IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
April 2023 Vol.:27, Issue:1

Development and Evaluation of Microemulsion for Transdermal Delivery of Lornoxicam

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

[1]Kashiram Kushwaha, [2]Pushpendra Ahirwar, [3]*Ravish Sahu

[1,2,3]Vedic Institute of Pharmaceutical Education &Research College, Sagar M.P. 470001 India.

Submitted: 25 March 2023
Accepted: 31 March 2023
Published: 30 April 2023

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Lornoxicam, Microemulsion, Nanoemulsion, Transdermal, Skin Penetration, Penetration Enhancer, Nanosystem.

ABSTRACT

Nano systems such as microemulsions (ME) and Nanoemulsions (NE) offer considerable opportunities for targeted drug delivery to and via the skin. ME and NE are stable colloidal systems composed of oil and water, stabilized by a mixture of surfactants and cosurfactants, that have received particular interest as topical skin delivery systems. There is considerable scope to manipulate the formulation components and characteristics to achieve optimal bioavailability and minimal skin irritancy. This includes the incorporation of established chemical penetration enhancers to fluidize the stratum corneum lipid bilayers, thus reducing the primary skin barrier and increasing permeation. This review discusses Nanosystems with utility in skin delivery and focuses on the composition and characterization of ME and NE for topical and transdermal delivery. The mechanism of skin delivery across the stratum corneum and via hair follicles is reviewed with a particular focus on the influence of formulation.

1. INTRODUCTION

1.1 Transdermal Drug Delivery Systems

One of the most promising drug application techniques at the moment is transdermal drug delivery. The list of therapeutic compounds that can be administered to the systemic circulation via the skin is being expanded to include an increasing number of medications. Transdermal drug delivery systems (TDDS) are self-contained discrete dose forms that release the medication(s) to the systemic circulation at a controlled pace through the skin when applied to intact skin. Since several years ago, it has been possible to administer drugs via unbroken skin. The idea of delivering drugs through the skin dates back to prehistoric times. Castor oil plant bark was ingested with water and applied to an aching head by Ebers Papyrus. In the past, the med-plaster might be regarded as the original transdermal drug delivery technology, and this medicated plaster quickly gained popularity in Japan as an over-the-counter medication dose form.

Transdermal delivery prevents pulsed entry into the systemic circulation, an often-unwanted side effect, and not only offers controlled, continuous drug administration. It also enables continuous input of medications with short biological half-lives.

For systemic effects, TDDS makes it easier for therapeutic doses of pharmacological compounds to pass through the skin and into the bloodstream.

Two parameters are taken into account while creating a transdermal delivery system: obtaining sufficient flux over the skin and reducing the lag time in skin permeation. The introduction of various chemical skin enhancers into the vehicle is one method of getting around this restriction. Another tactic is to select a suitable vehicle that matches the medication being administered via the cutaneous route.

When applied topically, microemulsions can interact with the stratum corneum to alter the lipid layers' structural organization, improving transdermal medication permeability and serving as a penetration enhancer.

1.2 Human Skin

Transdermal is a very effective alternate delivery technique. A typical adult's skin has a surface area of around 2 m2, and it gets about one-third of the blood that circulates through

the body. It is required to comprehend the skin in order to transport medicine into the body through the transdermal layer of the skin.

The skin serves as the body's outermost layer. It protects the underlying muscles, bones, ligaments, and internal organs in humans and is the largest organ of the integumentary system. It is made up of numerous layers of epithelial tissues.

1.3Anatomy of the Skin

The skin is composed of two main structural components. The epidermis is the outer, thinner layer that is made up of epithelium. The inner, denser, connective tissue layer known as the dermis is joined to the epidermis. There is a subcutaneous layer underneath the dermis. The superficial fascia or hypodermis are other names for this layer. Areoles and adipose tissues make up this tissue. The skin is fixed to the subcutaneous layer by fibers from the dermis that descend there. In turn, the subcutaneous layer adheres to the underlying organs and tissues. Epidermis, Dermis, Hypodermis (subcutaneous adipose layer).

1.4 Drug Delivery Routes Across Human Skin

Three possible routes exist for drug molecules in contact with the skin's surface to enter the body: directly across the stratum corneum, through the sweat ducts, and through the hair follicles and sebaceous glands (together known as the shunt or appendageal route) (Fig 2). Scientists have argued over the years (6–8) about the relative importance of transport via the stratum corneum against the shunt or appendageal routes, which is further confounded by the lack of an appropriate experimental model that would allow for the separation of the three paths.

In vivo tests frequently use hydrated skin or epidermal membranes to prevent appendages from closing due to hydration-related edema. Schoenlein and colleagues argued that the steady-state penetration of polar molecules and flux of large polar molecules or ions that have difficulty diffusing over the entire stratum corneum were caused by a follicular shunt channel.

1.5 Microemulsions

Hour and Schulman first used electron microscopy to identify tiny emulsion-like formations in 1943, and they later came up with the term "microemulsions." While the diameter of droplets in a kinetically stable emulsion is >500 nm, microemulsions are isotropic,

thermodynamically stable transparent (or translucent) systems of oil, water, and surfactant, commonly in combination with a co-surfactant. A microemulsion has benefits as a carrier for poorly soluble medications in water because of the microscopic droplets. These homogeneous systems are all low-viscosity fluids that can be created with a variety of surfactant concentrations and oil-to-water ratios.

1.5.1 Microemulsion as Drug Delivery Systems

- **Oral Medication Administration**

The oral route is the most used drug administration strategy since it is convenient and has a high patient compliance rate.

- **Parenteral Of Medication**

Microemulsion systems must be made using nontoxic, biocompatible components for parenteral application. Whereas water in oil microemulsion systems would be ideal for maximizing the delivery of hydrophilic drug molecules that are susceptible to harsh gastrointestinal conditions, oil in water microemulsion systems would be excellent for improving weakly solubility water-soluble drug molecules.

- **Ocular Drug Administration**

90% of the ophthalmic formulations on the market are aqueous solutions, primarily because they are straightforward and convenient. However, one of the main disadvantages of topical ocular medication delivery is substantial loss brought on by quick precorneal drainage and high tear turnover.

- **Transdermal Drug Administration**

Systemic circulation is one of the first channels to be utilized with microemulsion devices.

- **Topical drug delivery**

The delivery systems for topical medications, which are frequently used to treat skin problems, have advanced from crude mixtures. Advances in percutaneous absorption, product design based on a growing mechanistic understanding of interactions between drugs, products, and skin, related investigations, and a quality-by-design framework have all aided in their development. Drugs are transported from a topical product to a local target site via

diffusion, metabolism, and dermal circulation before being eliminated from the body and deeper tissues. Dermal Physiologically Based Pharmacokinetics,

1.5.2 Microemulsion Formulation Ingredients

There are many oils and surfactants that can be utilized as microemulsion system components, but their use is restricted due to their toxicity, potential for irritability, and unknown mode of action. In order to produce mild and non-aggressive microemulsions, one must select biocompatible, non-toxic, and clinically acceptable materials. Emulsifiers must also be used in the proper concentration range. Thus, the use of generally recognized as safe (GRAS) excipients is stressed.

Oil Phase: The capacity of the oil component to infiltrate and subsequently swell the tail group region of the surfactant monolayer affects curvature. Compared to long-chain alkanes, short-chain oils penetrate the tail group region more deeply, causing this region to expand and exhibit more negative curvature (and reduced effective HLB). Both saturated (such as lauric, myristic, and capric acid) and unsaturated (such as oleic, linoleic, and linolenic acid) fatty acids have long been researched for their ability to increase penetration. As the oil phase, fatty acid esters like the ethyl and methyl esters of lauric, myristic, and oleic acids have also been used. O/W microemulsions are preferred for solubilizing lipophilic medicines.

Surfactants: The chosen surfactant must have the ability to reduce interfacial tension to a very low value, which facilitates the dispersion process during the preparation of the microemulsion, and must provide a flexible film that can easily deform around the droplets. It must also have the right lipophilic character to provide the correct curvature at the interfacial region.

Co-surfactants: In the majority of circumstances, single-chain surfactants are unable to adequately lower the o/w interfacial tension to allow a microemulsion to develop on its own. Co-surfactants give the interfacial film the flexibility it needs to adopt the many curvatures needed to create microemulsion throughout a broad range of compositions.

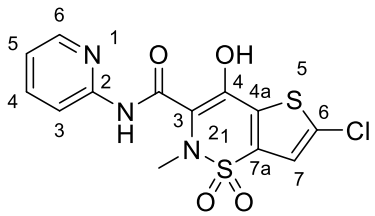
Oil in Water Microemulsions: The aqueous phase is continuously mixed with oil droplets. The o/w systems are intriguing because by solubilizing a hydrophobic medication in the interior oil droplets, they make it more soluble in an aqueous-based environment. Because hydrocarbon oils are more polar than small/medium molecular volume oils, most medications tend to prefer them over hydrocarbon oils.

Water in Oil Microemulsions: The continuous oil phase contains scattered water droplets. The continuous phase of oil surrounds the water droplets in water-in-oil microemulsions. The surfactant's polar head groups face the water droplets in these "reverse-micelles," while the fatty acid tails face the oil phase.

Bi-continuous Microemulsions: The system has interspersed microdomains of water and oil. In a bicontinuous microemulsion system, the phases of water and oil are both continuous. A "sponge phase" is created by the intertwining of irregularly shaped oil and water channels.

1.6 DRUG PROFILE

One of the NSAIDs in the oxicam class, lornoxicam (brand names Xefo, Xafon, Lorcam, Acabel) acts in part by non-selectively inhibiting cyclo-oxygenase-1 and -2 to generate analgesic and antipyretic effects. Osteoarthritis, rheumatoid arthritis, acute lumbar-sciatica pain, and postoperative pain management are the most common conditions for which it is recommended. There are several preparations, such as 4 mg or 8 mg injectable (intravenous or intramuscular) or oral (standard or quick-release) preparations. The usual oral preparation takes 1 to 2 hours to reach its peak plasma concentrations, whereas the quick-release oral preparation and intramuscular injection take about 30 minutes. 90% of oral formulations are bioavailable. The plasma half-life of lornoxicam, which is metabolized by cytochrome P450 2C9, is 3 to 4 hours.

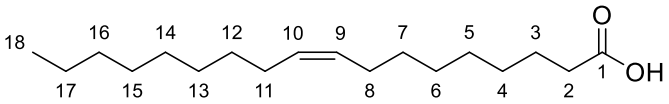


LORNOXICAM

Pharmacological effects: By inhibiting the enzyme cyclooxygenase, lornoxicam prevents the formation of prostaglandins. Both isoforms are inhibited by lornoxicam at the same concentrations, i.e., COX-1 inhibition: COX-2 inhibition = 1. With treatment of 4 mg twice daily, the ratio of plasma to synovial fluid AUC for lornoxicam is 0.5.

Oleic Acid

Oleic acid is the most prevalent fatty acid and is found in all oils and fats, at least partially. It is the main acid produced by saponification in oils such as olive, palm, peanut, and sunflower. Like other fatty acids, oleic acid, CH3(CH2)7CH=CH(CH2)7CO2H, does not naturally occur in the free state but is typically found as a glycerol ester.



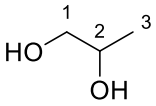
Oleic Acid

Pharmacological action: Oleic acid is utilized in foods and topical medicinal preparations as an emulsifier. It has been employed as a carrier in soft gelatin capsules, as a penetration enhancer in transdermal formulations, and to increase the bioavailability of medicines that are weakly water-soluble.

According to some reports, oleic acid acts as an ileal "break" that delays the passage of luminal contents through the distal part of the small intestine. Several parenteral formulations that are administered via the intramuscular route use oleic acid as a carrier. It has also been used to prepare microemulsions containing cyclosporine and as a solvent for medications created as biodegradable capsules for subdermal implantation.

Propylene Glycol

A synthetic liquid material that absorbs water is called propylene glycol. Furthermore, polyester compounds and the foundation for deicing solutions are made with propylene glycol. When a leak could result in contact with food, the chemical, food, and pharmaceutical industries utilize propylene glycol as an antifreeze. Propylene glycol is a food additive that is "generally recognized as safe" by the Food and Drug Administration (FDA). 1,2-dihydroxy propane, 1,2-propanediol, methyl glycol, and trimethyl glycol are further names for propylene glycol. At normal temperatures, propylene glycol is a transparent, colorless, slightly syrupy liquid. Propylene glycol can exist as a vapor in the air, but it needs to be heated or vigorously shaken in order to do so. Propylene glycol has almost little flavor or odor.



propane-1,2-diol

As a solvent, extractant, and preservative in numerous parenteral and nonparenteral preparations, propylene glycol has grown in popularity. It dissolves a wide range of materials, including corticosteroids, phenols, Sulfa medications, barbiturates, Vitamins (A and D), most alkaloids, and many local anesthetics, making it a better general solvent than glycerine. It is comparable to ethanol in terms of antiseptic properties and to glycerin in terms of effectiveness against molds.

TWEEN-20

In order to create stable oil-in-water pharmaceutical emulsions, hydrophilic non-ionic surfactants called polysorbates with 20 units of oxyethylene are frequently used. Used as wetting agents in the creation of oral and parenteral suspensions. Used as emulsifying agents for a variety of substances, including essential oils and oil-soluble vitamins.

2. PRE-FORMULATION STUDIES

Preformulating is a stage of the development process when the physical, chemical, and mechanical characteristics of the drug material are studied in order to create a dosage form that is efficient, stable, and secure. In order to properly develop the medication delivery system and characterize the drug, pre-formulation studies are crucial. The formulation research that this project utilized included,

2.1 Melting Point

A column of dry powder between 2.5 and 3.5 mm in diameter is charged into a capillary tube that is sealed at one end. The powder is packed as tightly as possible by mild tapping on a solid surface. According to the standard operating procedure, the device is used. Heat is applied to the block until it reaches a point that is roughly 30 °C below the predicted melting point. After inserting the capillary tube into the heating block, the temperature is raised by about 1 to 2 degrees Celsius per minute until the melting process is complete.

2.2 Solubility Studies

Separately suspended 10 mg of the medication in 10 ml of various solvents at room temperature in tubes that were tightly capped and shaken. Two medicines' solubility characteristics in various solvents.

2.3 Hygroscopic Nature

Two grams of the test specimens were precisely weighed in Petri dish, and the weight was recorded. The test specimens were then stored at ambient temperature for seven days while one was placed in an environment stability testing chamber with 75% RH at 40°C. After seven days, the specimen was weighed, and the weight change was recorded.

2.4 UV-Absorption

The maxima of absorption were discovered for medication identification. To learn more about the chromophore portion of the molecules, specific information has been gleaned using ultraviolet-visible spectrophotometry. When exposed to light in the visible and ultraviolet regions of the spectrum, organic molecules in solutions absorb light of a certain wavelength depending on the type of electronic transition involved in the absorption.

3. FORMULATION DEVELOPMENT

The correct dosage form and a stable formulation must be chosen as the main goals of pharmaceutical development studies. These studies provide a thorough explanation of every step taken in the creation of the finished method. Such information aims to identify crucial process variables that must be managed in order to produce a product of consistent, repeatable quality.

3.1 Selection of Oils

100 mg of lornoxicam was properly weighed into a 25 ml glass beaker with around 10 g of oil, and the mixture was then stirred at a moderate pace with a magnetic stirrer to dissolve the medication. Another 10 mg of lornoxicam was added when the medication had completely dissolved, and stirring was continued. Drug addiction was kept up until a saturated solution was attained. Finally, a UV spectrophotometer set to 377 nm was used to calculate the total amount of medication consumed. Oleic acid was discovered to have consumed the greatest quantity of lornoxicam, making it the vehicle of choice for the microemulsion oil phase.

S.no.	Drug solubility (in mg/10g of oil)	Oils
1	120	Olive oil
2	150	Castor oil
3	140	Isopropyl myristate
4	120	Isopropyl palmitate
5	180	Oleic acid

3.2 Co-surfactant and surfactant selection

Several nonionic surfactants, including span 20, tween 20, and co-surfactants including propylene glycol, isopropyl alcohol, and b-butanol, were titrated because they do not ionize to a significant level in the solution and are very compatible with both anionic and cationic chemicals. Ultimately, Tween-20 and propylene glycol were chosen as the system's optimal co-surfactant and surfactant, respectively.

Surfactant: co-surfactant	Concentration ratio	Appearance
Tween-20: propyleneglycol	1:1	Clear
	2:1	Clear
Tween-20: isopropylalcohol	1:1	Slightly cloudy
	2:1	Clear
Tween-20: n-butanol	1:1	Cloudy
	2:1	Clear
Span-20:propylene glycol	1:1	Clear
	2:1	Cloudy
Span-20:isopropyl alcohol	1:1	Slight cloudy
	2:1	Cloudy
Span 20:n-butanol	1:1	Cloudy
	2:1	Cloudy

3.3 Trial Compounds

A variety of test formulations were developed, and their physicochemical characterization and visual evaluation were evaluated. Get the formulation that is optimized at last.

The following recipe was used to create the microemulsion experimental formulations. Each trial formulation employed a different ratio of surfactant and co-surfactant, which was researched to have a controlled effect for a 24-hour period.

Formulation of trial batch I (F1-F5) Surfactant: co-surfactant (1:1)

S.no	Ingredients	Formulations				
		F1	F2	F3	F4	F5
1	Lornoxicam (mg)	10	10	10	10	10
2	Oleic acid (%w/v)	2	2	2	2	2
3	Tween-20 (%w/v)	1	2	3	4	5
4	Propylene glycol (%w/v)	1	2	3	4	5
5	Distilled water (%w/v)	26	24	22	20	18
6	Final volume (%w/v)	30	30	30	30	30

4. RESULTS

4.1 Melting Point Determination

Drug	*Melting point	Normal range
Lornoxicam	240 ± 0.145	239-241

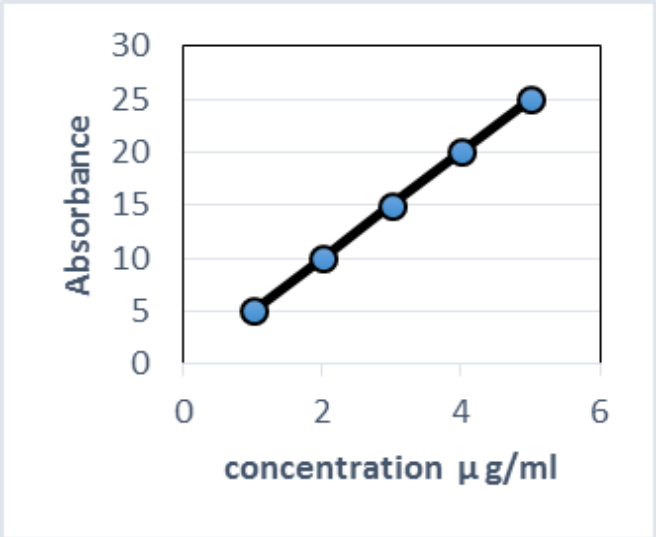
4.2 Solubility

S. No	Solvent	Solubility
1.	Distilled water	Slightly Soluble
2.	Phosphate buffer (pH 7.4)	Very Soluble
3.	Methanol	Very Soluble
4.	Ethanol	Slightly Soluble
5.	Chloroform	Slightly soluble
6.	0.1N NaoH	Very soluble

4.3 Hygroscopic Nature

At Room Temperature	75% RH at 40
Sample No-1	Sample No-1
Weight Gain Observed-Nil	Weight Gain Observed-Nil

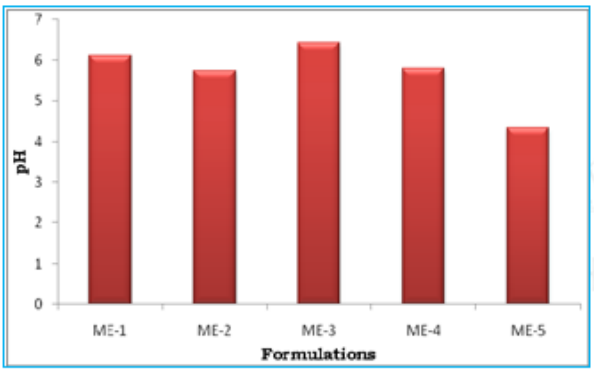
4.4 UV-Absorption



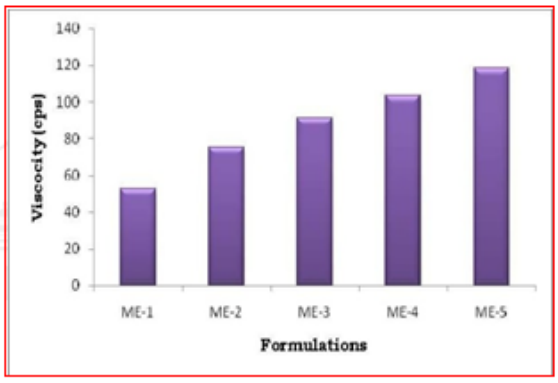
4.5 Characterization of Microemulsions

Appearance of Formulations

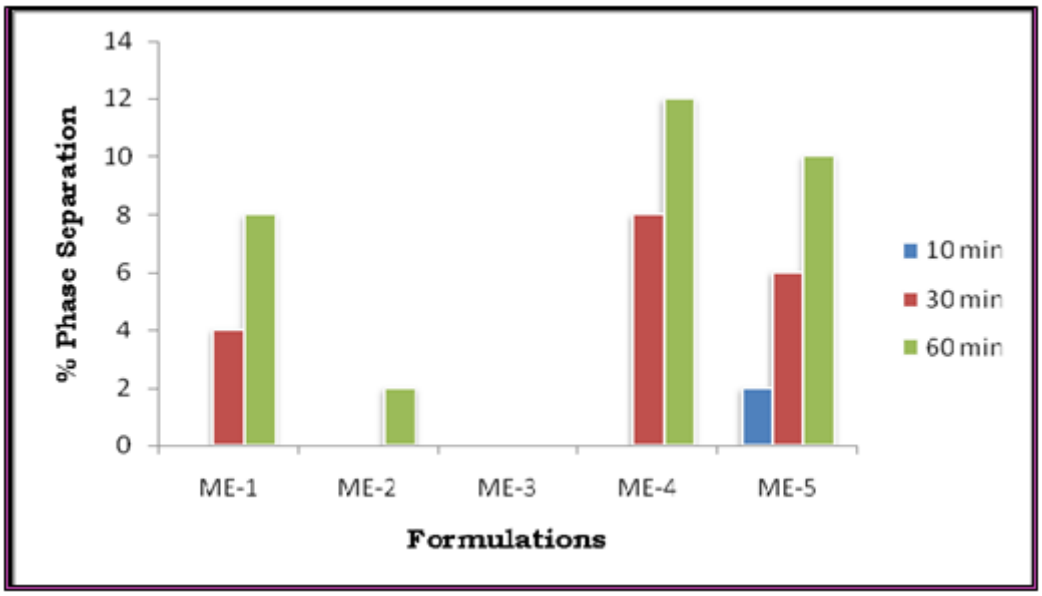
Formulation	Appearance
ME-1	Milky
ME-2	Opalescent
ME-3	Clear
ME-4	Milky
ME-5	Milky



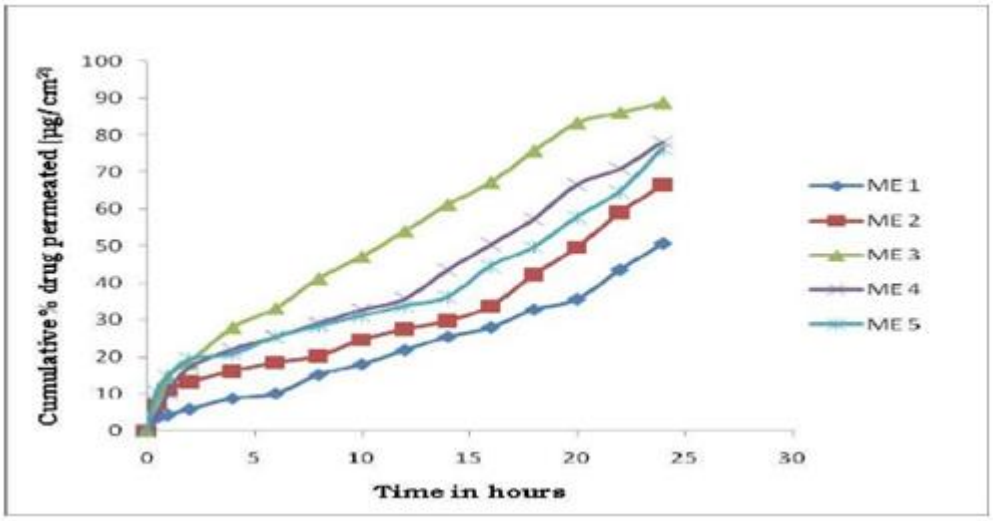
4.6 pH determination



4.7 Comparative Viscosity Values of Formulations



4.8 comparative drug content



4.9 Comparative *in vitro* Skin permeation rate of Lornoxicam Microemulsions

5. DISCUSSION

Microemulsion system transdermal delivery is made up of non-irritating, pharmaceutically approved components. Oleic acid was used as the oil phase, tween-20 was used as the surfactant, and propylene glycol was used as the co-surfactant to create the microemulsion.

Several oils, surfactants, and co-surfactants were evaluated to choose the best ingredients for microemulsions with good solubility and great skin penetration of lornoxicam. Oleic acid had the maximum lornoxicam solubility, followed by olive oil, castor oil, isopropyl myristate, and isopropyl palmitate.

Oleic acid is a model skin permeation enhancer that increases skin permeability via two mechanistic scenarios: (a) lipid fluidization and (b) lipid phase separation. Oleic acid makes it easier to penetrate the skin by reducing the fluidity of the stratum corneum. The formulation significantly accelerates the drug's thermodynamic activity and the release and penetration of the medication into the skin.

Non-ionic surfactants were chosen because they typically cause less skin irritation and are less harmful. The O/W kind of microemulsion's HLB value (9- 12). The needed HLB for the O/W type of emulsion for oleic acid (17), the HLB value of Tween-20 (16.7), and the HLB value of span-20 (20) (8.6). To achieve a superior penetration profile, the hydrophilic non-ionic surfactant Tween-20 was used to create these microemulsion systems. While other co-surfactants including butanol, ethanol, and isopropyl alcohol can be employed in place of

propylene glycol, it was discovered that propylene glycol provided the clarity and cumulative percent release that were required.

Lornoxicam may also partially solubilize in the exterior phase due to the surfactant and co-surfactant that may exist in each phase. The release of lornoxicam from the internal phase can replace any loss of lornoxicam that occurs from the exterior phase as a result of penetration into the skin. However, the oily concoctions of oleic acid, tween-20, and propylene glycol enhanced the solubility of the drugs. Final ratios of surfactants-cosurfactants were determined following comprehensive screening for physical properties and appearance.

The experimental formulations in the ratios (1:1, 2:1) in Tables 17 and 18 were chosen in order to determine the ideal ME formulation that contains oleic acid, Tween -20, and propylene glycol. By adjusting the amount of surfactant/co-surfactant, (F1-F10) trial formulations of microemulsions in the ratios of 1:1 and 2:1 was created.

Stable microemulsions were not generated in the tested formulations' 1:1 and 2:1 ratios. Using ocular observation, turbid and traditional emulsions. Ten experimental formulations were chosen, and one (F8) formulation was chosen on a 2:1 ratio for formulation optimization. Finally, the amount of oil was varied while the medication, surfactant, and co-surfactant were kept constant.

The produced formulations have gradually become more viscous, as seen by the microemulsion systems' viscosities (ME-1 to ME-5): 52.6 cps, 75.3 cps, 91.4 cps, 103.5 cps, and 118.2 cps. As would be expected from microemulsions, all samples had Newtonian flow characteristics. Because oil/water microemulsions have greater viscosities than those of water/oil systems in Table 33, it should be noted that the viscosity values tended to increase significantly as the water concentrations rose or the system changed from water to oil.

When centrifuged at 2000 rpm for 60 minutes, the centrifugation stress test of formulations ME-3 demonstrates good physical stability and no phase separation.

6. CONCLUSION

The study shows that the weakly water-soluble drug's solubility can be increased by using the microemulsion formulation. Oleic acid was chosen as the carrier for the microemulsion oil phase since it absorbed most lornoxicam. Tween-20 and propylene glycol were chosen as the best surfactant and co-surfactant in the right ratios.

The 24-hour controlled release formulation of lornoxicam microemulsion also lessened the negative effects brought on by oral traditional dosing.

A centrifuge stress test was used to characterize the chosen ME-3 formulation containing oleic acid (6%), Tween-20, and propylene glycol (30%). They are suitable for transdermal administration because of their viscosity and droplet particle size, and their pH values are within the physiological range.

The formulation's drug content was discovered to be 98.540.26%. The effectiveness of lornoxicam ME-3 for improved in vitro transdermal absorption through goat skin was highlighted in this investigation. The skin permeation of the ME-3 formulation follows non-fiction zero-order kinetics, which is suitable for the Korsemeyer-Peppas model (anomalous).

REFERENCES

1. Chien YW. Transdermal Drug Delivery and Delivery Systems, in: Y.W.Chien, Novel Drug Delivery Systems, 2nd ed, Chapter 7, Marcel Dekker,New York, 1992: 301-380.
2. Vyas SP and Khar RK. Targetted and Controlled Drug Delivery Novel Carrier System 1st ed., CBS Publishers and Distributors, New Delhi, 2002:411-447.
3. Hadgraft J, Guy R. In; Transdermal Drug Delivery, Marcel Dekker, Inc., NewYork and Basel,35,296.
4. Prausnitz MR, Mitragotri S, Langer R. Current Status and Futyre Potential of Transdermal Drug Delivery. Nature Reviews, Drug Discovery, 2004; (3):115-124.
5. Elias PM, Brown BE, Fritsch P, Goerke J, Gray GM, White RJ. J. InvestDermatol., 1979; 73: 339-48.
6. Govil SK, In; Tyle, P., Eds., Drug Delivery: Fundamentals and Application, Marcel Dekker, Inc., New York, 1998: 385-406
7. Jain NK. Contolled and Novel Drug Delivery, Cbs Publisher and Distributor,1st ed,100
8. Jayaswal SB, Sood R, the Eastern Pharmacist, 1987; 30(357): 47-50.
9. Hoar TP, Schulman JH, Transparent Water- In-Oil Dispersions, The Oleopathic Hydro-Micelle, Nature, 1943: 152; 102-103.
10. Schulman, J.H, Stoeckenius, W Prince, L.M, Mechanism Of Formation and Structure Of Microemulsions By Electron Microscopy, J. Phys. Chem, 1959: 63,1677-1680.
11. Vyas SP, Khar RK. Submicron Emulsions in Targeted and Controlled Drug Delivery, Novel Carrier System; Cbs Publishers and Distributors, New Delhi, 2002:(282-302).
12. Jadhav KR. et al., Applications Of Microemulsion Based Drug Delivery System. Curr Drug Deliv, 2006; 3(3):267-73.
13. Cordero J, Alarcon L, Escribano E, Obach R, Domenech J. A Comparative Study Of The Transdermal Penetration Of A Series Of Nonsteroidal Anti- Inflammatory Drugs, J. Pharm. Sci, 1997, 86:503–508.
14. Prince L M, Microemulsions. In: Lissant KJ (Ed), Emulsions And Emulsion Technology,New York : Marcel Dekker; 1974: 125-178.
15. Delgado-Charro MB, Iglesias-Vilas G, Blanco-Mendez J, Lopez QM, Marty Jp, Guy RH. Delivery Of A Hydrophilic Solute Through The Skin From Novel Microemulsion Systems. Eur J Pharm Biopharm 1997; 43: 37-42.
16. Celebi N, Kıslal O, Tarımcı N. The Effect of B- Cyclodextrin And Penetration Additives On The Release Of Naproxen From Ointment Bases. Pharmazie 1993; 48: 914-9179, Gasco M R, Gallarate M, Trotta M, Bauchiero L, Gremmo E, Chiappero O, J. Pharm. Biomed,1989; 7: 433.
17. Holmberg, K., Handbook of Applied Surface and Colloid Chemistry. 2002: Chichester, New York, Wiley.
18. Giustini MS, Murgia G, Palazzo. Does The Schulman's Titration Of Microemulsions Really Provide

Meaningful Parameters? Langmuir, 2004; 20(18):7381-4.
19. Giustini, M., et al., Microstructure and Dynamics of The Water-In-Oil Ctab/Npentanol/N-Hexane/Water Microemulsion: A Spectroscopic And Conductivity Study, Journal Of Physical Chemistry, 1996; 100(8): 3190-98.
20. Lawrence MJ, Rees GD. Microemulsion-Based Media As Novel Drug Delivery Systems, Adv Drug Deliv Rev, 2000; 45(1): 89-121.
21. Googman and Gilman's The Pharmacological Basis of Therapeutics, 11th Edition, 2005. P. 1415, Unit II, "Disease Of Organ System" 1304-1309