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Review Article

Organogel: An Ideal Drug Delivery Carrier for Non Steroidal Anti-Inflammatory Drugs through Topical Route

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ABSTRACT

Technological advancement in the field of medicine and pharmaceutics has made researchers to work in development of novel formulation and advancement in drug delivery systems using well advanced techniques. Among which conventional semi solid topical dosage form of lecithin organogel has got much significance. Lecithin organogel are three dimensional network of jelly like phase with lecithin macromolecule as major gelator compound and proportionate amount of organic and aqueous phase medium in them. They are thermodynamically stable with a nature of biphasic solubility of drugs, good partition coefficient, biocompatible nature with skin and ease of preparation with simple components. Lecithin organogel are mainly used as matrix delivery of various drugs through transdermal route of application. In this current review work, attempts have been made to explain about the types of organogels, gelation mechanism, properties of organogel, parameters influencing in gelation. More over the review mainly focused on categories of drugs loaded in them and their feasibilities in loading NSAID drugs in lecithin organogel.

Keywords: Organogel, NSAIDs, Topical

INTRODUCTION

Over a decade there has been much developments, but still there are many drawbacks in conventional dosage forms like tablets, capsules, parental, rectal, vaginal[1-4] etc, this lead to the development of novel drug delivery system[5]. Among which novel topical drug delivery systems using lipid based carrier such as Lecithin organogel has attained much importance and demands[6]. Topical drug delivery is the method of delivery of drugs through skin layers for local action and to systemic circulation using different carrier vehicles. Topical dosage forms include creams, pastes, ointments, solutions, gels, and plastizers[7,8]. They are mainly targeted on pain relief management, anti inflammatory effect, contraceptive devices and in would healing effects.

Compared to other semi solid topical dosage forms, gels have attained much importance among the other novel topical formulations because of their highlighted properties such as smooth texture, elegant appearance, miscibility with skin layer secretions, transparency, biocompatible, highly penetrable, spreadable, prolonged stability and ease of preparations with simple constituents. Gels constitute a network of structure formed by a solid gelator molecule in addition of solvents to it[9]. Novel semi-solid preparations of gels are mainly categorized in to organogel and hydrogel based on their solvent proportions[10]. And they are used in various forms like sustained release, controlled release, extended release, bio adhesive, and in-situ gels etc.

Using these techniques, a wide range of formulations and strategies has been employed for the delivery of various medicaments through skin layers. A recent research on lecithin lipid based molecules has made it as a potential carrier in topical delivery of various medicaments, which mainly includes bioactive agents, antiviral, muscle relaxants and NSAIDs. Recent studies on lecithin phospholipid have enriched lecithin organogel as better lipid based carrier system in novel drug delivery systems.

NSAID

Non Steroidal Anti-Inflammatory Drug (NSAID) is the medicaments mainly targeted in pain management and anti-inflammatory effect. They also possess mild antipyretic and analgesic property[11,12]. Generally they are available in various formulations like tablets, capsules, liquid orals, gels, eye drops, intravenous injections and suppositories etc., are administered through various routes like oral, ophthalmic, rectal, parental, and mainly through transdermal route. They are also available as over the counter drug and some commercially available drugs for example Aspirin, Ibuprofen, Ketoprofen, Piroxicam, Paracetamol etc. NSAIDs are mainly grouped into two categories, selective and non-selective NSAID. Non selective NSAIDs inhibit both COX-1 and COX-2 enzymes present in all parts of our body causing severe problems and side effects. Some of the commonly available non-selective NSAIDs are Aspirin, Ibuprofen, and Paracetamol etc.Whereas Selective NSAIDs are the COX-2 enzyme inhibitor drugs which are responsible in pain and inflammations. Celecoxib was the first

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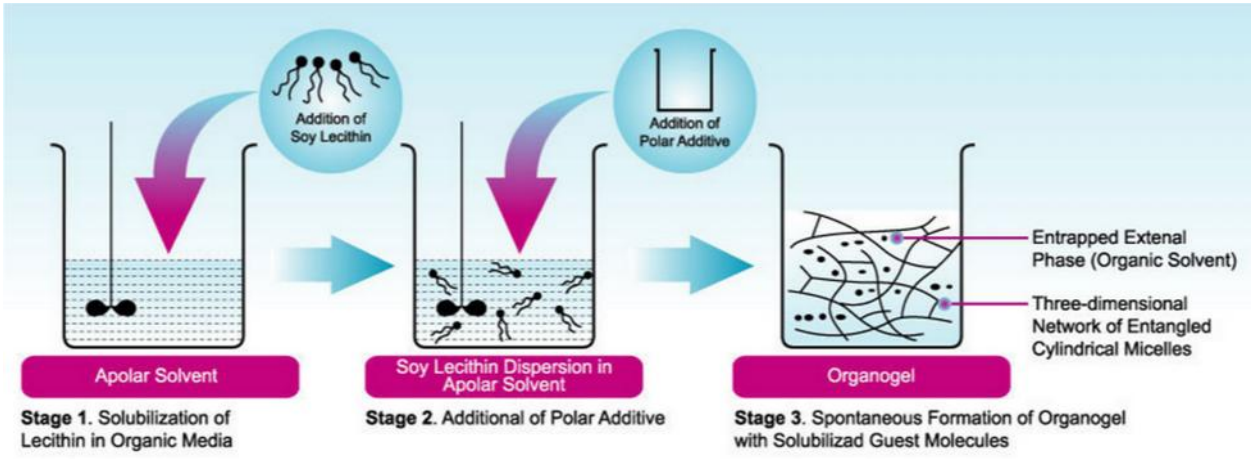

Figure 1: Schematic diagram of the preparation of lecithin organogels[51]

Table 1: Organogel types and model drugs loaded

S. No	Types of Organogel	Ingredients	Model Drugs loaded
1.	Lecithin organogels[15]	Egg Lecithin or soya lecithin, organic solvents, aqueous phase, sorbic acid.	Diclofenac[29], Indomethacin[31], Piroxicam[31], Aceclofenac[32], Fluriprofen[33,] Propranolol[34]
2.	Pluronic Lecithin organogels[17,18]	Pluronic F127 (poloxamer) polymer. Soya lecithin, sorbic acid, IPM, potassium sorbate, water,	Diclofenac[30,] Ibuprofen[31],Ketoprofen[34] Methimazole[38] Dexamethasone
3.	Limonene derived organogels[24]	Limonene incorporated within Dibutyl lauroylglutamide (GP1) in propylene glycol	Diclofenac[29], Ibuprofen[31], Ketoprofen[33], Progesterone[31]
4.	Non-ionic surfactant based Organogel[25]	Cetyl alcohol, Stearyl alcohol, Tween, isopropyl myristate, n-butanol, water	Cyclosporin A, Zidovudine[31], BSA
5.	Sorbitan monosterate organogel[26]	Span20, Tween80 , isopropyl myristate, non polar solvents like Eucalyptus oil, n-octanol, propylene glycol, PEG (polyethylene glycol), ethyl alcohol, isopropyl alcohol	Antigens, sumatriptan[39,] Clobetasol Propionate[39],Doxorubicin
6	Poly ethylene organogels[27]	Poly ethylene's, mineral oils, sorbic acid, Aqueous phase.	Leuprolide[31], Propranolol hydrochloride[33]
7.	Surfactant and polymer based Organogel	Oil phase: Gelucire 44/14, Plurol oleique, Lauroglycol 90 Water phase: Sodium alginate, Glycerin, water	Acyclovir, Salicylic acid[33]
08	Eudragit Organogel[27]	Copolymer of ethyl acrylate, methyl acrylate, polyhydric alcohols, ethylene glycol,	Salicylic acid[36], Ketoprofen[32], BSA.

commercially available sulfonamide COX-2 inhibitor in market followed by Rofecoxib, Etoricoxib etc[13].

Lecithin

Lecithin is a fatty substance with a complex mixture of triglycerides, choline, phosphoric acid, fatty acids and mainly of phosphatidylcholine compounds[14]. They are less soluble in water and have good emulsifying property. In aqueous solutions, its lipid compounds form micelles or liposomes which act as surfactant of amphiphilic surfactant possessing both lipophilic and hydrophilic characteristics. Although lecithin is available in natural sources like plant and animal tissues, milk, and marine sources, they are predominantly outsourced from soy bean and egg yolk. Lecithin has a wide range of applications in various fields and recent researches on lecithin phospholipids has got higher priority in pharmaceutical areas as it can act as an efficient wetting agent, surfactant, solublizer ,emulsifier and penetration enhancers. As a result they are now mainly utilized in preparation of organogel with addition other co-surfactants[15].

Lecithin Organogel

In general, Organogels[15,16] are semi-solid systems in which a three-dimensional network of gelator molecules are aggregates immobilise an organic liquid continuous phase, typically a non-polar solvent. They consists of an organogelators (lecithin) compounds in them. These compounds form a cross-linked structure either by physical or chemical interactions, thereby immobilising the organic phase within the network. Molecular interactions such as hydrogen bonding and dipolar interactions are responsible for the Organogel structure.

Pluronic lecithin organogel

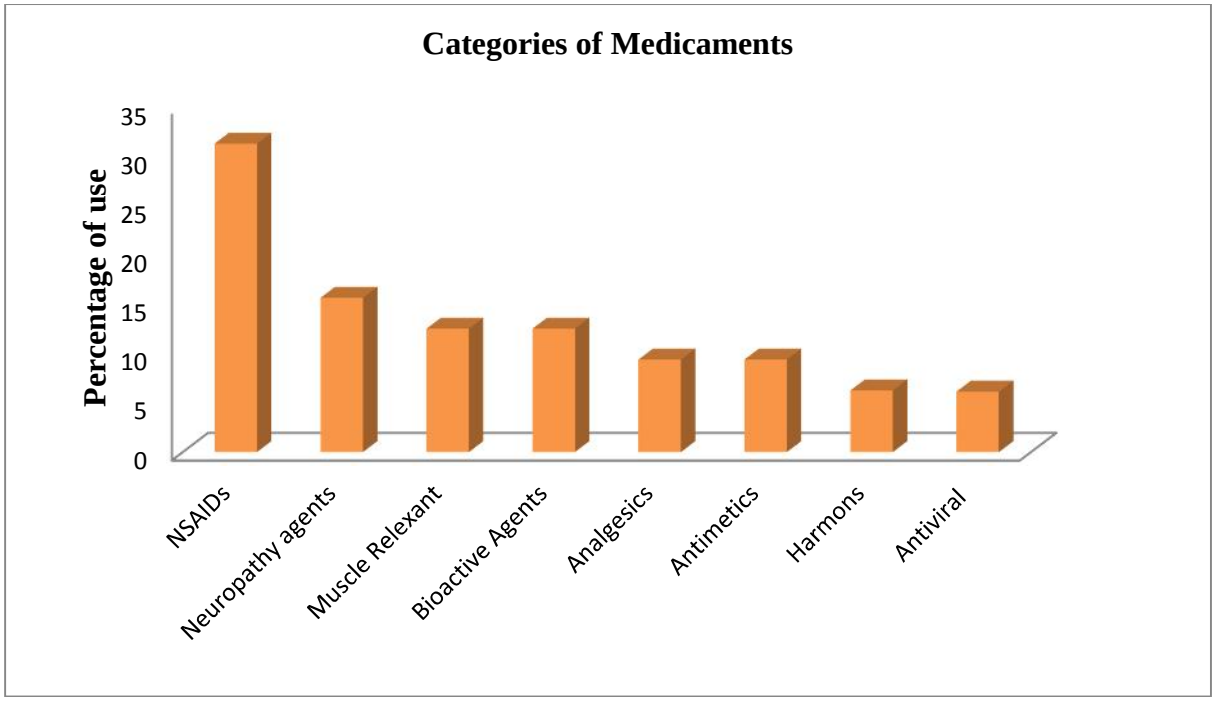

Figure 2: Categories of Medicaments loaded in Organogel

Pluronic F-127 is a copolymer of polyoxyethylene and polyoxypropylens, which are also called as poloxamer with a major compound of ethylene oxide makes it hydrophilic[17]. They are freely soluble in cold water and at low temperature (4-5°C) they exhibit more as solution form and turns into gel when reaches body temperature. Pluronic polymers are non-toxic, biocompatible and act as a good penetration enhancer without harming the skin layers. These properties confers to the use of Pluronic polymer in preparation of organogel loaded with various medicaments.

Main aspects of preferring Organogel in topical formulation is that drugs of both hydrophilic and lipophilic nature can be loaded in them and they have a good viscoelastic, thermodynamically stable, ease spreadable properties etc .They are mainly used in the targeted drug delivery. Lecithin organogels are attributed because of their importance like bypass first pass metabolism, targeted site of action, gastro intestinal complexity can be avoided, good pharmacological response through skin absorption into systemic circulation, problems of various pH change, gastric enzymes activity, and intravenous therapies etc can be avoided, medication can be stopped when needed, larger surface area of application gives good response, ease of preparation, cost efficient etc.

Properties of lecithin Organogel

Physiochemical properties of lecithin Organogel[18] includes

Viscoelaticity

Lecithin Organogel are three dimensional network structures formed by the physical interaction between the gelator molecules. It consists of surfactant (lecithin) dissolved in a non-polar phase and an aqueous phase. At low shear rate they act as a solid and possess elastic property and increase in shear rate disturbs the interactions between them and makes them to flow this shows the plastic nature of Lecithin organogel[18].

Non- birefringence

Isotropic nature of lecithin Organogel makes them non-birefringence, which do not allow polarized light to pass through their rigid matrices.

Thermal stability

Organogel when heated above its phase transition temperature undergo disruption in physiological interactions between the gelator molecules and flows as liquid phase and again on relaxed cooling, decrease in thermal energy makes them revert and thermally stable[18,20].

Optical clarity

Compositions of Organogel determine the transparency nature of the gel, where lecithin added Organogel are transparent and other gelator added gels are opaque in nature.

Biocompatibility

Organogel consists of organic solvents which on continuous administration on skin causes allergic reactions. However recent development in novel topical formulations made use of lecithin and many other mineral oils in Organogel development make them as biocompatible one[19,21].

Hydrophilic lipophilic balance

HLB values of lecithin Organogel are well balanced as they contain organic phase and aqueous phase together. Lecithin molecules are amphiphilic in nature and they contain polar head and non polar tail which can attract a wide range of molecules[20].

Microbial resistance

Aqueous phase act as a medium for growth of micro organism whereas, Lecithin Organogel consists of an external organic continuum phase which prevents the lecithin and aqueous phase from microbial contamination. Which got entrapped within the three dimensional network of gelation structure formed by the gelator molecule[15,21].

Organogelation mechanism

Table 3: Adverse effect of NSAIDs in various organs

S.No	Organ System	Adverse Effects
01	Gastrointestinal [44]	Dyspepsia, Gastroduodenal ulceration, Bleeding Colitis, Increased UGI ulceration [45]
02	Hepatic [46]	Elevated transaminases, Severe hepatic reactions [46,47]
03	Cardiovascular [48]	Arterial thrombosis [49]
04	Central nervous system[49]	Dizziness, Somnolence, Cognitive dysfunction, Aseptic meningitis
05	Renal [50]	Hypertension, Edema, Acute renal failure Interstitial nephritis, Papillary necrosis

Table 2: Categories of drug loaded in organogel

S. No	Category	Medicaments' loaded
01	Antiemetics	Dexamethasone, dimenhydrate, scopolamine
02	Muscle relaxants	Cyclobenzaprine, baclofen, buspirone, nircardipine[42]
03	Neuropathy drugs	Clonidine, capsaicin, amitryptiline, gabapentin, phenytoin
04	NSAIDs	Diclofenac[29], Ibuprofen[31,] Aceclofenac[33], ketoprofen[33], Sumatriptan[33],Indomethacin[33], Piroxicam[34], Ketorolac tromethamine[39], Fluriprofen[35],
05	Analgesics	Acetaminophen, hydromorphone, morphine sulphate[37]
06	Hormones	Progesterone[37], testosterone[37]
07	Bioactive agents	Vitamin A[37], vitamin C[34], Amino acids, Peptides[37]
08	Antiviral agent	Acyclovir

Organogel development mainly depends on two factors, first purity of lecithin used and second addition of aqueous phase to it. Mechanism of Organogel formation takes place by two steps, preparation of organic phase and aqueous phase separately. Organic phase is prepared by mixing calculated amount of lecithin in organic solvent and allowed to stand overnight for complete dissolution. And aqueous phase is prepared by adding Pluronic[17] F127 polymer in ice cold water and seen that complete dissolution takes place[21,22].

Later addition of aqueous phase to lecithin organic phase under controlled stirring leads to the formation of three dimensional networks of reverse micelles due to the interaction of hydrophilic molecules of lecithin with the polar phase. This confirms the Organogel formation, whereas Excess addition of water leads to deformation of gel.

Parameters influencing organogel formation

Purity

Purity of lecithin used in formulation plays an important role in organogel formation mechanism. Impurities results in deformation of gels[20].

Solvent addition

Amount of aqueous phase added to lecithin organic phase determines the organogel formation. Excess addition leads to unstable nature of the organogel and leads to hydrogel formation[22].

Surfactants

Different types of surfactants like span, tween, poloxamer, polyethylene, etc. are available with various concentrations and molecular weight, which influences the properties of organogel formed[20].

Other parameters like charge, solubility, phase transition temperature, molecular weight etc also influence in organogel formation[23].

Organogel types and drug loaded

Organogels can be prepared by using various gelator molecules and they are grouped bellow with some model drugs loaded in them.

From the above tabulations we could observe that compared to other drugs, NSAID has been incorporated numerous numbers in organogel.

Mechanism of NSAID action

NSAID mainly interact with different types of cyclooxygenases enzymes, which are present in our body performing various actions. Cyclooxygenases (COX-1 enzyme) catalyzes the formation of prostaglandins which are a protective lining layer of stomach preventing from its own acid secretions. Whereas COX-2 enzyme which controls the production of the prostaglandins, a messenger molecule responsible for pain and inflammation. However NSAID act as an anti inflammatory and pain reducing agent by inhibiting the cyclooxygenases enzymes (COX-1 and COX-2 enzyme) present in all parts of our body[12,13].

But there are tedious problems in uptake of NSAIDs in excess amount. They cause gastrointestinal ulcers, GIT Irritations, cardiovascular problems etc. Tabulation 3 shows the problems and side effects associated with excess uptake of NSAIDs. So precautions should be followed during administration of these drugs.

To avoid all these problems of NSAID it has been tried in organogel formulations via topical route was successful and benefits of loading in lecithin organogel were given below.

Benefits of NSAID loaded Organogel

a) Avoids gastrointestinal irritations, ulcers, bleeding.
b) Reduces drug toxicity.
c) Can be targeted to specific site of action.
d) Both lipophilic and hydrophilic compounds can be incorporated.
e) Drug potency can be maintained.
f) Ease of preparation with minimal constituents.

Future prospects

Lecithin organogel strongly proves to be a better carrier molecule in topical delivery when compared to other lipid based vesicular systems because of their higher significance values. Apart from phosphatidylcholine, fatty acids and various compounds, lecithin also constitutes many complex molecules and structures which are to be investigated further and their applications in various fields has to be sorted out. Research works on these prospects are focused and attempts were carried out.

CONCLUSION

NSAID being commonly used for anti inflammatory, anti-pyretic, and analgesic property via oral route cause severe problems make the researchers to concentrate on novel delivery system. Which focused in development of NSAID loaded organogels via topical route of administration has gained a better result. Among the other lipid based carrier systems Organogels proves to show an important advantage of increase in shelf life, thermodynamically stable, efficacy and feasibility of the drugs in them. Such novel delivery systems have coined lecithin organogel as a promising effective carrier over other route of delivery of NSAIDs. In future these prospects will lead to the improvisation and development of organogels loaded with other categories of drugs and so on.

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