SOLID LIPID NANOPARTICLES BASED NANOGEL FOR DERMAL DELIVERY OF MELOXICAM: REVIEW

Dr. Sandip .R. Pawar[1], Miss. Shivani Sandip Patil[2], Dr. Bharat .V. Jain[3], Mr. Tanveer .Y. Shaikh.[4]

Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda-425107, Maharashtra, India

Abstract

Nanogels composed of nanosize particles formed by physically or chemically cross linked polymer networks that swells in a good solvent. The nanogel methods have verified their potential to carry drugs in controlled, continuous and targetable mode. Through the promising field of polymer sciences it has now develop predestinated to make smart nano-system which can found effectual for treatment, diagnosing as well as experimental trials progress. 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.

Keyword: Nanogel, Meloxicam, Epidermis.

1.INTRODUCTION

1.1 General introduction to topical drug delivery system

For the successful delivery of any new developed pharmaceutical formulation it is expected to deliver the therapeutic active drug to the target site at minimum effective concentration with negligible discomfort, maximum patient compliance to the therapeutic use and minimum side effects. Among various routes of administration, the topical route is the most favored route for local delivery of therapeutic agent. Due to its advantage of easy of application, low cost of production and convenience, topical route has become more popular over last few years. Current trend of oral and parenteral route offer the challenges related to adverse effects of drug and dosage form along with patient compliance and issue related to stability. However, conventional topical drug delivery systems have limitations such as less retention time and low bioavailability. Hence existing topical drug delivery and innovations in this system aims to improve the efficacy of drug and to achieve an optimal concentration of a certain drug at its site of action for an appropriate duration [1,2].

Topical route of administration have several advantages over other drug delivery systems.

These advantages are enlisted below.

1.1.1. Advantages of topical drug delivery system [3-6]:

1. It avoids first pass metabolism.
2. Expedient and easy to apply.
3. Avoids the disadvantages and risks of intravenous therapy
4. Avoids the problem associated with oral therapy like the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
5. Lowers the total drug administration.
6. Avoids wavering in drug levels.
7. Medication can be easily terminated whenever needed.
8. Availability of larger application area than other like buccal or nasal cavity
9. Target the drug more selectively to a specific site.
10. Avoids the gastro-intestinal incompatibility.
11.The drugs with short biological half-life and narrow therapeutic window can be administered.

12. Improving physiological and pharmacological response.
13. Improve patient acceptance.
14. Self-medication is possible.

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 exogenetic 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 irreversible disturbing the skin barrier function can be achieved.

1.2 Anatomy and Physiology of Skin and barrier properties [7,8]

Skin is one of the largest organ, separates the most stable internal environment from the most unstable external environment. Skin compose of epidermis, dermis and subcutis, each plays a fundamental role of maintaining chemical balance and protection of skin from microorganisms, dust and varied climatic conditions. Refer Figure 1 for illustration of Skin.

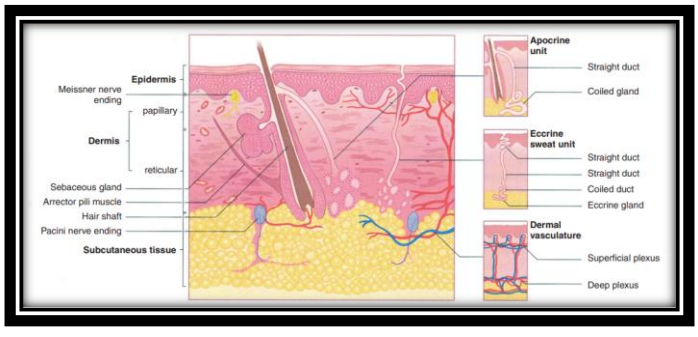


Figure 1: Cross-Section of Human Skin

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It executes many vital functions, with defence against external physical, chemical, and biologic assailants, as well as inhibition of excess water loss from the body and a role in thermoregulation. The skin is constant, with the mucous membranes liner the body's surface. The integumentary system is formed by the skin and it is derived structures. The skin include three layers 1st is epidermis 2nd dermis and 3 rd is subcutaneous tissue. The outermost level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role. The mid layer, the dermis, is basically made up of the fibrillar structural protein called as collagen. The dermis lies on the subcutaneous tissue, or panniculus, which encloses small lobes of fat cells as lipocytes. The thinness of these layers differs considerably, dependent on the geographic site on the anatomy of the body. The eyelid, for example, has the tinniest layer of the epidermis, measuring less than 0.1 mm, while the palms and soles of the feet have the thick epidermal layer, determining approximately 1.5 mm. The dermis is thickest on the back, wherever it is 30–40 times as thick as the covering epidermis
Epidermis forms the outermost layer of skin. The cells of epidermis travel upward and become dead flat cell called stratum corneum. Stratum corneum composed of corrneocytes and intercellular lipids which forms the compact impermeable layer. Dermis forms the elastic layer below the epidermis. Subcutaneous layer consist of sheet of fat rich areolar tissue attaching the dermis to the underlying structure of skin.

1.3. Biochemistry of skin: [8,9]

Epidermis composed of lytic enzymes and proteolytic enzymes generated from the end product of glucose metabolism. The end product of glucose metabolism i.e lactic acid accumulates in the skin which drops down the tissue pH from usual 7.0 to less than 6.0. The fibroblast cells of dermis increases the synthetic and proliferative activity during the wound healing.

1.4. Contribution of topical dosage form in pharmaceutical market [10,11,12]

The pharmaceutical industries are standing up with the building blocks of drug delivery system. Along with different diseases, limitations of drugs and difficulty in

formulating dosage form. A novel delivery system are gaining focus nowadays to overcome the limits of properties of drugs and to treat different disease conditions. Various factors have contributed in formulation of dosage form like the effective delivery of drug to target site, poor efficacies of drugs, minimizing side effects of drugs and patient compliance. Among the various drug delivery system topical/transdermal drug delivery system effectively delivers the drug to the skin. Low dose with continuous release of drug is possible with topical drug delivery systems for e.g. various hormones, nicotine and therapeutic agents can be successfully administered through skin. Hence the topical market has been increased up to 8% and gaining increasing acceptance and popularity among different dosage form. The topical route is also associated with challenges like delivery of large drug molecule, skin barrier properties and disease condition of skin hence the market participants are researching on novel technologies to enhance dermal drug delivery.

1.5. Solid lipid nanoparticles [13-15]

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 advantageous 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.

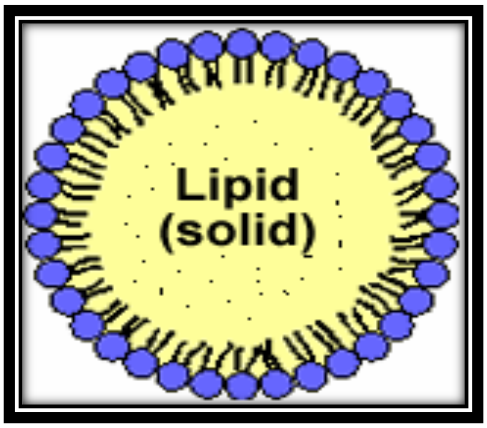


Figure 2: Structure of solid lipid nanoparticle (SLN)

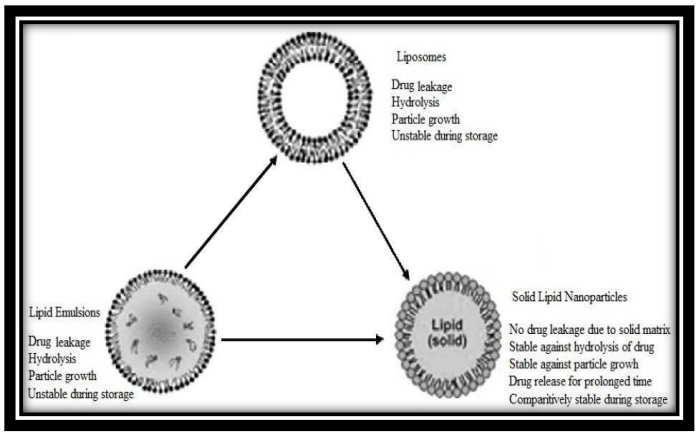


Figure 3: A diagrammatic representation on SLN over emulsions and liposomes

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 slts
Cyclic complexes	Sodium cholate
Cyclodextrin	Sodium glycocholate
Para-acyl-calix-arenes	Sodium taurocholate
	Sodium taurodeoxycholate
	Alcohols
	Ethanol
	Butanol

Solid lipid nanoparticles (SLNs) are considere to be the leading nominal lipid based colloidal carriers, make known to in early. This can be the one amongst the foremost popular approaches to boost the oral bioavailability of the poorly water soluble drugs. SLNs are inside the submicron size range of 50 to 1000 nm and are contain of physiologically tolerated lipid constituents which are in dense at temperature. The schematic representation of various particulate drug carriers like emulsions and liposomes and their advantages are compared with SLNs in Figure 3. SLNs combine all the benefits of polymeric nanoparticles, fat emulsions and liposomes.

1.5.1. Advantages of SLN [16]

• Control and / or target drug release.
• Excellent biocompatibility
• Improve stability of pharmaceuticals
• High and enhanced drug content.
• Easy to scale up and sterilize.
• Well controller over issue 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.

1.5.2. Disadvantages of SLN [17]

• Particle growth.

• Unpredictable gelation tendency.
• Unexpected dynamics of polymeric transitions.

1.6 Aims of solid lipid nanoparticles [18]

• Possibility of controlled drug release
• Increased drug stability.
• High drug pay load
• No bio-toxicity of the carrier.
• Avoidance of organic solvents.
• Incorporation of lipophilic and hydrophilic drugs.

1.7 Preparation of solid lipid nanoparticles [19-21] SLNs are ready from lipid, emulsifier and water/solvent through using dissimilar methods and are discoursed below.

1.7.1 Methods of preparation of solid lipid nanoparticles

1. High pressure homogenization (HPH)

It's a reliable and powerful technique, which is employed for the assembly of SLNs. high homogenizers push a liquid with high (100–2000 bar) through a narrow gap (in the range of some microns). The fluid accelerates on a awfully short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles right down to the submicron range. Generally 5-10% lipid content is employed but up to 40% lipid content has also been investigated. Dual general methods of HPH are hot homogenization and cold homogenization, effort on the matching idea of blending the drug in bulk of lipid melt.

Hot homogenization: Hot homogenization is dispensed at temperatures above the freezing point of the lipid and may therefore be thought to be the homogenization of an emulsion. A pre-emulsion of the medication load lipid melt and formerly the aqueous emulsifier phase is attained by high-shear mixing device. HPH of the pre-emulsion is allotted at temperatures above the freezing point of the lipid. In general, higher temperatures end in lower particle sizes thanks to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and also the carrier. Increasing the homogenization pressure or the quantity of cycles often ends up in a rise of the particle size because of high K.E. of the particles.

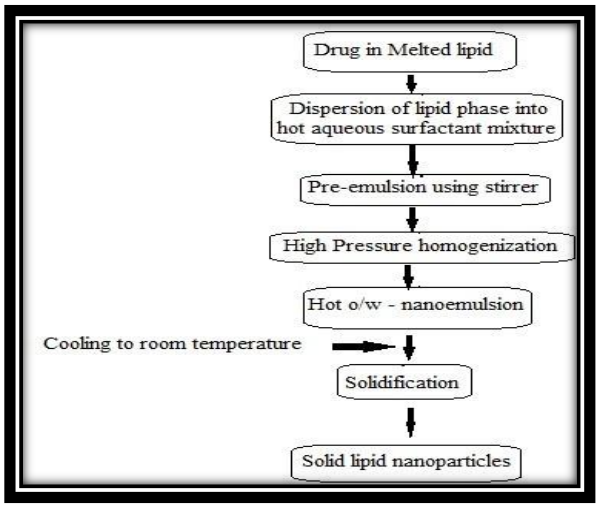


Figure 4: Solid lipid nanoparticles planning by hot homogenization process

Cold homogenization: Cold homogenization has been developed to beat various problems related to hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization phase of the nanoemulsion resultant in some changes and/or super cool melts. During this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a very cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or lower temperature, the gravity is robust adequate to interrupt the lipid micro particles on to solid lipid nanoparticles.

Advantages

- Low assets cost.
- Demonstrated at lab scale.

Disadvantages

- Energy intensive process.
- Demonstrated at lab scale Biomolecule damage.
- Polydisperse distributions.
- Unproven scalability.

2. Ultrasonication/high speed homogenization

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

Advantages

- Reduced shear stress.

Disadvantages

- Potential metal contamination.
- Physical instability like particle growth upon storage.

3. Solvent evaporation

SLNs may also prepared by solvent evaporation method. The lipophilic material is dissolved during a water-immiscible organic solvent (e.g. cyclohexane) that's emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is made by precipitation of the lipid within the aqueous medium by giving the nanoparticles of 25 nm mean size. the answer was emulsified in an aqueous phase by high homogenization. The carbon-based solvent was reserved from the mixture by evaporation under decrease pressure (40 to 60 mbar).

Advantages

- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.

Disadvantages

- Extremely energy intensive process.
- Polydisperse distributions.
- Biomolecule damage.

4. Solvent emulsification-diffusion method

The particles with average diameters of 30-100 nm are often obtained by this method. Voidance of warmth during the preparation is that the most vital advantage of this method.

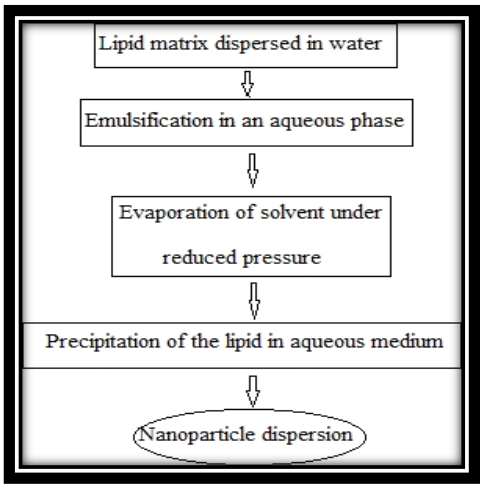


Figure 5: Systematic representation for emulsification-diffusion method

5. Supercritical fluid method

This is another method of preparing SLNs by particles from gas saturated solutions (PGSS).

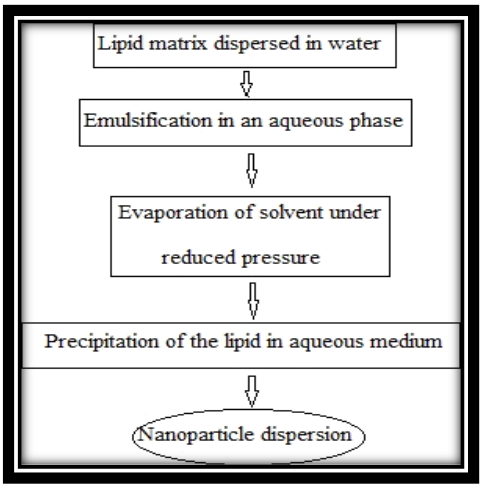
Advantages

- Avoid the usage of solvents.
- Particles are obtained as a dry powder, rather than suspensions..
- Mild pressure and temperature conditions.
- Carbon dioxide solution is that the good selection as a solvent for this method.

6. Microemulsion based method

This method is predicated on the dilution of microemulsions. As micro-emulsions are 2- stage systems contained of an internal and external phase (e.g. o/w microemulsions). they're made by stirring an optically transparent mixture at 65-70°C, which generally composed of an occasional melting carboxylic acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The novel micro emulsion is discrete in cold water (2 to 3°C) below stirring. SLN dispersion may be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but just in case of low particle content an excessive amount of of water must be removed. High-temperature gradients facilitate rapid

lipid crystallization and forestall aggregation. thanks to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.



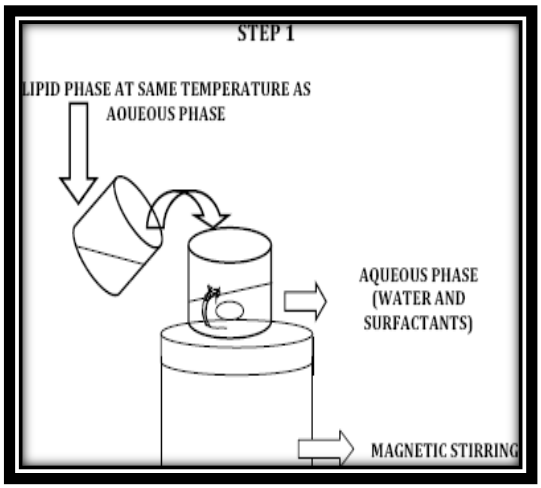


Figure 6: Microemulsion method

Advantages

- Low mechanical energy input.
- Theoretical stability.

Disadvantages

- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticle concentrations.

7. Spray drying method

It is another technique to the lyophilization process. This recommends the utilization of lipid with freezing point over 70oC. The greatest effective consequences were found by SLN concentration of 1% concluded a solution of trehalose in water or 20% trehalose in ethanol-H2O mixture.

8. Double emulsion method

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

9. Precipitation method

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

10. Film-ultrasound dispersion

The lipid and so the drug were placed into appropriate organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is created, then the solution which has the emulsions was additional. Using the ultrasound with the probe to diffuser eventually, the SLN with the miscroscopic and uniform particle size is created.

11. Secondary Production Steps

- **Freeze drying**

Lyophilization could be a promising thanks to increase the chemical and physical stability over extended periods of your time. Lyophilization had been required to attain future stability for a product containing hydrolysable drugs or an acceptable product for per-oral administration. Alteration into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. Just in circumstance of freeze drying of the merchandise, all the lipid mediums used, form bigger solid lipid nanoparticles with a broader size distribution since of occurrence of groups among the nanoparticles. The conditions of the freeze drying process and also the removal of water promote the aggregation among SLNs. A sufficient quantity of cryoprotectant can defend the

aggregation of solid lipid nanoparticles through the freeze drying process.

- **Sterilization**

Sterilization of the nanoparticles is desired for parenteral administration and autoclaving which is valid to preparations containing heat-resistant drugs. Effects of sterilization on particle size are investigated and it had been found to cause an explicit increase in particle size.

- Spray drying

Spray drying is often an alternate procedure to lyophilization so on rework an aqueous SLN dispersion into a dry product. this method has been used scarcely for SLN formulation, though spray drying is cheaper as associated with lyophilization. The lipids with melting points at temperature >70°C had been recommended for spray drying.

1.8 Drug incorporation models of SLN [23]

Influences affecting filling 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.

Drug incorporation models are as follows

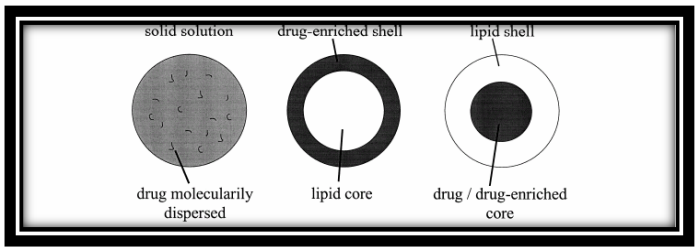


Figure 7: Drug incorporation models

1.8.1 Solid solution model:

1. Drug is molecularly discrete in lipid medium when SLN is prepared through cold homogenization.
2. Drug-enriched shell model.
3. A solid lipid main methods upon recrystalization temperature of the lipid is extended.
4. Drug-enriched core model.
5. Cooling the nanoemulsion results in a brilliant saturation of the drug which is dissolved within the lipid melt ends up in recrystalization of the lipid.

1.9. Fate of SLN after oral administration [24]

The oral route continues to be a challenge moreover because the most tasty thanks to administer drugs due to its unquestionable commercial potential. Incorporation of medicine into lipid nanoparticles opens the angle of enhanced and / or less variable bioavailability and prolonged plasma levels. While these systems may provide the best flexibility within the modulation of the drug release profile within GIT and supply protection against chemical degradation for labile drug molecules (Peptide drugs)

2. DRUG PROFILES

2.1 Meloxicam [38]

Table 2: MLX Drug Profile

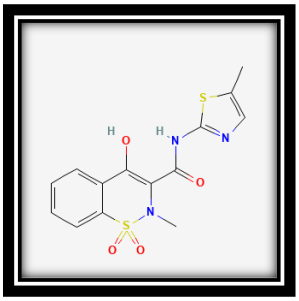
Name	Meloxicam
Chemical Structure	

Figure 8: MLX Chemical Structure

IUPAC Name	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-1λ6,2-benzothiazine-3-carboxamide
CAS No.	71125-38-7
Molecular Weight	351.4 g/mol
Molecular Formula	C14H13N3O4S2
Melting point (°C)	254 °C
Boiling point (°C)	581.3±60.0 °C
logP	1.9
pKa	4.08
Solubility	48.7 [ug/mL] in water, Very slightly soluble in methanol. Practically insoluble in water, with higher solubility observed in strong acids and bases.
Bioavailabiltiy	~89%
Half Life	15-20 Hours
Description	This Drug could be a long acting nonsteroidal antiinflammatory drug (NSAID) available by prescription only and utilized in therapy of chronic arthritis. Meloxicam has remained connected to rare samples of acute, clinically apparent liver injury.
Indication	This drug is showed for relief of the signs and indications of osteoarthritis. Use rock bottom effective dose for the shortest duration according to individual patient treatment goals
Mechanism of action	This Drug inhibits prostaglandin synthetase (cylooxygenase 1 and 2) enzymes resulting in a decreased synthesis of prostaglandins, which normally mediate painful inflammatory symptoms. As prostaglandins sensitize neuronal pain receptors, inhibition of their synthesis ends up in analgesic and inflammatory effects. Meloxicam specially Prevent COX-2, but also exerts certain action against COX-1, causing GIT irritation.
Absorption	he complete bioavailability oral pills after a dosage were 89% in one pharmacokinetic study. Cmax was reached 5–6 hours after administration of one dose given after the primary meal of the day. The Cmax doubled when the drug was administered within the fasting state. Despite this, meloxicam will be taken without relevance food, unlike many other NSAIDS. Meloxicam formulated for instillation with [bupivacaine] produced varied systemic measures following one dose of varying strength. In patients undergoing bunionectomy, 1.8 mg of meloxicam produced a Cmax of 26 ± 14 ng/mL, a median Tmax of 18 h, and an AUC∞ of 2079 ± 1631 ng*h/mL. For a 9 mg

	dose used employed in herniorrhaphy, the corresponding values were 225 ± 96 ng/mL, 54 h, and therefore the AUC∞ wasn't reported. Lastly, a 12 mg dose utilized in total knee arthroplasty produced values of 275 ± 134 ng/mL, 36 h, and 25,673 ± 17,666 ng*h/mL.
Protein Binding	This Drug is about 99.4% protein bound, mainly to albumin.
Volume of Distribution	The volume of distribution of meloxicam is 10-15L. thanks to its high binding to albumin, it's likely to be distributed in highly perfused tissues, like the liver and kidney. Meloxicam concentrations in secretion, measured after an oral dose, are estimated at 40% to 50% of the concentrations measured within the plasma. This drug is thought to cross the placenta in humans.
Route of elimination	This Drug is especially eliminated through metabolism. Its metabolites are cleared through renal and fecal elimination. but <0.25% of a dose is eliminated within the urine as unchanged drug. About 1.6% of the parent drug is excreted within the feces.
Clearance	After an oral dose, the entire clearance of meloxicam is 0.42–0.48 L/h. The FDA label indicates a plasma clearance from 7 to 9 mL/min. No dose changes are required in mild to moderate renal or hepatic impairment. the employment of meloxicam in patients with severe renal or hepatic impairment has not been studied. FDA prescribing information advises against it. The absolute bioavailability of meloxicam capsules was 89% following one oral dose of 30 mg compared with 30 mg iv bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown within the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of seven.5 mg to fifteen mg. Mean Cmax was achieved within four to 5 hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a protracted drug absorption. With multiple dosing, steady state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.
Metabolism/Metabolites	This Drug is nearly completely metabolized. CYP2C9 is that the main enzyme chargeable for the metabolism of meloxicam with minor contributions from CYP3A4. Meloxicam has 4 major metabolites with no activity determined. About 60% of the ingested dose is metabolized to 5'-carboxy meloxicam from hepatic cytochrome enzyme oxidation of an intermediate metabolite, 5′-hydroxymethylmeloxicam. Two other metabolites are likely produced via peroxidation.

3. CONCLUSON

Nanogels composed of nanosize atoms made by physically or chemically cross linked polymer networks that swells in a very decent solvent. The nanogel systems have proven that potential to deliver drugs in controlled, continuous and targetable mode. With the promising field of polymer sciences it's now become predestinated to organize smart nano-system which might establish effectual for treatment, diagnosing likewise as clinical trials progress. Nanogels is been proving as a promising drug delivery system and offers sort of characteristics like on site drug delivery system, sustained release formulation, high drug entrapment properties, water solubility, biodegradability, low toxicity etc. because of these multi functionality properties and features nanogel utilized extensively in many drug deliver fields. Composite with polymers, metals and other active molecules nanogel clothed as excellent drug delivery system. Topical administration of the MLX drug is seemingly a lovely choice since it'd reduce the possibilities of drug associated gastrointestinal and systemic side effects, and would allow an increased level of drug locally. Although, topical application of MLX offers the advantage of delivering a drug on to the disease site so as to maximise local effects without concurrent systemic activity yet, no formulation of MLX is accessible within the marketplace for topical use. the foremost difficult aspect of the topical drug delivery system is that the formidable barrier properties of the corneum (SC), the outermost layer of the skin that forestalls percutaneous absorption of medicine. Although, MLX possesses some favorable properties for topical administration like low relative molecular mass, low daily therapeutic dose yet, the inherent poor aqueous solubility and high temperature make it unsuitable for topical application. variety of topical/transdermal drug delivery systems,

which vary in their compositions and structures are developed to enhance the skin permeation of MLX. However, the poor drug loading capacity, poor drug controlled and sustained release capacities have limited their use as topical/transdermal carriers. the amount of interest in lipid-based carrier systems have increased substantially for topical administration of medication thanks to the utilization of fats and oils of natural origin and pharmaceutically accepted surfactant as excipients.

REFERENCES

[1] Chen HY, Fang JY. Therapeutic patents for topical and transdermal drug delivery systems. Expert Opinion on Therapeutic Patents. 2000 Jul 1;10(7):1035-43.

[2] Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. International journal of pharmaceutics. 1999 Jul 5;184(1):1-6.

[3] Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Advanced drug delivery reviews. 2002 Nov 1;54:S77-98.

[4] Singh SK, Durrani MJ, Reddy IK, Khan MA. Effect of permeation enhancers on the release of ketoprofen through transdermal drug delivery systems. Die Pharmazie. 1996 Oct 1;51(10):741-4.

[5] Ramesh P. Transdermal delivery of drugs. Indian journal of pharmacology. 1997 May 1;29(3):140.

[6] Sinha VR, Kaur MP. Permeation enhancers for transdermal drug delivery. Drug development and industrial pharmacy. 2000 Jan 1;26(11):1131-40.

[7] Gerard J. Tortora., Brayan Derrickson., Principles Of Anatomy and Physiology.

[8] Mithal BM, Saha RN. A handbook of cosmetics. Vallabh Prakashan, New Delhi. 2000;141.

[9] Jain NK. Controlled and novel drug delivery CBS publishers & distributors. Daria Gang, New Delhi. 1997:101-27.

[10] http://www.frost.com/prod/servlet/market-insight-print.pag?docid=134287829 [Accessed: Feb. 7, 2022].

[11] https://www.boomer.org/c/p4/c07/c07.pdf [Accessed: Feb. 7, 2022].

[12] https://www.marketsandmarkets.com/market-Reports/topical-drug-deliverymarket-124871717.html [Accessed: Feb. 7, 2022].

[13] Müller RH, Runge SA, Ravelli V, Thünemann AF, Mehnert W, Souto EB. Cyclosporine-loaded solid lipid nanoparticles (SLN®): Drug–lipid physicochemical interactions and characterization of drug incorporation. European journal of pharmaceutics and biopharmaceutics. 2008 Mar 1;68(3):535-44.

[14] Lippacher A, Müller RH, Mäder K. Preparation of semisolid drug carriers for topical application

based on solid lipid nanoparticles. International journal of pharmaceutics. 2001 Feb 19;214(1-2):9-12.

[15] Pandya JB, Parmar RD, Soniwala MM, Chavda JR. Solid lipid nanoparticles: overview on excipients. Asian Journal of Pharmaceutical Technology & Innovation. 2013;1(3):01-9.

[16] Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian journal of pharmaceutical sciences. 2009 Jul;71(4):349.

[17] Müller RH, 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. 2000 Jul 3;50(1):161-77.

[18] Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. Journal of Controlled release. 2008 Apr 21;127(2):97-109.

[19] Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Advanced drug delivery reviews. 2007 Jul 10;59(6):478-90.

[20] Vyas SP, Khar RK. Controlled drug delivery concepts and advances. vallabh prakashan. 2002;1:411-7.

[21] Vyas SP, Khar RK. Controlled drug delivery concepts and advances. vallabh prakashan. 2002;1:411-7.

[22] Lee CH, Chien YW. Drug delivery: Vaginal route. InEncyclopedia of Pharmaceutical Science and Technology, Fourth Edition 2013 Jul 1 (pp. 1236-1259). CRC Press.

[23] Üner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. International journal of nanomedicine. 2007 Sep;2(3):289.

[24] Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. Journal of Controlled release. 2008 Apr 21;127(2):97-109.

[25] zur Mühlen A, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) for controlled drug delivery–drug release and release mechanism. European journal of pharmaceutics and biopharmaceutics. 1998 Mar 1;45(2):149-55.

[26] Kuo YC, Chen HH. Entrapment and release of saquinavir using novel cationic solid lipid nanoparticles. International journal of pharmaceutics. 2009 Jan 5;365(1-2):206-13.

[27] Paliwal R, Rai S, Vaidya B, Khatri K, Goyal AK, Mishra N, Mehta A, Vyas SP. Effect of lipid core material on characteristics of solid lipid nanoparticles designed for oral lymphatic delivery. Nanomedicine: Nanotechnology, Biology and Medicine. 2009 Jun 1;5(2):184-91.

[28] Suresh G, Manjunath K, Venkateswarlu V, Satyanarayana V. Preparation, characterization, and in vitro and in vivo evaluation of lovastatin solid lipid nanoparticles. Aaps Pharmscitech. 2007 Mar;8(1):E162-70.

[29] Teja VC, Chowdary VH, Raju YP, Surendra N, Vardhan RV, Reddy BK. A glimpse on solid lipid nanoparticles as drug delivery systems. J Glob Trends Pharm Sci. 2014;5(2):1649-57.

[30] Ekambaram P. Formulation and Evaluation of PH Triggered In Situ Gelling System of Levofloxacin (Doctoral dissertation, Madurai Medical College, Madurai).

[31] Abdelbary G, Fahmy RH. Novel Drug Delivery. AAPS Pharm. Sci. Tech. 2009;10(1):1.

[32] Harivardhan Reddy L, Murthy RS. Etoposide-loaded nanoparticles made from glyceride lipids: formulation, characterization, in vitro drug release, and stability evaluation. AAPs PharmSciTech. 2005 Jun;6(2):E158-66.

[33] Sandhu P, Bilandi A, Kumar S, Rathore D, Bhardwaj S. Additives in topical dosage forms. IJPCBS. 2012;2(1):78-96.

[34] Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995 Mar;12(3):413-20.

[35] Dao Thanh T. Desarrollo galénico de nuevas formulaciones inyectables de meloxicam y amoxicilina sódica para uso veterinario.

[36] Burke A, Smyth E, FitzGerald GA. Analgesic-antipyretic agents; pharmacotherapy of gout. The pharmacological basis of therapeutics. 2006;1:706.

[37] Oliveira IM, Fernandes DC, Cengiz IF, Reis RL, Oliveira JM. Hydrogels in the treatment of

rheumatoid arthritis: Drug delivery systems and artificial matrices for dynamic in vitro models. Journal of Materials Science: Materials in Medicine. 2021 Jul;32(7):1-3.

[38] PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 54677470, Meloxicam; [cited 2022 Apr. 30]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Meloxicam

[39] Rowe RC, Sheskey P, Quinn M. Handbook of pharmaceutical excipients. Libros Digitales-Pharmaceutical Press; 2009.