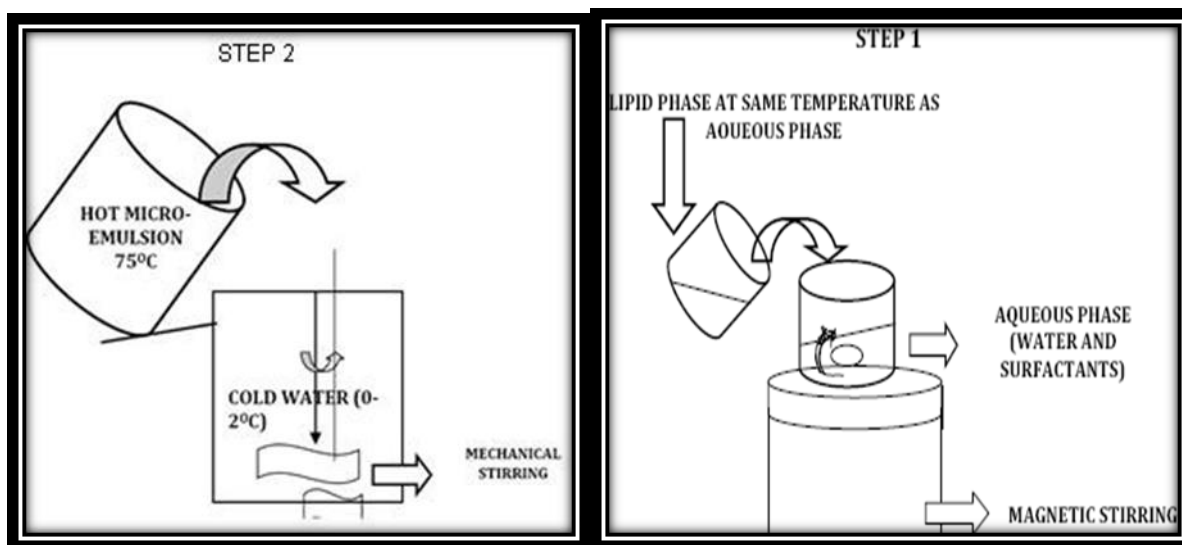


Fig. No.11. Microemulsion method

➤ Advantages

1. Low mechanical energy input.
2. Theoretical stability.

➤ Disadvantages

1. Extremely sensitive to change.
2. Labor intensive formulation work.
3. Low nanoparticle concentrations.

Spray drying method:

It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than 70°C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

Double emulsion method:

Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

Precipitation method:

The glycerides are dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

Film-ultrasound dispersion:

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

Secondary Production Steps:

a. Freeze drying:

Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time. Lyophilization had been required to achieve

long term stability for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. In case of freeze drying of the product, all the lipid matrices used, form larger solid lipid nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process.

b. Sterilization:

Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving which is applicable to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it was found to cause a distinct increase in particle size.

c. Spray drying:

Spray drying might be an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method has been used scarcely for SLN formulation, although spray drying is cheaper as compared to lyophilization. The lipids with melting points at temperature $>70^{\circ}\text{C}$ had been recommended for spray drying.

Influence of excipients:

Particle size:

Alteration of the size significantly affects the physical stability, biofate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated systems (liposomes, nanospheres and nanoparticles) should display a narrow particle size distribution in the submicron size range (as having size below $1\mu\text{m}$), according to the definition of colloidal particles.

Influence of the ingredients on product quality:

The particle size of lipid nanoparticles is affected by various parameters such as composition of the formulation (such as surfactant/ surfactant mixture, properties of the lipid and the drug incorporated),

production methods and conditions (such as time, temperature, pressure, cycle number, equipment, sterilization and lyophilization). Large particle size is obtained at lower processing temperature. The hot homogenization technique gives a smaller particle size, generally below 500 nm, and a narrow particle size distribution as compared to cold homogenization. Mean particle size as well as polydispersity index (PI) values are reported to be reduced at increasing homogenization pressure up to 1500 bar and number of cycles (3-7 cycles).

Influence of the lipids:

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area).

Further, increasing the lipid content over 5-10% resulted in larger particles (including microparticles) and broader particle size distribution in most cases.

Influence of the emulsifiers:

The concentration of the surfactant/surfactant mixture strongly affects the particle size of the lipid nanoparticles. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration resulted in increase of particle size during storage.

Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.

Drug incorporation models of SLN:

Factors affecting loading capacity of a drug in lipid are:

1. Solubility of drug in lipid melt.
2. Miscibility of drug melt and lipid melt.
3. Chemical and physical structure of solid matrix lipid.
4. Polymorphic state of lipid material.

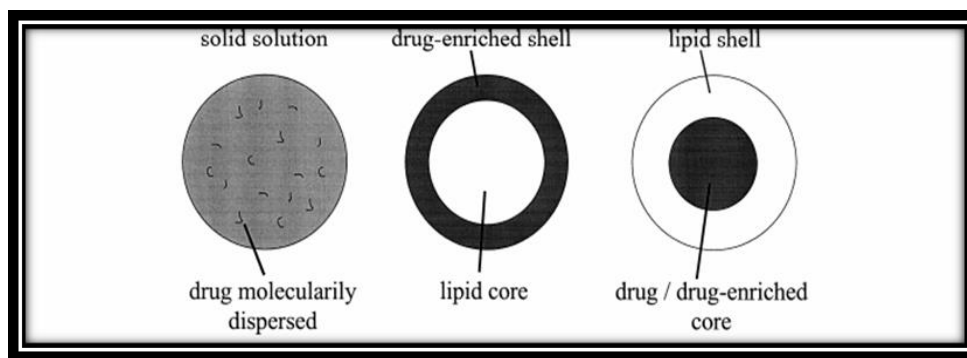


Fig. No.12. Drug incorporation models

Solid solution model:

1. Drug is molecularly dispersed in lipid matrix when SLN is prepared by cold homogenization.
2. Drug-enriched shell model.
3. A solid lipid core forms upon recrystallization temperature of the lipid is reached.
4. Drug-enriched core model.
5. Cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt leads to recrystallization of the lipid.

SLN in cosmetic and dermatological preparations:

An area of big potential for SLN and with a short time-to market are topical products based on the SLN technology, that means pharmaceutical but also cosmetic formulations. SLN are considered as being the next generation of delivery system after liposomes. Due to the lower risk of systemic side effects topical treatment of skin disease appears favourable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. Particulate carrier systems may mean an option to improve dermal penetration. Since epidermal lipids are found in high amounts within the penetration barrier, lipid carriers attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Besides liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been studied intensively. Following the evaporation of water from the lipid nanodispersion applied to the skin surface, lipid particles form an adhesive layer occluding the skin surface. Then hydration of the stratum corneum may increase by which reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug penetration into deeper skin strata. Occlusive effects appear strongly related to particle size.

SUMMARY AND CONCLUSION:

The aim of the present study was to develop Review of of Apigenin Loaded Anti-inflammatory Nanogel. Nanogels is been proving as a promising drug

delivery system and offers variety of characteristics like on site drug delivery system, sustained release formulation, high drug entrapment properties, water solubility, biodegradability, low toxicity etc. Due to these multi functionality properties and features nanogel utilized extensively in many drug deliver fields. Composite with polymers, metals and other active molecules nanogel turned out as excellent drug delivery system..

Acknowledgement:

The authors are thankful to the Principal, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India. Necessary facilities for work.

Conflicts of interest:

Authors have no conflicts of interest to declare.

REFERENCES:

1. Amarowicz R., Carle R., Dongowski G., Durazzo A., Galensa R., Kammerer D., Maiani G., Piskula M.K. Influence of postharvest processing and storage on the content of phenolic acids and flavonoids in foods. *Mol. Nutr. Food Res.* 2009;53:S151–S183. doi: 10.1002/mnfr.200700486
2. Cermak R., Durazzo A., Maiani G., Böhm V., Kammerer D.R., Carle R., Wiczowski W., Piskula M.K., Galensa R. The influence of postharvest processing and storage of foodstuffs on the bioavailability of flavonoids and phenolic acids. *Mol. Nutr. Food Res.* 2009;53(Suppl. 2):S184–S193. doi: 10.1002/mnfr.200700444.
3. Falcone Ferreyra M.L., Rius S.P., Casati P. Flavonoids: Biosynthesis, biological functions, and biotechnological applications. *Front. Plant. Sci.* 2012;3:222. doi: 10.3389/fpls.2012.00222.
4. Kabera J.N., Semana E., Mussa A.R., He X. Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. *J. Pharm. Pharmacol.* 2014;2:377–392.

5. Patel D., Shukla S., Gupta S. Apigenin and cancer chemoprevention: Progress, potential and promise (review) *Int. J. Oncol.* 2007;30:233–245. doi: 10.3892/ijo.30.1.233.
6. Miccadei S., Di Venere D., Cardinali A., Romano R., Durazzo A., Foddai M.S., Fraioli R., Mobarhan S., Maiani G. Antioxidative and apoptotic properties of polyphenolic extracts from edible part of artichoke (*Cynara scolymus* L.) on cultured rat hepatocytes and on human hepatoma cells. *Nutr. Cancer.* 2008;60:276–283. doi: 10.1080/01635580801891583.
7. Shukla S., Gupta S. Apigenin: A promising molecule for cancer prevention. *Pharm. Res.* 2010;27:962–978. doi: 10.1007/s11095-010-0089-7.
8. D'Evoli L., Morroni F., Lombardi-Boccia G., Lucarini M., Hrelia P., Cantelli-Forti G., Tarozzi A. Red chicory (*Cichorium intybus* L. cultivar) as a potential source of antioxidant anthocyanins for intestinal health. *Oxid. Med. Cell. Longev.* 2013;2013:704310.
9. Azzini E., Maiani G., Garaguso I., Polito A., Foddai M.S., Venneria E., Durazzo A., Intorre F., Palomba L., Rauseo M.L., et al. The potential health benefits of polyphenol-rich extracts from *Cichorium intybus* L. studied on Caco-2 cells model. *Oxid. Med. Cell. Longev.* 2016;2016 doi: 10.1155/2016/1594616.
10. Abenavoli L., Izzo A.A., Milić N., Cicala C., Santini A., Capasso R. Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. *Phytother. Res.* 2018;32:2202–2213. doi: 10.1002/ptr.6171.
Madunić J., Madunić I.V., Gajski G., Popić J., Garaj-Vrhovac V. Apigenin: A dietary flavonoid with diverse anticancer properties. *Cancer Lett.* 2018;28:11–22. doi: 10.1016/j.canlet.2017.10.041.
11. Hostetler G.L., Ralston R.A., Schwartz S.J. Flavones: Food sources, bioavailability, metabolism, and bioactivity. *Adv. Nutr.* 2017;8:423–435. doi: 10.3945/an.116.012948.
12. Thomas M.B. *The Systematic Identification of Flavonoids*. Springer Verlag; Berlin, Germany: 1970.
13. Dewick P.M. *Chimica, Biosintesi e Bioattività delle Sostanze Naturali*. Piccin; Roma, Italy: 2001.
14. Ornano L., Venditti A., Donno Y., Sanna C., Ballero M., Bianco A. Phytochemical analysis of non-volatile fraction of *Artemisia caerulea* subsp. *densiflora* (Viv.) (Asteraceae), an endemic species of La Maddalena Archipelago (Sardinia-Italy) *Nat. Prod. Res.* 2016;30:920–925. doi: 10.1080/14786419.2015.1079189.
15. Venditti A., Maggi F., Vittori S., Papa F., Serrilli A.M., Di Cecco M., Bianco A. Antioxidant and α -glucosidase inhibitory activities of *Achillea tenorii*. *Pharm. Biol.* 2015;53:1505–1510. doi: 10.3109/13880209.2014.991833.
16. Venditti A., Guarcini L., Bianco A., Rosselli S., Bruno M., Senatore F. Phytochemical analysis of *Achillea ligustica* all. from Lipari Island (Aeolian islands) *Nat. Prod. Res.* 2016;30:912–919. doi: 10.1080/14786419.2015.1079188.
17. Sharifi-Rad M., Nazaruk J., Polito L., Morais-Braga M.F.B., Rocha J.E., Coutinho H.D.M., Salehi B., Tabanelli G., Montanari C., Del Mar Contreras M., et al. *Matricaria* genus as a source of antimicrobial agents: From farm to pharmacy and food applications. *Microbiol. Res.* 2018;215:76–88. doi: 10.1016/j.micres.2018.06.010.
18. Venditti A., Frezza C., Sciubba F., Serafini M., Bianco A., Cianfaglione K., Maggi F. Volatile components, polar constituents and biological activity of tansy daisy (*Tanacetum macrophyllum* (Waldst. et Kit.) Schultz Bip. Ind. Crop. Prod. 2018;118:225–235. doi: 10.1016/j.indcrop.2018.03.056.
19. Venditti A., Frezza C., Guarcini L., Foddai S., Serafini M., Bianco A. Phytochemical study of a species with ethnopharmacological interest: *Sideritis romana* L. *Eur. J. Med. Plants.* 2016;12:1–9. doi: 10.9734/EJMP/2016/23809
20. Venditti A., Frezza C., Trancanella E., Zadeh S.M.M., Foddai S., Sciubba F., Bianco A. A new natural neo-clerodane from *Teucrium polium* L. collected in Northern Iran. *Ind. Crop. Prod.* 2017;97:632–638. doi: 10.1016/j.indcrop.2017.01.010.
21. Venditti A. Secondary metabolites from *Teucrium polium* L. collected in Southern Iran. *AJMAP.* 2017;3:108–123.
22. Venditti A., Frezza C., Foddai S., Serafini M., Bianco A. A rare bis-rhamnopyranosyl-aromadendrin derivative and other flavonoids from the flowers of *Genista carentina* Vals. an endemic species of Southern Italy. *Arab. J. Chem.* 2016 doi: 10.1016/j.arabjc.2016.02.012.
23. Fatma W., Taufeeq H.M., Shaida W.A., Rahman W. Biflavonoids from *Juniperus macrocarpa* Boiss and *Juniperus phoenicea* Linn. (Cupressaceae) *Indian J. Chem. B Org.* 1979;17:193–194.
24. Stassi V., Verykokidou E., Loukis A., Harvala C. Polyphenolic compounds from the leaves of *Juniperus oxycedrus* L. subsp. *macrocarpa* (Sm.) Ball. *Pharm. Acta Helv.* 1998;72:311–312. doi: 10.1016/S0031-6865(97)00037-X.

25. Alquasoumi S.I., Farraj A.I., Abdel-Kader M.S. Study of the hepatoprotective effect of *Juniperus phoenicea* constituents. *Pak. J. Pharm. Sci.* 2013;26:999–1008.
26. Venditti A., Maggi F., Quassinti L., Bramucci M., Lupidi G., Ornano L., Bianco A. Bioactive Constituents of *Juniperus turbinata* Guss. from La Maddalena Archipelago. *Chem. Biodivers.* 2018;15:e1800148. doi: 10.1002/cbdv.201800148.
27. Forkmann G. Flavonoids as Flower Pigments: The Formation of the Natural Spectrum and its Extension by Genetic Engineering. *Plant. Breed.* 1991;106:1–26. doi: 10.1111/j.1439-0523.1991.tb00474.x.
28. Herrmann K.M. The shikimate pathway as an entry to aromatic secondary metabolism. *Plant. Physiol.* 1995;107:7–12. doi: 10.1104/pp.107.1.7.
29. Martens S., Forkmann G., Matern U., Lukacin R. Cloning of parsley flavone synthase I. *Phytochemistry.* 2001;58:43–46. doi: 10.1016/S0031-9422(01)00191-1.