ORGANOGELS

PREPARATION AND EVALUATION OF EUDRAGET ORGANOGELS FOR MODEL DRUG

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ABSTRACT:

Organogels have been explored as a versatile tool in pharmaceuticals for topical as well as a transdermal delivery of various drugs. These are semisolid system consists of a polar phase and a solid phase. Gels are formed by the mechanisum of entrapment of a polar phase into the three dimensional network structure of solid phase. A polar phase is used as a solvent such as isopropyl palmitate, isopropyl myristate etc.. solid phaseis an organogelator such as sorbitanmonosterate , lecithin etc.. these system are good carrier for both hydrophilic and lipophillic therapeutic agent. This study aims at preparing the eudraget organogels by solid fiber mechanisum. Diclofenae as the model drug and studying the properties with different concentrations of eudrget and a polar phase.
PREPARATION AND EVALUATION OF EUDRAGIT ORGANOGELS FOR NEBIVOLOL

1. INTRODUCTION

Organogels are thermodynamically stable, visco-elastic biphasic systems comprising of a gelator [any substance capable of forming gel] and a nonpolar phase, with or without the presence of water molecules within the network formed by the gelator system. When compared with hydrogel they have a lower degree of hydration. Because of their non-irritating property and biocompatibility they gained importance in the delivery of drugs over the past few years. Although organogel comprised of large amount of liquid systems but it exhibit morphological and rheological properties similar to solids. The thermodynamic and kinetic stability of these systems can be attributed to the opposing forces which are operating and are associated with the organogelator‘s partial solubility in the continuous phase. The Gelling matrix governs by the resulting interaction and physicochemical properties of gel components. Gels can be classified on the basis of the properties of gelators, solvents and the intermolecular interactions which converted into gels. Organogelators are mostly small molecules, while gelators in a hydrogel are polymeric in nature. Hence, the organogelators are well known by the name Low Molecular Weight [LMW] Organogelators. Depending upon the route of administration, organogel required the change in its formula to Administered the drugs. Solvent system in organogels are non-aqueous liquids, which is a useful topical deliveries for lipophilic drug and aqueous liquids, which is useful for hydrophilic drug mentioned in various pharmacopoeias as well as for hydration of skin. Through percutaneous absorption Organogel achieved the local as well as systemic effect by the presence of a penetration enhancers: their lipophilic nature and occlusive effect are potentiated.

Structure of Organogels

Gels are an intermediate state of the matter, containing both solid and liquid components. The solid component comprises a three dimensional network of interconnected molecules which immobilizes the liquid continuous phase. Hydrogels have an aqueous continuous phase, and organogels have an organic solvent as the liquid continuous medium. Organogels exhibit interesting properties such as the ability to solublize guest molecules, uses for purification and separation purposes and as transdermal delivery vehicles.

Advantages of organogel Template vehicle:

The wide range of substances can be incorporated in organogel with diverse physicochemical characters viz: chemical nature, solubility, molecular weight, and size etc.

Process benefits: The process is very simple and easy to handle because of organogels formulation by virtue of selfassembled super molecular arrangement of surfactant molecules makes the process very simple and easy to handle.

Structural/ physical stability: The organogel do not form semisolids on standing as an organogel consists of macromolecules existing as twisted matted strands. The units having the strong Vanderwaal forces so as to form crystalline amorphous regions throughout the entire system and it maintained for longer periods of time as it is thermodynamically stable, the structural integrity of organogel.

Chemical stability: Organogel is organic in character also resist microbial contamination and are moisture insensitive.

Topical delivery potential: Since having both hydrophilic and lipophilic character, they can efficiently partition with the skin and therefore enhance the skin penetration and transport of the molecules. Drug delivery into the skin layers [cutaneous or dermal delivery] and beyond [percutaneous or transdermal delivery] is advantageous because it provides a non-invasive, convenient mode of administration, avoid the first pass metabolism of the active ingredient, an important aspect for highly hepatic metabolized molecules and for drug with short elimination half-life.

Disadvantage

When a gel stands for some time, it often shrinksϖ naturally, & some of its liquid is pressed out, known as syneresis, therefore stored in a proper condition. When the gel is taken up of liquid with an increasingϖ volume known as swelling. In most cases the effect is slow and sustained.ϖ Chances of irritation to the skin from the penetrationϖ enhancers Only drugs small enough to penetrate the skin can be effectively delivered with less then 500 Dalton Less stable to temperature. If contamination present then no gelling will occur.ϖ Raw material like lecithin is not available on largeϖ scale. therefore expensive in production. Permeability of drug through skin depends on the partition coefficient of drug therefore required reasonable partition coefficient. The route is not suitable for the drugs which causeϖ irritation to the skin or sensitive to skin.

Application Pharmaceutical:

Organogels as Matrix for Transdermal Transport of Drugs

Organogels as Iontophoretic Transdermal Drug Delivery system:

Organogel as Opthalmic Drug Delivery Systems:

Organogels in cosmetics

Nutraceutical applications

DRUG PROFILE

Name: Nebivolol

Category: Anti hypertensive agent

Structural formula:

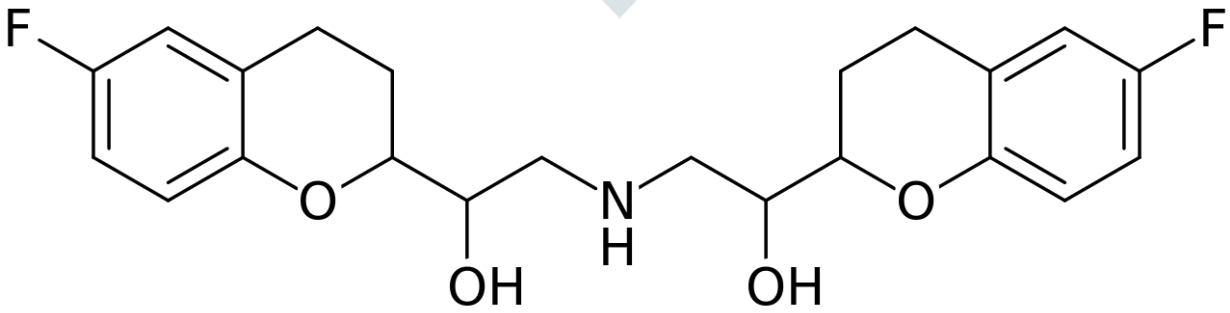

Fig-: Molecular structure of Nebivolol

Description: Nebivolol is a highly cardio selective vasodilatory beta1 receptor blocker used in treatment of hypertension. In most countries, this medication is available only by prescription.

Molecular formula: C_{22} H $_{25}$N O $_{4}$F $_{2}$

Molecular weight: 405.435 g/mol

Storage: Store in well-closed, light-resistant containers.

Pharmacodynamics: Nebivolol is a competitive and highly selective beta-1 receptor antagonist with mild vasodilating properties, possibly due to an interaction with the L-arginine/nitric oxide pathway. In preclinical studies, nebivolol has been shown to induce endothelium-dependent arterial relaxation in a dose dependent manner, by stimulation of the release of endothelial nitric oxide. Nitric oxide acts to relax vascular smooth muscle cells and inhibits platelet aggregation and adhesion.

Mechanism of action: Nebivolol is a selective β1-receptor antagonist. Activation of β1-receptors by epinephrine increases the heart rate and the blood pressure, and the heart consumes more oxygen. Nebivolol blocks these receptors which reverses the effects of epinephrine, lowering the heart rate and blood pressure. In addition, beta blockers prevent the release of renin, which is a hormone produced by the kidneys which leads to constriction of blood vessels. At high enough concentrations, this drug may also bind beta 2 receptors.

Pharmacokinetics

Bioavailability: 12 %

Metabolism: Hepatic

Elimination: hepatic

Half life: 10 hours

Uses: Nebivolol is used alone or in combination with other medications to treat high blood pressure. Nebivolol is in a class of medications called beta blockers. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decreaseblood pressure

2. LITERATURE REVIEW

Sahar et al., Etodolac (ETD) is a non-steroidal anti-inflammatory drug used for the acute and chronic treatment of rheumatoid arthritis. It exhibits poor water solubility so its bioavailability is limited. Long term use of ETD causes serious gastrointestinal disturbance. Lecithin organogels (Los) have generated considerable interest over the years as potential topical drug delivery vehicle. Therefore, the objective of this study was to formulate ETD in lecithin organogels as a transdermal delivery system. Methods: Based on the preliminary studies, pseudoternary phase diagrams were constructed using isopropyl myristate (IPM), water and lecithin as a surfactant with different cosurfactants (CoS) and organogel areas were identified and three systems each of 36 formulae were prepared. A number of organogels were selected and loaded with 1% ETD then evaluated for visual inspection, spreadability, pH, rheological and in vitro release studies to select the optimum formulae. The selected formulae were subjected to ex-vivo permeation through excised abdominal rabbit skin and their stability was studied for one year of storage under ambient conditions. The therapeutic efficacy of ETD including analgesic activity and antiinflammatory effect was monitored. Results: The prepared ETD organogels showed suitable properties for topical application and the selected formulae (F3, F14 & F39) showed enhanced permeation. The In vivo study showed a significant difference in the therapeutic efficacy of formula F14, containing 10% IPM, 40% lecithin/PG in the ratio of (5:1) and 50% water, compared to a market product. Skin irritation test and histopathological studies proved the safety of this formula. Conclusion: So this organogel formula (F14) is considered to be a potential vehicle for a sustained release transdermal delivery system for ETD.

Jadhav et al., The purpose of the present study was to develop and investigate the suitability of microemulsion based lecithin organogel formulations for topical delivery of fluconazole in order to bypass its gastrointestinal adverse effects. The ternary phase diagrams were developed and various organogel formulations were prepared using pharmaceutically acceptable surfactant (lecithin) and ethyl oleate (EO). Solubility of fluconazole in EO and EO-lecithin reverse micellar system was determined. The transdermal permeability of fluconazole from different concentrations of lecithin organogels containing EO as oil phase was analyzed using Keshary-Chien diffusion cell through excised rat skin. Solubility of fluconazole in EO-lecithin reverse micellar system was almost 3 folds higher than that in EO. Gelation and immobilization of oil require critical solubility-insolubility balance of gelator. The occurrence of gel phase was lecithin concentration dependent and was observed in 10-60% w/v of system. Organogel containing 300 mM of lecithin showed the higher drug release and better relative consistency. Hence, it was selected for antifungal activity. The increase in antifungal activity of fluconazole in lecithin organogel may be because of the surfactant action of the lecithin and EO that may help in the diffusion of drug. The histopathological data showed that EO-lecithin organogels were safe enough for the topical purpose. Hence, the present lecithin based organogel appears beneficial for topical delivery of fluconazole in terms of easy preparation, safety, stability and low cost.

Chethana et al., Skin aging is one of the prominent problems associated with skin as each part of body ages with the time, skin is the external organ where the sign and symptoms of aging are readily evident. However cosmetics as well as pharmaceutical approaches delayed skin aging. Gel are best fitted in all these essential criteria because of their excellent appearance, smoothness, desired consistency, fast drug release, ease of manufacturing and quality assessment and admirable stability. Recently gel formulation have been modified to yield an advance drug delivery system known as ―organogels‖. Gel define as a semi-solid preparation having an external solvent phase, apolar [organogel] or polar [hydrogel] immobilized within the space available of a three dimensional network structure. Lecithin is a natural surfactant isolated from eggs or soya bean, when it combined with water and non-polar solvent, it form gels. PLO gels have gained importance in recent years as transdermal drug delivery system. It is a thermodynamically stable, visco-elastic system, which is non-irritating, odorless and biodegradable. Pluronic F127 or poloxamer is a copolymer of polyoxyethylene and polyoxypropylene which forms a thermoreversible gel in concentrations between 15-30%w/v. Water plays the role of a structure-forming agent and stabilizes the process of gel formation as it solubilizes the pluronic and other hydrophilic drugs. PLO gel system facilitates the delivery of hydrophilic as well as lipophilic drugs owing to the presence of both oil and aqueous phases within the gel system.

Shashikanth et al., A gel may be defined as a semi-solid formulation having an external solvent phase, a polar (organogel) or polar (hydrogel) immobilized within the spaces available of a three dimensional networked structure. Organogel can be prepared by Fluid-Filled fiber mechanism and Solid fiber mechanism. The chemical enhancer used in dermal formulation for permeation of drug through the skin, it may be produce irritation as in chronic application. Organogel does not require use of chemical enhancer for facilitate drug through the skin. Lecithin, Sorbitan ester base or gelatin use for gellating agent. This article gives information about types of organogelator, types of organogel, properties and Evaluation parameter of organogel with application.

3.AIM AND OBJECTIVES

Aim:

The main aim of this study is to achieve prolonged release of Nebivolol such that the dosing frequency of the drug can be reduced by which we may reduce the side effects and increase the patient compliance. By formulating Nebivolol eudragit organo gel used in the treatment of hypertention.

Objectives:

- The present study involves preparation and evaluation of organo gel containing Nebivolol .
- The organo gel are prepared by using the polymers as eudragit L and S.
- To reduce side effects of the drug.
- To prepare controlled delivery of drug at a particular site.
- To increase bioavailability of the drug.
- To increase skin penetration of the drug.

- To increase amount of drug retention into the skin.
- To delay clearance from circulation.
- To improve the stability

4. PLAN OF WORK

PART-I:

1. Extensive literature survey.
2. Procurement of excipients.
3. Procurement of drug Nebivolol

PART-II:

Preparation of organogel formulations.

PART-III:

Evaluation of batches of eudragit organo gel containing Nebivolol for the following parameters:

a) pH determination
b) Spreadability measurements
c) Rheological studies
d) Entrapment efficiency
e) In- vitro drug release.
f) Stability studies

PART-IV:

Conclusion and discussion.

5. METHODOLOGY

Formulation development

Eudragit organogels: Eudragit organogels are really mixtures of Eudragit (L or S) and polyhydric alcohols, such as glycerol, propylene glycol and liquid polyethylene glycol containing high concentrations (30 or 40% w/w) of Eudragit. Gel consistency and spreading is described using a penetrometer. Gel viscosities were found to increase with increasing concentrations of Eudragit and to decrease with increasing drug content.

Ingredients	F1	F2	F3	F4

Drug	20	20	20	20
Eugragit L	500	-	750	250
Eugragit S	-	500	250	750
Glycerol	10	10	10	10

Fourier-Transform Infrared (FT-IR)

FT-IR spectra of all samples of pure ETD, plain organogels without drug and the selected medicated formulae were examined, the samples were mixed separately with KBr powdered crystals, then loaded into DRS-8000A unit installed into FTIR spectrometer (IRAffinity-1) (Japan), connected to IBM-PC computer loaded with IR solution software version 1.60 in wave number range of 400 – 4000 cm-1 with laser jet printer according to diffuse reflectance method.

Evaluation of physicochemical properties of the prepared organogels

Visual inspection

The prepared organogels were examined for optical clarity, fluidity, homogeneity, and phase separation.

Thermodynamic stability of organogels

To overcome the problem of metastable formulae, the prepared organogels were subjected to centrifugation and freeze-thaw stress tests to assess their thermodynamic stability. The Organogels were centrifuged at 7000 rpm for 30 min. Formulae that did not show any phase separation was considered to be stable and were subjected to freeze-thaw stress test . Three complete cycles, each cycle consisting of 24 h at 25 °C followed by 24 h at-5 °C were carried out. These cycles were important for determining the ability of the organogels to withstand thermal shock . The formulae that survived thermodynamic stability tests were selected for further studies.

pH determination

The pH was measured for each organogel using a pH meter (Hanna-213, Portugal) by direct immersion of the electrode .

Spreadability measurements

Spreadability test was carried out by pressing 0.5 g of the prepared formulae between two slides of glass and left for about 5 min where no more spreading was expected. The diameter of the formed circle was measured and taken as a comparative value for Spreadability.

Rheological studies

The selected organogels were tested for their rheological behavior at 25±1 °C using a rotational Brookfield viscometer of cone and plate structure, spindle 52 (Brookfield, cone and plate viscometer, model III, USA).

In-vitro drug release studies:

The release studies were carried out by franz diffusion cell. It containing 10 ml Phosphate buffer. Phosphate buffer pH 7.4 (100 ml) was placed in a 10 ml of beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37±5^{0}C. Dialysis membrane was taken and one end of the membrane was sealed. After separation of non entrapped gel dispersion was filled in the dialysis membrane and other end was closed. The dialysis membrane containing the sample was suspended in the medium. 1ml of aliquots were withdrawn at specific intervals, filtered after withdrawal and the apparatus was immediately replenished with same quantity of fresh buffer medium.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

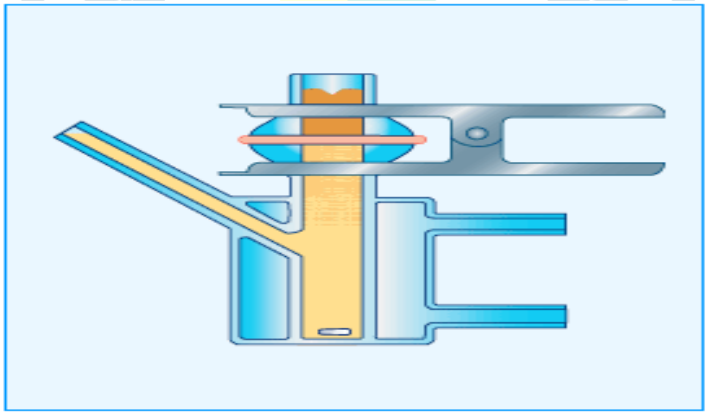

Fig-: Franz diffusion cell

Conditions:

Medium: Phosphate buffer pH 7.4
RPM: 200
Temperature: 37 ± 0.5^{0}C
Time intervals: 1, 2, 3, 4, 5, 6, 7, 8 hours

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 25^0C/60% RH analyzed every month for period of one month.
2. 30^0C/75% RH analyzed every month for period of one month.
3. 40^0C/75% RH analyzed every month for period of one month.

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