DEVELOPING A NOVEL MICROEMULSION CONTAINING IBUPROFEN FOR TRANSDERMAL APPLICATION

By:

Waseem Nawaf Sayeh

Supervisor:

Dr. Jamal Alyoussef Alkrad

This Thesis Was Submitted in Partial Fulfillment of the Requirements for the Master's Degree in pharmaceutical sciences

Faculty of Pharmacy

Isra University, Amman, Jordan

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COMMITTEE DECISION

Thesis (developing a novel microemulsion containing ibuprofen for transdermal application).

Was successfully defended and approved on (Tuesday 1-9-2020).

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Date: 3/8/2020

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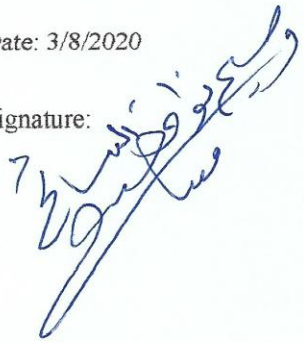

DEDICATION

To my parents Nawaf & Laila who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

To my brothers, Firas, Emad, Samer and my lonely sister Lamis.

Finally, to everyone who helps, teaches me and take my hand to the right way in seeking knowledge.

Waseem Nawaf Sayeh

2020

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There have been many people who have walked an alongside me during when I came to Jordan until now. They have guided me, placed opportunities in front of me and showed me the doors that might be useful to open. I would like to thank each and every one of them.

Waseem Nawaf Sayeh

2020

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List of Abbreviations

Abbreviation	***Meaning***
%	Percentage
℃	Degree celsius
Ibu	Ibuprofen
cm^2	Square centimeter
HPLC	High performance liquid chromatography
h	Hour
L	Litter
µL	Microliter
ml	Milliliter
kg	Kilograms
g	Gram
mg	Milligram
min	Minute
m^2	Square meter
mwt	Molecular weight
nm	Nanometer
mm	Millimeter
pH	Negative logarithm of hydrogen ion concentration
DMSO	Dimethyl sulfoxide
IPM	Isopropyl myristate

UV	Ultraviolet
N	Normality
ME	Microemulsion
rpm	Revolutions per minute
mV	Millivolts
PEG600	Polyethylene glycol 600
E	Absolute ethyl alcohol
TDDS	Transdermal drug delivery system
kHz	Kilohertz
MHz	Megahertz
HLB	Hydrophilic-lipophilic balance
µm	Micrometre
NSAID	Non-steroidal anti-inflammatory drugs
COX-1	Cyclo-oxygenase 1
COX-2	Cyclo-oxygenase 2
°F	Fahrenheit
cm^3	Cubic centimetre
mmHg	Millimetre of mercury
GIT	Gastrointestinal tract
w/w	Weight/weight
ex	Example
No.	Number
Kp	Permeability coefficient

Dsc	Diffusion coefficient through stratum corneum
Ksc	Partition coefficient between the excipient and the stratum corneum
A	Skin surface area
Q	The cumulative mass penetrating a membrane
Cv	The constant drug concentration in the donor solution
hsc	The thickness of the membrane or the diffusion path length or stratum corneum
PDI	Poly disparity index
Pa.s	Pascal-second
AUC	The area under the curve
K01	The absorption constant
K10	Elimination rate constant
Tmax	Time of maximum concentration
Cmax	Maximum concentration
t1/2	Half life

Abstract

Developing a novel microemulsion containing ibuprofen for transdermal application

By:

Waseem Nawaf Sayeh

Supervisor:

Dr. Jamal Alyoussef Alkrad

Abstract:

Transdermal Drug Delivery System (TDDS) nowadays is one of the most important topics to deliver certain drugs in a safe, efficient and sustained manner and to achieve the acceptance of the patient. Microemulsions (MEs) are known to be good drug delivery systems for transdermal application. The droplet size and rheological properties play a vital role in the quality of MEs. In this study, Non-ionic surfactants were used to formulate MEs containing ibuprofen. The MEs were characterized for their droplet size, poly disparity index (PDI), rheological properties. Furthermore, the flux of Ibuprofen was evaluated by Franz diffusion cell *in-vitro* over 24h where the penetrated amount of ibuprofen was estimated using high performance liquid chromatography (HPLC). The *in-*

vivo bioavailabilities of encapsulated ibuprofen in MEs were studied in rats. The results showed that the MEs complies with their colloidal characteristics, transparency, and have ideal viscosity. Moreover, the highest achieved flux value of MEs containing ibuprofen through the skin using Franz diffusion cell was 0.039 mg/cm^2 hr. The in vivo results showed a maximum plasma level 0.064 mg/ml at 8 hr for tested ME containing ibuprofen. The developed non-ionic MEs containing ibuprofen can be an ideal carrier and promising formulation for transdermal administration of ibuprofen.

Table of Content

جامعة الإسراء
Isra University

CHAPTER ONE

Introduction

Chapter One: Introduction

Ibuprofen is a phenyl propionic acid derivative which is a nonsteroidal anti-inflammatory agent that is widely used in the treatment of mild to moderated pain, fever, acute and chronic rheumatic, and rheumatoid arthritis (Adeyeye, 2001, Główka, 2000). The transdermal application of ibuprofen can eliminate the side effect which associated with oral application using a carrier such as microemulsion(Tombs *et al.*, 2018), also, to enhance the tranderaml bioavailability and provides the ibuprofen to the blood at a constant rate.(Bushra & Aslam, 2010a)

1.1. Skin overview:

Skin is the largest human organ of our body. It covers the entire body and has a surface area of 1.2-2.2 m^2, weigh about 4-5 kg, and about 16% of total body weight in the average adult (Wu *et al.*, 2006, Sorg *et al.*, 2017). It has a function of protecting the body and regulating body temperature. (Coon *et al.*, 2017, Romanovsky, 2014)

1.2. Anatomy of the Skin:

It has three main layers, The first one is epidermis which is the superficial layer of the skin, and it is the seen part (Gurusamy *et al.*, 2014). Its providing new skin cells at the base of this layer, the new cells then move up to the top of the skin and shedding as dead coenocytes after a month (keratinization process), it also gives the skin tone by producing melanin in different amount depending on genetics (Everett & Sommers, 2012). The second layer of skin is the dermis which is thicker than the epidermis. This layer has a function of making sweat, help grows hair, producing oil, and supplying epidermis with blood. The third layer is subcutaneous fat that controls body temperature and store fats (Bragazzi *et al.*, 2019, Hwang *et al.*, 2001).

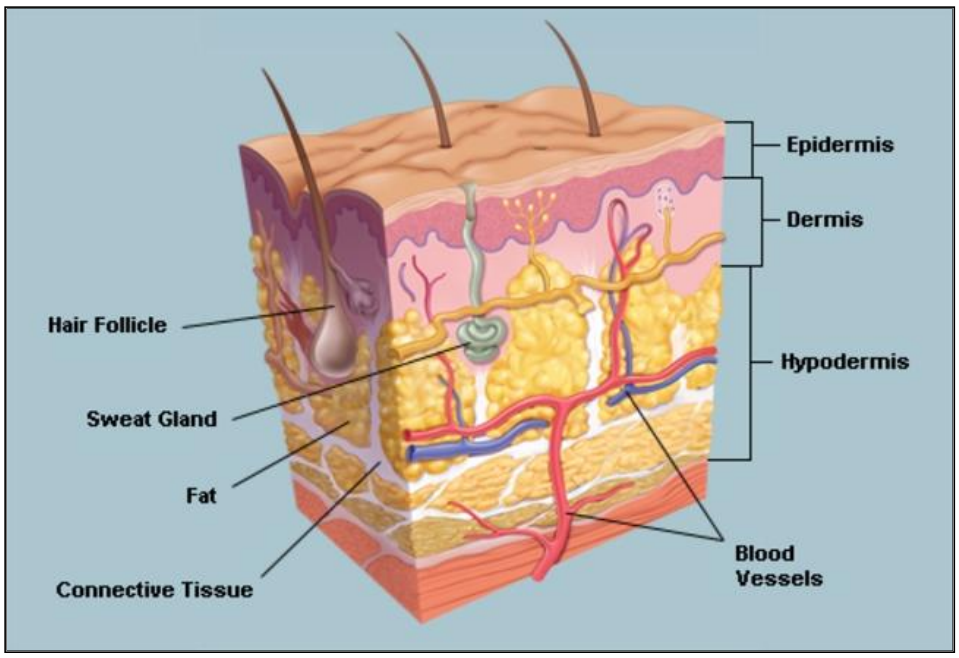

Figure (1): main layers of skin(Jordan, 2017)

1.2.1. Epidermis:

It is the outer layer of the skin. It is made of four to five layers of epithelial cells. These layers from superficial to deep:(Baroni *et al.*, 2012, Rawlings & Harding, 2004, Lee & Friedman, 2016)

- Stratum corneum is the layer exposed to the outside environment and is the most superficial layer of epidermis that contains about 25 layers of flattened dead cells.
- Stratum lucidum is the smooth, translucent, and thin layer. It contains about five layers of flat dead cells, only can be found in the skin of the palms and soles of the feet.
- Stratum Granulosm is the middle layer in the epidermis which consists of three to five layers. It contains granule known as keratohyalin that is secreted to provide a water repellent sealant.
- Stratum spinosum consists of eight to ten layers of cells. It has a spiny appearance, also contains Langerhans cells.
- Stratum basal: consists of a single layer of cubical dead cells. Also, this layer is the deepest layer in epidermis.

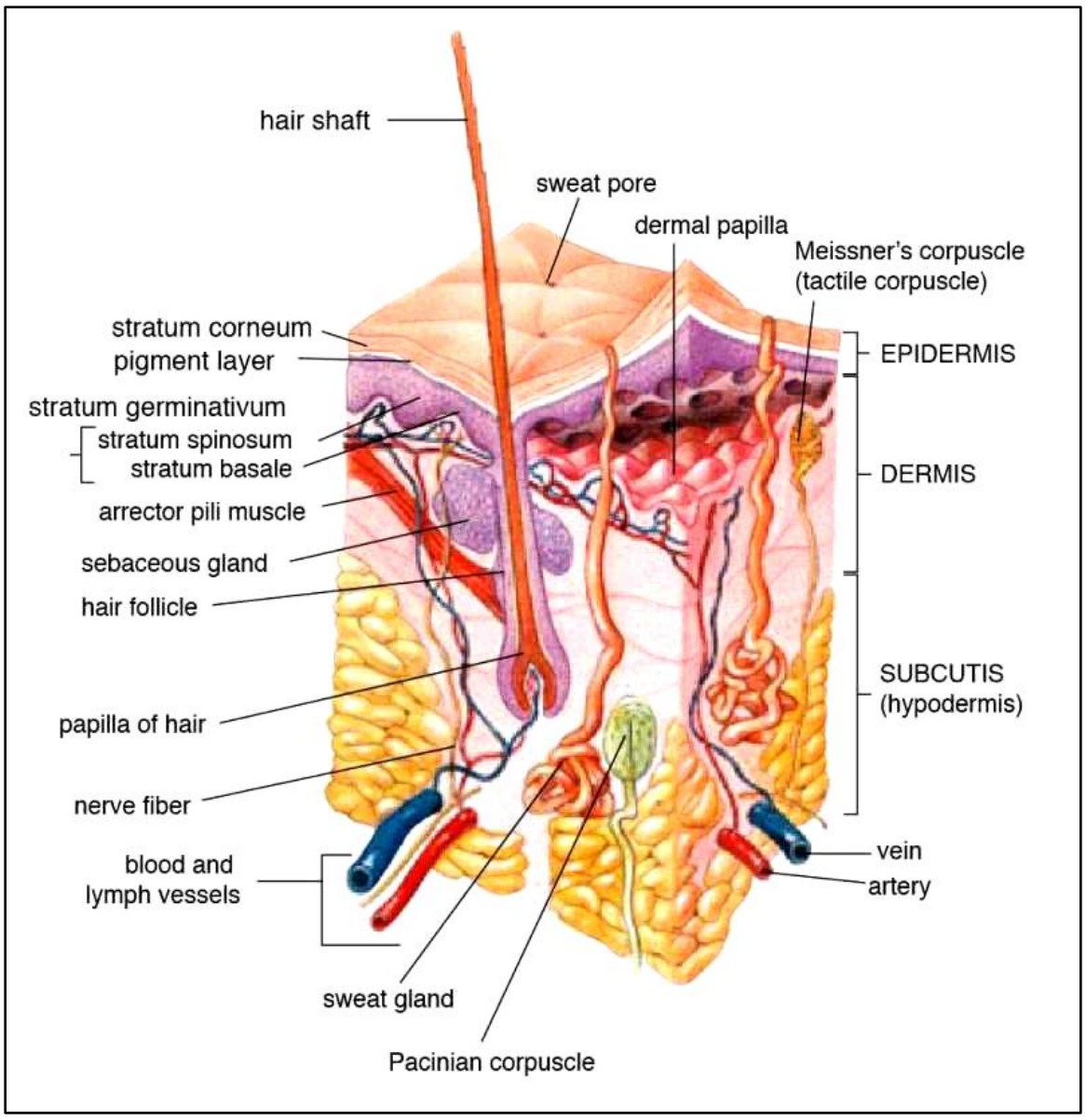

Figure (2): Anatomy of the epidermis (Yousef *et al.*, 2019)

1.2.2. Dermis:

The second layer in the skin, it provides structural support & elasticity because it consists of strong connective tissue that is containing collagen and elastic fibers. (Brown & Krishnamurthy, 2020) it supports the epidermis structurally and nutritionally. Like all connective tissues, the dermis has three components cells, fibers, and amorphous ground substances.(Tobin, 2017, Rognoni & Pisco, 2018)

1.2.3. Hypodermis:

This layer is located below the dermis, it is also known as subcutaneous tissue, and it consists of many cell types like fibroblast, leukocytes, and fat cell. This helps to insulate the body by monitoring heat gain and heat loss(Kim *et al.*, 2019, da Cunha *et al.*, 2017).

1.3. Transdermal Drug Delivery System (TDDS):

Transdermal drug delivery systems (TDDS) are a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin(Hao *et al.*, 2017). The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer(Szunerits & Boukherroub, 2018). When the drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. Transdermal drug delivery systems can improve the therapeutic efficacy and safety of the drugs, because drugs are delivered through the skin at a predetermined and controlled rate (Arora, Prausnitz and Mitragotri, 2008; Langer, 2008).The transdermal drug delivery system could deliver drugs to the body locally and systematically.

1.3.1. Advantages of Transdermal Drug Delivery Systems:

The main advantages of Transdermal Drug Delivery Systems are 1) Avoidance of first-pass metabolism and other variable associated with gastrointestinal tract 2) Predictable and extended duration of an activity. 3) Reducing undesirable side effects .4) Improving physiological and pharmacological response 5) Avoiding the fluctuation in drug levels and maintaining plasma concentration of potent drugs .6) Termination of therapy is easy at any point of time 7) Greater patient compliance due to elimination of multiple dosing profiles and self-administration (Ranjan *et al.*, 2018, Paudel *et al.*, 2010).

1.3.2. Disadvantages of Transdermal Drug Delivery Systems:

Disadvantages of Transdermal Drug Delivery Systems include: 1) Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin. 2) the formulation may cause irritation or sensitization. 3) Not practical when

molecular size is great enough to prevent the molecules from diffusing through the skin (Ranjan et al., 2018, Alkilani *et al.*, 2015).

1.3.3. Routes of Transdermal Drug Delivery Systems:

TDDS could happen through three main routes 1) intercellular route in which the drug must pass through the spaces between the skin's cells. 2) A transcellular route in which the active ingredient must pass through the cells. 3) Transappendagal route in which the drug across the skin via sweat glands, hair follicles, and sebaceous glands (Langer, 2008)(Garg & Singh, 2018).

1.3.4. Properties that influence Transdermal Drug Delivery Systems:

Many Properties influence transdermal delivery of the drug such as 1) release of the medicament from the vehicle, 2) Penetration through the skin barrier, 3) Activation of the pharmacological response (Pandey, Anushree and Mittal, Ashu and Chauhan, Nitesh and Alam, 2014; Ramteke, K.H., Dhole S.N., 2018).

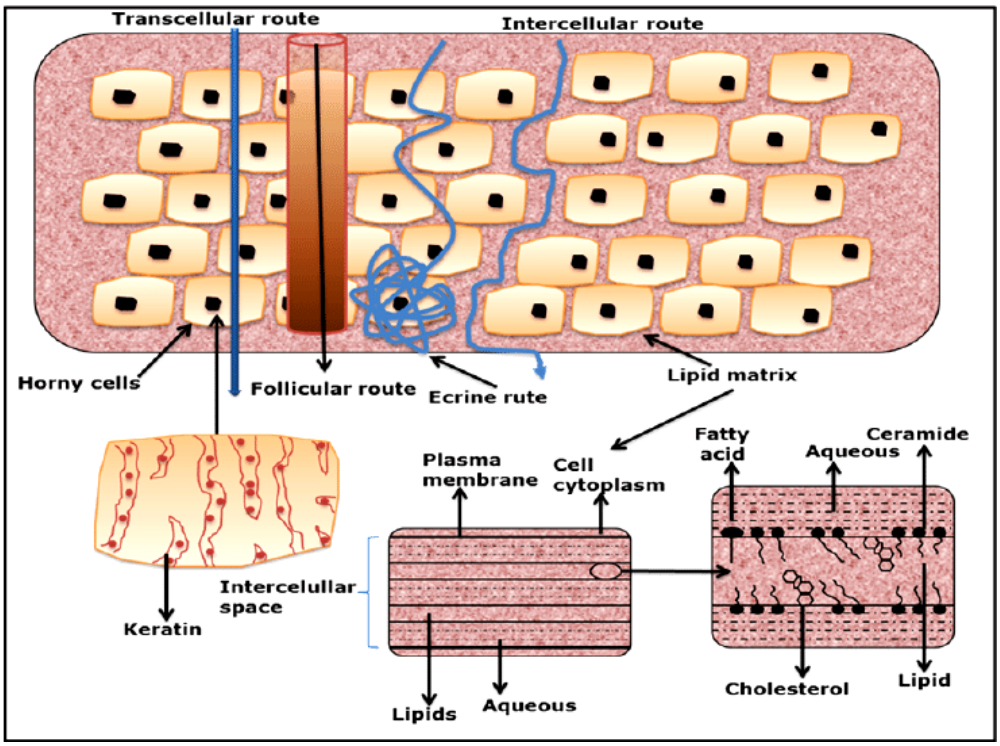

Figure (3): Route of transdermal drug delivery (Escobar-Chávez *et al.*, 2012)

1.3.5. Techniques for enhancement of skin permeability for transdermal delivery drug system:

As a barrier, skin could cause difficulties for transdermal drug delivery for many drugs and this makes the researchers think of many technologies to enhance permeation through the skin. One of these techniques is by using surfactants to enhance penetration through the skin and the studies show that the chemical structure of surfactants as penetration enhancers plays a major role in the permeation process. The good Selection of surfactants is very helpful in the development of a successful transdermal product (Pandey, Anushree and Mittal, Ashu and Chauhan, Nitesh and Alam, 2014). Another used technique is Sonophoresis which includes using ultrasound at frequencies in the range of 20 kHz–16 MHz to enhance skin permeability for various drugs including high molecular weight and hydrophilic compounds (Park *et al.*, 2014)(Benson, 2005).

1.4. Microemulsions:

At the beginning of the 1940s of the last century, the concept of microemulsions was presented by Hawar and Schulman by titrating a milky emulsion with hexanol which lead to a clear single phase. In 1959, Schulman and his colleagues were able to prepare the first microemulsion by dispersing the oil in an aqueous solution and adding alcohol as co-surfactant which resulted in a clear stable formulation. MEs are mixtures of lipophilic phase (oil),

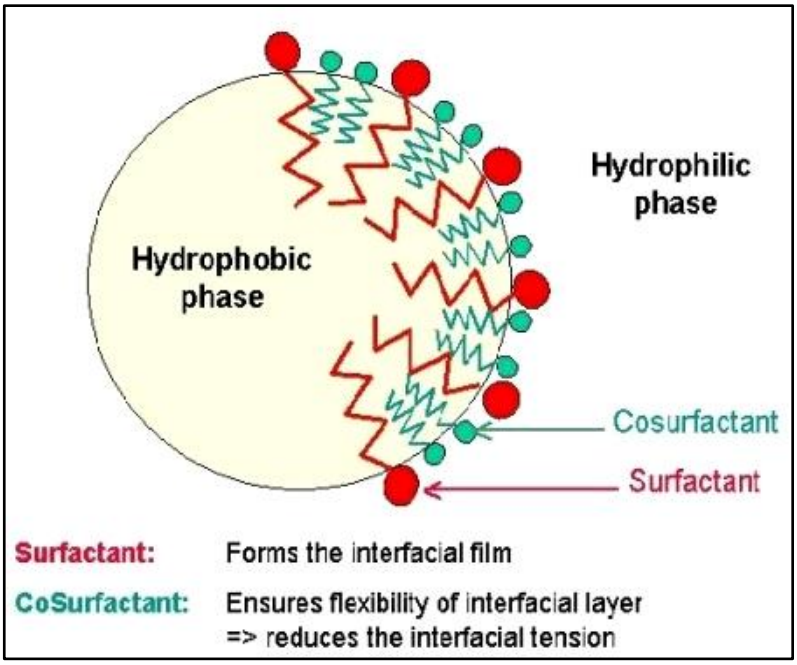

Figure (4): Structure of ME (K *et al.*, 2012, Yong *et al.*, 2004)

hydrophilic phase (water), and surfactants leading to the formation of a clear single phase that makes thermodynamically stable, isotropic mixtures with a dispersed diameter approximately from one to one hundred nm (Lawrence & Rees, 2000, Kale & Deore, 2017, Sujatha *et al.*, 2020). MEs are topical drug vehicles that can improve transdermal and dermal delivery properties. In addition to protect labile drug, control drug release, reduce patient variability, and increase drug solubility.(Heuschkel *et al.*, 2008, Alkrad *et al.*, 2016).

Microemulsions are innovative carrier systems for systemic application compared to conventional semisolid formulations because of their penetration enhancing capacities and rheological properties. MEs are modern colloidal drug carrier systems. They are created spontaneously by combining appropriate amounts of a lipophilic phase (oil) and hydrophilic ingredient, surfactant, and co-surfactant (Yuan *et al.*, 2006, Narang *et al.*, 2007). MEs are thermodynamically stable dispersions of oil in water or water in oil which are stabilized by surfactants and co-surfactants (Lawrence & Rees, 2000). Furthermore, MEs can increase the local or systemic availability of drugs by different mechanisms: First, their composition and structure enable them to incorporate a greater amount of drug than other conventional topical formulations such as ointments, creams, gels, and lotions. Second, the diffusion barrier of the skin may be modified depending on the composition of the ME. Third, the increased thermodynamic activity of the drug may favor its partitioning into the skin (Kale & Deore, 2017, Siqueira Leite *et al.*, 2018).

1.4.1. Advantages of MEs

- MEs doesn't require energy for the formation and they are thermodynamically stable.
- Highly cutaneous absorption for hydrophilic and hydrophobic drugs compared to conventional vehicles.
- Easy to prepare, highly diffusion, a spontaneous formation, and large absorption rates.
- Reversible formation occurs when unstable at high or low temperature but when the temperature may stable, the MEs reforms.

- Helps in the solubilization of lipophobic and lipophilic drugs, so microemulsions act as super solvent of a drug.
- Provide various route of administration like oral, topical and parental can be used to deliver the ingredients.
- MEs could help in masking the taste and smells.
- Prevent hydrolysis and oxidation when drug is soluble in the oil phase of MEs.
- Low viscosity when compared with other dosage form, that ensures good contact with the skin (Sarkhejiya *et al.*, 2013, Goswami *et al.*, 2019).

1.4.2. Disadvantages of MEs

- Require large amounts of surfactant or surfactant mixtures. These surfactants should be non-irritating and non-toxic for pharmaceutical applications.
- Limited solubilizing capacity for high melting substances.
- Stability is sensitive by environmental parameters such as pH, temperature (Sarkhejiya et al., 2013, Goswami et al., 2019).

1.4.3. Types of MEs

Four types of MEs are classified according to Winsor depending on composition (Nguyen & Sabatini, 2011, Čilek *et al.*, 2006):

- Water in oil: the droplets of water exist in equilibrium with the continuous oil phase which represents two-phase systems.
- Oil in water: the droplets of oil exist in equilibrium with continuous water phase which represents two-phase systems.
- Middle bicontinuous: the droplet of oil in water or water in oil exists in equilibrium with continuous water phase or oil phase which represents three-phase systems.
- Bi continuous: a mixture of oil, water, and surfactant form homogenous phase which represents single-phase systems.

1.4.4. Component of MEs

MEs are mixtures of lipophilic phase, hydrophilic phase, and surfactants leading to the formation of a clear single phase that makes thermodynamically stable, isotropic mixtures with involving the following main components(Ghosh & Murthy, 2006):

1.4.4.1. Lipophilic phase (oil):

This phase is important in MEs formulation because it can solubilize the lipophilic drugs. Also, can be used as a penetration enhancer for different types of drugs. The lipophilic phase includes different types of oils such as fatty acid esters, saturated fatty acids, and unsaturated fatty acids. Thus, selecting the appropriate lipophilic phase (oil) component depends on the solubility of the drug (McClements & Rao, 2011).

1.4.4.2. Aqueous phase

In some cases of MEs formulation, a buffer solution may be used as an aqueous phase. Also, water is mainly used as the aqueous phase (Warisnoicharoen *et al*., 2000).

1.4.4.3. Surfactants:

The main function of surfactants is to lower the interfacial tension. They are small molecules composed of hydrophilic head group and lipophilic tail part in the same molecule to facilitate the dispersion process during MEs preparation. Which is made easier to form the correct curvature at the interfacial region for desired MEs type water in oil, oil in water or bicontinuous (Kralova & Sjöblom, 2009). Surfactants have four types that can be classified based on the charge present in the hydrophilic group:

- Non-ionic surfactants: have two types (oil-soluble and water-soluble): used to formulate both water in oil and oil in water MEs. This category is preferable because they are more stable, compatible, and safe. Most important example are sorbitan esters, macrogols, tween series, and fatty alcohol groups (McClements, 2015).

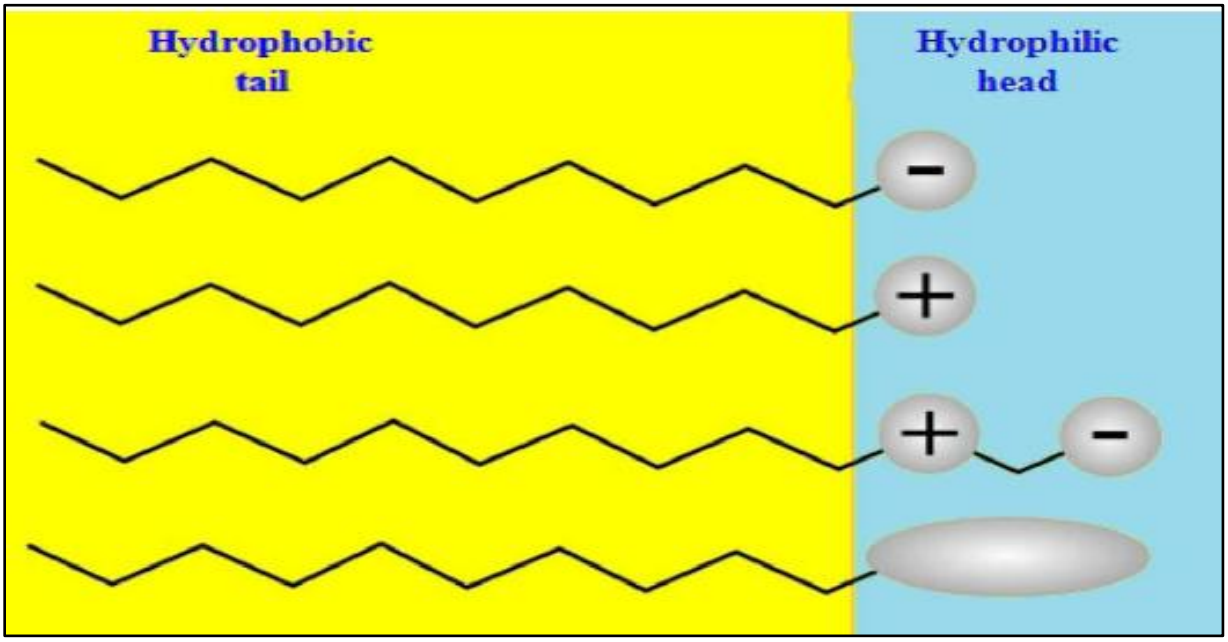

Figure (5): Classification of surfactants according to charged groups (Liu *et al.*, 2013)

- Cationic surfactants: have a positive charge in their polar parts. They are used in the pharmaceutical formulation as a preservative such as quaternary ammonium.
- Anionic surfactants: have a negative charge in the polar part. The main examples are sulfate and carboxylate.
- Zwitterionic surfactants: have positive and negative charges in the head part. They have many uses in pharmaceutical forms. Examples include alkyl betaines and sulpho betaines.

1.4.4.4. Co-surfactants

The main functions are enhancement of the efficacy of surfactant in MEs formulation or enhancement of the penetration enhancer to skin. They work to reduce interfacial tension. In addition to reducing the HLB value for surfactants that have value more than 20 to an appropriate range for formulating stable MEs(Pavoni *et al.*, 2020).

1.4.5. Comparison between emulsion and MEs

The most important characteristics that differentiate between emulsion and MEs are mentioned in the below table (Patel *et al.*, 2007, Kayes, 1999, Muzaffar *et al.*, 2013, Naimish *et al.*, 2000):

Table (1): Comparison between emulsion and MEs according to properties

Property	Emulsion	Microemulsion
Appearance	Milky	Transparent
Phases	Biphasic	Monophasic
Thermodynamic stability	Unstable (kinetically stable) will eventually phase separate	Stable, long shelf life
Formation	Energy input	Spontaneous
Microstructure	Dynamic (fluctuating surfaces)	Static
Interfacial tension	High	ultra-low
Optical isotropy	Anisotropic	Isotropic
Droplet size	More than 500 nm	10 to 100 nm
Shape	The spherical droplet of one phase dispersed into another phase	Spherical, lamellar swollen micelles to bi-continuous structure
Energy to formulate	Large energy, higher cost	No energy, low cost
Viscosity	Higher viscosity	Low viscosity

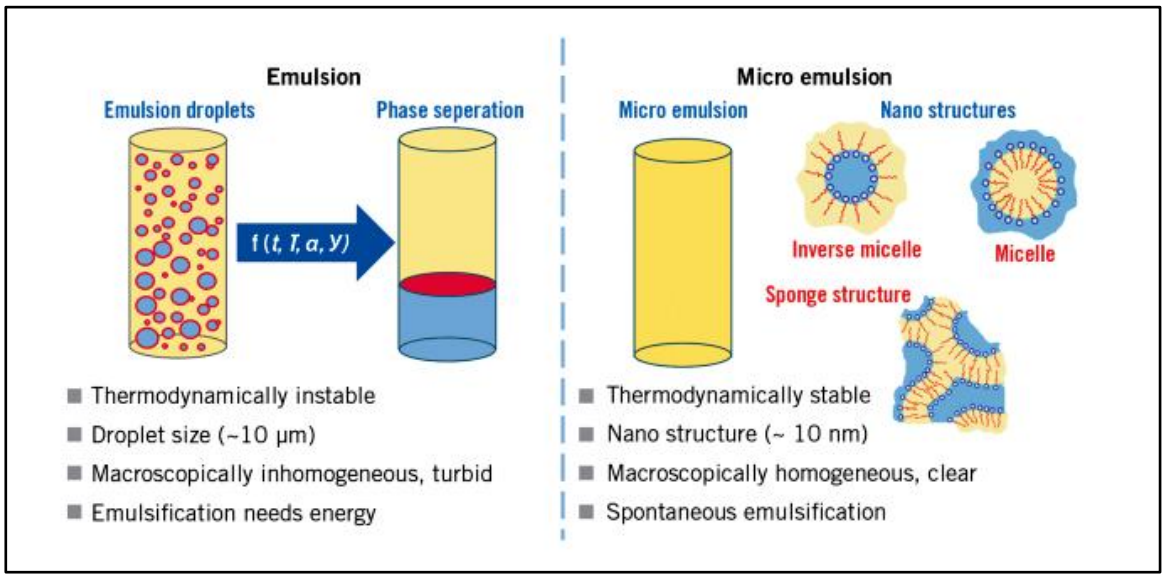

Figure (6): Differentiation between emulsion and MEs (Dittmann *et al.*, 2015)

1.5. Franz diffusion cell:

a device used in formulation development for in vitro skin permeation studies, because it's simple and has low cost. The Franz diffusion cell is composed of two main compartments called the donor compartment and receptor compartment separated by a membrane usually can be used animal skin. The skin is stored in a deep freezer at temperature -70℃ and the epidermis is separated. It also contains a thermal jacket connected with a water bath to maintain the temperature at 32℃, a cell clamp, and a stir bar in the receptor compartment. When the compartments are fully installed with skin, the test product is applied to the membrane directly via the top chamber. The bottom compartment usually filled by an isotonic saline solution or other appropriate medium and should avoid the formation of bubbles under the skin membrane. The fluid in the bottom compartment is kept homogenous in concentration and temperature by a magnetic stirring bar. The bottom compartment contains fluids that are sampled at regular time intervals for analysis and replaced with the same volume of a solution after every collection. This testing determines the amount of active drug that has permeated the membrane at each time point(Farner *et al.*, 2019, Liu *et al.*, 2015, Kshirsagar *et al.*, 2012, Alkrad, 2019).

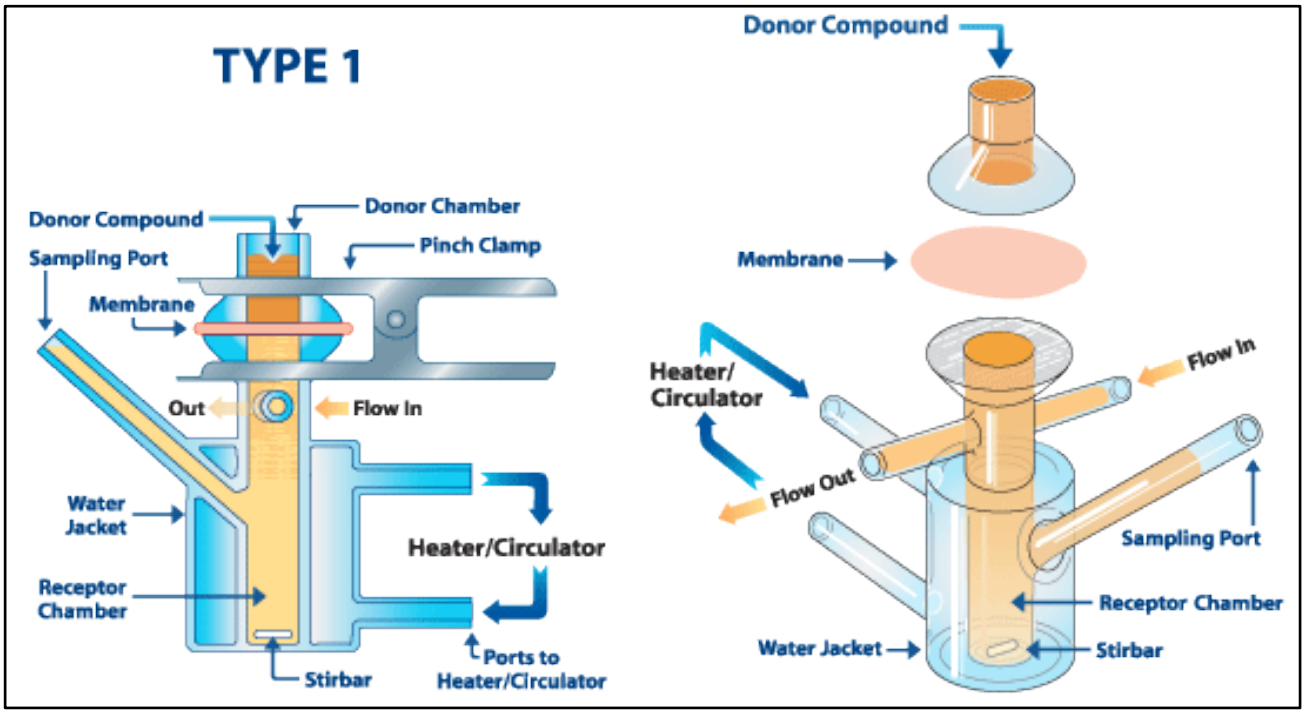

Figure (7): Franz Diffusion Cell (Kumar & Maurya, 2018)

1.6. Ibuprofen:

Ibuprofen is a propionic acid derivative. It is initial development was in the 1960s and considered as a non-steroidal anti-inflammatory drug (NSAID).

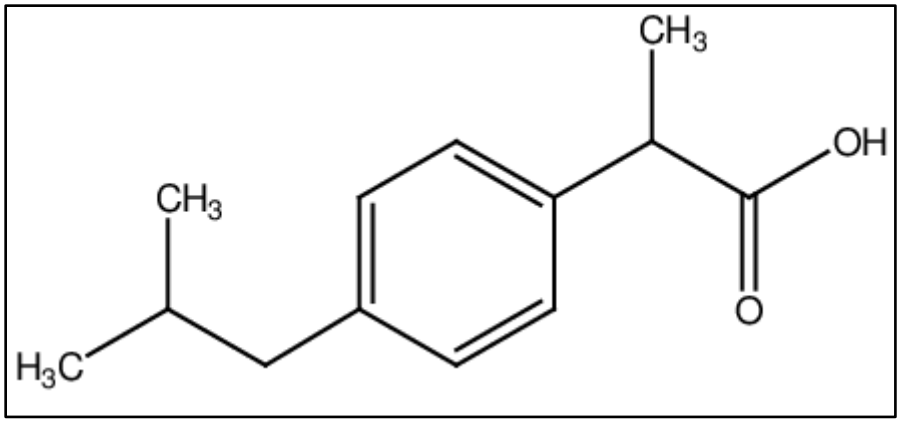

Figure (8): Chemical structure of Ibuprofen (Abualhasan *et al.*, 2015)

1.6.1. Pharmacology of ibuprofen:

Ibuprofen has analgesic, antipyretic, and anti-inflammatory effects due to prostaglandin synthetase inhibition like other non –steroidal anti-inflammatory mechanisms.

The specific mechanism of action for ibuprofen through inhibits the activity of COX-1 and COX2. which inhibits COX-2 leads to decrease the synthesis of prostaglandins and that leads to mediating and relieve inflammation, fever, swelling, and pain but the inhibition of the COX-1 lead to a gastrointestinal side effect(Vane & Botting, 1995).

1.6.2. Physiochemical properties of Ibuprofen:

Table (2): Physiochemical properties of ibuprofen (Higgins *et al.*, 2001)

Chemical Name	(RS)-2-(4-(2-methyl propyl)phenyl) propanoic acid
Molecular Formula	$C_{13}H_{18}O_2$
Molecular Weight	206.285 $g \cdot mol^{-1}$
Cas No.	15687-27-1
Melting Point	75 to 78 °C (167 to 172 °F)
Boiling Point	157 °C (315 °F) at 4 mmHg
Density	1.03 g/ml g/cm^3
Solubility	Insoluble in water 0.021 mg/mL (20 °C), freely soluble in acetone, methanol, and methylene chloride. Soluble in ethanol (66.18 g/100mL at 40 °C for 90% E).
Appearance	White crystalline powder or colorless crystals
Odor	Characteristic odor
Taste	Bitter taste

1.6.3. Medical use of ibuprofen:

Ibuprofen in all pharmaceutical forms is prescribed for the relief of acute chronic pain in which there is an inflammatory component. Also indicated for persons suffering from juvenile rheumatoid arthritis, pyrexia, rheumatoid arthritis, primary dysmenorrhoea, and osteoarthritis(Moore, 2003).

1.6.4. Side effects and contraindications of ibuprofen:

Ibuprofen has reported side effects with oral use involving (Katzung, 2012, Wolfe *et al.*, 1999):

- Gastrointestinal symptoms: include nausea, heartburn, epigastric pain, abdominal distress, diarrhea, vomiting, dyspepsia, abdominal cramps or pain, constipation, flatulence, tinnitus, and gastrointestinal hemorrhage.
- Central nervous system symptoms: include hearing impaired, headache, dizziness, nervousness, fatigue, and decreased appetite.

The most important contraindication of ibuprofen usage:

- Hypersensitivity to ibuprofen as a drug and any component of excipient in the pharmaceutical dosage form.
- Anyone who has a history of GIT bleeding related to NSAIDs therapy.
- Anyone who has severe ulcerative colitis, liver failure, heart failure, and renal failure.
- Pregnant during the thirds trimester.

1.6.5. Dosage forms and dose administration:

Table (3): Pharmaceutical dosage form of ibuprofen and dose administration (Bushra & Aslam, 2010b, Katzung, 2012, Potthast *et al.*, 2005)

<table>
<tr><th>Dosage form</th><th>Available dose</th><th>Age</th><th>Daily dose</th><th>Notes</th></tr>
<tr><td>Tablet, capsules</td><td rowspan="3">200 , 400 , 600 , 800 mg</td><td>Adult</td><td>1200-1800 mg daily</td><td>Total daily maximum dose of 2400 mg</td></tr>
<tr><td>Granules</td><td rowspan="3">Children</td><td rowspan="3">20mg -40mg per kg daily</td><td>In case the weight of child less than 30 kg should be not given exceed 500 mg in 24h</td></tr>
<tr><td>Suspension</td><td>100, 200 mg</td><td>Should be shaken well before using</td></tr>
<tr><td>Suppositories</td><td>60,100,125, 300,500 mg</td><td>Do not use in children weighing less than 6 Kg.</td></tr>
<tr><td>Gel</td><td>5% - 10%</td><td>Adult</td><td>50 to 125mg daily</td><td>Should not apply on the skin more than 500mg in 24h</td></tr>
</table>

1.6.6. Pharmacokinetics of ibuprofen:

Ibuprofen is well absorbed when given orally on an empty stomach producing peak serum concentration after approximately 45 minutes. If it is take after food, this leads to slower absorption which appears peak levels at 1.5 to 3 hours. A metabolite of ibuprofen readily cross the placental barrier in pregnant and the apparent volume of distribution is 140 ml /kg. Ibuprofen has high protein binding and should not be prescribed with drugs that have high protein binding because they will be bounded on the same site. The major route of excretion for ibuprofen is kidney, a high percentage of ibuprofen is excreted within 24 hours in urine. Two major metabolites of ibuprofen that are dextrorotatory and other metabolites devoid of anti-inflammatory as also analgesic activity. Ibuprofen half-

life ranges between 1.9 -2.2 h (Katzung, 2012, Mazaleuskaya *et al.*, 2015, Potthast et al., 2005).

1.7. Previous studies about transdermal application and development of the MEs formulation for Ibuprofen:

A study explained formulation and characterization of ibuprofen loaded ME system using D-optimal Mixture design by using various oils (oleic acid, cottonseed oil, olive oil, argan oil, and labrafac® WL 1349), surfactants (tween® 80, tween® 40, tween® 20) and co-surfactants including polyethylene glycol 400, ethanol, 1-butanol, and propylene glycol were selected after solubility studies. The best MEs results that were obtained was composed of oleic acid (6.88% w/w), tween® 80/1-butanol (3:1, 63.11% w/w), and water (30.00% w/w). The results showed an average globule size of 117.5 nm, a zeta potential of-6.47 mV, and transmittance of 96.95±0.77%. (EL ALAOUI *et al.*, 2019)

A second study explained the evaluation of the effect of saturated fat acid chain length on the transdermal behavior of ibuprofen-loaded microemulsions. In this study, the effect of the saturated fatty acid chain length in the oil phase on the behavior of Ibuprofen -loaded transdermal microemulsion was evaluated in vitro, ex vivo, and in vivo. Three oils classified as long fatty acid, medium fatty acid, and short fatty acid chain length oils, Cremophor RH40 (surfactant), and Transcutol P (cosurfactant) were selected after experimental optimization. The physicochemical properties of ME were characterized and found the medium fatty acid was an optimal oil phase with appropriate fatty acid chain length for IBU-loaded transdermal microemulsion, which exhibited excellent physicochemical properties, low toxicity, and good permeability profile (Ren *et al.*, 2014).

1.8. Objectives :

This work aims to develop a new microemulsion for the application of transdermal ibuprofen concerning the various micro-emulsions mentioned and updated in previous studies to improve their bioavailability. What distinguishes this study from the previous studies is the selection of a new formulation using a non-ionic surfactant that is non-toxic, safe, and can be used in food products. Few studies were reported about preparing microemulsion containing Ibuprofen (previous studies). However, we are planning in this study to develop a new microemulsion containing ibuprofen using non-toxic components (not used before for preparing microemulsions containing ibuprofen), in an attempt to improve the systemic and local effect of the drug with control release and can be used transdermally.

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CHAPTER TWO

Experiments and Methods

Chapter two: Experiments and Methods

2.1. Materials:

Table (4): Materials used in the preparation and analysis of ibuprofen MEs.

Materials	Suppliers	Notes
Ibuprofen (IBU)	Iol chemicals and pharmaceuticals limited, China Batch No. 4001/1201/18/A-4661	Gifted From ITQAN pharmaceutical company – Jordan
Isopropyl Myristate (IPM)	Sigma – Aldrich, USA Batch No. MKBV0742V	
Absolute Ethyl Alcohol (E)	Shandong aojin chemical technology, China Batch No.2020040802	
Polyoxyethylene sorbitan mono-oleate (TWEEN® 80)	Sigma – Aldrich, France Batch No. BCBT0817	
Sorbitan monolaurate (Span® 20)	Sigma – Aldrich, USA Batch No. MKBX8187V	Gifted From Almaerifa pharmaceutical (ALMA) company- Syria
Polyethylene glycol 600 (PEG600)	Nitika pharma company, India Batch No.PEGY3G107T	Gifted From ITQAN pharmaceutical company – Jordan
Acetonitrile (HPLC Grade)	Alpha – Chemika, India Batch No. A0037	
Methanol (HPLC Grade)	Sigma – Aldrich, France Batch No. I256HS	
Water (HPLC Grade)	Labchem, USA Batch No. W170605	
Chloroacetic acid	Schalau, Barcelona, Spain Batch No. AC07471000	
Ammonium hydroxide	Ricca Chemical Company, Batch No. IL-905	
Perchloric acid	Xilong chemical industry, China Batch No. 110301	

2.2. Instruments:

Table (5): Instruments used in this study

Instrument	Manufacture	Model	Serial Number	Origin
Sensitive electrical balance	Mettle Toledo ,	AB204	1114421517	Switzerland
Hot plate Magnetic stirrer	Labinco	L 34	34000	Notherlands
pH Meter	Martini instruments	MI 150	MA917B/1	Romania
Balance	OHAUS	TS4KS	3425	USA
Micro capillary Centrifuge	Sigma	201 M	42320	Germany
Refrigerator (Ultra-Low Temperature Freezer)	Haier Medical and laboratory products.	DW-86L628	BE060KEIT00B2E2 H0012	China
High-Performance Liquid Chromatography (HPLC)	Thermo Scientific Dionex Ultimate 3000	4 D-82110	For Pump: 8078897 For autosampler: 80778903 For detector: 8079207	Germany
Franz diffusion cells	Orchid scientific	EMFDC-08	FDC08/16-17/03	India
Rheometer	Brookfield	DV3T	M13-2100-A0415	India
Zeta-sizer	Malvern Instruments Ltd	NANO S	MAL1076435	United Kingdom

2.3. Methods:

2.3.1. Microemulsions (MEs) Preparation:

Ibuprofen was dissolved in the lipophilic phase (IPM), then the hydrophilic phase was added to the solution. The surfactant or surfactant mixture (Span 20 and Tween 80) was added dropwise with continuous stirring over a magnetic stirrer to a mixture that contains the lipophilic phase and hydrophilic phase until a transparent microemulsion was formed. The consumed surfactant or surfactant mixture amount from the burette was recorded. Different constituents of developed ibuprofen MEs are listed in table (6):

Table (6): Composition and concentration of formulated ibuprofen microemulsion

MEs Name	Lipophilic Phase (IPM) ml	Hydrophilic phase (ml)	Ibuprofen amount (mg)	Surfactant or Surfactant mixture ratio (ml)	Surfactant amount (ml)	Ibuprofen concentration (mg/ml)
System G2	3ml	2ml (50%E / 50% W)	1000 mg	3 Tween80 / 2 Span 20	1.5ml	154mg
System G9	3ml	2ml (50%E / 50% W)	1000 mg	4 Tween80 / 1 Span 20	1.5ml	154mg
System G14	3ml	2ml (25%E / 75% W)	1000 mg	4 Tween80 / 1 Span 20	1.4ml	156mg
System G18	3ml	2ml (25%DMSO / 75% W)	1000 mg	4 Tween80 / 1 Span 20	1.2ml	161mg
System G26	3ml	1.25ml (20%E / 80% W)	1000 mg	4 Tween80 / 2 Span 20	1.6ml	171mg
System G30	3ml	1.5ml (33.3%E / 66.7% W)	1000 mg	Tween80	1.3ml	172mg
System G27	1ml	2.3ml (87%PEG600 / 13% W)	1000 mg	1 Tween80 / 1 Span 20	1.1ml	227mg
System B1	4ml	1.25ml (20% E / 80% W)	1000 mg	4 Tween80 / 1 Span 20	1.2ml	155mg

System C1	3ml	1.5ml (16.7% E / 16.7% DMSO / 66.6% W)	1000 mg	Tween80	1.2ml	175mg
System F3	3ml	1.3ml (76.9%PEG600 / 23.1% W)	1000 mg	Tween80	0.8ml	196mg

2.3.2. Pseudo – ternary phase diagrams of the microemulsion system for ibuprofen :

Three-phase diagrams were drawn to find microemulsion existences area. The used three components are: lipophilic phase, surfactant or surfactant mixture, and hydrophilic phase either with ibuprofen or without ibuprofen for testing the influence of ibuprofen on this area. One formulation made for each cross point of the drawn three parallel lines to the three bases of the triangle. More formulations were made between the cross points on the border of the MEs area. Only the clear, stable formulation after mixing was identified to be a ME. One hundred mg of ibuprofen was added for each of these formulations for testing the influence of ibuprofen on the MEs area.

Table (7): Pseudo – ternary phase diagrams of microemulsion system

IPM (ml)	Surfactant Tween80: Span 20 (ml)	W50% E 50% (ml)
0.1	0.8	0.1
0.1	0.7	0.2
0.1	0.6	0.3
0.1	0.5	0.4
0.1	0.4	0.5
0.1	0.3	0.6
0.1	0.2	0.7
0.1	0.1	0.8
0.2	0.7	0.1
0.2	0.6	0.2
0.2	0.5	0.3
0.2	0.4	0.4
0.2	0.3	0.5
0.2	0.2	0.6

0.2	0.1	0.7
0.3	0.6	0.1
0.3	0.5	0.2
0.3	0.4	0.3
0.3	0.3	0.4
0.3	0.2	0.5
0.3	0.1	0.6
0.4	0.5	0.1
0.4	0.4	0.2
0.4	0.3	0.3
0.4	0.2	0.4
0.4	0.1	0.5
0.5	0.4	0.1
0.5	0.3	0.2
0.5	0.2	0.3
0.5	0.1	0.4
0.6	0.3	0.1
0.6	0.2	0.2
0.6	0.1	0.3
0.7	0.2	0.1
0.7	0.1	0.2
0.8	0.1	0.1

2.3.3. Viscosity Measurement :

An electric rheometer made by Brookfield model DV3T (India) was used to determine the viscosity and rheological property of MEs. Rheograms were established for the MEs with increasing and decreasing shear force at 25℃ on the bob and cup viscometer. Used a sufficient quantity of each MEs for applied the measurement.

2.3.4. Droplet size and zeta potential measurements :

A laser Doppler electrophoresis was carried out on the MEs with ibuprofen and without ibuprofen using a zeta-sizer made by Malvern in India. This is capable of measuring particle size ranging between 0.8 nm to 6.54 mm, in addition to measure zeta potential range -125 mV to +125mV.

2.3.5. Preparation of rat's skin:

Wistar rats were supplied from Jordan University of science and technology then kept in the animal house of Isra University. The used rats in this study were weighing between 200-250 g. Rat's hair was shaved by an electrical shaver before executing the rats. Then the skin was peeled. After that, the peeled skin was cleaned from adipose tissue carefully to avoid any injury formation. Then the skin was divided to small circular pieces with a diameter larger than 1.5 cm to fit Franz diffusion cell surface area . The skin prepared was wrapped in aluminum foil then put in a close plastic container and stored in a deep freezer at temperature -70℃. Thus, it was ready to use in the study for the Franz diffusion cell.

2.3.6. In vitro ibuprofen MEs penetration study using Franz diffusion cell:

A multiple Franz diffusion cell made by orchid scientific (India origin) that contains eight glass cells (10mm diameter, acceptor volume 5ml) fitted with thermo circulator water bath to maintain the temperature of the glass diffusion cells at 32± 1 ^{o}C. Eight frozen rat skin pieces were removed from the deep freezer and aluminum foils, and then thawed in a water bath at 32 ^{o}C before using in Franz diffusion cell. The acceptor compartments were filled with 5 ml of mobile phase composed of water: acetonitrile (40:60) and chloroacetic acid 4g/L neutralizing by ammonium hydroxide to adjust pH equal to three. The skin was fixed with a ring over the acceptor compartment medium (the upper surface of epidermis must be toward the donor compartment and the lower surface toward the acceptor compartment). Only 0.3 ml of each MEs system was applied over the skin. A flange was used to fix a glass disc and the ring over the donor compartment with acceptor compartment using 1.5 ml were removed after 1, 2, 4, 8, 24 h and replaced immediately by an equal volume of the same acceptor solution to maintain the volume constant. The removed sample for ibuprofen was injected into HPLC for analyzing the penetrated ibuprofen through the skin.

2.3.7. In vivo transdermal bioavailability study of MEs containing ibuprofen:

A 0.5 ml of ME C1 and 5g of Ibuprofen gel from the local market that contains 5% ibuprofen were applied over a rat skin in three white male rats for each preparation. A one ml blood sample was collected at zero time, 1, 2, 4, 8, 12, 16, and 24 h in heparin blood tubes. The blood samples were centrifuged at 5000 rpm at 4℃ for 10 min. the plasma parts were transferred into Polypropylene 1.5 ml Micro-centrifuge tube with a snap cap then 200 microliters (µL) of cold 0.5 N perchloric acid in methanol and 100 microliters (µL) of methanol were add (Canaparo *et al.*, 2000). The tubes were centrifuged at a rate of 11000 rpm at 4℃ for 10 min. the supernatant was transferred to the HPLC sample tube for analysis.

2.3.8. In vivo oral bioavailability study of ME containing ibuprofen:

A 0.5 ml of system C1 MEs was applied orally in three white male rats for this preparation. A one ml blood sample was collected at zero time , 1, 2, 4, 8, 12, 16, and 24 hin heparin blood tubes . The blood samples were centrifuged at 5000 rpm at 4℃ for 10 min. the plasma parts were transferred into Polypropylene 1.5 ml Micro-centrifuge tube with a snap cap then add 200 microliters (µL) of cold 0.5 N perchloric acid in methanol and 100 microliters (µL) of methanol were add (Canaparo et al., 2000). The tubes were centrifuged at a rate of 11000 rpm at 4℃ for 10 min. the supernatant was transferred to an HPLC sample tube for analysis.

2.3.9. Ibuprofen analysis using high-pressure liquid chromatography method :

Quantification of ibuprofen was performed on thermo scientific, Dionex ultimate 3000 HPLC chromatography system made in Germany connected with diode array detector using suitable standards. 10 µL were injected into C18 column system and separated using a mobile phase composed of water: acetonitrile (40:60) and chloroacetic acid 4g/L neutralizing by ammonium hydroxide to adjust pH equal to three (Asmus, 1985). Ibuprofen was detected at a wavelength of UV 254 nm for assaying ibuprofen in removed samples from Franz diffusion cell and samples from the supernatants that were collected

in vivo transdermal MEs study in addition to samples from bioavailability study at same conditions as above.

Table (8): Method parameters of HPLC system

Column	C18, 250*4.6mm, 5 μL particle size
Flow rate	1 ml / minute
Mobile phase	Acetonitrile : Water (60:40)
Run time	10 minutes
Wave length	254 nm
Temperature of column	40℃
Injectable volume	10 μL
Sample solvent	Methanol

A calibration curve was established for concentration 0.1, 0.5, 1, 2, 4, 6, 8, and 10 mg/ml to determine the content penetrated ibuprofen amount through the skin to the receptor and in the blood of rats.

2.3.10. Pharmacokinetic and statistical analysis :

The analysis and penetration studies related tests are all triplicated. Both the mean value and standard deviation are calculated. Origen program was used for statistical evaluation with a confidence interval of 95%. Passive diffusion is the way of transport across the skin.

Jss is the steady-state flux, calculated from the slope by plotting the penetrated amount per cm^2 (Q/A) against the time (t) as in equation 1 and 2:

$$Q/A = J_{ss} * t \quad \text{..... (1)}$$

From equation 1 :

$$J_{ss} = \frac{Q}{A(t - t_{lag})} = K_p C_v \quad \text{..... (2)}$$

From equation 2 :

$$K_p = \frac{K_{sc} D_{sc}}{h_{sc}} = \frac{J_{ss}}{C_v} \quad \text{..... (3)}$$

Table (9): abbreviations of pharmacokinetic parameters

Kp	Permeability coefficient
Dsc	Diffusion coefficient through stratum corneum
Ksc	Partition coefficient between the excipient and the stratum corneum
A	Skin surface area
Q	The cumulative mass penetrating a membrane
Cv	The constant drug concentration in the donor solution
hsc	The thickness of the membrane or the diffusion path length or stratum corneum

The elimination rate constant (K10), absorption rate constant (K01), area under the curve (AUC) were estimated for the drug from data after transdermal and oral application of preparation using pheonix® program (Phoenix Version 7.0, Certara, L.P.). Moreover the percentage relative bioavailability was calculated using equation 4:

$$\text{Percentage relative bioavailability} = \frac{\{AUC\}ME / DoseME}{\{AUC\}Gel / DoseGel} * 100 \quad \text{..... (4)}$$

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CHAPTER THREE

Results

Chapter three: Results

3.1. HPLC Method and calibration curve

The calibration curve was established by plotting the area under curve against the concentration of ibuprofen using Origin program for concentration 0.1-10 mg/ml showed linearity of 99.99% and regression standard division of 2.4332. The straight-line equation number (1) was used for further calculation of penetrated ibuprofen amount.

$$A=7.78682\ C+0.50036 \quad \text{(1)}$$

A: Area under the curve

C: ibuprofen concentration

For calculating total penetrated ibuprofen amount the following developed equation number (2) was used:

$$IBU_{amount} = \left[\frac{(A-0.50036)}{7.78682} * 5 \right] + (IBU_{previous-amount}) \quad \text{(2)}$$

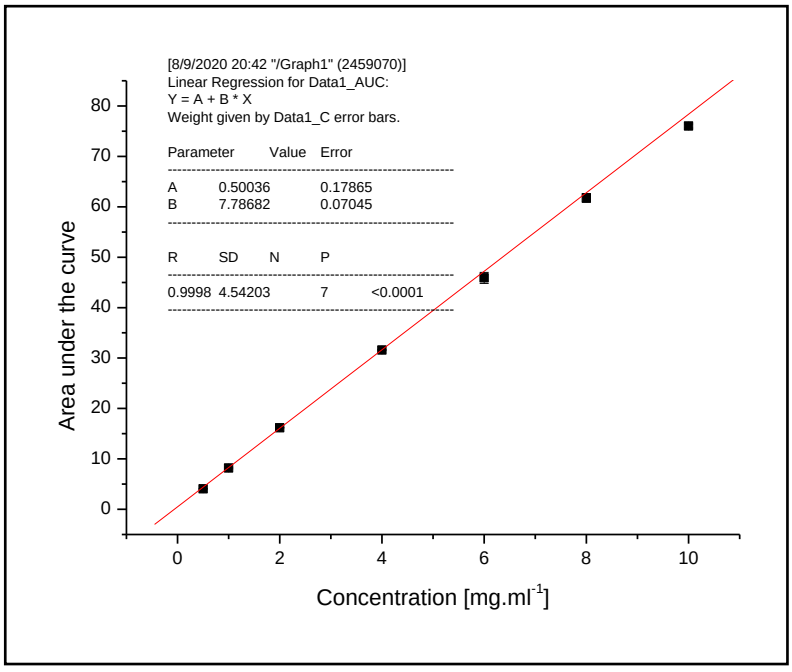

Figure (9): Calibration curve of ibuprofen

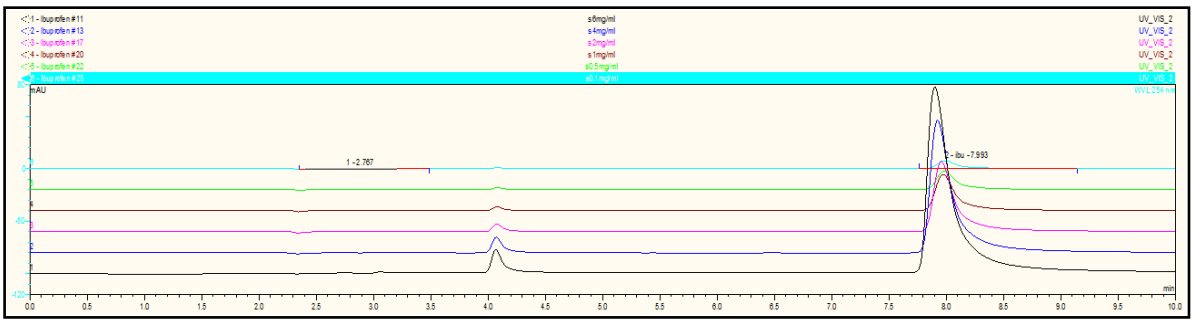

Figure (10): HPLC Calibration curve of ibuprofen

3.2. Droplet size and zeta potential measurements for ibuprofen :

The droplet size of different MEs was less than 100 nm. All MEs zeta potentials measurements were around zero as expected. However, the PDI of MEs system ranges between (0.3 to 0.7).

The PDI of MEs containing hydrophilic phase that is composed of a mixture of ethanol and water, varied with the surfactant ratio and the composition of MEs.

Using tween80 only as a surfactant in MEs results in the lowest PDI comparing with samples using mixture of other surfactants. Besides, the use of a high amount of surfactant or mixture of surfactants leads to reduce PDI. Furthermore, the consumed surfactant amount decreased with decreasing the proportion of water in hydrophilic phase which in turn led to increase the concentration of incorporated ibuprofen.

The PDI of ME which contains a hydrophilic phase composed of a mixture of DMSO and water, increased proportionally with increasing hydrophilic phase and which resulted in an increase in droplet size diameter. Furthermore, the MEs containing ethanol have lower PDI and droplets size. In contrast, adding DMSO to ME led to higher PDI and Droplets size.

The MEs which had a hydrophilic phase composed of a mixture of PEG 600 and the lowest percentage of water showed the highest droplet sizes and lowest PDI.

The results of zeta sizer including droplet size diameter, zeta potential, and poly dispersity index of MEs with ibuprofen are summarized in the table (10):

Table (10): The measured droplet size, poly disparity index (PDI) and zeta potential for different formulated ibuprofen MEs using zeta-sizer

ME System Name	Z-Average Diameter.nm	PDI	Zeta Potential
ME G26	12.9	0.395	-0.0704
ME C1	18.92	0.561	0.0238
ME F3	11.69	0.352	-0.426
ME G30	18.14	0.466	0.00617
ME G27	89.1	0.361	-0.0182
ME G2	12.13	0.494	-0.126
ME G9	11.1	0.313	-0.0245
ME G14	59.03	0.399	0.0356
ME B1	50.05	0.568	-0.142
ME G18	24.33	0.7	-0.0892

3.3. Three-phase diagrams :

A three-phase diagram of MEs was established for MEs composed of IPM, the hydrophilic phase which contains water: ethanol (1:1) and the mixture of tween 80: span 20 (4:1) without ibuprofen in below figure (11)

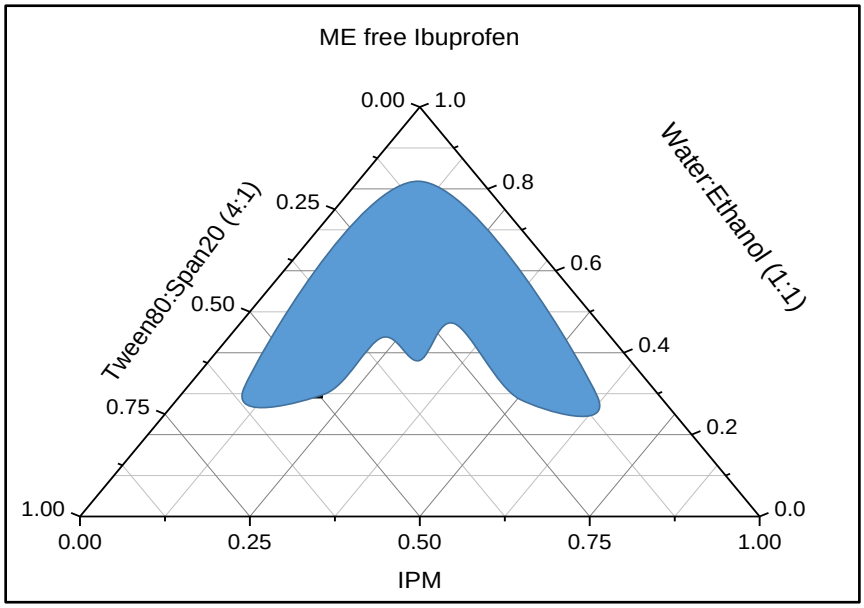

Figure (11): The three-phase diagrams for MEs composed of IPM, Water: ethanol (1:1) and the mixture of tween80:span20 (4:1) without ibuprofen

Also, another three-phase diagram of MEs was established for MEs composed of IPM, the hydrophilic phase which contains water: ethanol (1:1) and the mixture of tween 80: span 20 (4:1) with 100 mg of ibuprofen in figure (12)

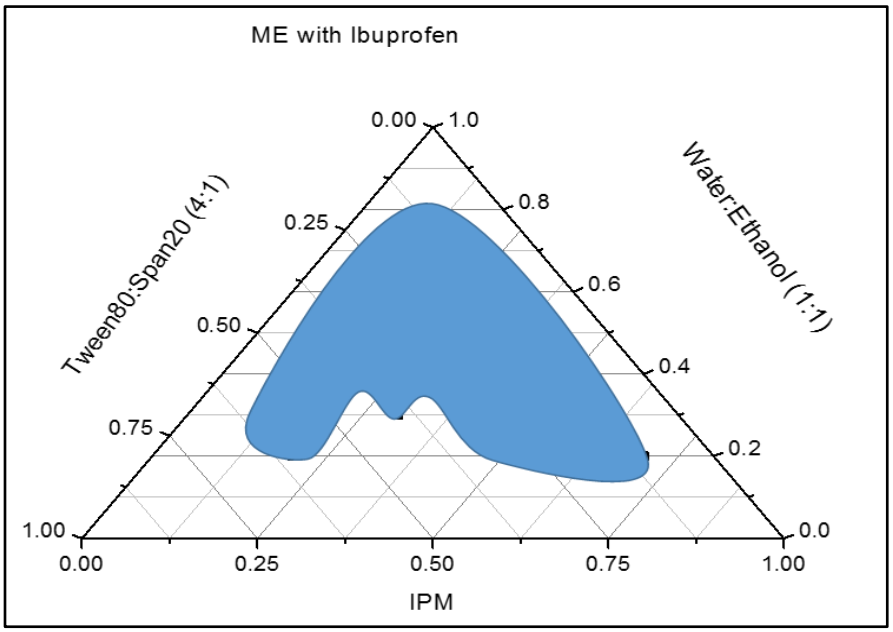

Figure (12): The three-phase diagrams for MEs composed of IPM, Water: ethanol (1:1) and the mixture of tween80:span20 (4:1) with ibuprofen

The area of clear ME without ibuprofen was estimated at fractions of more than 0.7 of IPM and less than 0.3 of the hydrophilic phase. After the addition of 100 mg of ibuprofen, this area of ME was shifted in the lower part to increase the range of fractions of hydrophilic from (0.8 -0.3 to 0.8-0.2). Consequently, More MEs were formed for lower fractions of the hydrophilic phase.

3.4. Rheological properties :

Rheological properties were measured by bob and cup instrument with increase share rate for different MEs and the results are represented in the figure (13). The rheological properties show that the share rate is proportional to share stress. However, the plotting of shear rate against the shear stress gives a straight line. This result gives evidence that

MEs in our study has Newtonian characteristics. Furthermore, the viscosity for different MEs formulation against shear rate was constant (figure 14). Consequently, all formulation exhibited ideal viscosity (Newtonian viscosity).

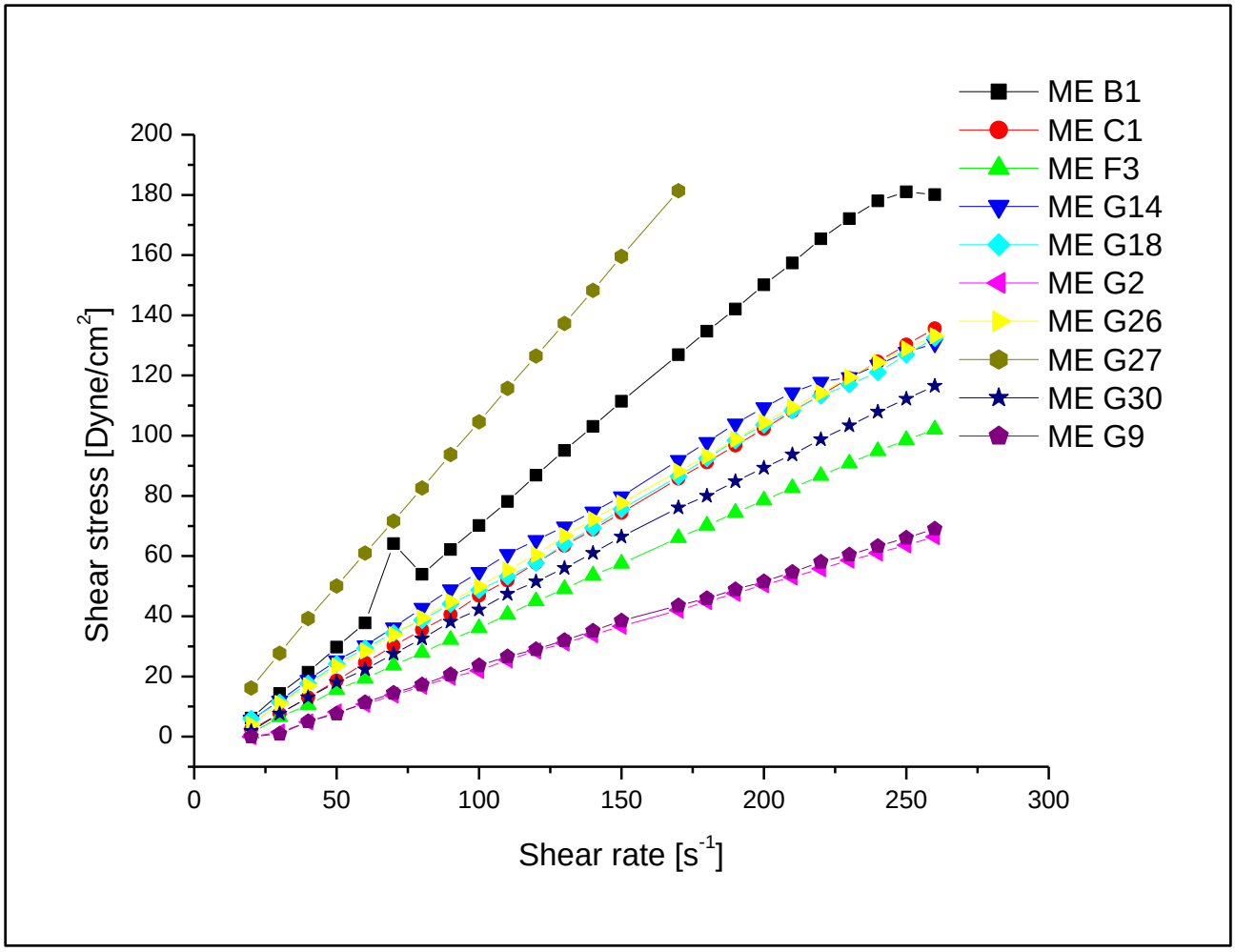

Figure (13): The rheograms of different ibuprofen MEs that illustrate the relationship between shear rates and shear stress

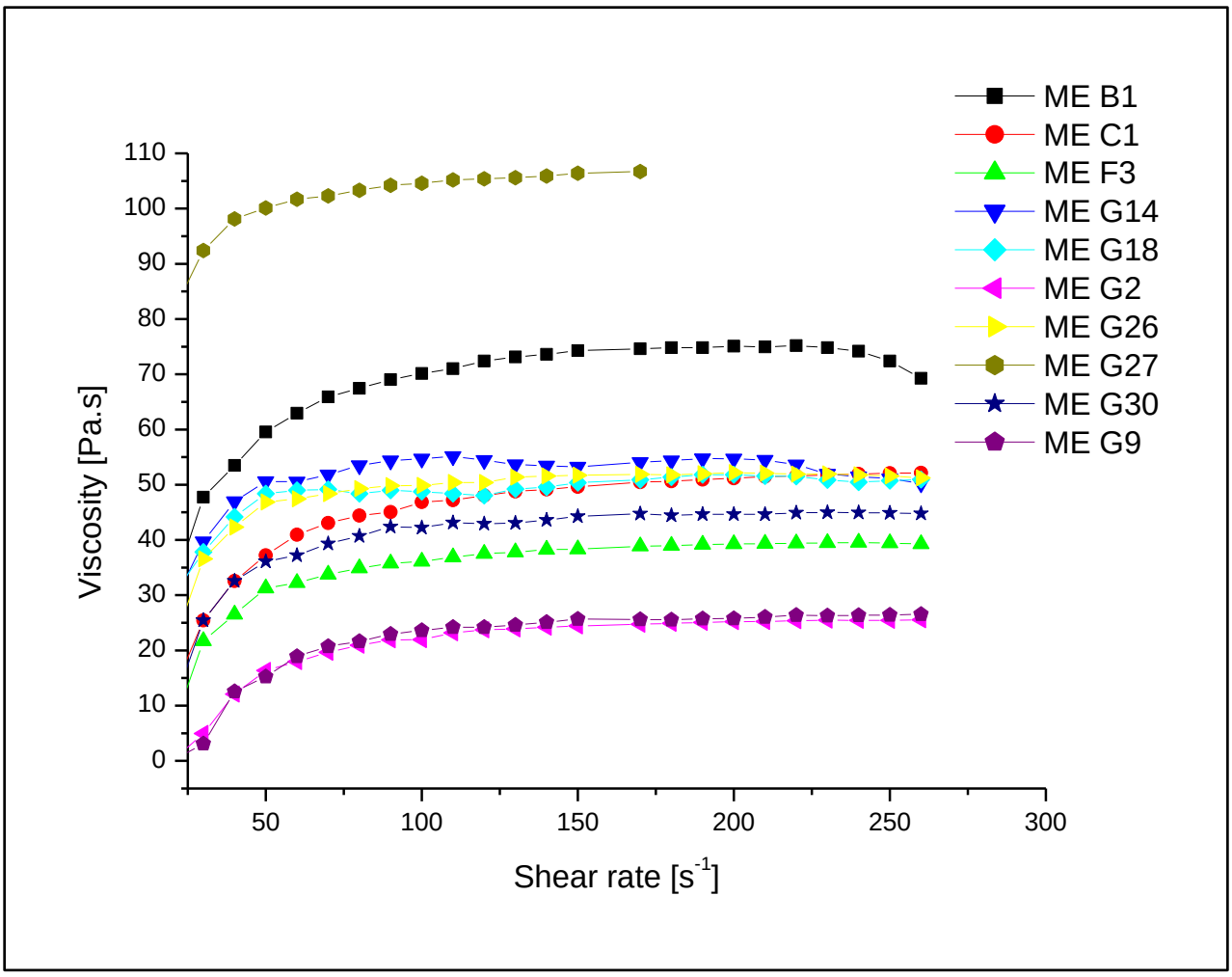

Figure (14): The rheograms of different MEs containing ibuprofen that illustrate the relationship between shear rate and viscosity

3.5. In vitro study of MEs containing ibuprofen using Franz diffusion cells:

Eight formulas were tested by the Franz diffusion cells. Six of them contains different ratios of ethanol and water. The other two MEs are different in the composition of the hydrophilic phase. One of the remaining MEs contains PEG600 with water (ME F3) and the other one contains ethanol, DMSO, and water. Although, ME C1 to study the effect of the addition of DMSO to the ibuprofen on the penetration. The dermal penetrability of Ibuprofen through shaved rat skin was monitored using Franz diffusion cell over 24 h. The penetrated ibuprofen was evaluated by removing 1.5ml periodically from the acceptor medium. The samples were analyzed for ibuprofen using HPLC. The removed

ibuprofen in each sample was calculated and added to the subsequent estimated amount. Penetrated ibuprofen per cm^2 was measured over 24 h and the cumulative measured amount per cm^2plotted against the time. The penetration profiles for different MEs are represented in the below figure (15).

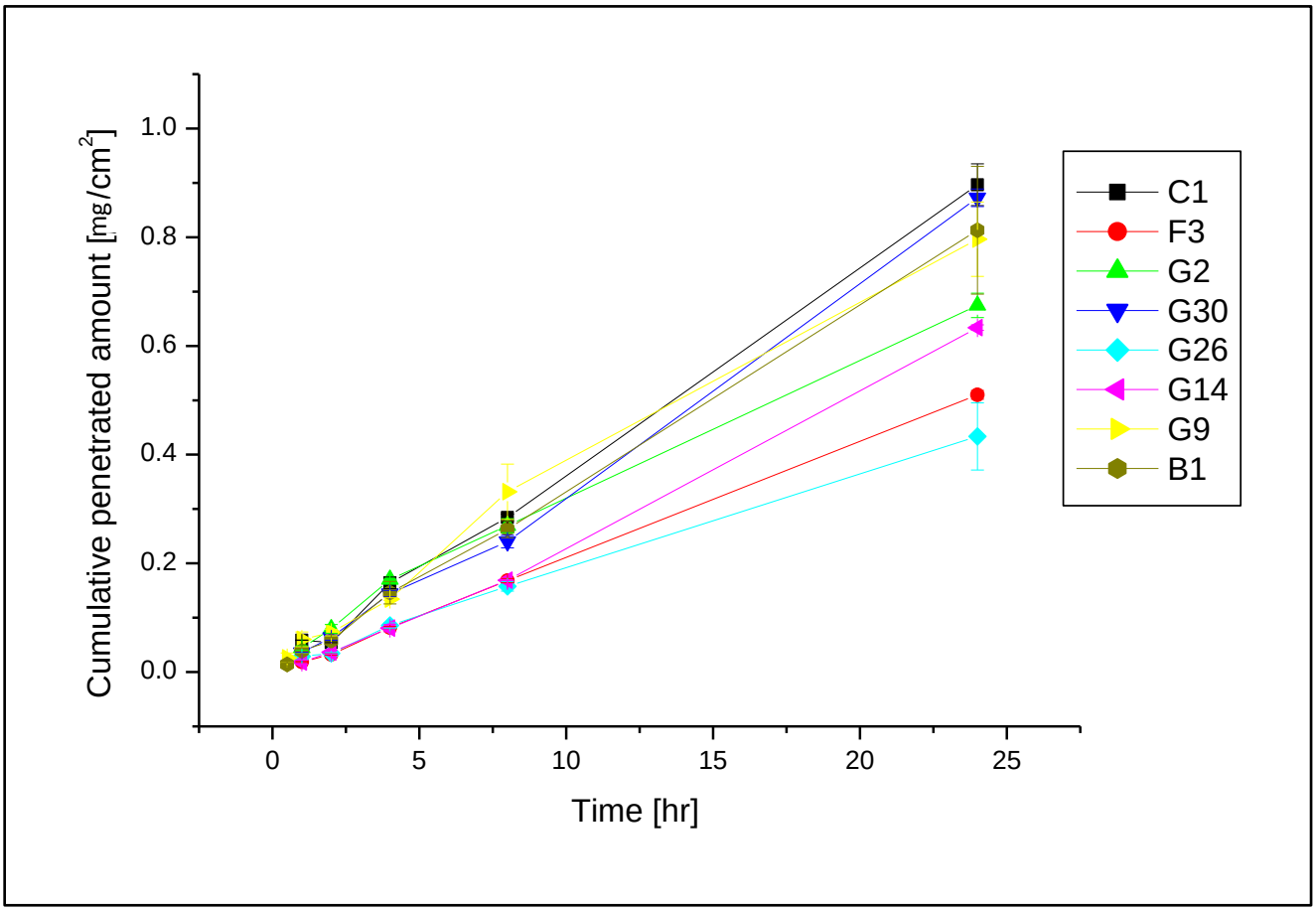

Figure (15): cumulative penetrated ibuprofen amounts per mg/cm^2 in different MEs formulations against the time per hour (h)

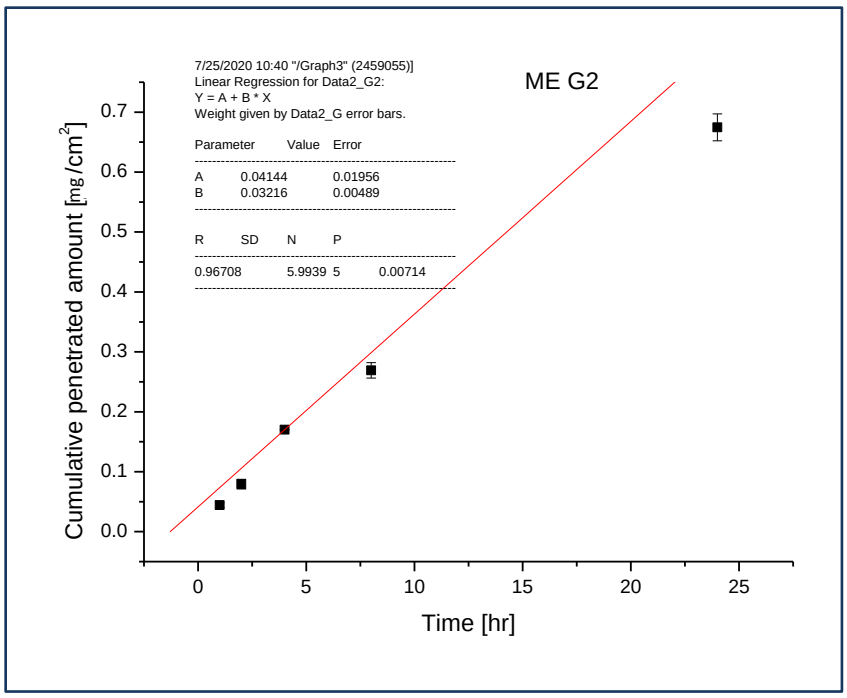

Figure (16): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (G2) formulation against the time per hour (h)

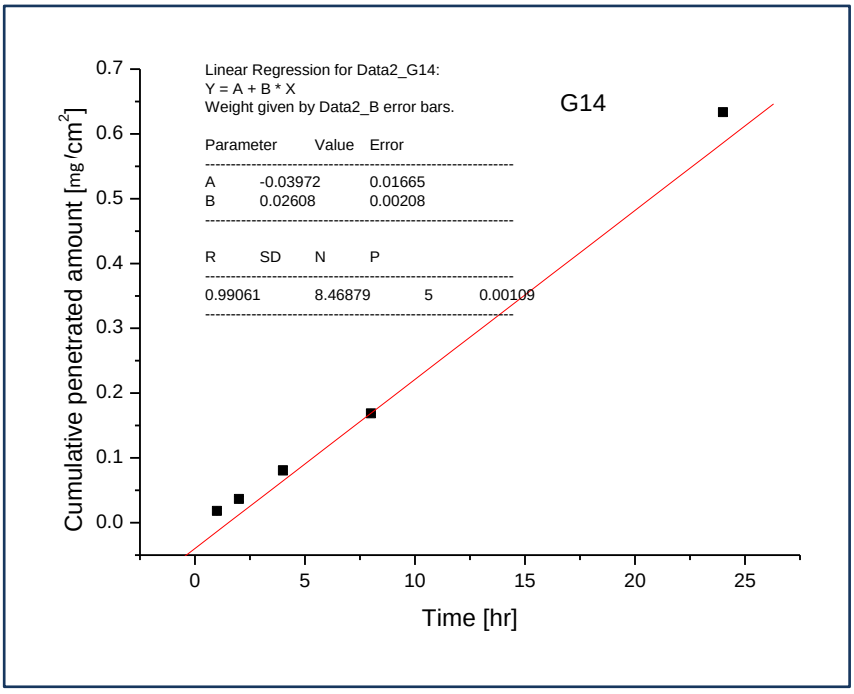

Figure (17): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (G14) formulation against the time per hour (h)

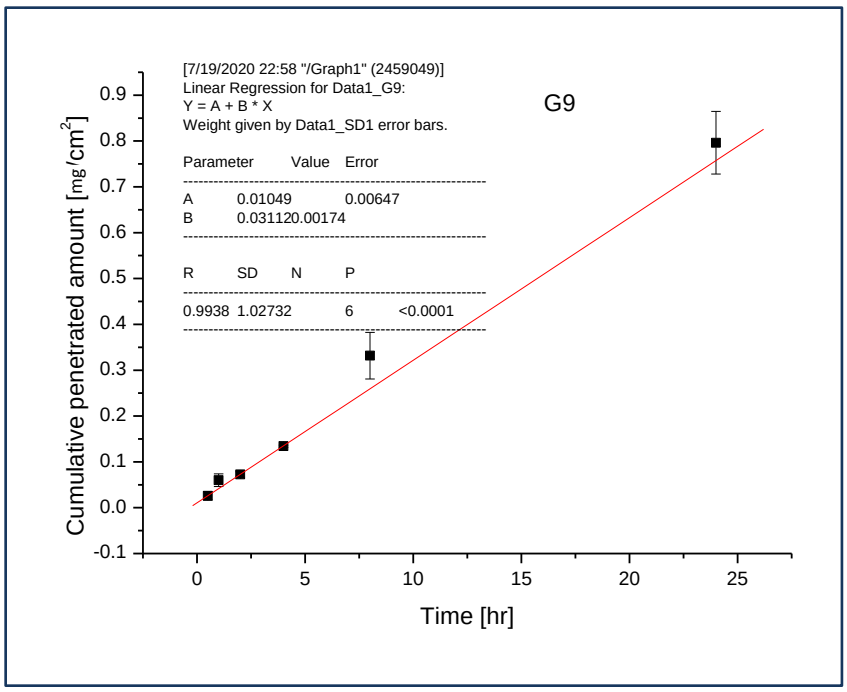

Figure (18): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (G9) formulation against the time per hour (h)

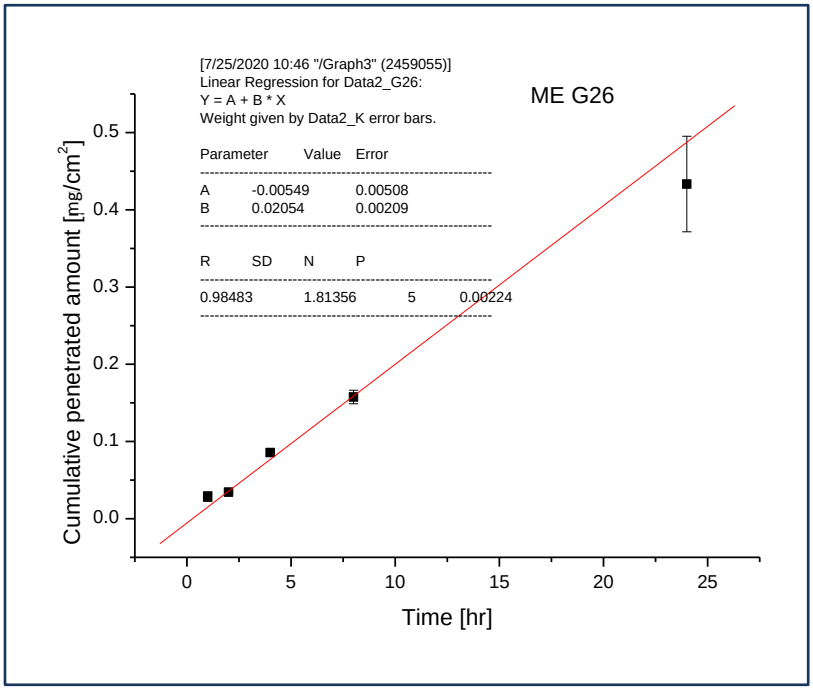

Figure (19): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (G26) formulation against the time per hour (h)

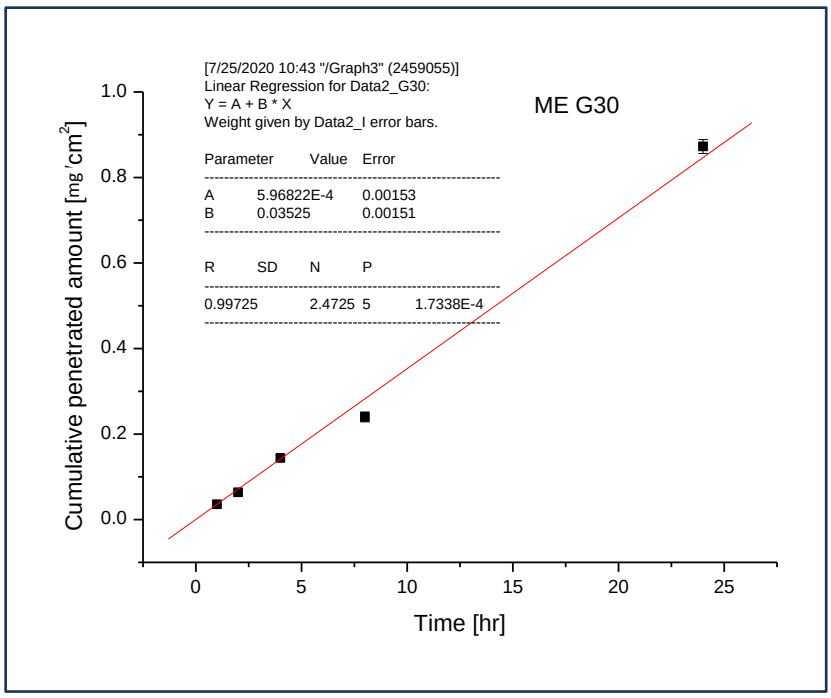

Figure (20): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (G30) formulation against the time per hour (h)

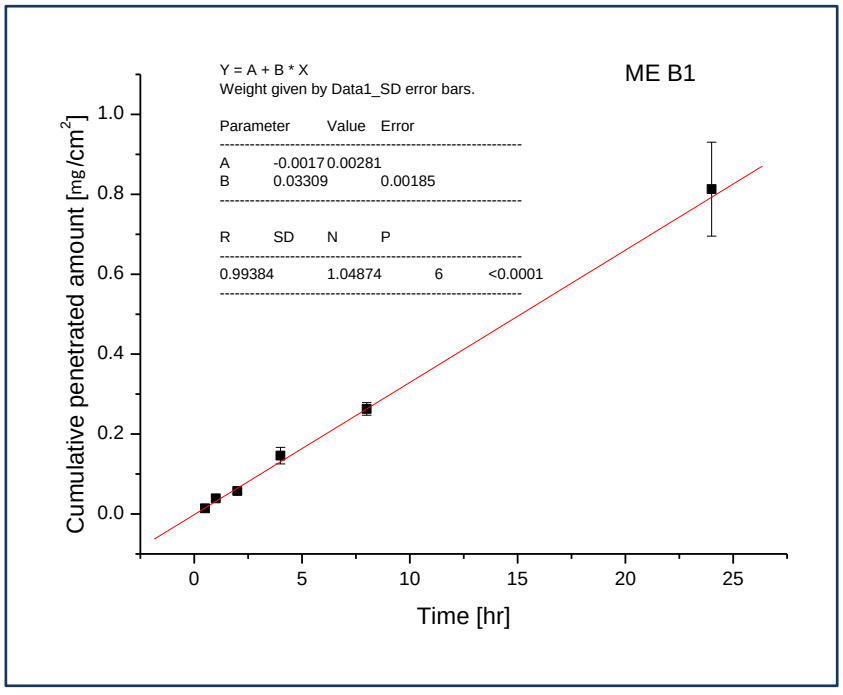

Figure (21): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (B1) formulation against the time per hour (h)

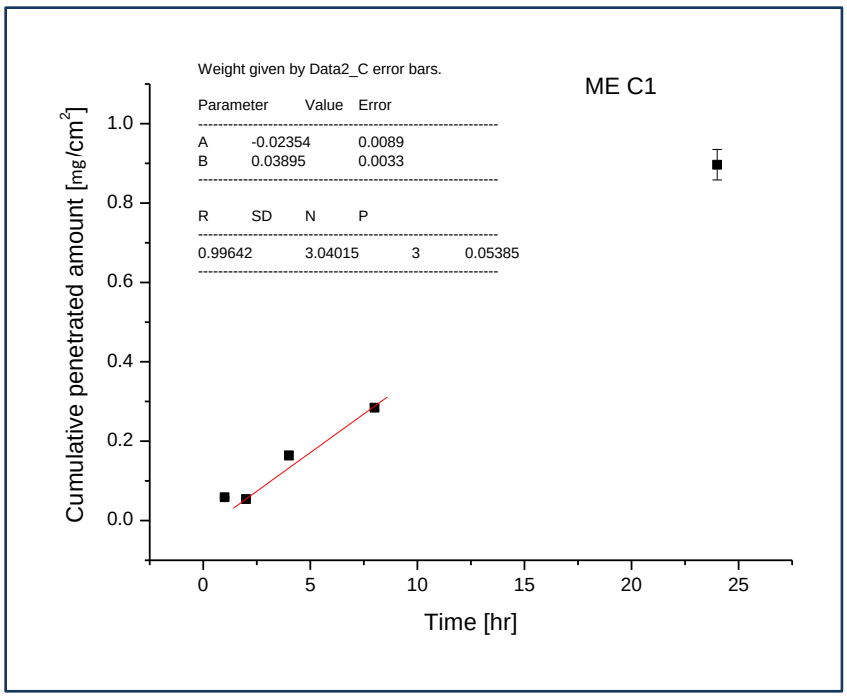

Figure (22): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (C1) formulation against the time per hour (h)

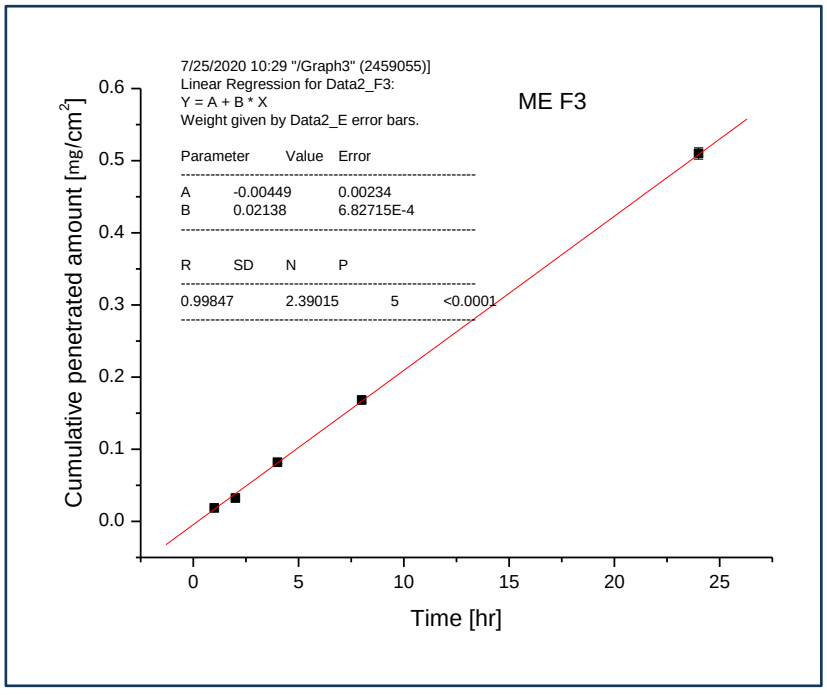

Figure (23): Cumulative penetrated ibuprofen amounts per mg/cm^2 in ME (F3) formulation against the time per hour (h)

Table (11): The Flux of different ibuprofen MEs through rat's skin using Franz diffusion cell

MEs	Flux (Jss) (mg/ml.hr)	SD
G14	0.02608	0.00208
G26	0.02054	0.00209
G30	0.03525	0.00151
G9	0.03112	0.00174
B1	0.03309	0.00185
C1	0.03895	0.0033
F3	0.02138	$6.83E^{-04}$
G2	0.03216	0.00489

The ME (C1) had the highest flux where the ME formulation (G30) had the second value of flux among developed MEs. The flux of ME (C1) is higher than ME (G30). Since, the use of DMSO in ME (C1) increases the flux. The lowest flux in all MEs was observed for ME (G26). This may related to the use of little quantity co-surfactant in ME (G26).

3.6. In vivo transdermal ibuprofen study in rats:

Volume of 0.5 ml of ME (C1) and 5g of gel from local marketed Ibuprofen were tested on shaved rat skin for the transdermal bioavailability. The amount of penetrated ibuprofen through the skin in plasma was quantified using the HPLC method over 24h. Furthermore, the area under the curve (AUC), the absorption constant (K01), elimination rate constant (K10), maximum concentration Cmax, time of maximum concentration (Tmax) were estimated for both ME C1 and ibuprofen gel calculated using phoenix program. The results are mentioned in the table (12).

Table (12): The area under the curve (AUC), elimination rate constant (K10), maximum concentration (C_{max}), time of maximum concentration ($_{Tmax}$) of the transdermal ME C1 and ibuprofen gel

Parameter	**Unit**	ME (C1)	Gel
		Value	**Value**
Lambda_z (K10)	1/h	0.122912354	N/A
t1/2	hr	5.639361356	N/A
Tmax	hr	8	24
Cmax	mg/ml	0.06434	0.0212
Tlag	H	0	0
Clast_obs/Cmax		0.107553621	1
AUC 0-t	mg/ml*h	0.464408	0.291854
AUC 0-inf_obs	mg/ml*h	0.52070828	N/A
AUC 0-t/0-inf_obs		0.891877501	N/A

The results show a difference in the maximum time of absorption between two formulation dosage forms. In the case of ME C1, the maximum time of absorption was 8h while ibuprofen gel 24h. In addition to the maximum concentration of ME C1 is higher approximately three times than ibuprofen gel. Also, no lag time was estimated for both two dosage forms. In addition, the estimated percentage of relative bioavailability of transdermal ME C1 in comparison to ibuprofen gel was approximately 453%. We can conclude that the bioavailability of ME C1 is higher than ibuprofen gel.

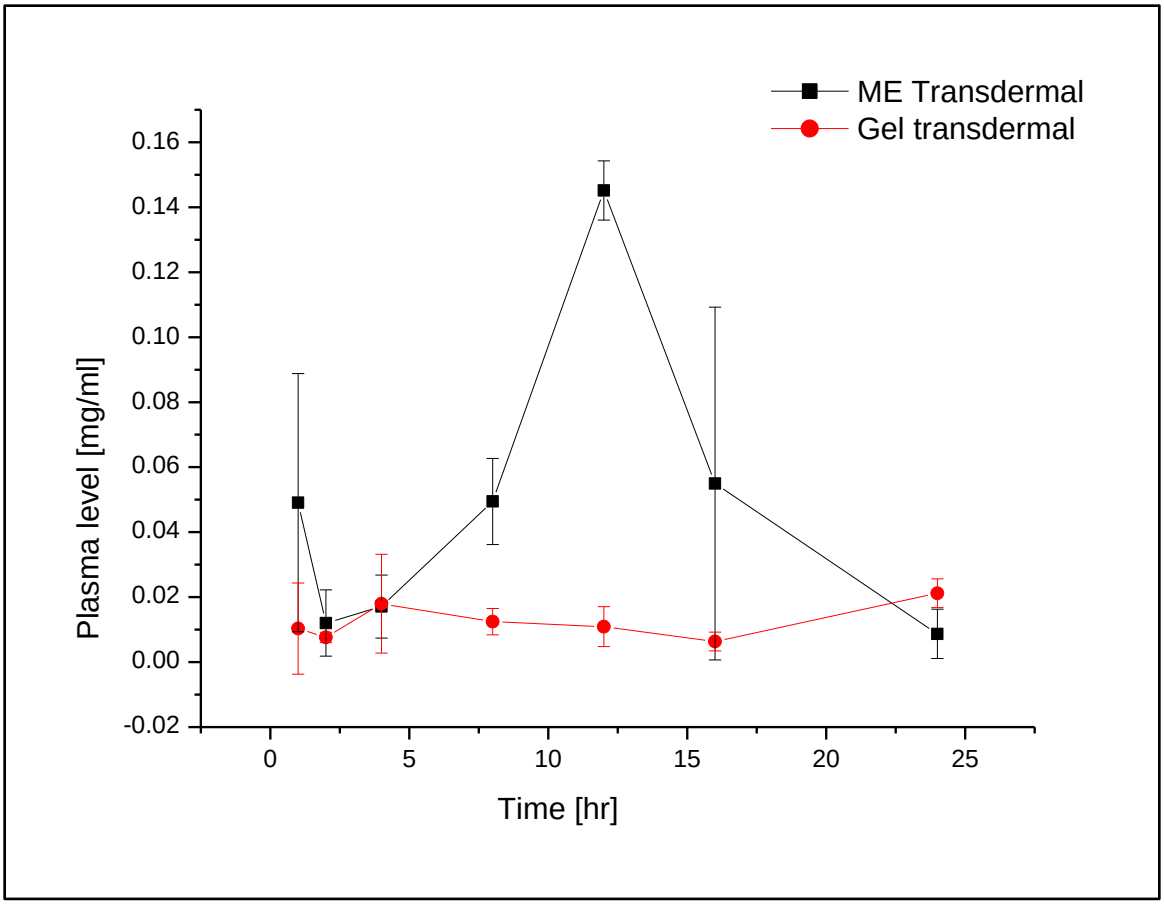

Figure (24): Plasma level time curve of transdermal ibuprofen in rats

3.7. The oral bioavailability of ibuprofen MEs in rats :

ME formulation (C1) was chosen to be tested for oral bioavailability in rats. The absorbed amount of ibuprofen was monitored in plasma using the HPLC method over 24 h.

The plasma level versus time curve was plotted over 24 h. Furthermore, the area under the curve (AUC), the absorption constant (K01), elimination rate constant (K10), maximum concentration Cmax, time of maximum concentration (Tmax) were estimated for ME (C1) using phoenix program. The results are mentioned in the table (13).

Table (13): The area under curve (AUC) , elimination rate constant (K10) , maximum concentration (C_{max}), time of maximum concentration (t_{max}) of the oral ME C1

Parameter	Unit	Value
Lambda_z (k10)	1/h	0.205128297
t1/2	H	3.379090999
Tmax	H	12
Cmax	mg/ml	0.09696
Tlag	H	0
Clast_obs/Cmax		0.089727723
AUC 0-t	mg/ml*h	1.068621
AUC 0-inf_obs	mg/ml*h	1.111033481
AUC 0-t/0-inf_obs		0.9618261

The results show that the maximum time of absorption of orally given ME C1 was 12h and the estimated maximum concentrations 0.096 mg /ml while in case of transdermal ME C1 the estimated maximum concentration 0.064 mg/ml. In addition, the estimated percentage of relative bioavailability of oral ME C1 in comparison to transdermal was approximately 658%. Also a no lag time was observed for orally ME C1.

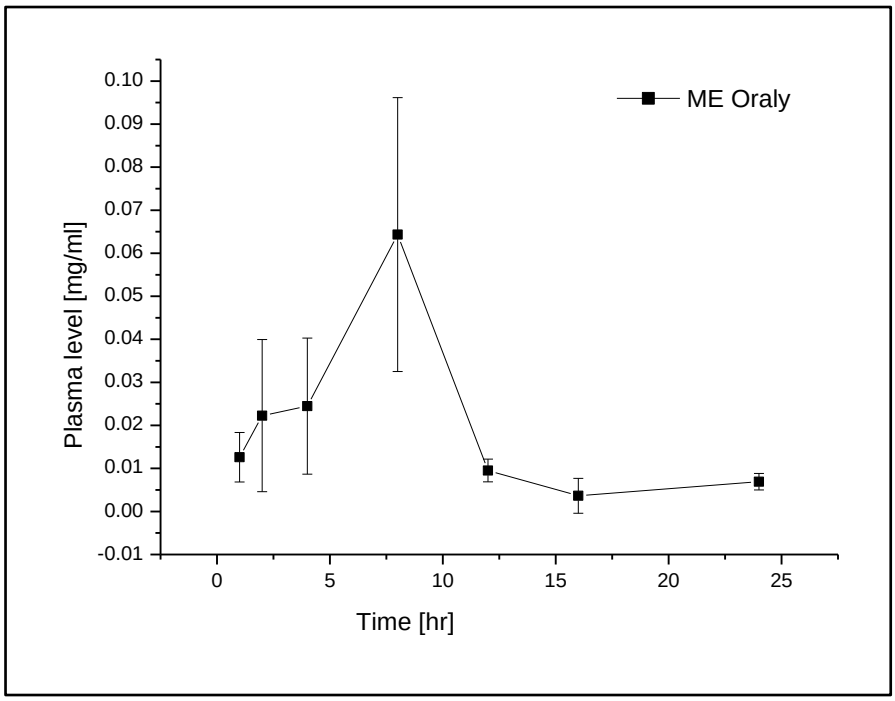

Figure (25): Plasma level time curve of oral ibuprofen in rats using ME

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CHAPTER FOUR

Discussion

The system ME G27 had the highest concentration of ibuprofen where ME G2 and ME G9 had the lowest concentration of ibuprofen. This may be related low fraction of water in the hydrophilic phase in ME G27 comparing to the higher amount of water in ME G2 and G9. The use of low content of water led to decrease the consumed surfactant amounts which in its turn led to increase the concentration of incorporated ibuprofen (Alyoussef alkrad *et al.*, 2016).

Three groups of ME containing ibuprofen were prepared according to the composition of the hydrophilic phase. The first group contains ethanol and water as the hydrophilic phase with different ratios. ME G9 which consumes the relatively high surfactant amount showed the lowest droplet size in this group. ME F3 which contains only tween80 as a surfactant in the second group (containing PEG 600 and water as the hydrophilic phase with different ratios) had the lowest droplet size. However, the PDI for MEs in this group was similar approximately. The lowest droplet size was observed in the third group containing DMSO was observed for ME C1 which contains tween80 only as a surfactant.

Furthermore, the droplets size decrease with increasing the tween80 content or proportion in the mixture of the surfactant. However, all MEs had Newtonian properties. Also, the viscosity of ME G27 was higher than other formulated systems which may be related to presence of PEG600. The ME G9 is the lowest viscosity than other formulated systems which contains ethanol and water as a hydrophilic phase. However, it was observed a decrease in the viscosity with increasing in ethanol content. The MEs (C1 and G18) containing DMSO showed moderate viscosity in comparison to other MEs.

The present investigation revealed that both the rate and extent of ibuprofen delivery across rat's skin were highly dependent on the concentration, type of oil, surfactant, co-surfactant, and water amount of developed formulations. Regarding the measurement of flux using Franz diffusion cell for the different systems, ME G9 which has similar formula as ME G2 showed higher flux which may be related to higher content of tween80 in ME G9 in comparison to ME G2. However, the highest flux among studied MEs systems was observed for ME C1 while the lowest flux was for ME G26. However,

the difference between them in the structure is the addition of DMSO to ME C1, which may be the responsible for the increase in the flux (Shabbir *et al.*, 2018). MEs G30 and C1 containing Tween80 alone as a surfactant showed highest flux except ME F3. The using of higher fraction of ethanol (50%) in ME G9 led to incase the flux of ibuprofen comparing to ME G14 which contains (25 %) faction of the hydrophilic phase. The use of Tween80:Span20 (4:1) as a surfactant led to increase the flux in ME B1 comparing to Tween80:Span20 (4:2) which used in ME 26. However ME 26 contains less amount of IPM (3ml) and it has higher concentration of ibuprofen. In vivo study, the maximum concentration of transdermal ME C1 higher three times than traditional ibuprofen gels. That the flux of ibuprofen in MEs as carriers higher than of ibuprofen in gel. This may be related to rheological properties and droplets size of MEs. As well as, the bioavailability of oral ME C1 results showed that using ME as a carrier for ibuprofen increased the absorption rate compared to the transdermal ME.

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CHAPTER FIVE

Conclusion

Chapter Five: Conclusion

Using non-ionic surfactants was possible to formulate stable MEs containing ibuprofen successfully. These MEs had colloidal characteristics regarding their droplet size, transparency, and rheological properties. Also, MEs as carriers facilitated the penetration of ibuprofen though rats' skin as well as via the gastrointestinal tract into the blood circulation. The flux of MEs containing ibuprofen was related to two main factors which are hydrophilic phase and surfactant nature. Finally the developed ME C1 which has higher flux compared to other MEs had also higher in vivo oral and transdermal bioavailability in rats in comparison to marketed tested gel.

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Appendices

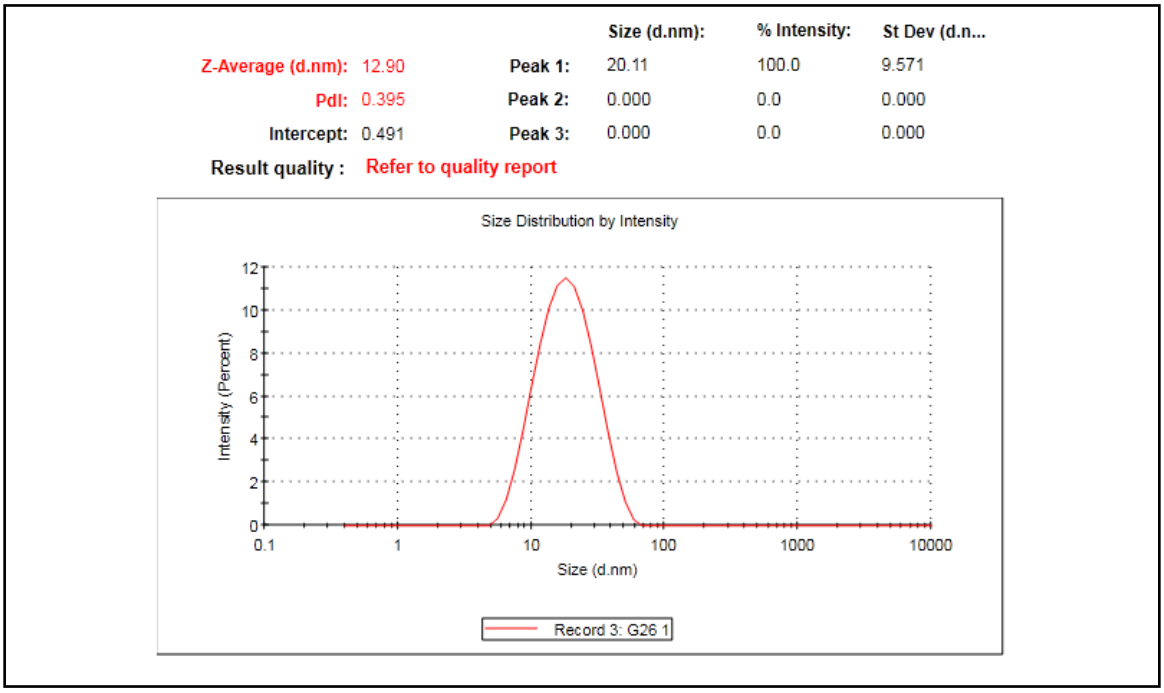

Figure (26): Droplet size with PDI of microemulsion G26 system

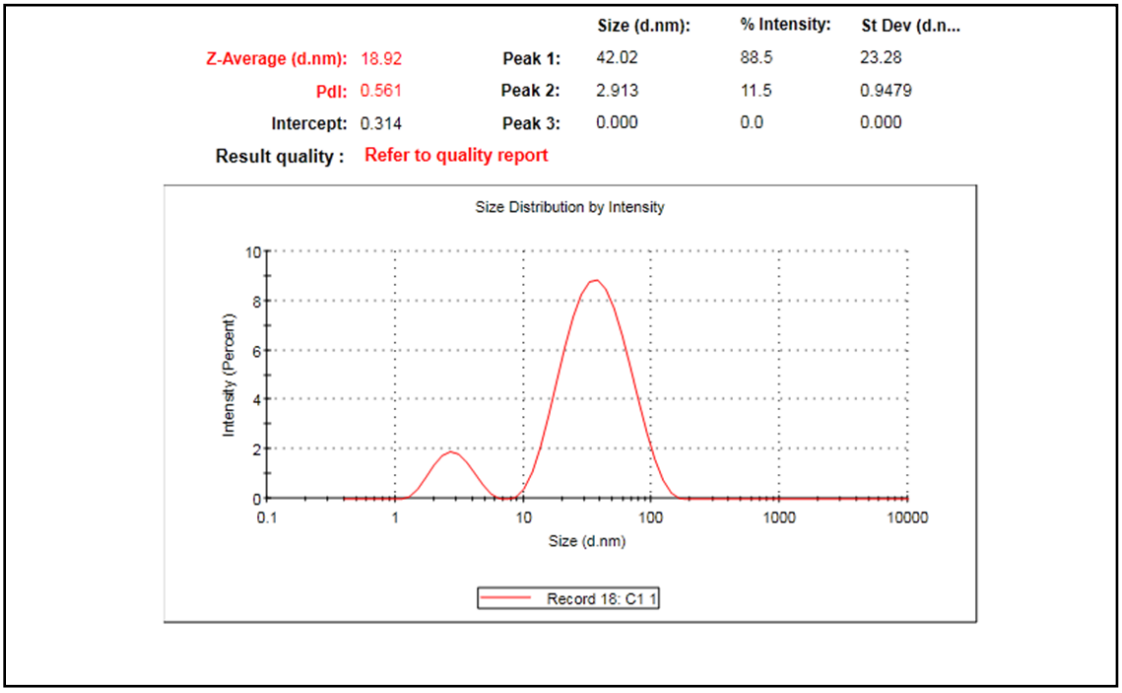

Figure (27): Droplet size with PDI of microemulsion C1 system

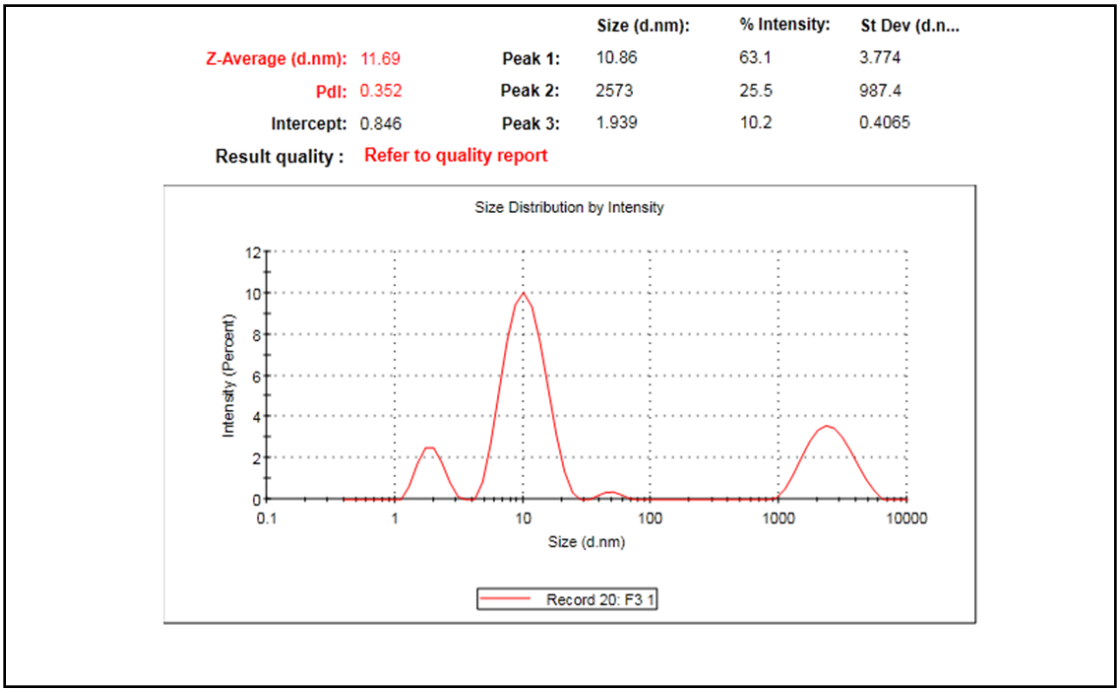

Figure (28): Droplet size with PDI of microemulsion F3 system

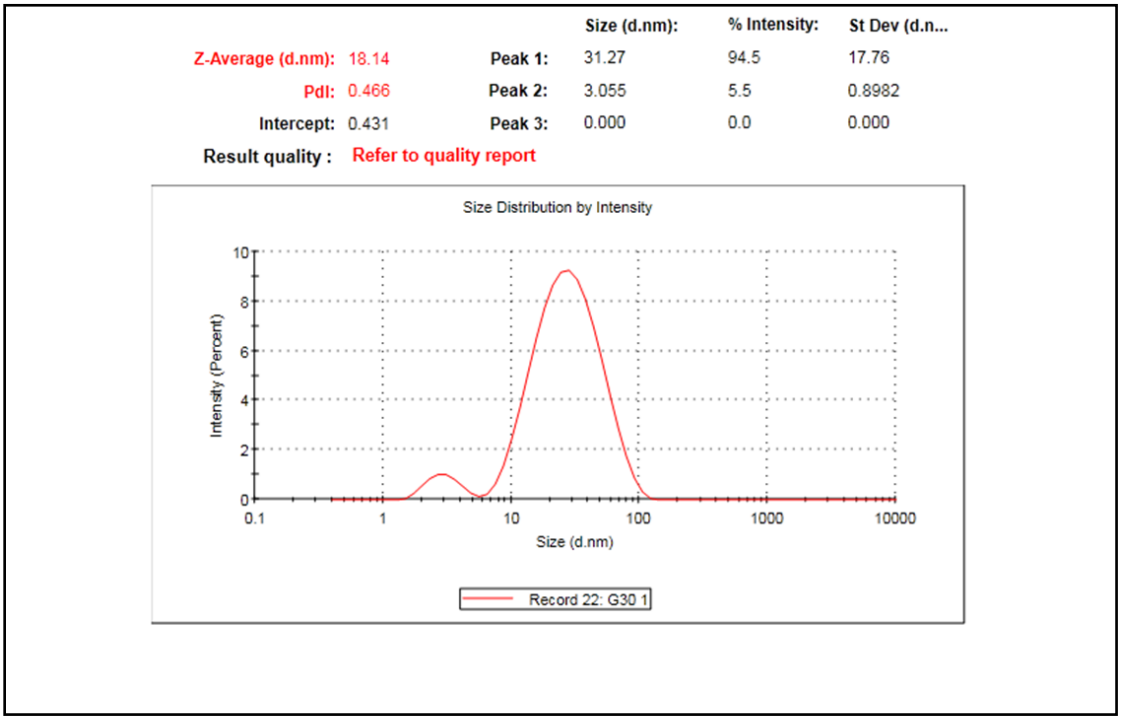

Figure (29): Droplet size with PDI of microemulsion G30 system

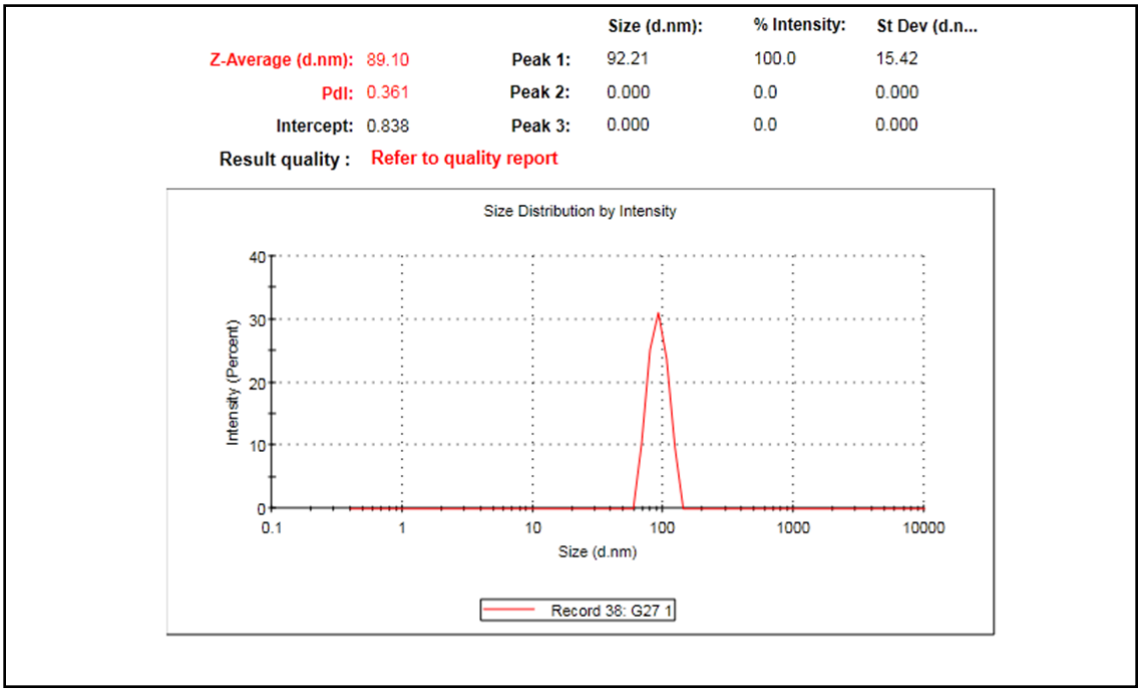

Figure (30): Droplet size with PDI of microemulsion G27 system

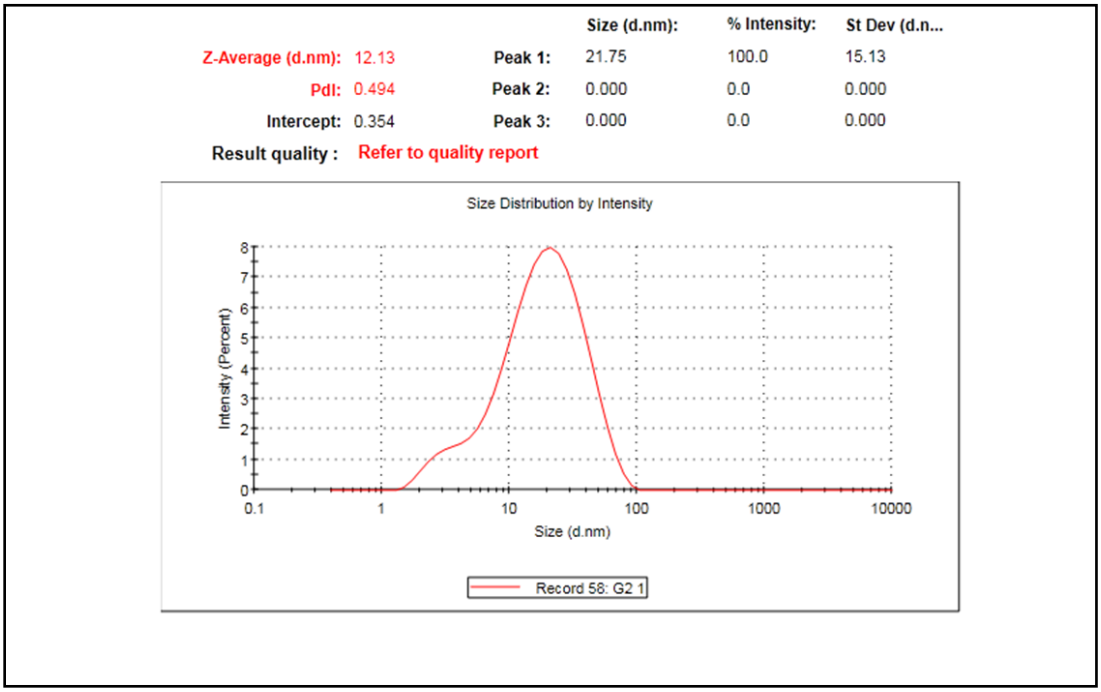

Figure (31): Droplet size with PDI of microemulsion G2 system

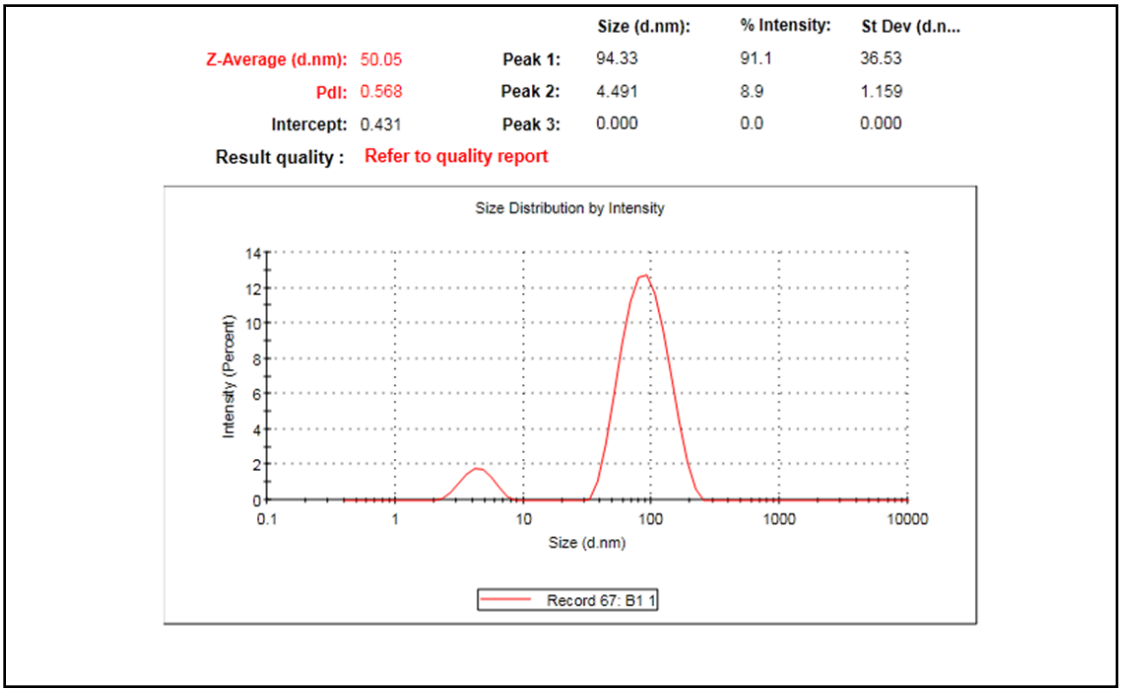

Figure (32): Droplet size with PDI of microemulsion B1 system

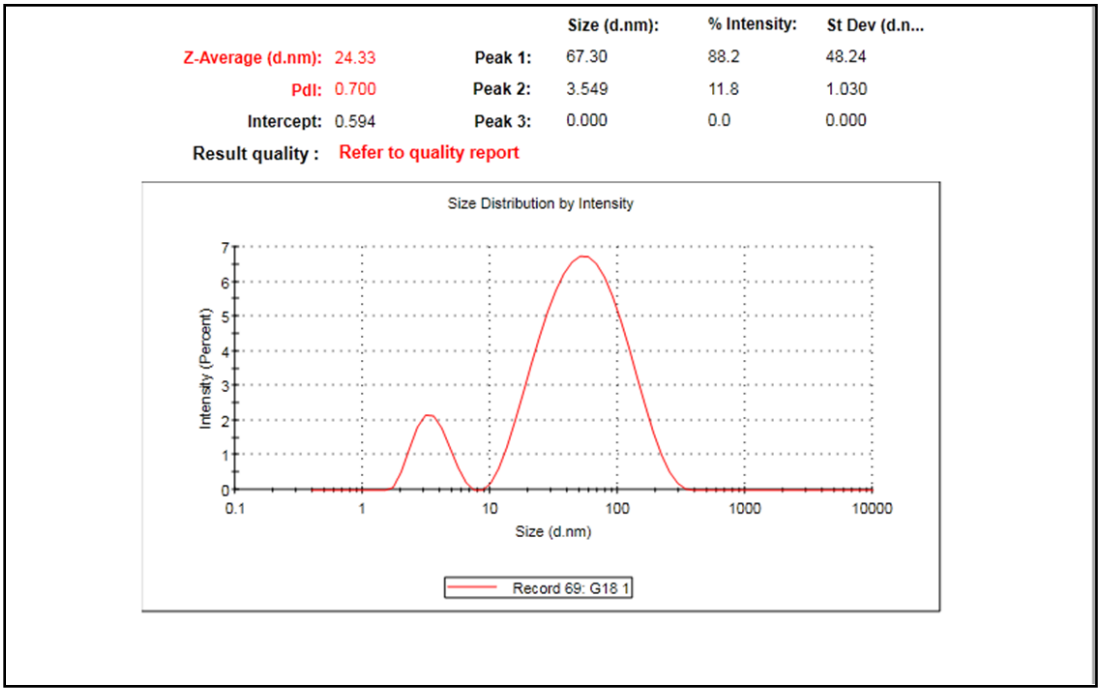

Figure (33): Droplet size with PDI of microemulsion G18 system

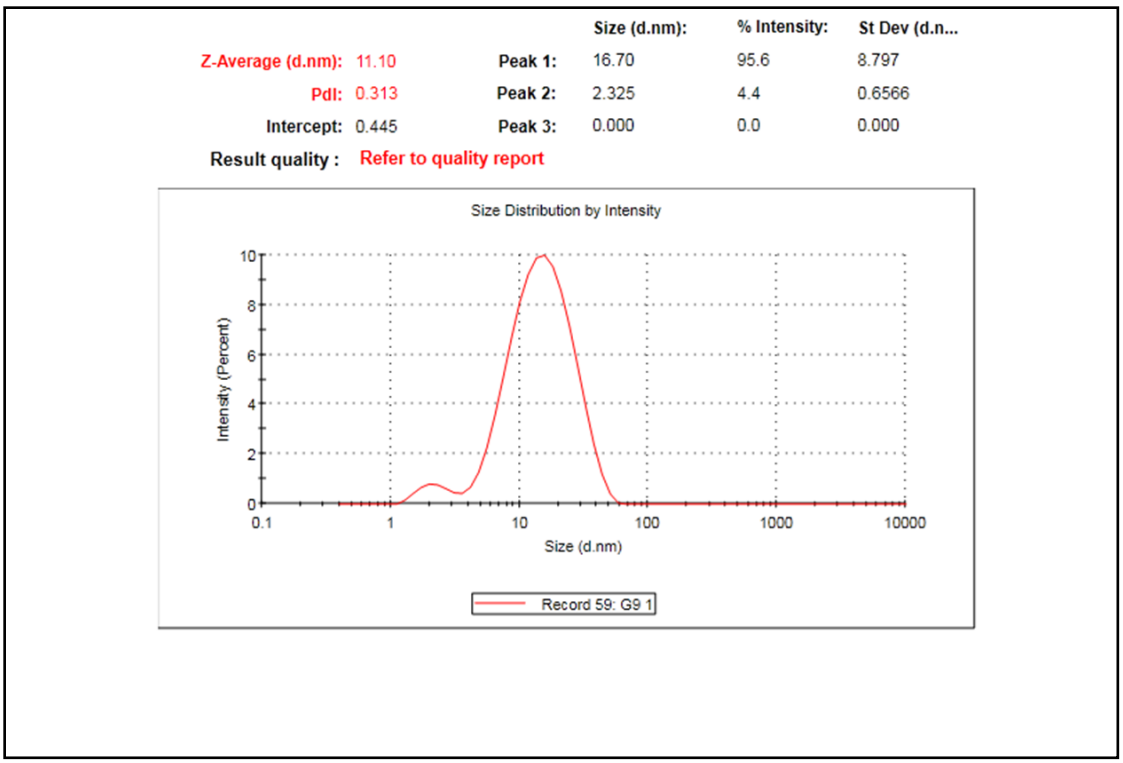

Figure (34): Droplet size with PDI of microemulsion G9 system

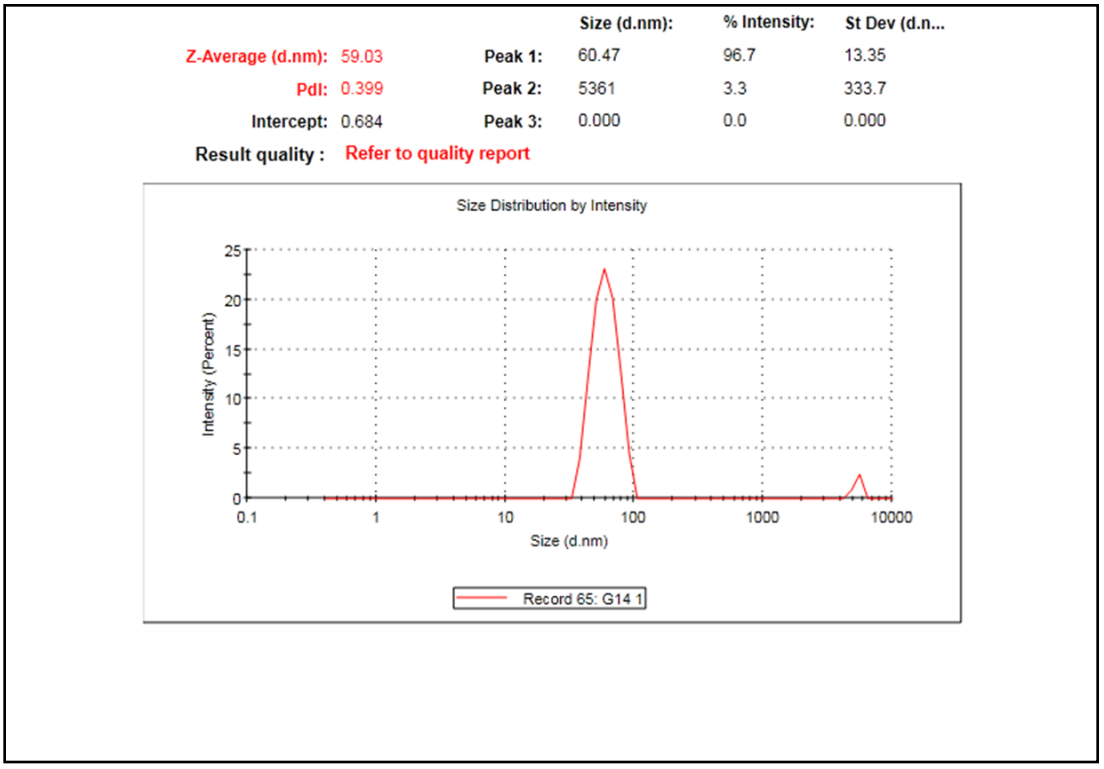

Figure (35): Droplet size with PDI of microemulsion G14 system

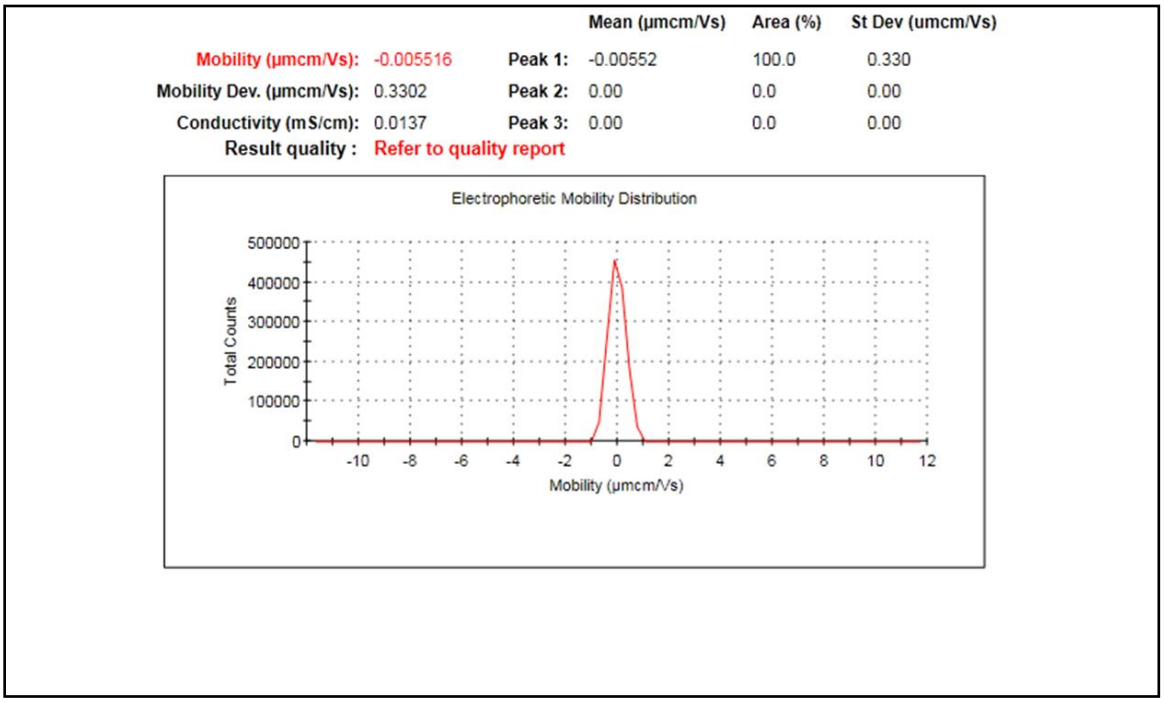

Figure (36): Average zeta potential of microemulsion G26 system

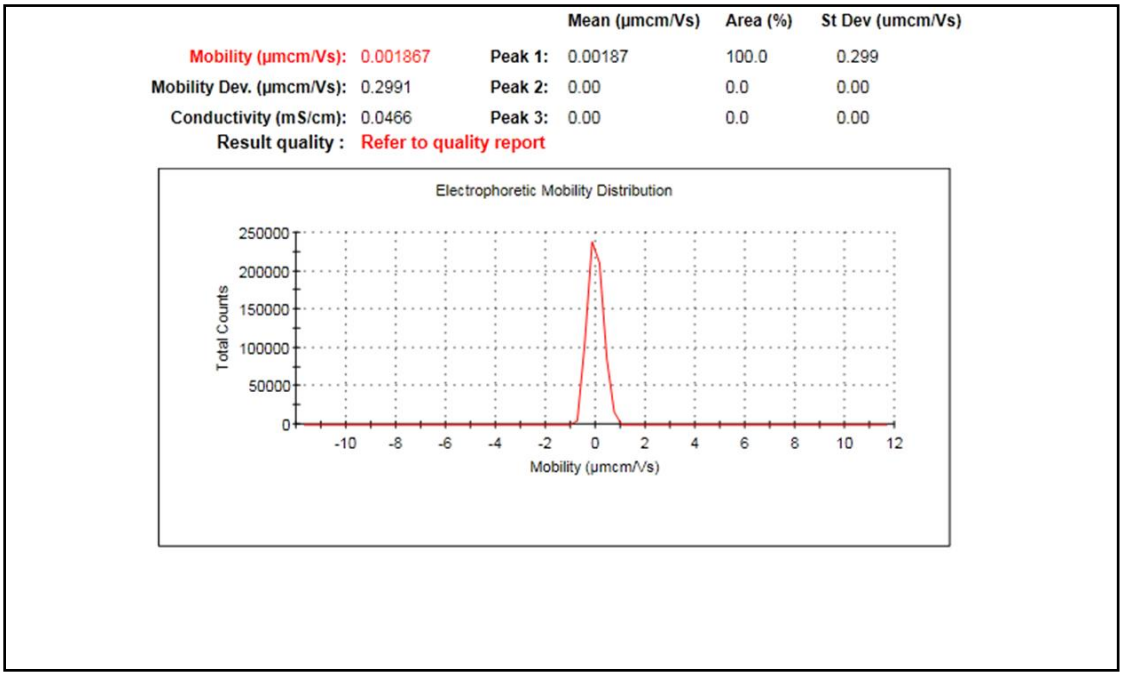

Figure (37): Average zeta potential of microemulsion C1 system

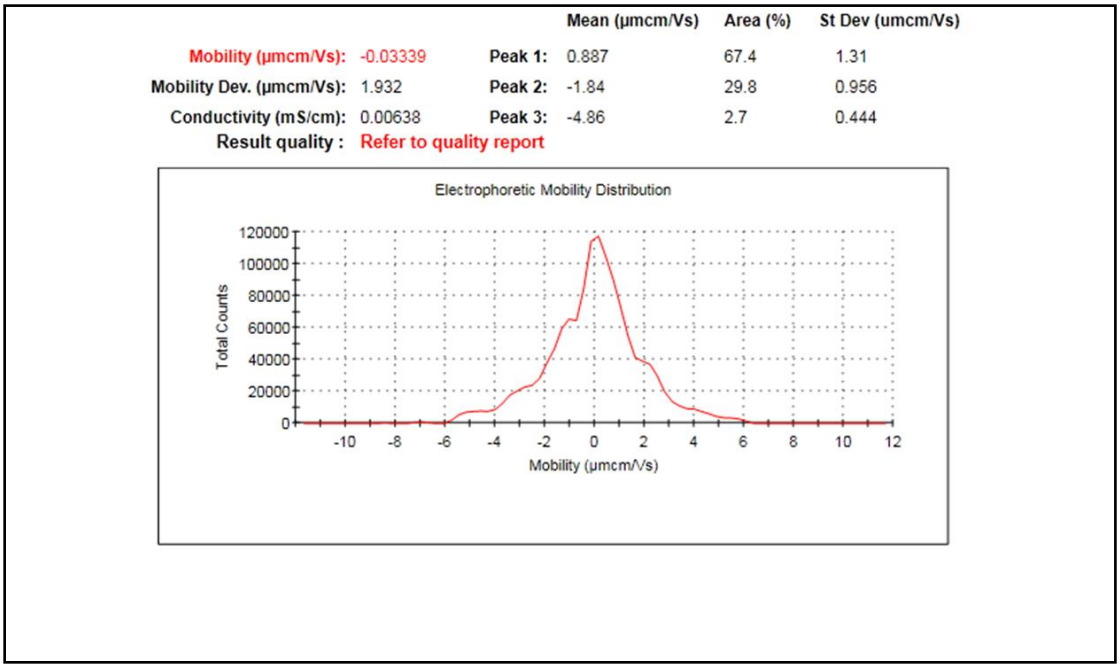

Figure (38): Average zeta potential of microemulsion F3 system

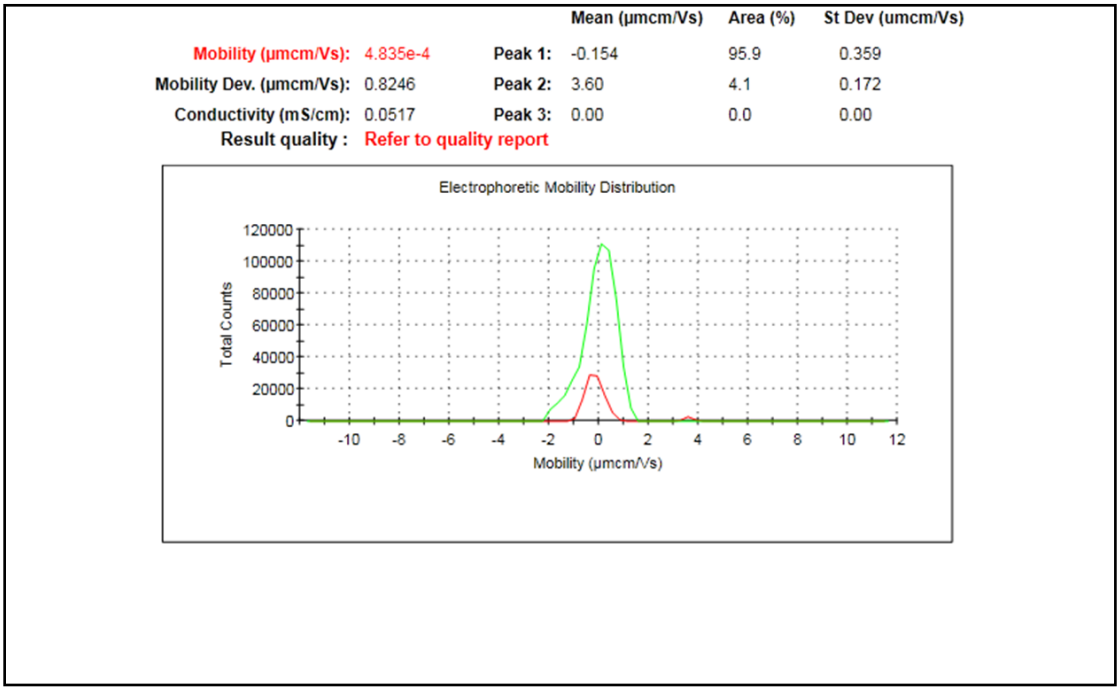

Figure (39): Average zeta potential of microemulsion G30 system

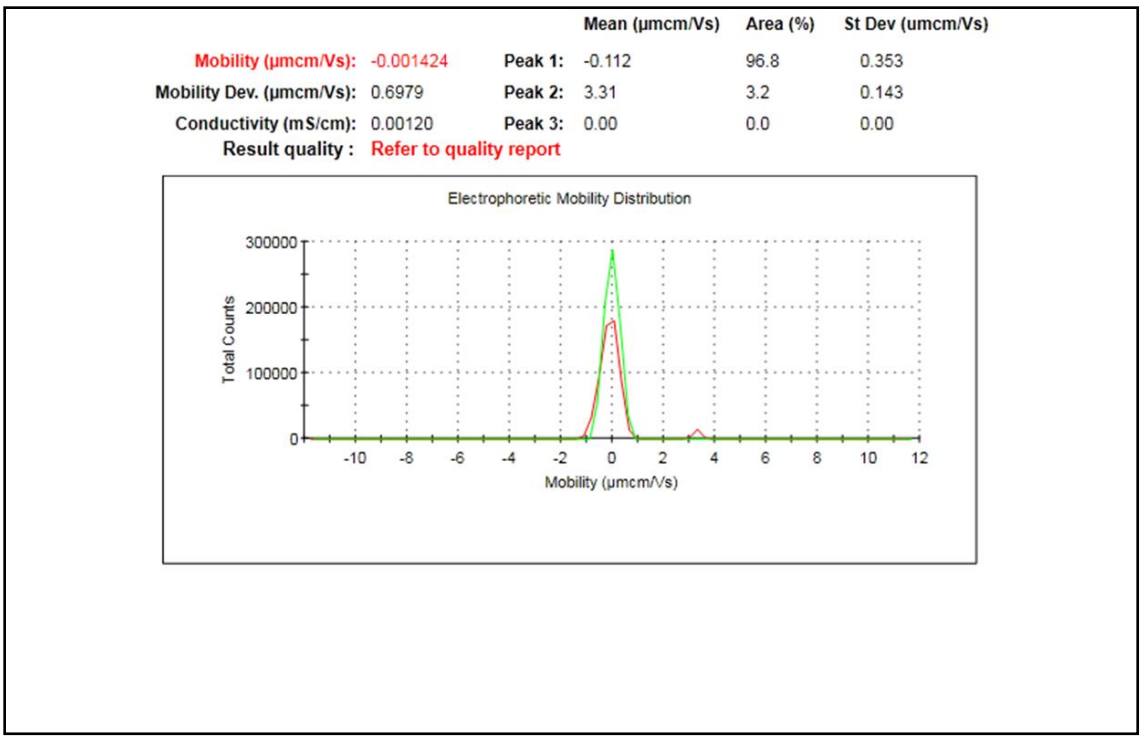

Figure (40): Average zeta potential of microemulsion G27 system

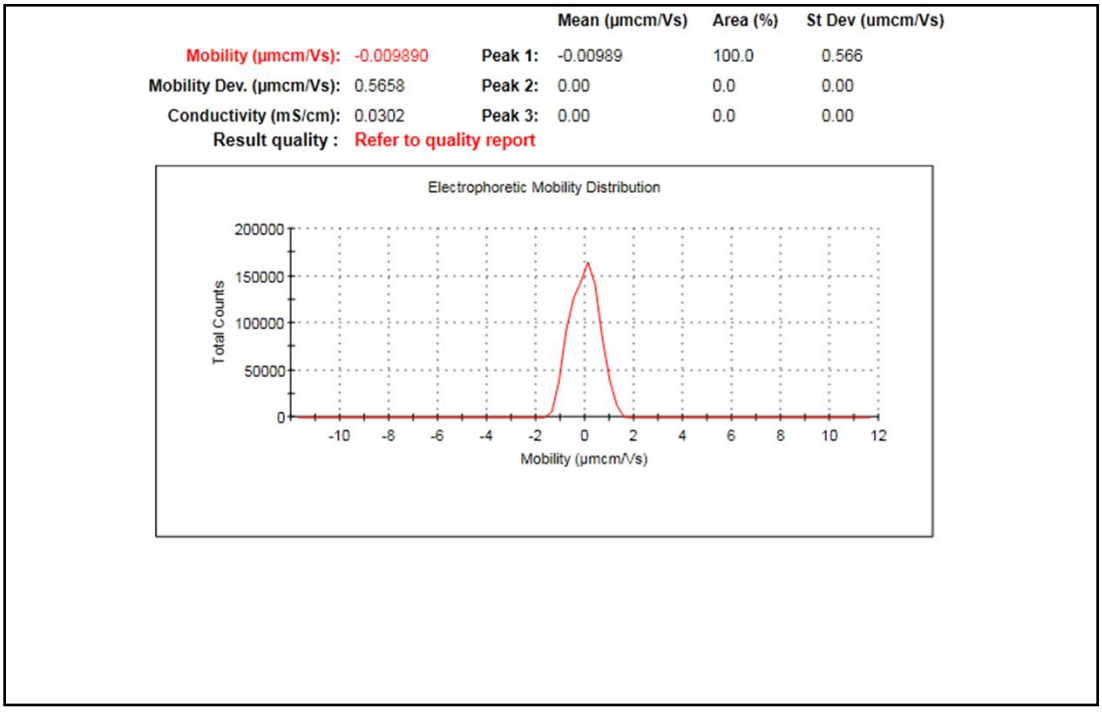

Figure (41): Average zeta potential of microemulsion G2 system

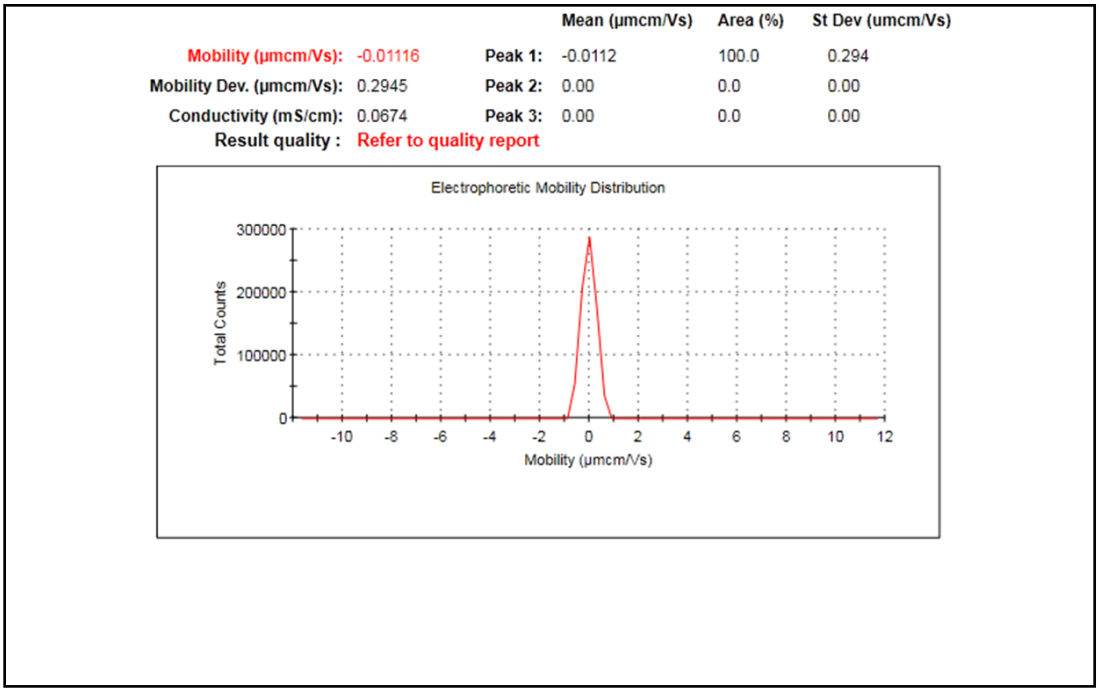

Figure (42): Average zeta potential of microemulsion B1 system

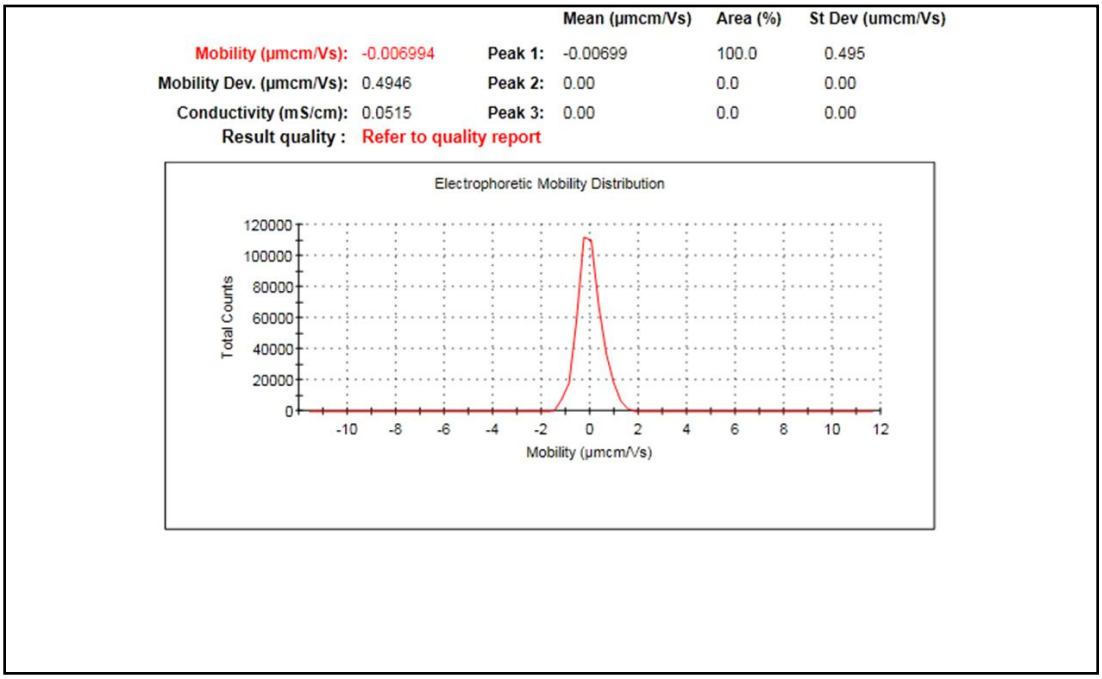

Figure (43): Average zeta potential of microemulsion G18 system

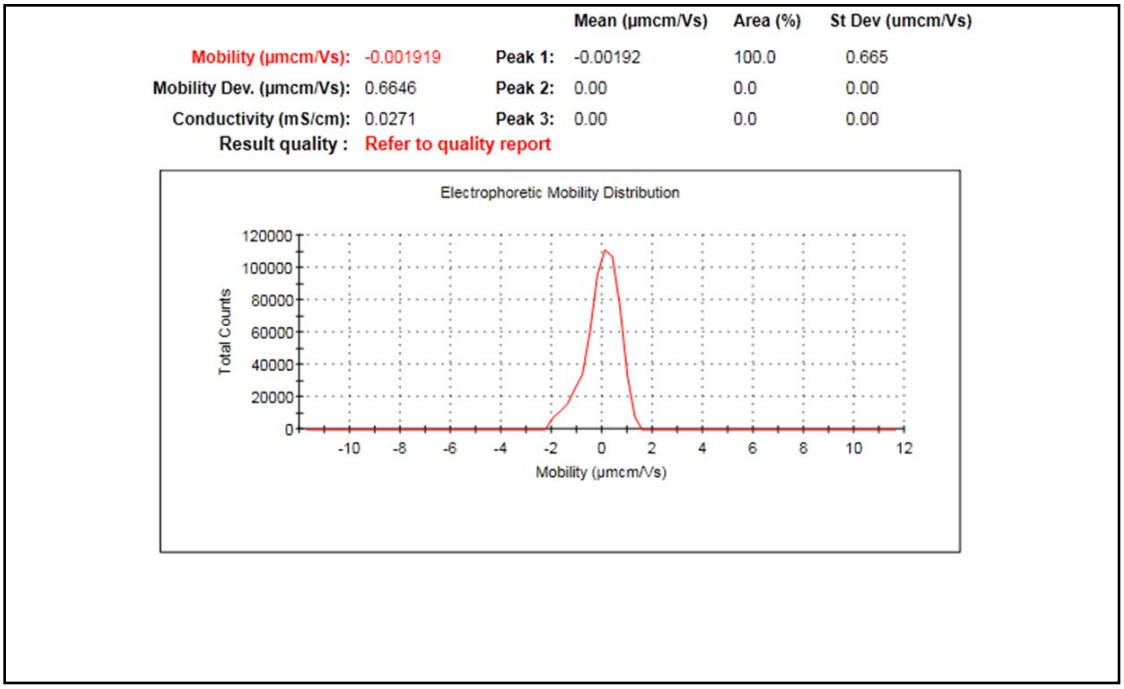

Figure (44): Average zeta potential of microemulsion G9 system

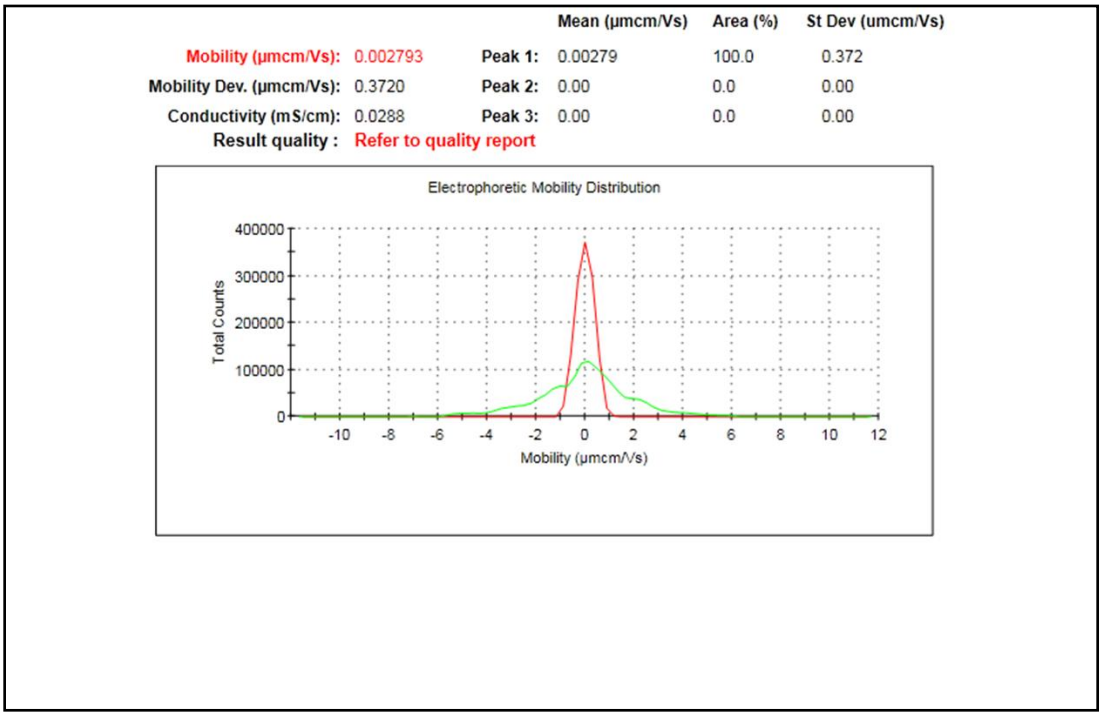

Figure (45): Average zeta potential of microemulsion G14 system

رسالة ماجستير بعنوان

تطوير مستحلب دقيق جديد يحتوي الإيبوبروفين بغرض التطبيق الجلدي

اعداد الطالب

وسيم نواف السائح

إشراف

الدكتور جمال اليوسف الكراد

قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في العلوم الصيدلانية

كلية الصيدلة

جامعة الاسراء – عمان – الأردن

آب 2020

ملخص الدراسة

تطوير مستحلب دقيق جديد يحتوي الإيبوبروفين بغرض التطبيق الجلدي

اعداد الطالب

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إشراف

الدكتور جمال اليوسف الكراد

ملخص:

يعد نظام توصيل الأدوية عبر الجلد (TDDS) أحد أهم الموضوعات اليومية لتقديم بعض الأدوية بطريقة آمنة وفعالة ولها قبول لدى المريض.

من المعروف أن المستحلبات الدقيقة (MEs) هي أنظمة جيدة لتوصيل الدواء وتطبيقها عبر الجلد.

يلعب حجم القطرة والخصائص الانسيابية دورًا حيويًا في جودة صياغة المستحلبات الدقيقة (MEs).

في هذه الدراسة ، تم استخدام المواد الخافضة للتوتر السطحي الغير المتأينة لتكوين المستحلبات الدقيقة MEs التي تحتوي على الإيبوبروفين. تميزت هذه المستحلبات الدقيقة بحجم القطرة ، معامل توزع ابعاد الجزيئات ، الخصائص الريولوجية. تم تقييم تدفق الإيبوبروفين في المختبر بواسطة خلية انتشار فرانز على مدار 24 ساعة حيث تم حساب الكمية المخترقة من الإيبوبروفين باستخدام جهاز الكروماتوجرافيا السائلة عالية الأداء (HPLC).

تمت دراسة التوافر الحيوي في الجسم الحي للمستحلبات الدقيقة الحاوية على الإيبوبروفين على الفئران. أظهرت النتائج أن هذه المستحلبات الدقيقة تتوافق مع الخصائص الغروية ،الشفافية واللزوجة المثالية.

كانت أعلى قيمة تدفق للمستحلبات الدقيقة MEs التي تحتوي على إيبوبروفين عبر الجلد باستخدام خلية انتشار فرانز هي 0.039 مجم / سم 2 ساعة.

أظهرت النتائج في الجسم الحي الحد الأقصى لمستوى البلازما 0.064 مجم / مل عند 8 ساعات لاختبار المستحلب الدقيق ME الحاوي على الإيبوبروفين.

يمكن ان تكون المستحلبات الدقيقة غير الأيونية المطورة التي تحتوي على إيبوبروفين ناقلًا مثاليًا وصياغة واعدة لإدارة الجلد للإيبوبروفين.