Archives of Pharmaceutical Sciences and Research
Vol 13 Issue 2 125 - 131 June 2023
Review Article

Recent Developments in Microemulsion Based Transungual Delivery System

Anupama R, S. Rajarajan, Beny Baby, Tejas. R and K Ramesh

Department of Pharmaceutics and Industrial Pharmacy, Karnataka College of Pharmacy, Bangalore-560064

ABSTRACT

Transungual microemulsion is a new approach for the fungal infection of the nail . The topical therapy is preferred since the risk of systemic side effects is reduced. By literature information microemulsion transungual formulation will give information on microemulsion which is an isotropically transparent, thermodynamically stable dispersion of two immiscible liquids, such as oil and water, in the size range of 10 to 100 nm that is stabilised by surfactant and co-surfactant molecules they will helps to solubilize lipophilic drugs. The solubility study, construction of pseudo-ternary phase diagram and two preparation methods with Evaluation and Characterization of microemulsions for transungal delivery is described and some commercially available oral and topical preparations are listed. To enhance the transungual penetration physical, chemical, and mechanical techniques are used. Iontophoresis is a physical method to deliver therapeutic compounds across a membrane with the assistance of an electric field, Transungual Iontophoresis may improve drug diffusion through the moist keratin of a nail.

Keywords: Microemulsion, Transungual, Iontophoresis, pseudo-ternary phase diagram

INTRODUCTION

The term "*microemulsion*" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, in the range of 10–100 nm which is stabilized by an interfacial film of surfactants and co-surfactant molecules.(1) Microemulsions have more benefits over other formulations as topical drug delivery. They were used to increase solubility of drugs and to improve rate of absorption , Helps to solubilize lipophilic drug, Provides an aqueous dosage form for water insoluble drugs. Several authors have revealed that the use of microemulsion will increase the antimicrobial activity.(2)

The chronic fungal infection of the nail apparatus, the nail plate and nail bed is a more and more frequently emerging disease . The topical therapy is preferred since the risk of systemic side effects such as nausea, vomiting and liver dysfunction is reduced. However, it is quite difficult to achieve adequate bioavailability of the antifungal agents inside the nail after ungual application because it possesses a unique anatomical structure and special properties . The human nail apparatus comprises the nail plate and four specialized epithelia: the proximal nail fold, the nail matrix, the nail bed and the hyponychium (3)

Antifungals have been available in market in the form of cream, ointment, lotion, powder, and solutions. These formulations require high concentration of active agents to be incorporated for effective therapy because of their low efficacy. To overcome the limitations of conventional formulations there is a need of an effective system that can deliver the antifungals deep into the nail bed. However, the development of a formulation for safe and effective topical delivery is still under in fancy.(4)

Materials used for the preparation of microemulsion;

Surfactant

The surfactant, also called emulsifier or amphiphilic compound, plays an important role in microemulsion preparation by reducing the interfacial tension between the hydrophobic tails of the surfactant and the polar solvent reduce the overall free energy of the system, thus facilitating microemulsion formation.

Oils

hydrocarbon mineral oils have been the basis of many microemulsion studies, mainly due to ease of microemulsion formation and also probably due to the purity of the hydrocarbon systems.

Co-surfactant

The cosurfactant has the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface, thereby increasing the entropy of the system. (5)

Methods

Solubility study

The solubility of the drug in various oils , surfactants and co-surfactants is an essential step for the micro emulsion formulation .So before starting the phase diagram one must have to choose the oil, surfactant and co-surfactant in which the drug shows maximum solubility. Drug powder was added in excess to each of the oils, surfactants , cosurfactants and then vortexed for mixing. After vertexing the samples were kept for 72 hours at ambient temperature for attaining equilibrium. The equilibrated samples were then centrifuged at 5000 rpm for 30 minutes to separate the undissolved drug. the supernatant was taken and diluted with methanol and observed by UV spectrophotometric method.(6)

Construction of pseudo-ternary phase diagram

The water titration method was used for the construction of pseudoternary phase diagrams . From the solubility study results the oil, surfactant and co-surfactant were selected respectively for the construction of the phase diagram. The mixture of surfactant and co-surfactant (Smix) was prepared in a different ratio (1:1, 1:2, 1:3, 2:1, and 3:1). This different Smix was mixed with oil in serial dilution from 1:9 to 9:1 respectively and titrated using an aqueous phase till the homogeneous, clear, and transparent microemulsion solution was obtained. All these batches were kept at room temperature for 48 h to observe the stability of the formulation before constructing a pseudo-ternary diagram. The microemulsion batches were analyzed using Chemix School 3.51 software for plotting the pseudo-ternary phase diagram.(7)

Microemulsion preparation

The formulation of microemulsion include two main method, these are First method by Phase Inversion Method and Phase Titration Method

Phase Inversion Method

In the phase inversion method phase inversion of microemulsions occurs by addition of excess amount of the dispersed phase. During phase inversion quick physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. For non-ionic surfactants, this can be completed by changing the temperature, forcing a transition from oil in water microemulsion at low temperatures to water in oil microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is also known as phase inversion temperature (PIT) method. Other than temperature, other parameters such as pH value or salt concentration may be considered more effectively instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. By increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point.

Phase Titration Method

Microemulsions are formulated by the spontaneous emulsification method (phase titration method) and can be shown with the help of phase diagrams. The phase diagram is a useful approach to study the complex of interaction that can occur when different components are mixed. depending on the chemical composition and concentration of each component. The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspects of the study.(8) ME formulae were selected at different component ratios according to the microemulsion areas in phase diagrams.(2)The ME was prepared by the water titration method. The calculated amount of drug (5 mg/mL) was added to the oily phase of ME and magnetically stirred until dissolved. This was followed by the addition of Smix in a fixed proportion to produce a clear mixture. Then, a defined proportion of water was added and stirred to produce clear micro emulsion.(9)

Evaluation and Characterization of microemulsions for transungal delivery

Visual inspection

The formulation were inspected visualy for optical transparency and homogeneity by observation against strong light. The systems were also checked for the presence of undissolved drug, fluidity, and phase separation.(2)

Measurement of pH

The pH values of microemulsions were measured at laboratory temperature (23 ± 2^0C) using a calibrated pH meter. The electrode was directly immersed into the formulation and waited for reading to get equilibrated.(10)

Viscosity measurement

The viscosity is determined by using Brookfield viscometer. The spindle number 2 was dipped in microemulsion and rotated at 5, 10, 20, and 50 rpm at room temperature.(11)

Morphological characterization

Transmission electron microscopy was employed to study structure and morphology of ME. A drop of diluted sample was directly placed on holey film grid, was allowed to dry and examined under the microscope.(12)

In vitro drug release study

In in vitro diffusion study, the diffusion medium used was phosphate buffer pH 7.4. Assembly of diffusion cell for in-vitro diffusion studies the diffusion cell was designed as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm2 was used for in-vitro permeation studies. The egg membrane was mounted on the cell carefully so as to avoid the entrapment of air bubble under the egg membrane. Intimate contact of egg membrane was ensured with receptor fluid by placing it tightly with clamp. The diffusion cells were placed on the receptor compartment with magnetic stirrer. Then add 1gm of microemulsion to the donor compartment and 200ml of phosphate buffer pH 7.4 to receptor compartment. The speed of the stirrer and temperature was kept constant throughout the experiment. With the help of 1ml pipette 1 ml of sample was withdrawn at a time interval of 60 min (0 to 6hrs) from receptor compartment and same volume was replaced with receptor medium in order to maintain sink condition. The samples were appropriately diluted and the absorbance was measured at 262 nm using UV spectrophotometer.(11)

Ex vivo permeation study

Freshly collected bovine hoof membrane was obtained from the local slaughterhouse. The bovine hoof membrane is prominently used in ex vivo nail permeation study. The bovine hoof membrane resembles human nail plates for releasing keratin protein upon incubation with keratinase as per the literature report. The

bovine hoof membrane was immersed in a pH 7.4 phosphate buffer solution for 24 h before use. Ex vivo permeation study was performed using a modified Franz diffusion cell (effective diffusion area 2.54 cm^2). The bovine hoof membrane was carefully mounted between the donor and receptor compartments. The receptor chamber was filled with 5 mL phosphate buffer pH 7.4 solution and was maintained at 32±0.5◦C with continuous magnetic stirring at 50 rpm. The microemulsion (5.03%w/w) have simultaneously experimented. At predetermined time intervals (0.5, 1, 2, 4, 8, and 12 h), samples were withdrawn and filtered through a 0.45 μm pore size cellulose membrane filter and were analyzed by the HPLC method . After each sampling, an immediate replacement was done with a fresh buffer solution into the receptor chamber. The following equation was used for determining the cumulative amount of drug permeated through the membrane:

$$Qn = \frac{CnxV0 + \Sigma n-1\ i = 1\ CixVi}{S}$$

Where Cn is the drug concentration of the receptor medium after each sampling time, Ci is the drug concentration for ith sample, V0 and Vi are the volumes of the receiver solution, and sample, respectively, and S is the effective diffusion area . The data were plotted in the form of cumulative permeation of drugs in the receptor chamber versus time (h) for all the tested formulations. The ex vivo study data were extrapolated to various kinetic models to find out the order of drug release viz. zero-order (cumulative percentage of drug release versus time), first-order (log cumulative of drug remaining versus time), Higuchi (cumulative percentage of drug release versus square root of time), Korsmeyer-Peppas (log cumulative percentage drug release versus log time) and Hixon-Crowell (cube root of drug percentage remaining in formulation versus time.(7)

Transungual

Nail infections have a propensity to reoccur, infrequently resolve on their own, and can significantly affect quality of life. Due to the deep-seated, persistent nature of this type of infection and the fact that topically applied medications have not consistently been proved to adequately penetrate the nail plate, oral antifungal therapy continues to be a mainstay. As opposed to oral antifungal therapy, topical therapy is highly preferred because of its localised effects, which should reduce any negative systemic drug effects and reactions.(13)

Commercially Available Oral and Topical Preparations.(14)

Formulation type	Commercial Product	API	Company
Nail lacquers	Loceryl® Eco Nail™ Ciclopoli® Curanil® Nailon	Amorolfine (5%) Econazole (5%) Ciclopirox (8%) Amorolfine (5%) Ciclopirox amine (8%)	Galderma, Switzerland. Macrochem, Massachusetts. Polichem, Switzerland Galderma, Switzerland. Protech Biosystem, India.
Topical solution	Penlac® Jublia® Trosyl® Kerydin®	Ciclopirox (8%) Efinaconazole (10%) Tioconazole Tavaborole (5%)	Aventis Pharma, India. Bausch Health, United states. Pfizer Ltd., United Kingdom. Anacor Pharmaceuticals, United states.
Nail film	Umecta ®	Urea (40%)	Pharmaceuticals, United states.
Nail patch	Zalain®	Sertaconazole nitrate	Labtec GmbH, Germany.

Nail paint	Phytex® Monphytol®	Salicylic acid Methyl undecenoate	Pharmax Healthcare Ltd. LAB. United Kingdom.
Cream	Loprox® Avage® Ertaczo®	Ciclopirox (1%) Tazarotene Sertaconazole nitrate (2%)	Sanofi-Aventis, France. Allergan Inc., United states. Ortho Neutorgena, United states
Gel	Tazorac® Zorac®	Tazarotene (0.1%) Tazarotene (0.05% & 0.1%)	Allergan Inc., United states. Allergan Inc., United states

Methods to enhance the transungual penetration

Since the nail has about 25 layers of densely connected keratinized cells and is 100 times thicker than the stratum corneum, effective penetration through the nail is not as simple. Along the nail, the thickness of the toe nail rises.

The nail barrier's strength has been reduced through physical, chemical, and mechanical techniques.

Methods

1. Physical - Iontophoresis, Etching, Carbon dioxide laser, Hydration and occlusion ,Micro needle

2. Chemical - Sulfhydryl group compounds, Keratolytic enhancers, Enzymes

3. Mechanical - Nail abrasion, Nail avulsion(15)

Iontophoresis

In order to transfer therapeutic chemicals into and across a biological membrane or tissue, iontophoresis is used by applying an electric current to the membrane or tissue. The idea of utilising an electric in the delivery of drug was introduced in 18th century while the 19th century saw substantial advancements in distribution methods. Drug distribution to several tissues and membranes, including the skin, nails, eyes, buccal cavity, and tympanic membrane, has been improved via iontophoresis.(16)

Mechanisms of iontophoresis

The processes of iontophoresis-enhanced transport include electro-permeabilization (field-induced membrane modification and an increase in membrane permeability), electroosmosis (convective solvent flow), and electrophoresis (direct field effect or Nernst-Planck effect).(17)

Transungual iontophoresis

In iontophoresis, a substance is delivered across a membrane using an electric field (also known as an electromotive force). Iontophoresis may improve drug diffusion through the moist keratin of a nail.(18) It has been effectively used to improve drug distribution over the nail plate by iontophoresis. Delgado-Charro has addressed specifics on iontophoresis's theoretical concepts and its use in transungual drug delivery. It has been proven that iontophoresis effectively improves the transungual distribution of charged ciclopirox, salicylic acid, and terbinafine using electrophoresis. The transungual distribution of uncharged griseofulvin and glucose by electroosmosis was also demonstrated to be improved by iontophoresis.(19) Hydration increases the nail matrix's pore size, which affectps ungual penetration. Hydrated nails have been observed to be more elastic and porous. This characteristic is used in iontophoresis-based studies to improve the penetration.(20)

CONCLUSION

From this review article it can be concluded that the development of transungual drug delivery by microemulsion technique can be a superior tool in the management of transungual drug delivery. By above literature information the transungual penetration of the active pharmaceuticals can be enhanced by microemulsion formulation Nail barrier's strength can been reduced through physical, chemical, and mechanical techniques. In that iontophoresis is one of the physical technique in which substance is delivered across a membrane using an electric field this will improve drug diffusion through the moist keratin of a nail.

Acknowledgement: Authors are thankful to Management and Director, Karnataka College of Pharmacy, Bangalore for their Extensive support to carry out this Review Work.

REFERENCES

1. Szumała P, Jungnickel C, Kozłowska-Tylingo K, Jacyna B, Cal K. Transdermal transport of collagen and hyaluronic acid using water in oil microemulsion. Int J Pharm. 2019;572(July).

2. Badawi AA, Sakran WS, Ramadan MA, El-Mancy SMS. Improvement of the microbiological activity of topical ketoconazole using microemulsion systems. J Drug Deliv Sci Technol [Internet]. 2012;22(6):473–8. Available from: http://dx.doi.org/10.1016/S1773-2247(12)50083-3

3. Naumann S, Meyer J, Kiesow A, Mrestani Y, Wohlrab J, Neubert RHH. Controlled nail delivery of a novel lipophilic antifungal agent using various modern drug carrier systems as well as in vitro and ex vivo model systems. J Control Release [Internet]. 2014;180:60–70. Available from: http://dx.doi.org/10.1016/j.jconrel.2014.02.013

4. Gunt HB, Kasting GB. Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. 2007;2:254–60.

5. Taylor P, Flanagan J, Singh H. Microemulsions : A Potential Delivery System for Bioactives in Food Microemulsions : A Potential Delivery System for Bioactives in Food. 2007;(May 2013):37–41.

6. Okore VC, Attama AA, Ofokansi KC, Esimone CO, Onuigbo EB. Formulation and evaluation of niosomes. Indian J Pharm Sci. 2011;73(3):323–8.

7. Agrawal V, Patel R, Patel M, Thanki K, Mishra S. Design and evaluation of microemulsion-based efinaconazole formulations for targeted treatment of onychomycosis through transungual route: Ex vivo and nail clipping studies. Colloids Surfaces B Biointerfaces [Internet]. 2021;201(February):111652. Available from: https://doi.org/10.1016/j.colsurfb.2021.111652

8. Plants M, Anti W, Activity C. International Journal of Universal. 2013;2(June):285–97.

9. Patel RB, Patel MR, Bhatt KK, Patel BG. Risperidone-loaded mucoadhesive microemulsion for intranasal delivery: Formulation development, physicochemical characterization and ex vivo evaluation. J Drug Deliv Sci Technol [Internet]. 2013;23(6):561–7. Available from: http://dx.doi.org/10.1016/S1773-2247(13)50085-2

10.Alam MA, Al-Janoobi FI, Alzahrani KA, Al-Agamy MH, Abdelgalil AA, Al-Mohizea AM. In-vitro efficacies of topical microemulsions of clotrimazole and ketoconazole; and in-vivo performance of clotrimazole microemulsion. J Drug Deliv Sci Technol [Internet]. 2017;39:408–16. Available from: http://dx.doi.org/10.1016/j.jddst.2017.04.025

11.Sabale V, Vora S. Formulation and evaluation of microemulsion-based hydrogel for topical delivery. Int J Pharm Investig. 2012;2(3):140.

12.Kansagra H, Mallick S. Microemulsion-based antifungal gel of luliconazole for dermatophyte infections: formulation, characterization and efficacy studies. J Pharm Investig. 2016;46(1):21–8.

13.Hafeez F, Hui X, Chiang A, Hornby S, Maibach H. Transungual delivery of ketoconazole using novel lacquer formulation. Int J Pharm [Internet]. 2013;456(2):357–61. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.08.082

14.Aggarwal R, Targhotra M, Sahoo PK, Chauhan MK. Onychomycosis: Novel strategies for treatment. J Drug Deliv Sci Technol. 2020;57(February).

15.Kumar K, Fateh V, Ahmad S, Pant NC, Pandey S. Review Article DRUG DELIVERY ACROSS HUMAN NAIL : A NEWER APPROACH. 2014;3(6):1225–30.

16.Hao J. Topical iontophoresis for local therapeutic effects. J Drug Deliv Sci Technol [Internet].

2014;24(3):255–8. Available from: http://dx.doi.org/10.1016/S1773-2247(14)50043-3

17.Hao J, Smith KA, Li SK. Iontophoretically Enhanced Ciclopirox Delivery into and Across Human Nail Plate. J Pharm Sci [Internet]. 2009;98(10):3608–16. Available from: https://www.sciencedirect.com/science/article/pii/S0022354916330982

18.Muralidhar P, Bhargav E, Reddy KR. Transungual Drug Delivery : An Over View Transungual Drug Delivery : An Over View. 2017;(August).

19.Elsayed MMA. Development of topical therapeutics for management of onychomycosis and other nail disorders : A pharmaceutical perspective. J Control Release [Internet]. 2015;199:132–44. Available from: http://dx.doi.org/10.1016/j.jconrel.2014.11.017

20.Akhtar N, Sharma H, Pathak K. Onychomycosis: Potential of Nail Lacquers in Transungual Delivery of Antifungals. Scientifica (Cairo). 2016;2016.