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MICROEMULSION FORMULATION AND OPTIMIZATION OF NABUMETONE FOR TOPICAL DELIVERY

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ABSTRACT: This research developing a transdermal delivery system, two primary criteria are achieving adequate flux across the skin and minimizing the lag time in skin permeation. Transdermal drug delivery systems facilitate the passage of therapeutic quantities of drug substances through the skin into the general circulation, enabling systemic effects. This method of topical administration offers advantages over other methods, such as avoiding hepatic first-pass metabolism and related toxicity effects, controlling the rate of delivery, and modulating the distribution of the drug in the systemic circulation. A transdermal delivery system using a microemulsion can be particularly effective. Microemulsions are composed of non-irritating, pharmaceutically acceptable ingredients. They can be prepared by the water titration method, using oleic acid as the oil phase, tween-20 as the surfactant, and propylene glycol as the co-surfactant. The selection of oils, surfactants, and co-surfactants is critical to ensuring good solubility and excellent skin penetration of the drug, such as piroxicam. Oleic acid is especially advantageous due to its dual mechanistic scenarios as a skin permeation enhancer: lipid fluidization and lipid phase separation. As a model skin permeation enhancer, oleic acid facilitates penetration into the skin by disrupting the fluidity of the stratum corneum. The thermodynamic activity of the drug in the formulation is a significant driving force for the release and penetration of the drug into the skin.

KEYWORDS: Transdermal delivery system, Adequate flux, Skin permeation, Lag time, Topical administration, Systemic effects and Hepatic first-pass metabolism.

I. INTRODUCTION

INTRODUCTION: Transdermal Drug Delivery Systems: Currently, transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. Transdermal drug delivery systems (TDDS) can be defined as self contained discrete dosage forms which, when applied to the intact skin, delivers the drug(s) through the skin at a controlled rate to the systemic circulation. The potential of using intact skin as the route of drug administration has been known for several years. The inspiration of using skin for delivery of drug is from ancient time. Ebers papyrus used the husk of castor oil plant bark imbibed with water placed on aching head. Historically, the medicated plaster can be viewed as the first development of transdermal drug delivery; this medicated plaster became very popular in Japan as over the counter pharmaceutical dosage form Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half- life and eliminates pulsed entry into systemic circulation, which often undesirable side effect. TDDS facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. In developing a transdermal delivery system, two criteriaare considered: one is achieving adequate flux across the skin and the other is minimizing the lagtime in skin permeation. One strategy overcoming this constraint is the incorporation of various chemical skin enhancers into the vehicle. Another strategy is a choice of an appropriate vehicle that corresponds to the drug being used for the dermal route of administration Concerning dermal application the microemulsions can interact with the stratum corneum changing structural rearrangement of its lipid layers and consequently increasing transdermal drug permeation and soact as penetration enhancer.[1,2]

Advantages of TDDS

- Avoidance of first pass metabolism Avoidance of gastro intestinal incompatibilityPredictable and extended duration of activity Minimizing
- Provides utilization of drugs with short biological half lifeNarrow therapeutic window

- Improving physiological and pharmacological response[3]

Drug Delivery Routes Across Human Skin

Drug molecules in contact with the skin surface can penetrate by three potential potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands, (collectively called the shunt or appendageal route), or directly across the stratum corneum(Fig 2). The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years (6-8) and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways. In vivo experiments tend to involve the use of hydrated skin or epidermal membranes so that appendagesare closed by the swelling associated with hydration. Scheuplein and colleagues proposed that a follicular shunt route was responsible for the presteady-State permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum.[4,5]

Factors Affecting Transdermal Permeation

Physicochemical factors:

A. Biological factors

1) Skin condition Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skinis better barrier but the above mentioned conditions affect penetration.
2) Skin age The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.
3) Blood supply Changes in peripheral circulation can affect transdermal absorption.

MICROEMULSION AS DRUG DELIVERY

Systems Oral drug delivery

The most common method for drug delivery is through the oral route as it offers convenienceand high patient compliance.

Parenteral Drug Delivery

Microemulsion systems intended for parenteral application have to be formulated using nontoxic and biocompatible ingredients. The oil in water microemulsion systems would be suitable to improve the solubility of poorly water soluble drug molecules whereas water in oil microemulsion systems would be best suited for optimizing the delivery of hydrophilic drug molecules that are susceptible to the harsh gastrointestinal condition.

Ocular Drug Delivery

Aqueous solutions account for around 90% of the available ophthalmic formulations, mainly due to their simplicity and convenience However, extensive loss caused by rapid precorneal drainage and high tear turnover are among the main drawbacks associated with topical ocular drug delivery.

Topical Drug Delivery

Transdermal Drug Delivery To the systemic circulation is one of the oldest routes that have been exploited using microemulsion systems.[10]

Components of Microemulsion Formulations

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions. The emphasis is, therefore, on the use of generally regarded as Safe (GRAS) excipients.

Oil Phase: The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group region to a greater extent than long chain alkanes, and hence swell this region to a greater extent, resulting inincreased negative curvature (and reduced effective HLB). Saturated (e.g. lauric, myristic and capric acid) and unsaturated fatty acids (e.g. oleic acid, linoleic acid and linolenic acid) have penetration enhancing property of their own and they have been studied since a long time. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase. When the synovial membrane is attacked, it becomes inflamed (synovitis) and can thicken and erode. As the synovial membrane is destroyed, the synovial fluid fluid is also destroyed because it is not being secreted. The surrounding structures can also become involved leading to the joint deformities that can be seen in rheumatoidarthritis.

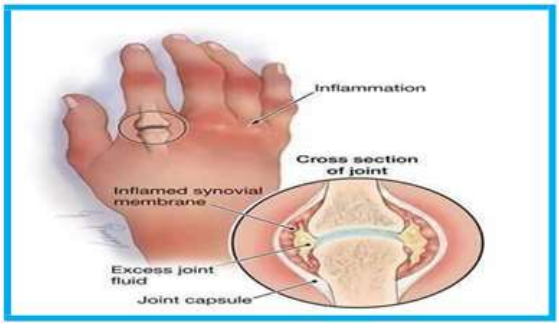


Fig. 1: Rheumatoid Arthritis.

II. LITERATURE REVIEW

Jadupati *et al.*, 2011 developed the Insulin-loaded microemulsions for transdermal delivery using isopropyl myristate or oleic acid as the oil phase, Tween 80 as the surfactant, and isopropyl alcohol as the co-surfactant. The insulin permeation flux of microemulsions

containing oleic acid through excised mouse skin and goat skin was comparatively greater than that of microemulsions containing isopropyl myristate. The insulin-loaded microemulsion containing 10% oleic acid, 38% aqueous phase, and 50% surfactant phase with 2% dimethyl sulfoxide (DMSO) as permeation enhancer showed maximum permeation flux (4.93 ± 0.12 g/cm2/hour) through goat skin. The in vitro insulin permeation from these microemulsions was found to follow Zero order and the Korsmeyer-Peppas model (R2 = 0.923 to 0.973) over a period of 24 hours(19) **Bhavika et al., 2011** developed a microemulsion for enhancing the permeation of acyclovir using different penetration enhancer like DMSO, Menthol, and Eucalyptus oil. They concluded that 1% menthol incorporated as a penetration enhancer and it showed 10% increase in permeation rate of drug. The microemulsion system was investigated for viscosity, pH, refractive index, electrical conductivity, and permeation. The optimum formulation provided 76% drug release in 12 hr. (20) **Xiaohui et al., 2011** studied the microstructure characterization of microemulsion consisting of oleic acid, cremophor RH40, ethanol and water and investigate the influence of microstructure on the solubilization potential of the microemulsion to meloxicam. They concluded that the solubilization capacity of microemulsion is closely related with its microstructure. The solubilization of W/O microemulsion is the best, compared with other two (O/W, Bi continuous), where as the O/W is the weakest(21). **Ying et al., 2011** investigated a microemulsion system for transdermal delivery of ligustrazine phosphate. Microemulsions containing isopropyl myristate, labrasol, plurol were investigated in pseudo-ternary phase diagrams. The optimized microemulsion with permeation flux of 41.01µg/cm2/h across rat skin in vitro, showed no obvious irritation on backskin of rabbits. The results indicated that the studied microemulsion system might be a promising vehicle for transdermal delivery of ligustrazine phosphate. (22) **Manish et al., 2010** formulated Glipizide Microemulsion by water titration method using oleic acid as oil phase, tween-80 as surfactant and propylene glycol as cosurfactant. Microemulsions were characterized for pH, viscosity, droplet size, in vitro release profile, ex-vivo diffusion study, irritancy tests, stability and in vivo evaluation. Five microemulsion formulations were prepared.Oleic acid is used as oil phase in 2, 4, 6, 8, 10% concentration of formulation content and then 6% (ME-3) obtained in clear form and have higher cumulative percent release than others. Non–ionic surfactant Tween-80 was selected because they are generally less toxic, produce less skin irritation. In vivo studies were carried out on wistar rats. The optimized microemulsion formulation was found to be o/w type emulsion and having mean particle sizeof 138±4.5 nm. The results indicated that the developed microemulsion systems, especially ME-3, may be promising vehicles for the transdermal delivery of glipizide. (23).

III. METHODOLOGY

Preformulation may be described as a stage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, preformulation studies are essential to characterize the drug for proper designing of the drug delivery system. The preformulation studies which were performing in this project include.

Description

Organoleptic characters of drug was observed and recorded by using descriptive terminology.

Melting Point

Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of the tube 2.5mm to 3.5mm, and packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until the temperature is about 30o C below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1o C to 2o C per minute until melting is completed.

The temperature at which the detector signal first leaves its initial value is defined as the beginning of melting, and the temperature at which the detector signal reaches its final value is defined as the end of melting, or the melting point. The two temperatures fall within the limits of the melting range.

Solubility Studies

The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 10 mg of drug was a suspended separately in 10 ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table.

Table 1: Solubility Profile I.P. 1996.

Descriptive term	Parts of solvent required for 1 part of solute.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10, 000
Practically insoluble of Insoluble	Greater than or equal to 10,000

Hygroscopic Nature
Procedure
2 gm of the test specimens were weighed accurately in petridish and the weight were noted down. Then the test specimens were exposed to 75% RH at 40□C in environment stability testing camber and the other was kept at room temperature for 7 days period. The specimen was weighed after 7 days and the difference in weight was noted down.

Identification of Drug Sample
Finding the absorption maxima max)
The absorption maxima were found for drug identification. Ultraviolet visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength on the type of electronic transition associated with the absorption. Preparation of Phosphate Buffer Solution [pH 7.4] I.P1996

- 27.218 g of potassium dihydrogen ortho phosphate was dissolved in 1000 ml of distilled water to give a 0.2N solution
- 8 g of sodium hydroxide was dissolved in 1000ml of distilled water to give 0.2N solution
- 1250ml of 0.2N potassium dihydrogen ortho phosphate and 977.5ml of 0.2N sodium hydroxide were mixed together and made upto 5000ml with distilled water
- The drug solution (10, 20, 30, 40, 50, 60 □g/ml) in Phosphate buffer pH 7.4 was taken in standard cuvette, and scanned in the range of 200-300nm in a UV spectrophotometer. It exhibits maxima at 377nm. UV spectrum of drug taken in phosphate buffer pH 7.4 also exhibits maxima at 377nm. Therefore, further all measurements were taken at 377nm

FORMULATION DEVELOPMENT
The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process of development of the finished procedure. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product.

DOSE CALCULATION
The total dose of drug, Dt in a prolonged action preparation comprises the normal (prompt) dose, Dn and the sustaining dose Ds i.e., Dt = Dn + Ds if the first order elimination rate constant is K, the rate at which drug is eliminated when a normal dose is given is Dn K which is the rate at which drug must be replaced if the peak blood level is to be maintained. Given a maintenance period‘t’ the maintenance dose (Ds) is Dn kt. The total dose is therefore:
Dt = Dn+ Ds
= Dn + DnKt
= Dn (1+Kt)
= Dn (1+0.693t/t1/2)
Dt = Di (1+ 0.693 x tm/t1/2)
Where, Dt = Total dose
Di = initial dose
tm = time to which the drug is sustained
t1/2 = half life of the drug.
Di= 10 mg t1/2 = 5 hrs tm = 24 hrs
Dt = 10 (1 + 0.693 x 24/5) Dt= 35.26mg
Dt = 35 mg (app)

Calculation of HLB value for O/W type of Microemulsions
The HLB of a non-o-ionic surfactant whose only hydrophilic portion is polyoxyethylene is calculated by using the formula
HLB= *E*/5
Where, *E* is the percentage by weight of ethylene oxide. A number of polyhydric alcohol fatty acid esters, such as glyceryl monostearate, can be estimated the formula

HLB= 20(1-*S*/A)
Where, *S* is the saponification number of the ester and A is the acid number of the fatty acid. The HLB of polyoxyethylene sorbitan monolaurate (tween-20),
For which *S*=45.5 and A=276, is
HLB= 20(1-45.5/276) =16.7
The HLB values of some commonly used amphiphilic agents are given in table (13)

The oil phase of an oil-in water (O/W) emulsion requires a specific HLB, called Required Hydrophile- Liphophile Balance (RHLB). A different RHLB is required to form water-in oil (W/O) emulsion from the same oil phase. The RHLB values for both O/W and W/O emulsions have been determined empirically for a number of oil and oil-like substance.

Table 2: HLB Values of Some Agents.

Substance	HLB Value
Oleic acid	1
Span-80	4.3
Span-20	8.6
Brij-30	9.5
Tween-20	16.7
Sodium oleate	18

Table 3: Oil Phase Ingredients For (O/W) and (W/O) Emulsions.

Oil phase ingredients	O/W emulsion	W/O emulsion
Cottonseed oil	6-7	-
Mineral oil	10-12	5 - 6
Castor oil	14	-
Lauric acid	16	-
Oleic acid	17	-

Selection of Oils

Tofind out the suitable oil, which can be used as oil phase in microemulsion, and provide excellent skin permeation rate of nabumetone. The solubility of nabumetone in various oils including olive oil, castor oil, isopropyl myristate, isopropyl palmitate, oleic acid was measured at 25°C. The solubility of olive oil, castor oil, isopropyl myristate, isopropyl palmitate, and oleic acid in oily mixtures was also measured.[52]

Procedure

About 10 gm of oil was accurately weighed in 25 ml glass beaker and 100 mg of nabumetone was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10 mg nabumetone of was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 377 nm. It was found that, oleic acid has consumed maximum amount of nabumetone and thus chosen as a vehicle for microemulsion oil phase(15).

IV. RESULT

Pre-formulation studies

Description

Nature	Yellow Powder
Taste	Weakly Acidic

Melting Point

Table: Melting Point Determination.

Drug	*Melting point	Normal range
nabumet one	247 ± 0.138	239-241

SOLUBILITY

The solubility of drug in various solvents was shown in the table

Table: Solubility Profile of nabumetone.

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

HYGROSCOPIC NATURE

Table: Hygroscopic Nature of nabumetone (nabumetone is non hygroscopic in Nature).

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

Identification of Drug Sample

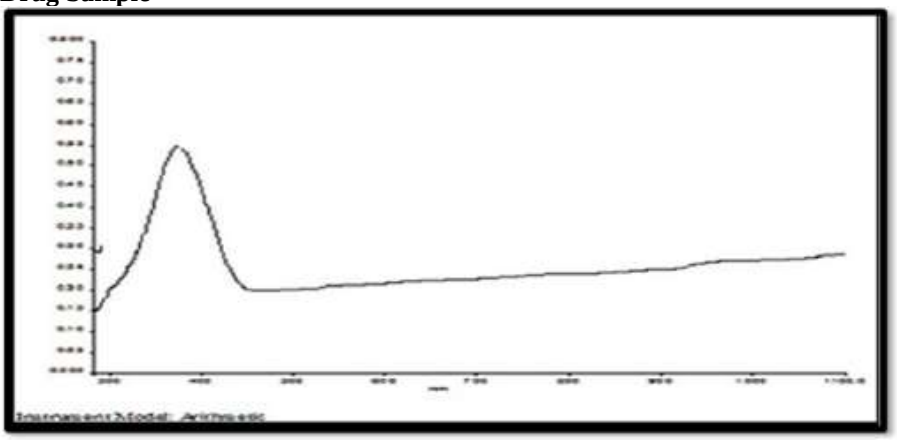


Fig. 2: UV spectrum of nabumetone in phosphate buffer pH 7.4.

Table 4: Absorption maxima of nabumetone in phosphate buffer pH 7.4.

Solvent	Concentration (μg)/ml	λ max (nm)	Absorbance
Phosphate buffer pH 7.4	5 0	379	0.5869

Table : UV Absorbance of phosphate buffer pH 7.4.

S. No.	Concentration (μg/ml)	Absorbance at 379nm
1	10	0.1316
2	20	0.2795
3	30	0.3862
4	40	0.4958
5	50	0.5869

Characterization of Microemulsions OPTICAL TRANSPARENCY

Table 31: Appearance of Formulations.

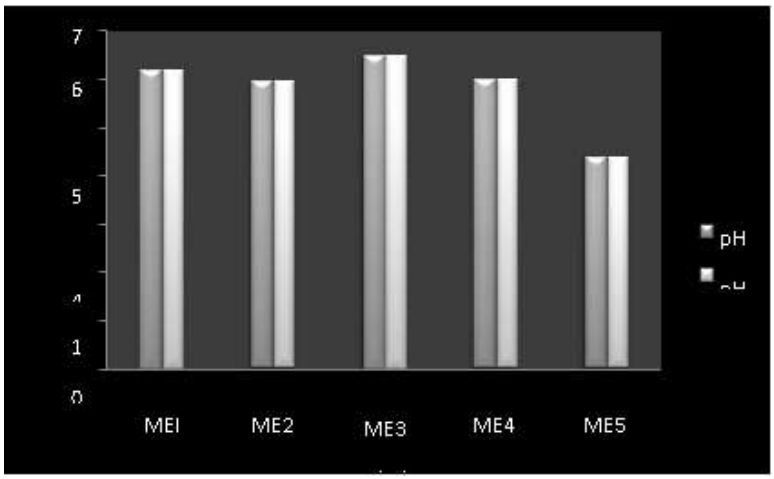
Formulation	Appearance
ME-1	Milky
ME-2	Opalescent
ME-3	Clear
ME-4	Milky
ME-5	Milky

PH DETERMINATION

Table 32: Comparative pH values of Formulations.

Formulations	pH*
MEI	6.19±0.05
ME2	5.95±0.04
ME3	6.49±0.03
ME4	5.98±0.04
ME5	4.38±0.05

***Values are mean ±SD, n=3**



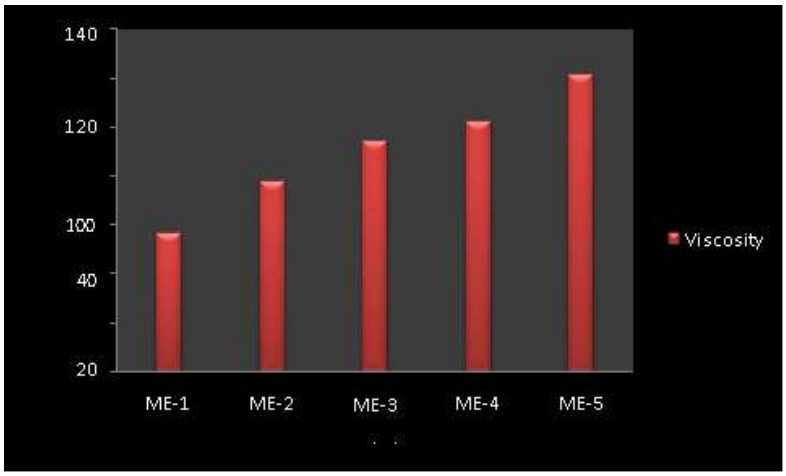


Fig. : Comparative pH values of Formulations.

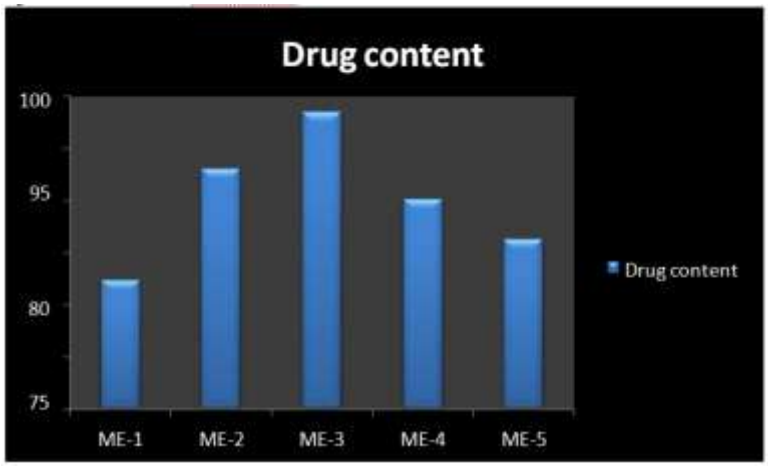
MECHANICAL STRESS STUDY

Table: Comparative study of mechanical stress in Formulations.

S. No	Centrifugation time (min)	% Phase separation				
		ME -1	ME -2	ME -3	ME -4	ME -5
1	10	-	-	-	-	2
2	30	4	-	-	8	6
3	60	8	2	-	12	10

Table : Comparative *in vitro* Skin permeation rate of nabumetone Micro emulsions.

Formulations	Drug content (%)
ME-1	82.42±0.32
ME-2	93.12±0.54
ME-3	98.54±0.26
ME-4	90.21±0.42
ME-5	86.34±0.28



Time in hours	Cumulative % drug permeated (µg/cm2)*				
	ME-1	ME-2	ME-3	ME-4	ME-5
0	0	0	0	0	0
0.5	3.71±0.12	7.06±0.032	6.59±0.42	4.22±0.12	10.70±1.02
1	4.32±0.02	11.03±0.42	14.56±0.31	10.02±0.02	14.70±0.34
2	5.84±2.11	13.15±2.12	18.59±2.10	17.23±0.31	19.39±0.15
4	8.76±0.21	16.22±1.25	27.96±0.24	21.98±1.02	20.79±0.52
6	10.09±1.13	18.52±0.02	33.12±0.15	25.44±1.32	25.41±0.12
8	15.14±0.02	20.25±1.01	41.24±1.02	29.05±2.01	28.36±0.32
10	18.02±0.21	24.65±0.21	47.14±0.21	32.72±0.02	31.14±2.53
12	21.80±1.04	27.53±1.31	53.98±2.25	35.68±0.12	33.80±1.28

***Values are mean** ±SD, n=3

V. CONCLUSION

In developing a transdermal delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation.

Transdermal drug delivery systems facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. Topical administration of drugs with systemic effect can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism of the drug and related toxicity effects, controlling the rate of delivery and modulating distribution of drug in the systemic circulation.

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