WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 10, Issue 9, 2276-2283 Review Article ISSN 2278 – 4357

A REVIEW ON PREPARATION AND CHARACTERIZATION OF REVERSE MICELLES BASED LECITHIN ORGANOGELS

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Article Received on
22 July 2021,

Revised on 12 August 2021,
Accepted on 01 Sept. 2021

DOI: 10.20959/wjpps20219-20071

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ABSTRACT

The solubility and permeation of hydrophilic drugs across skin barrier system are the limiting steps for any topical drug delivery system. Although several approaches have been investigated by the researchers for the development of an efficient drug delivery system but all have their own limitations. Several novel approaches are taken into consideration and reverse micelles based Lecithin organogels are one of them. The reverse micelles have inner hydrophilic core and outer hydrophobic core. The hydrophilic drug can be easily incorporated within inner core. The reverse micelles based Lecithin organogels has shown high efficient in drug permeation through skin. They can be formulated by either of two methods. Method 1 includes the addition of lecithin, isopropyl Myristate and water [RMS-1] whereas Method 2 involves the addition sodium bis (2-ethylhexyl) sulfo-succinate, isooctane, and water [RMS-2]. The reverse micelles formation change the polarity of water allows the solubilization of hydrophilic drug. These reverse micelles are then used for the formation of Lecithin organogels by addition of any gelation agent or by adjusting the water ratio. These systems are evaluated for physical properties, drug content, toxicology, in vitro and in vivo transdermal permeation.

KEYWORDS: Lecithin, Organogels, Reverse micelles, topical route, transdermal, hydrophilic drugs, skin barrier system.

INTRODUCTION

The reverse micelles are self aggregated molecules which are formed in the presence of any non-polar solvent.[1] In reverse micelles, the surfactant polar head is directed inwards to form hydrophilic core and solubilise hydrophilic drugs and can solubilise water whereas the lipophilic part of the surfactant is exposed to outer portion of micelle and protect the inner

core from external environment.[2] The reverse micellar system has a tendency to deliver hydrophilic or less skin permeable drugs across the skin barrier system.[3] The properties of water molecules present in reverse micelles differ from that of bulk water. Reverse micelles have nano-sized 1-10 nm water droplets that are obtained by addition of surfactant in organic solvent.[4] The reverse micellar system is cost-effective, non-toxic, and controlled drug release efficient.[5] These advantages of reverse micelles have made it useful for applications in pharmaceutical industries. The reverse micellar solution cannot be used as such for the topical or transdermal route and hence reverse micellar system are added with gelating agent or excess amount of water in order to obtain an organogel or Reverse Micelle based Lecithin Organogel.[6] Organogel are solid, visco-elastic systems that are non-crystalline, thermostable, thermo-reversible.[7] These organogels can be easily applied onto skin, have patient compliance and compatibility with skin.[8]

Lecithin is a natural product extracted mainly from egg yolk and also from plants and animal tissues.[9] Lecithin is a phospholipid that was designed by Scartazzini and Luisi in 1988 specifically for organogels.[10] Natural Lecithin contains more than 95% of phosphotidyl content. The Lecithin has a unique property of procuring gel structure in presence of any organic or non-polar solvent and has unsaturated chemicals within. Because of this property a lot of research has been conducted on lecithin based organogels. The lecithin-based organogels have been found to be viscoelastic, thermodynamically stable, thermoreversible (solto-gel transition temperature at 40°C), transparent, biocompatible and non-irritant.[11,12] The organogels prepared using lecithin has been found to have an isotropic structure. This unique property was only found in natural lecithin whereas synthetic and soy lecithin failed to show the property of gelling. The natural lecithin should be pure molecule and presence of even small amount of guest molecules can lead to destruction or failure of organogels formation. The hydration ratio (molar ratio of water to lecithin) in lecithin organogels may vary from 1 to 12.[13] The lecithin organogels have unique properties along with unique chemical structure. The lecithin based organogels are generally formed by entanglement of fluid-fiber reverse micellar tubular structures and consist of 3 main components i.e., a non-polar solvent, an aqueous phase and a surfactant (Lecithin).[11]

The other most commonly used surfactants which have been studied in this respect are sodium bis (2-ethylhexyl) sulfosuccinate (AOT), Tweens 1, Spans 1, poly (ethylene oxide), alkyl trimethyl ammonium halides e.g. CTAB and phospholipids e.g. phosphotidyl choline.

The organic solvents used as dispersing media include n-octane, iso-octane, heptane, cyclohexane, benzene and chloroform.[14] In the present study, the literature review was conducted to determine the most suitable method for preparation of reverse micelles consisting of surfactant, an organic solvent and water. The most commonly used surfactant for the preparation of reverse micelles based Lecithin organogels is Lecithin because of its amphiphilic character. On a further note, combination of lecithin and iso-propyl myristate is bio-compatible and hence can be helpful for topical and transdermal delivery of drugs for treatment of skin disorders.

Preparation of Reverse micelles

The most suitable method for the formulation of reverse micelles based organogels is addition of lecithin, isopropyl Myristate and water. Before formulation, the critical micelle concentration is determined for finding the optimum concentration of surfactant at which micelles start forming.

Determination of Critical Micelle concentration (CMC): The CMC is determined using the Abbe Refractometer. Different concentration of lecithin solution was observed for refractive index in Abbe Refractometer. The point at which there is sharp change in refractive index is considered as CMC. This amount of lecithin is used for preparation of reverse micelles.[1]

Preparation of drug loaded reverse micelles: Drug loaded reverse micelles are prepared in different batches by measuring different quantities of lecithin and dissolving it in optimum quantity of isopropyl Myristate with continuous stirring at 80^{o}C for about 60 minutes using measuring stirrer.[2] Measured quantity of distilled water is then added to above solution with constant stirring to obtain stable reverse micelles. The hydrophilic drug is also added to above prepared micellar solution by firstly dissolving the drug in water. The solution is further stirred for atleast 120 minutes for obtaining optimum solubilization of drug in micellar solution.[15,16]

Characterization of drug loaded reverse micelles

Particle size determination and polydispersity index: The particle size and polydispersity index is measured by Zetasizer at 25°C. The samples from different batches are placed in neat and clean cuvette of polystyrene and the readings are determined at a fixed angle.[17,18]

Drug encapsulation efficiency: The drug loaded reverse micelles are also determined for the drug encapsulation efficiency using ultra-centrifugation technique**.** About 1ml of formulation is centrifuged at a speed of 13,000rpm for 10 min at controlled temperature. The supernatant liquid is collected from the above solution using micropipette and analyzed at particular wavelength by UV spectrophotometer.[17,18,19] The percentage of the encapsulated drug was calculated using the formula**:**

$$Entrapment\ Efficiency = \frac{Amount\ of\ drug\ encapsulated}{Total\ amount\ of\ drug\ incorporated} X\ 100$$

Preparation of Reverse micelles based Organogels

The reverse micelle based organogels are prepared by mixing oil phase i.e., drug loaded reverse micelles and aqueous phase in the ratio of 30:70 w/v. The aqueous phase used in formulation is water for Lecithin organogels and for Pluronic Lecithin organogels pluronic F 127 and cold water is used. The oil and aqueous phase is constantly mixed using magnetic stirrer to obtain Reverse micelles based Organogels.[1,2]

Characterization of Reverse micelles based Organogels

Macroscopic examination: The physical appearance of the PLO are checked and compared visually for their colour, homogeneity, consistency and by physical examination.[20]

Determination of pH: The pH values of PLO gel formulations are determined by using digital pH meter. Gel (1 g) is dissolved in 100 ml distilled water and stored for 2 h. The measurement of pH of formulation is done in triplicate and average values are calculated. Since the formulation is topical formulation to be applied to the skin, therefore, pH measurement is essential to ensure non-irritating nature of the formulation.[21,22]

Gel Transition Temperature: PLO is filled in transparent vial containing a magnetic bar and placed in water bath and stirred continuously at 60 rpm. At the point of gelation, the magnetic bar stops and the temperature of gelation is measured.[23]

Water Content: The water content of the gel is determined by weighing the gel before and after evaporation. The difference is measured and the water content is calculated. The gel stability gets affected if the water content is not maintained. Another approach is Near-infrared (NIR) spectroscopy.[24,25]

Determination of Viscosity: Brookfield digital viscometer is used to measure the viscosity (in cps) of the prepared PLO formulation. The spindle (T-D) is rotated at 6 rpm. The viscosity of formulations is more correct which is near to 100% torque. Samples are measured at 30 ± 10^0C. Reading is detected 30 sec after measurement is made, when the level is stabilized.[26]

Determination of Drug content: 1g formulation is taken in a 50 mL volumetric flask and made up to volume with desired solvent. The solution is filtered through Whatman filter paper and 0.1 mL of the filtrate is pipetted out and diluted to 10 mL with hexane. The content of active constituents is estimated spectrophotometrically by using standard curve.[27]

Determination of spreadability: Spreading coefficient is determined by apparatus which consist of a wooden block that is attached to a pulley at one end. Spreading coefficient is measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground glass slide is fixed on the wooden block. An excess of PLO (about 2 g) under study is placed on this ground slide. The preparation is then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. A weight of 500 mg is placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the gel between the two slides. Measured quantity of weight is placed in the pan attached to the pulley with the help of hook. Time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load is to be measured. Lesser the time taken for separation of two slides, better the spreadability.[28] It is calculated by using the formula:

S= M.L/ T,

Where, M= weight placed on upper slide (20 g), L= Length of upper slide (7.5 cm), T= time taken to separate the slide (in sec)

***In vitro* permeation test:** The *in vitro* permeation tests are performed using Franz diffusion cell. The diffusional area of the cell is 1.75 cm^2 and the receptor compartment had a capacity of approximately 10.5 ml. The membrane is cut to a diameter of 25 mm and saturated for 30 minutes in receptor medium (phosphate buffer pH 7.4) before starting the experiment. The cell is filled with degassed receptor medium and the membrane is placed in the top of the receptor compartment and checked for air bubbles. An aliquot of the sample is measured with the aid of a syringe and then placed in the cavity of a dosage wafer (donor compartment), on top of the membrane. The amount applied is around 50 mg of PLO. With a spatula, PLO is

spread uniformly filling the donor compartment. A glass disk is carefully placed on the sample to occlude it, and an aligner cap is then used to centralize the assembly, which is held together by a clamp. The receptor medium is maintained at 37 ± 2°C under constant stirring. To characterize the drug release, 1ml samples are collected after 1, 2, 3, 4, 5, 6 and 7 hrs. After sampling, the volume collected is replaced with fresh receptor medium. The amount of drug is assayed by UV analysis.[29]

Stability Studies: Stability study of the formulation is conducted at different temperature conditions according to ICH guidelines at 25^{o} C ± 2^{o}C / 60 % ± 5% RH for real and 40^{o} C ± 2^{o} C / 75 % ± 5% RH for accelerated stability studies as per ICH guidelines for a period of 3 months. Samples were withdrawn at 1 month time intervals and evaluated for physical appearance, pH and rheological properties.[30]

REFERENCES

1. Nithya R, Kumari B, Development and Characterization of Reverse Micelle based Pluronic Lecithin Organogel containing Imatinib Mesylate, Res J Pharm Technol, 2021; 14(3): 1209-14.
2. Agrawal GP, Juneja M, Agrawal S, Jain SK, Pancholi SS, Preparation and characterization of reverse micelle based organogels of piroxicam, Pharmazie, 2004; 59(3): 191-3.
3. Jain SK, Chandra R, Rai AK, Characterization of Ocular Delivery of Reverse Micelles Bearing Insulin, Res J Pharm Technol, 2008; 1(4): 370-3.
4. Melo EP, Aires-Barros MR, Cabral JM, Reverse micelles and protein biotechnology, Biotechnol Ann Rev, 2001; 7: 87-129.
5. Esposito C, Kirilov P, Roullin VG. Organogels, promising drug delivery systems: an update of state-of-the-art and recent applications, J Control Rel, 2018; 271: 1-20.
6. Almeida H, Amaral M, Lobão P, Lobo J, Pluronic F-127 and Pluronic Lecithin Organogel (PLO): Main Features and their Applications in Topical and Transdermal Administration of Drugs, J Pharm Pharma Sci, 2012; 15(4): 592-605.
7. Saha S, Shivarajakumar R, Karri VVSR, Pluronic Lecithin Organogels: An Effective Topical and Transdermal Drug Delivery System, Int J Pharma Sci Res, 2018; 9(11): 4540-50.
8. Fu Y, Liu Y, Fang Y, Qi X, Cao D, Physicochemical Characterization of Lecithin/Isopropyl Myristate Reverse Micelles. Chem Sel, 2017; 2(24): 7439-44.

9. Sahoo S, Kumar N, Bhattacharya C, Sagiri SS, Jain K, Pal K, Ray SS, Nayak B, Organogels: Properties and Applications in Drug Delivery, Desig Monomers Polymers, 2011; 14(2): 95-108.
10. Scartazzini R, Luisi PL, Organogels from lecithins, J Phys Chem, 1988; 92: 829.
11. Kumar R, Katare OP, Lecithin organogels as a potential phospholipid-structured system for topical drug delivery: a review, AAPS PharmSciTech, 2005; 6(2): E298-310.
12. Schurtenberger P, Scartazzini R, Magid LJ, Leser ME, Luisi PL, Structure and Dynamics of Viscoelastic Surfactant Solutions - An Application of Concepts from Polymer Science, J Phys Chem, 1990; 94: 3695.
13. Luisi PL, Scartazzini R, Haering G, Schurtenberger P, Organogels from water-in-oil microemulsions, Col Polym Sci, 1990; 268: 356–374.
14. Jhawat V, Gupta S, Saini V, Formulation and evaluation of novel controlled release of topical pluronic lecithin organogel of mefenamic acid, Drug del, 2016; 23(9): 3573-81.
15. Vrignaud S, Anton N, Gayet P, Benoit JP, Saulnier P, Reverse micelle-loaded lipid nanocarriers: a novel drug delivery system for the sustained release of doxorubicin hydrochloride, Eur J Biopharm, 2011; 79(1): 197-204.
16. Vrignaud S, Hureaux J, Wack S, Benoit JP, Saulnier P, Design, optimization and in vitro evaluation of reverse micelle-loaded lipid nanocarriers containing erlotinib hydrochloride, Int J Pharma, 2012; 436(1-2): 194-200.
17. Jones M, Leroux J, Reverse micelles from amphiphilic branched polymers, Soft Matter, 2010; 2010: 6.
18. Kim Hyunjoo, Lee B, Sah H, Reverse Micelle-Based Microencapsulation of Oxytetracycline Hydrochloride into Poly- d, l -Lactide- co -Glycolide Microspheres, Drug del, 2007; 14: 95-9.
19. Liu J, Gong T, Wang C, Zhong Z, Zhang Z, Solid lipid nanoparticles loaded with insulin by sodium cholate-phosphatidylcholine-based mixed micelles: Preparation and characterization, Int J Pharma, 2007; 340: 153-62.
20. Mohamed MI, Optimization of chlorphenesin emulgel formulation, The AAPS J, 2004; 6(3): 1-7.
21. Murthy TEGK, Kishore VS, Formulation and evaluation of transdermal gels of diltiazem hydrochloride, Indian J Pharma Edu Res, 2008; 42(3): 272-6.
22. Queiroz M, Marcelino NB, Ribeiro MV, Espindola LS, Cunha F, Silva MV, Development of gel with Matricaria recutita L. extract for topic application and evaluation of physical-chemical stability and toxicity. Latin American J Pharm, 2009; 28(4): 574-9.

23. Pisal S, Shelke V, Mahadik K and Kadam S, Effect of organogel components on in-vitro nasal delivery of propranolol hydrochloride, AAPS PharmSciTech, 2004; 5: 92-100.
24. Singh S, Gajra B, Rawat M, Muthu MS, Enhanced transdermal delivery of ketoprofen from bioadhesive gels, Pakistan J Pharma Sci, 2009; 22 (2): 193-8.
25. Nandgude T, Thube R, Jaiswal N, Deshmukh P, Chatap V, Hire N, Formulation and evaluation of pH induced in situ nasal gel of salbutamol sulphate, Int J Pharma Sci Nanotechnol, 2008; 1(2): 177-83.
26. Patel AR, Babaahmadi M, Lesaffer A and Dewettinck K, Rheological profiling of organogels prepared at critical gelling concentrations of natural waxes in a triacylglycerol solvent, J Agri food chem, 2015; 63(19): 4862-9
27. Ba W, Li Z, Wang L, Wang D, Liao W, Fan W, Wu Y, Liao F and Yu J, Optimization and evaluation of pluronic lecithin organogels as a transdermal delivery vehicle for sinomenine, Pharma Develop Technol, 2016; 21: 535-45.
28. Saha S, Shivarajakumar R, Karri VVSR, Pluronic Lecithin Organogels: An Effective Topical and Transdermal Drug Delivery System, Int J Pharma Sci Res, 2018; 9(11): 4540-50.
29. Shirsath SC, Patil PB, Mutha SS, Bhosale AV, Hardikar SR, A review of pluronic lecithin organogel (PLO) as a topical and transdermal drug delivery system, Res J Pharm Technol, 2009; 2(1): 1-7.
30. Alsaab H, Alzhrani RM and Boddu SH, Evaluation of the percutaneous absorption of chlorpromazine from PLO gels across porcine ear and human abdominal skin. Drug Develop Ind Pharm, 2016; 42: 1258-66.