Formulation and Evaluation of Pluronic lecithin organogel of Flurbiprofen

Choukse R. *,1, Sangameswaran B.2
1Suresh Gyan Vihar University, Jaipur, Rajasthan, India.
2Adesh Institute of Pharmacy & Biomedical Sciences, Bathinda, Punjab, India.

ABSTRACT

The aim of the present work was to generate an index to predict topical efficiency of a series of nonsteroidal anti-inflammation drugs. Organogel, a viscoelastic system, can be regarded as a semi-solid preparation which has an immobilized external apolar phase. The apolar phase gets immobilized within spaces of the three-dimensional networked structure formed due to the physical interactions amongst the self-assembled structures of compounds regarded as gelators. In general, organogels are thermodynamically stable in nature and have been explored as matrices for the delivery of bioactive agents. In the current manuscript, attempts have been made to understand the properties of organogels, various types of organogelators and some applications of the organogels in controlled delivery.

KEYWORDS: Organogel, Gel, Gelator, Drug delivery, Biocompatibility

INTRODUCTION

The fundamentals of successful formulation are to deliver the active substance at target organ with minimal discomfort and side effects. In this respect, transdermal route excels because of avoidance of hepatic first pass metabolism, typical peak trough plasma profile, ease of administration etc. Drug delivery through the skin has been used to target the epidermis, dermis and deeper tissues and for systemic delivery. The major barrier for the transport of drugs through the skin is the stratum corneum, with most transport occurring through the intercellular region. Topical application can potentially limit systemic adverse events by increasing local effects, and minimizing systemic concentrations of the drug. Different type of topical formulations includes creams, ointments, pastes, gels, etc. Out of which gels are getting more popular now a days because they are more stable and also can provide controlled release than other semisolid preparations. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic particles form a three-dimensional “house of cards” structure. A topical gel is a gel substance, which often contains some form of medicine and is applied to the skin or the mucus membranes. In most cases a topical gel is clear and it tends to be more readily absorbed by the skin than is a lotion or ointment. Individual drugs have different degrees of penetration. A balance between lipid and aqueous solubility is needed to optimize penetration, and use of prodrug esters has been suggested as a way of enhancing permeability. Methods of Preparation of gels include fusion method, cold method, and dispersion method. The permeation of drugs through skin can be enhanced by physical methods such as mechanical disruption, electrical disruption, chemical modification and by chemical penetration enhancers e.g. sulphoxides (di methyl sulfoxides), pyrrolidine, alcohols, glycols, surfactants and terpenes. These compounds increase skin permeability by increasing the partition coefficient of the drug into the skin and by increasing the thermodynamic activity of the drug in the vehicle. Chemical penetration enhancers modify barrier properties of the stratum corneum and hence increase drug permeability across skin. Ideally, the effects of the penetration enhancer on the skin should be reversible, non-toxic, non-allergenic, compatible with drugs and excipients and non-irritating.

GENERAL METHOD OF PREPARATION OF PLURONIC LECITHIN ORGANOgel:

Pluronic lecithin organogel is mainly composed of Pluronic F-127, soya lecithin, and IPP/IPM. In general, it is made up of two phases, first pluronic phase (aqueous phase) and second lecithin phase (oil phase), i.e., pluronic gel combined with a lecithin based oil. Pluronic lecithin organogel gel looks and feels like a cream but is actually a gel. When the aqueous phase (pluronic gel) is combined with the lecithin oil base creates an emulsion that forms together due to the pluronic gel and the viscosity of that gel at room temperature. Chilling of PLO converts the gel into liquid, which later gets separated in to oil and aqueous phases (usually takes weeks for separation to occur).

PLURONIC GEL (AQUEOUS PHASE):

Pluronic gel is prepared by taking specified amount of Pluronic F-127 NF in ice cold water, agitating continuously and placing the mixture overnight for complete dissolution of Pluronic F-127. About 0.2% w/w potassium sorbate is added as preservative.

*Corresponding author: R. Choukse | Email: raju.choukse@gmail.com
LECITHIN PHASE (OIL PHASE):
Lecithin phase is prepared by taking specified amount of lecithin, IPP/IPM, and 0.2-0.3% w/w sorbic acid as preservative, then keeping the mixture overnight for complete dissolution of lecithin. Lastly, the PLO gel is being prepared by mixing lecithin: IPP liquid phase and the Pluronic phase together well. Incorporation of air should be minimized.

1.5.2 CHARACTERIZATION OF PLURONIC LECITHIN ORGANOGELS:
In contrast to the ease of preparation, characterization of LOs is relatively complicated on account of their interior structural design built-up on the self-associated supramolecules. These microstructures, the result of varied polar-nonpolar interactions, are highly sensitive and pose difficulties in the investigative studies. However, different characterization studies are extremely useful when investigating the potential applications of organogel systems as a topical vehicle.

STRUCTURAL FEATURES:
An efficient characterization methodology for any organogel system begins with its structural elucidation. The isotropic nature and the optical clarity of LOs makes their study feasible by various spectroscopic techniques, namely, nuclear magnetic resonance (NMR) spectroscopy (ie, 2H NMR, 31P NMR), and Fourier transformed infrared (FTIR) spectroscopy.

RHEOLOGICAL BEHAVIOR:
For any vehicle to be used for topical drug delivery applications, it is essential to study its rheological behavior. The critical parameters such as spreadability, adhesiveness (property related to bioadhesion on skin site), cohesiveness (which indicates structural reformation following application of shear stress), and gel consistency need to be modified in a favorable manner. These systems, prior to gelling (ie, before the addition of polar phase) exhibit Newtonian behavior but follow Maxwell’s rheological (viscoelastic) behavior on addition of the polar phase.

PHASE: TRANSITION TEMPERATURES:
The phase behavior of organogels varies on changing temperature conditions. The phase transition temperature (PTT) (ie, sol-to-gel, TSG, or gel-to-sol, TGS) gives an insight into the nature of microstructures that form the gelling cross-linked network. The phase transition temperatures also help in optimizing the organogel composition. For the determination of PTTs, hot stage microscopy (HSM) and high sensitivity differential scanning calorimetry (HSDSC) have been reported to be useful as accurate and sensitive techniques. However, the inverse flow method, a simple technique based on visual observations has also been employed.

WATER CONTENT:
Water content of an organogel system is critical, as the water loss by evaporation can lead to consequent decrease in viscosity thus affecting the gel stability. Nastruzzi and Gambri have proposed near-infrared (NIR) spectroscopy as a simple, rapid, and nondestructive technique for determining the water content in LOs. The researchers performed NIR studies on lecithin/IPP/water organogel system by measuring the water absorption in the NIR region (1800–2200 nm).

1.5.3 ADVANTAGES OF PLURONIC LECITHIN ORGANOGEL SYSTEM:
Pluronic lecithin organogels have following advantages over other transdermal drug delivery system:
The inclusion of pluronic as cosurfactants in organogel makes the organogelling feasible with lecithin of relatively lesser purity.

- More stable than other types of gel.
- Easy to formulate.
- Have a high uptake capacity for active drugs.
- Do not grow mold if the gel becomes contaminated.
- Enhanced the drug penetration through the skin.
- The drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles / joints, while maintaining low blood levels.
- Poorly water soluble drug can be easily formulated using PLO.
- They can substitute for oral administration of medication when that route is unsuitable.
- They are less greasy and can be easily removed from the skin.
- Localized effect with minimum systemic side effects.
<table>
<thead>
<tr>
<th><strong>PLO GEL FORMULATION</strong></th>
<th><strong>APPLICATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen PLO gel</td>
<td>Administration of ketoprofen in PLO gel offered convenience, produced fewer side effects, and alleviated pain in a specific location</td>
</tr>
<tr>
<td>PLO gel of diclofenac, ibuprofen, ketamine</td>
<td>● Randomized, placebo-controlled study on lateral epicondylitises employing diclofenac in PLO gel reduced pain and increased functional status. ● Preparation also found to be effective treatment for osteoarthritis</td>
</tr>
<tr>
<td>PLO gel of ondansetron</td>
<td>Ondansetron in PLO gel exhibited dose-dependent attenuation of nociceptive and inflammatory effects of intradermally injected capsaicin in humans</td>
</tr>
<tr>
<td>Lecithin (20%-40% vol/vol) in isopropyl myristate or isopropyl myristate containing suitable amount of pluronic and water with or without short chain alcohol</td>
<td>The components of PLO gel provide desired hydration state to the skin, thus effective in the treatment of eczema or psoriasis</td>
</tr>
<tr>
<td>Lecithin organogel in combination of pluronic F-127 (poloxamer 407) solution/cyclobenzaprin</td>
<td>Effective formulation for topical treatment of carpal tunnel syndrome</td>
</tr>
<tr>
<td>PLO formulation of local anesthetics and nonsteroidal anti-inflammatory (NSAIDs)</td>
<td>Rapid onset of action, associated with low side-effect profile</td>
</tr>
<tr>
<td>PLO gel containing extract of Arnica Montana in combination with opioid</td>
<td>Effective treatment for pain management</td>
</tr>
<tr>
<td>Soy lecithin (18%-32% vol/vol) in isopropyl myristate and pluronic F-127 (10%-40%)/ketamine</td>
<td>PLO gel maximizes the effectiveness of the ketamine, effectively alleviates neuropathic, sympathetic, and myofacial pain</td>
</tr>
<tr>
<td>Isopropyl palmitate and Poloxamer 407 containing PLO gel of saw palmetto extract</td>
<td>Selective delivery of antiandrogens into the pilosebaceous units for the treatment of androgenic alopecia</td>
</tr>
<tr>
<td>Bromelain (15%) and capsaicin in PLO gel</td>
<td>Excellent matrix for topical delivery of macromolecule</td>
</tr>
<tr>
<td>Hormones (eg, progesterone) in PLO gel</td>
<td>Transdermal delivery of hormone</td>
</tr>
<tr>
<td>Micronized testosterone in PLO gel</td>
<td>Systemic delivery of hormone</td>
</tr>
<tr>
<td>Fluoxetine hydrochloride incorporated in PLO gel</td>
<td>Systemic delivery of the compound in feline patients</td>
</tr>
</tbody>
</table>

Table No.1: Topical delivery of therapeutic substances incorporated in Pluronic Lecithin Organogels
Therapeutic Category | Therapeutic Agents
---|---
Antiemetics | Dexamethasone, dimenhydrate, scopolamine
Muscle relaxants | Cyclobenzaprine, baclofen, buspirone
Neuropathy drugs | Clonidine, capsaicin, amitryptiline, gabapentin, phenytoin, NSAIDs
NSAIDs | Diclofenac, ibuprofen, ketoprofen, indomethacin
Systemic analgesics | Acetaminophen, hydromorphone, morphine sulfate
Systemic hormones | Progesterone, testosterone

Table No.2 Commercially available Pluronic Lecithin Organogels

PREFORMULATION STUDY:
- Identification Of Drug
- Organoleptic Properties
- Solubility Determination
- Partition Co-efficient (Shaking Flask Method)
- Particle Size (Microscopic Method)
- Melting Point (Capillary Method)
- Standard Curve Of Flurbiprofen In Ethanol (Uv Spectroscopy)

5.1.2 METHODS FOR PREFORMULATION STUDIES OF FLURBIPROFEN:

A) DETERMINATION OF Λ MAX:

100 mg of Flurbiprofen was dissolved in 100ml of ethanol. 1ml of the prepared stock solution was further diluted to 100 ml and finally scanned for maximum absorbance using double beam U.V. spectrophotometer in the range from 230 to 360 nm. Average of triplicate readings was taken.

B) SOLUBILITY DETERMINATION:

Qualitative: 10 mg of drug dissolved in 10 ml of solvent to detect the solubility of drug in the different solvents. The different solvents used for the solubility determination are:-
- Methanol
- Ethanol
- Acetone
- Chloroform
- Hexane
- Octanol
- Water

C) PARTITION COEFFICIENT:

A drug solution of 1mg/ml was prepared in Chloroform 25ml of this solution was taken in a separating funnel and shaken with an equal volume of distilled water(aqueous phase) for 10 minutes and allowed to stand for two hrs then seperated. Both the phases were analyzed for the drug concentration using U.V. spectrophotometer. Partition coefficient was calculated by taking the ratio of the drug concentration in Chloroform to drug concentration in aqueous phase readings were taken.

\[ P_{o/w} = \frac{C_{oil}}{C_{water}} \]

D) Particle Size

I) Calibration Of Eyepiece: Use standard stage micrometer to calibrate the eyepiece micrometer and calculate for the least count (1 eye piece division)


II) Mounting Of The Sample: Transfer a small portion of the given sample on clean slide and disperse it uniformly and place the slide on the stage of microscope.

III) Measurement Of Particle Size: Focus the slide in low magnification (10x). observe the particles than shift to high power (45x) and focus the slide. measure the size of each particle in terms of eyepiece divisions. a total of 100 particles should be considered. tabulate the particles in terms of division of eyepiece and no. of particles (frequency) obtained above. classify the diameter into size ranges and average frequency of particles in terms of no. distribution.

E) Melting Point Determination

Melting point of the drug was determined by taking a small amount of the drug in a capillary tube closed at one end and was placed in Thiel’s melting point apparatus and the temperature at which the drug melts was noted. average of triplicate readings was taken.

F) Standard curve Of Flurbiprofen In ethanol
100 mg of Flurbiprofen was accurately weighed and dissolved in ethanol in a 100 ml volumetric flask and the volume was made upto the mark using ethanol. The above prepared solution of Flurbiprofen was subsequently diluted with ethanol to get 2, 4, 6, 8, 10, 12 μg per ml of the final solution. Then the absorbance was measured by spectrophotometer at 248nm using ethanol as blank. Average of triplicate readings was taken.

G) DRUG- EXCIPIENT INTERACTION STUDY:
A small amount of drug substance with excipients that is, physical mixture of the drug and excipients (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and rubber stopper was placed on the vial and sealed properly. A storage period of 2 weeks at 60°C, and the same sample was retained for 2 months at 40°C. After storage the sample were observed physically for liquefaction, caking, odour or gas formation, discoulouration.

MATERIALS AND METHODS:
Flurbiprofen was obtained from sun pharma india Ltd.,Mumbai. Pluronic F-127 was obtained from Sigma Aldrich, Delhi. Lecithin was purchased from Ruchi soya Pvt. Ltd.Isopropyl myristate and Polyethylene glycol 400 was purchased from SDFCL, Potassium sorbate and Sorbic acid was purchased from CDH, Potassium di hydrogen phosphate was purchased from Sunchem, Di sodium hydrogen phosphate, Sodium chloride and Sodium hydroxide was procured from Merck and n-octanol from Triza.

METHOD OF PREPARATION OF PLO: (BY COLD METHOD):
The various formulation of PLO were developed with different compositions. Four formulation of different compositions were made as given in Table 6.3. All the 4 formulation were coded from F1 to F4. Pluronic Lecithin Organogel is a two phases based gel. It is made up of 2 phases an oil phase and a aqueous phase. Oil Phase was prepared by mixing soya lecithin and sorbic acid in appropriate quantity of isopropyl myristate. The mixture was kept overnight at room temperature in order to dissolve its constituents completely. Aqueous phase was prepared by dispersing weighed amount of pluronic F-127 and potassium sorbate in cold water. The dispersion was stored in refrigerator for effect for effective dissolution of Pluronic F-127. The next day, active ingredient flurbiprofen was dissolved in Polyethylene glycol-400 and mixed with the lecithin-isopropyl solution. Polyethylene glycol-400 was used for solubilization of flurbiprofen . Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring using mechanical stirrer. Following PLO formulations were prepared by altering the concentration of Lecithin , while keeping the concentration of Pluronic and other excipient and drug unchanged.

RESULTS:
Any drug for its permeation through skin should be thermodynamically active, must be lipophilic as well as hydrophilic in nature having a favourable partition coefficient.The preformulation study for the drug was conducted. The λmax of Flurbiprofen was found at 247-248 nm, which is comparatively same as given in Merck Index. This shows that the drug is pure. By the determination of organoleptic properties, it was observed that the Flurbiprofen is white or slightly yellow crystalline powder , bitter in taste and odourless drug. Results of qualitative solubility studies shows that the Flurbiprofen is more soluble in organic solvents and insoluble in water. The partition coefficient was found to be 3.89, which is suitable for transdermal drug delivery. The obtained value of partition coefficient of Flurbiprofen was more than 1 which showed that the Flurbiprofen is lipophilic in nature . The average particle size of Flurbiprofen was measured by microscopy method was found to be 7.145 micrometer. The melting point was observed at 110-112 °C and this range is nearly same as reported in Merck Index, it shows the drug is crystalline in nature. The preformulation study of Flurbiprofen showed satisfactory results to select the drug for transdermal drug delivery system.

REFERENCES:
22. Kumar, R., Katare, O.P., 2005. Lecithin organogels as a potential phospholipid-structured system for topical drug delivery: a review. A. A. P. S. Pharm. Sci. Tech. 6(2), E298-


