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MICROEMULSION GEL OF IRBESARTAN: A POTENTIAL TRANSDERMAL DELIVERY SYSTEM

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Keywords:

Irbesartan, Microemulsion gel, Skin permeation, Pharmacokinetics

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ABSTRACT: The transdermal delivery route is increasingly being used for drug delivery primarily because the route avoids drawbacks encountered with oral and parenteral routes of drug administration. Irbesartan is an angiotensin II receptor antagonist used clinically to treat hypertension. The objective of the present study was to investigate microemulsion gel as a transdermal delivery system of irbesartan while envisaging drug bioavailability enhancement. The microemulsion based gel of irbesartan was prepared by incorporating optimized microemulsion containing 0.075% w/w of irbesartan into the gelling vehicle. The gelling vehicle was made by dispersing 2% w/w of polycarbophil in distilled water. Irbesartan-loaded microemulsion gel was characterized by droplet size and polydispersity index determinations. Physicochemical properties of irbesartan-loaded microemulsion gels were studied using reported procedures. Diffusion Franz cell was utilized for *in-vitro* skin permeation while an *in-vivo* study in rats was by non-compartmental pharmacokinetic model. Activation energy measurement was used to assess the skin permeation mechanism. The droplet size and polydispersity of the microemulsion based gel of irbesartan were in the range of 80 - 82 nm and 1.040 - 1.087, respectively. The *in-vitro* skin permeation result gave a higher permeability coefficient and steady-state flux when compared with the irbesartan suspension. In the pharmacokinetics study, higher plasma concentration and larger area under the curve were also observed when compared with irbesartan suspension. The *in-vitro* and *in-vivo* results suggest that microemulsion gel could be a more potential transdermal drug delivery system of irbesartan than microemulsion.

INTRODUCTION: The transdermal drug delivery system is a self-contained, discrete dosage form containing active agent(s) that has to cross the tissue when applied to the intact skin and be absorbed into the systemic circulation in order to reach its site of action [1].

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The transdermal route could be of use to drugs with short half-lives, gastrointestinal disorders, first-pass liver metabolism, inter and intrapatient variability, and low potencies [2].

The skin is a route to deliver active agent(s); however, the stratum corneum (SC) of the skin provides a barrier to this route of administration. Thus, to ensure the effective and efficient delivery of drugs and other active compounds, the tissue's barrier has to be surmounted [3]. Various techniques [4], including microemulsion based gels, have been developed and utilized to overcome this barrier to transdermal delivery.

Microemulsion consisting of oil, surfactant, cosurfactant, and water is a clear or translucent, optically isotropic and thermodynamically stable system [5].

A gel is a colloidal preparation immobilized by surface tension between it and macromolecular network of fibers built from a small amount of a gelatinous substance [6, 7]. Gels lack the ability to deliver hydrophobic drugs through the skin, and to overcome this limitation, microemulsion or nanoemulsion approach is employed.

The properties of microemulsion-based gels such as inertness, compatibility with other additives, stability, high loading capacity, control release, non-invasiveness, and increase in the rate of absorption and bioavailability, *etc*. make them be carrier systems of interest in the transdermal delivery of drugs. For instance, microemulsion gels have been used for transdermal delivery of antifungal (econazole, fluconazole, voriconazole, miconazole, antimicrobial (metronidazole, nadi-floxacin), antiviral (penciclovir), anti-inflammatory (ibuprofen, ketoprofen) and antioxidant (quercetin) agents [8, 9, 10].

Irbesartan **Fig. 1**, chemically defined as 2-n-Butyl-4-spirocyclopentane-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one is a potent long acting AII receptor antagonist with high specificity for the AT1 subtype [11, 12]. It has very poor aqueous solubility.

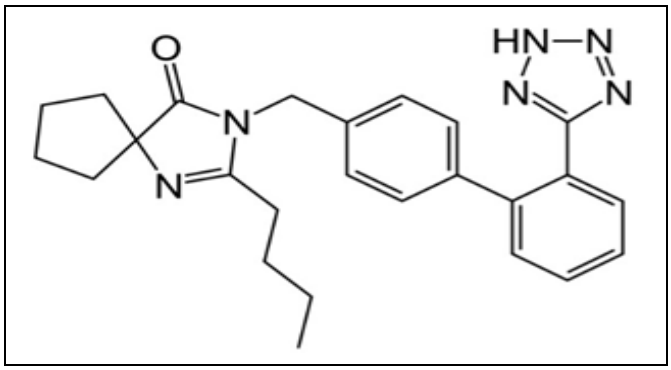

FIG. 1: CHEMICAL STRUCTURE OF IRBESARTAN

Clinically, it is used in the treatment of hypertension and very often prescribed by clinicians because of its advantages (efficacy, safety, *etc*.) when compared to other antihypertensive agents, including angiotensin II receptor blockers [13-15]. Thus, it was thought that having the drug in various pharmaceutical dosage forms, patients would have the opportunity of exploiting these advantages. Currently, the oral route is the only route of administration.

In our previous report [16], we investigated microemulsion and found it to be a potential transdermal delivery system for irbesartan. However, in the present study, microemulsion gel formulation (based on its characteristics such as high loading capacity and increase in the rate of systemic absorption) was investigated as a delivery system for irbesartan while envisaging more transdermal enhancement of the drug. Transdermal administration of irbesartan as a pharmaceutical microemulsion or microemulsion gel formulation other than the oral route could be very beneficial to a patient, especially geriatric patients. As literature review has shown that no study has reported transdermal delivery of irbesartan utilizing micro-emulsion-based gel as the delivery system, the present study, therefore, considered it of interest to investigate the bioavailability enhancement of irbesartan through transdermal route by using microemulsion-based gel as a delivery system. The probable mechanism of skin permeation was also studied.

MATERIALS AND METHODS:

Materials: Irbesartan ((Bristol-Myers Squibb, USA), polycarbophil, glycerol monocaprylocaprate (Inwitor 742 - Cremer Oleo GmbH & Co, Germany), polyethylene glycol 400 and polysorbate 80 (Sigma and Aldrich, USA). All other chemicals and reagents purchased from Sigma and Aldrich (USA) were of analytical or high-performance liquid chromatography (HPLC) grade.

Microemulsion Preparation: [16] Microemulsions were prepared by aqueous phase titration method. Glycerol monocaprylocaprate was used as oil phase while polysorbate 80 and polyethylene glycol 400 were used as surfactant and cosurfactant respectively. Various pseudo ternary phase diagrams were constructed. Thermodynamic stability study was carried out on selected formulations that were subjected to centrifugation, heating-cooling cycles and freeze-thaw cycles. Optimization of the thermodynamically stable microemulsions was by droplet size and polydispersity index

determinations using photon correlation spectroscopy [Zetasizer 1000 HS (Malvern Instruments, UK)].

Preparation of Irbesartan-Loaded Optimized Microemulsion Gel: Microemulsion gel was prepared by dispersing 2% w/w of polycarbophil in sufficient quantity of distilled water. The dispersion was left in the dark for 24 h for complete swelling of the polymer. A 0.075% w/w of irbesartan was dissolved in 20% w/w oil. This was followed by a slow addition of 35% w/w mixture of surfactant and co-surfactant (3:1) into oil phase. The remaining quantity of distilled water was added to get the final preparation of 100 %w/w. Ease of spreadability, feel and compatibility with the micro-emulsion structure were criteria used to select the suitable gelling agent.

Characterization of Microemulsion Gels:

Droplet Size and Polydispersity Index: Irbesartan -loaded microemulson gel was sufficiently diluted with double-distilled water, gently mixed for droplet size and polydispersity index analyses.

pH Measurement: The apparent pH of the microemulsion gels was measured in triplicate at 25 °C using a pH meter with a combination electrode (Eutech, Japan).

Spreadability Measurement: [17, 18] The analysis was performed by placing 0.5 g of microemulsion-based gel within a circle of 1 cm diameter pre-marked on a glass plate. A second glass plate was placed over it. A weight of 10 g was allowed to rest on the upper glass plate for 5 min. The increase in diameter due to the spreading of microemulsion gel was observed and recorded in cm/gm-sec. The spreadability was calculated using equation 1:

$$S = ml / t \quad \text{---------- Equation 1}$$

Where m = weight on the upper glass plate (g), l = length moved on the glass slide (cm), t = time taken

Viscosity Measurement: Viscosity of the samples was measured at 25 °C using, a cone and plate viscometer (NDJ 5s viscometer, England). The test was carried out in triplicate.

Drug Content Measurement: About 1 g micro-emulsion based gel was dissolved in methanol by sonication and filtered through a membrane filter (0.45µm). Irbesartan concentration was analyzed spectrophotometrically (UV- Visible spectrophoto-meter, Shimadzu 1800, Japan) at a maximum wavelength of 244 nm after appropriate dilution with methanol. The test was carried out in triplicate.

Preparation of Full-Thickness Rat Skin: The Faculty of Veterinary Medicine, University of Nigeria, Nsukka animal ethics committee gave approval for the animal studies. Institutional guidelines were followed in caring for the animals. Male Wister rats were sacrificed with prolonged exposure to chloroform. Hairs on the skin of animals were removed with an electrical clipper, and the abdominal skin of each rat was excised. Isopropyl alcohol was used to remove residual adhering fat from the dermis side after the subcutaneous tissues were removed. The skin was washed with distilled water prior to preparing the epidermis from it. The unused full-thickness skin was wrapped in aluminum foil and stored at -20 °C till further use.

Preparation of Epidermis: The epidermis was prepared from the full-thickness skin by heat separation technique [19]. It involved soaking the entire abdominal skin in the water at 60 °C for 1 min. The epidermal sheet was cleaned using distilled water and dried under vacuum. The sheet was cut into 4.5 × 4.5 cm^2 pieces and employed for the permeation study. The unused epidermis was wrapped with aluminum foil and stored at −20 °C until required.

***In-vitro* Skin Permeability Studies:** The studies were carried out in Franz diffusion cells. The diffusion area of the cells was 3.14 cm^2. The diffusion cells were connected with a circulating water bath, and the temperature was controlled at 37 °C. The phosphate buffer saline (PBS) used as a receiver fluid was placed in the receiver compartment (15 ml). The prepared epidermis was sandwiched between the receiver compartment and the donor compartment with the stratum corneum facing upwards. The donor compartment was clamped. One gram of drug-loaded microemulsion gel was applied onto the skin surface facing the donor compartment that was covered with a glass lid. Aluminum foil was used to cover the sampling arm of the donor compartment. While the receiver

fluid was being stirred, a 0.5 ml of each sample was withdrawn at a suitable time interval (0, 1, 2, 3, 4, 6, 8, 10, 12 h) from the center of the receiver compartment with a syringe connected with a needle. An equal volume of fresh PBS (37 °C) was immediately replaced. The amount of irbesartan in the receiver fluid was determined spectrophotometrically at a maximum wavelength of 244 nm.

Data Analysis: The data obtained from skin permeation measurement were evaluated as the cumulative drug permeation per skin surface area Q_t/S. The cumulative drug permeation (Q_t) was calculated from equation 2:

$$Q_t = V_t C_t + \sum_{t-o}^{t-i} V_s C_i$$ ----------Equation 2

Where, C_t is the drug concentration of the receiver fluid at each sampling time t, C_i is the drug concentration of the ith sample, V_r and V_s are the volumes of the receiver fluid and sample respectively. A linear plot was obtained by graphing cumulative drug permeation per skin surface area versus time. Steady-state flux and lag time of the drug was calculated using linear regression analysis. The slope of the linear portion of the graph produced the steady-state flux (Jss, µg/cm^2/h). The lag-time was obtained by extrapolating the linear portion of the graph to the X-axis [20]. The permeability coefficient (P) was calculated as

P = Jss / C----------Equation 3

Where C is the drug concentration in donor compartment

One-way analysis of variance (ANOVA) was utilized to compare the flux obtained. A *p*-value of 0.05 was taken to be statistically significant. The penetration enhancing effect of each micro-emulsion gel was calculated in terms of enhancement ratio (ER) from equation 4:

ER = Kp (test – microemulsion) / Kp (control) -----Equation 4

Determination of Activation Energy: *In-vitro* skin permeation study of irbesartan across rat skin was also determined at 25 °C, 37 °C, and 50 °C respectively in methanolic PBS of pH 7.4 (30:70) as previously described. The permeability coefficient was calculated at each temperature, and the activation energy of irbesartan was calculated from the Arrhenius relationship.

$$P = P_o\ e^{-(Ea/RT)}$$

Or

$$\text{Log } P = Ea / 2.303\ RT + \log P_o$$

Where Ea is the activation energy, R is gas constant (8.143 kJ/mol), T is the absolute temperature in Kelvin, P is the permeability coefficient, and Po is the Arrhenius factor.

Pharmacokinetic Studies: An approval on the pharmacokinetic studies was obtained from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka animal ethics committee. The studies were in accordance with the guidelines of the ethics committee. Optimized irbesartan-loaded micro-emulsion gels and commercial tablets were used in the pharmacokinetic studies. Albino male rats weighing between 200–240 g were used for the study. The rats were kept under standard laboratory conditions (temperature 25 ± 2 °C and relative humidity of 55 ± 5%) and housed in polypropylene cages (six per cage). They were allowed free access to standard laboratory diet and water *ad libitum*. About 5 cm^2 of skin was shaved on the abdominal side of rats in each group for transdermal administration except the group treated with the commercial tablet. The animals were divided into 3 groups (n = 6). Group I received irbesartan-loaded microemulsion gel (MGa) transdermally, Group II received irbesartan-loaded microemulsion gel (MGb) transdermally while group III received commercial tablet suspension orally. Irbesartan dose was 30 mg/kg of body weight. Chloroform was used to anesthetize the rats. Blood samples (1.0 ml) were withdrawn from the retro-orbital plexus of rat at 0, 0.5, 1, 2, 4, 8, 12, 24 h in EDTA bottles. Centrifugation was done at 5000 rpm for 20 min following proper mixing of the blood collected with the EDTA. The plasma was separated and stored at -21 °C until drug analysis was carried out.

Following the thawing of the drug sample at room temperature, precipitation of the plasma protein was done by adding acetonitrile: methanol mixture (4:1) and centrifuged at high speed (5000 rpm) for sufficient time. The separated clear supernatant liquid was analyzed using a UV spectrophotometer. The concentration of unknown irbesartan ± in

plasma samples was calculated from the previously constructed calibration curve plotted between absorbance against irbesartan concentrations.

Pharmacokinetic and Statistical Analyses: Irbesartan plasma concentration at different time intervals was subjected to pharmacokinetic (PK) analysis to calculate various pharmacokinetic parameters. The values of maximum plasma concentration (C_{max}) and time to reach the C_{max} (T_{max}) were read directly from the plot of time against the plasma concentration of irbesartan. The area under the curve (AUC) was calculated using the linear trapezoidal method.

RESULTS:

Pseudoternary Phase Diagrams: The compositions of microemulsion gel formulations using optimized microemulsions are given in Table 1. Out of various pseudoternary phase diagrams constructed, **Fig. 2 A-B** showed two of such phase diagrams having 3:1 and 3:2 S_{mix} ratio of surfactant to cosurfactant, respectively. Two representative microemulsion formulations (oil in water, o/w) were identified from the microemulsion region of S_{mix} 3:1 and S_{mix} 3:2, respectively. These formulations were used to prepare microemulsion gels and designated as MGa and MGb respectively.

TABLE 1: COMPOSITIONS OF MICROEMULSIONS AND MICROEMULSION GELS

Ingredients	MEa (o/w)	MEb (o/w)	MGa	MGb
Irbesartan (% w/w)	0.75	0.75	0.75	0.75
Imwitor 742 (%w/w)	20	10	20	10
Smix	35	40	35	40
Polycarbophil	0	0	2.0	2.0
Distilled water to (% w/w)	100.0	100.0	100.0	100.0

Thermodynamic Studies: The results of thermodynamic stability studies showed no signs of cloudiness, phase separation or precipitation and therefore enabled very stable formulations to be selected for further optimization studies.

Characterization of Irbesartan-Loaded Microemulsion Gels: Microemulsions gels prepared from microemulsion regions of **Fig. 2** for each percentage of oil selected, while utilizing the minimum concentration of Smix from the pseudoternary phase diagrams were characterized in terms of droplet size and polydispersity index. The characterization studies results are presented in **Table 2**. When compared to the blank counterparts the results indicated that the morphological and physicochemical properties of microemulsion gels were not altered after 0.75% w/w of the drug was incorporated. The low droplet size values indicated uniformity of droplets within the formulations.

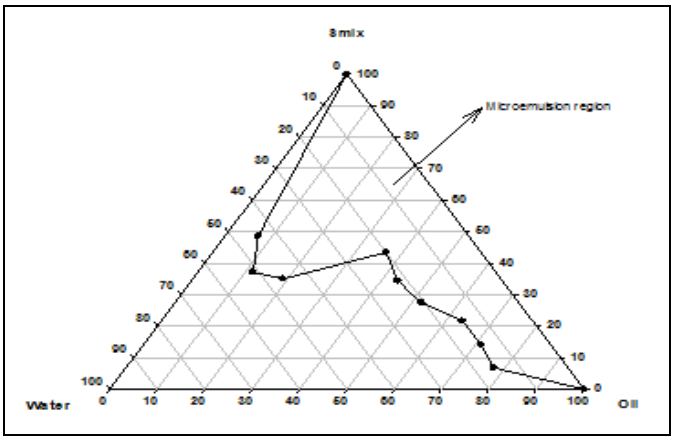

FIG. 2A: PSEUDOTERNARY PHASE DIAGRAM OF S_{mix} RATIO 3:1

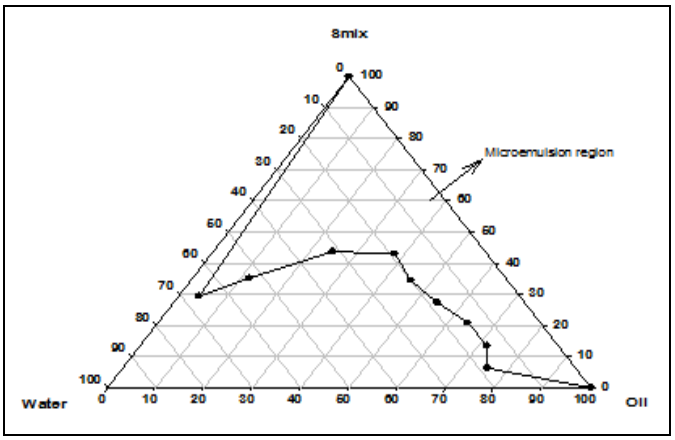

FIG. 2B: PSEUDOTERNARY PHASE DIAGRAM OF S_{mix} RATIO 3:2

Drug Content Analysis: The results of drug content in irbesartan-loaded microemulsion gels are given in **Table 2**. The results indicate a very significant recovery of irbesartan from the formulations.

TABLE 2: CHARACTERISTICS OF IRBESARTAN-LOADED MICROEMULSION GELS

Test	Blank	MGa	Blank	MGb
Droplet size (nm)	80.3	80.6±0.24	82.4	81.8±0.15
PDI	1.046	1.038±0.02	1.076	1.083±0.04
pH	6.54	6.28±0.03	6.62	6.33±0.01
Spreadability cm/gm-sec	0.026	0.024±0.001	0.027	0.025± 002
Viscosity (mpas)	5750	5742±7.57	4544	4539±1.31
Assay		98.7±0.7		98.2±0.4

***In-vitro* Permeation Studies:** The permeability study results are given in **Table 3** and **Fig. 3** respectively. The results showed that micro-emulsion gel formulations gave permeability coefficients (*K*p) and fluxes (*J*ss) that were greatly increased when compared to the tablet formulation. The lag time for the drug permeation through the stratum corneum from the control vehicle (distilled water) and the gel formulations is less than one hour. Statistical analysis of permeation studies showed that microemulsion gel formulations results were statistically significant when compared to tablet formulation.

TABLE 3: *IN-VITRO* PERMEATION OF IRBESARTAN -LOADED MICROEMULSION GEL THROUGH THE RAT SKIN AT 37 °C

Parameter	Aqueous suspension of irbesartan	MGa	MGb
Permeability coefficient ($\times 10^3$cm/h)	1.66 ±0.04	5.37 ±0-06	4.71 ±0.03
Steady-state flux (µg/cm^2/h)	8.30	26.86	23.56
Enhancement ratio		3.22	2.84

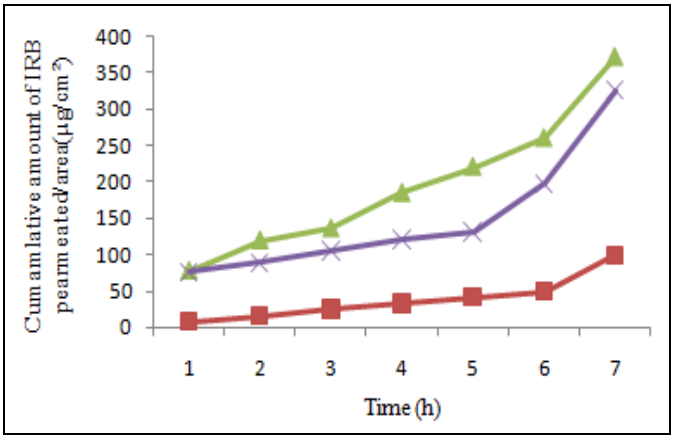

FIG. 3: *IN-VITRO* PERMEATION OF IRBESARTAN-LOADED MICROEMULSIONS-BASED GEL THROUGH THE RAT SKIN AT 37 °C

□----- □ - Aqueous suspension of irbesartan
× -----× - Oil in water microemulsion-based gel (MGb)
Δ -----Δ - Oil in water microemulsion-based gel (MGa)

Determination of Activation Energy: The activation energy determination results are shown in **Fig. 4**. The results show that microemulsion-based gel decreased the activation energy of permeation through the rat skin when compared to aqueous suspension of irbesartan. Arrhenius plots **Fig. 4** between logarithm of permeability coefficient versus reciprocal of absolute temperature were found to be linear in the temperature range between 25-50 °C. The values of activation energy (Ea) for irbesartan permeability across rat skin was calculated from the slope of Arrhenius plot and were found to be 57.98 kJ/mol, 36.44 kJ/mol and 36.68 kJ/mol for aqueous suspension of irbesartan, microemulsion-based gel MGa and microemulsion-basd gel MGb respectively.

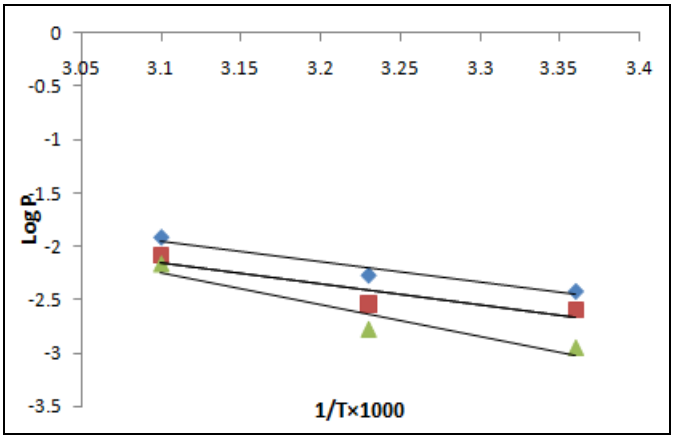

FIG. 4: ARRHENIUS PLOT BETWEEN LOGARITHMS OF PERMEABILITY COEFFICIENT VERSUS RECI-PROCAL OF ABSOLUTE TEMPERATURE FOR MICROEMULSION-BASED GELS

◊ ----- ◊ - Oil in water microemulsion-based gel (MGa)
Δ -----Δ - Aqueous suspension of irbesartan
□----- □ - Oil in water microemulsion-based gel (MGb)

Pharmacokinetic Studies: Plasma concentration of irbesartan from microemulsion gel formulations and tablet suspension at various time intervals was determined by UV spectrophotometry. The results are given in **Table 4** and **Fig. 5** respectively. The pharmacokinetic data (collected for a period of 24 h), for irbesartan tablet formulation are 1160.18 ± 5.86 µgh/ml, 0.0258 ± 0.0028 L/h/kg, 1.1416 ± 0.0234 L/kg, 44.25 ± 1.15 h, 0.0226 ± 0.0014 h^{-1} and 30.7 ± 0.41 h for area under curve at infinity ($AUC_{0\rightarrow\infty}$), total clearance (CL_{total}), volume of distribution at a steady-state (Vss), mean residence time (MRT), elimination rate constant (Ke) and elimination half-life ($t½$) respectively.

The irbesartan-loaded microemulsion gel formulations were found to enhance the bioavailability of irbesartan through transdermal delivery by 2.8 and 2.4- fold increase for MGa and MGb respectively, when compared with the oral tablet. The significant ($p < 0.05$) $AUC_{0\rightarrow24h}$ values observed with irbesartan-loaded microemulsion implied increased bioavailability of the irbesartan

from the formulations in comparison with oral tablet formulation.

TABLE 4: PHARMACOKINETIC PARAMETERS OF IRBESARTAN AFTER ORAL ADMINISTRATION OF REFERENCE TABLET AND MICROEMULSION GEL

Parameter	MGa	MGb	Aqueous suspension of irbesartan
C_{max} (µg/ml)	3.50 ±0.06	2.70 ±0.08	1.62 ±0.03
T_{max} (h)	8	8	4
AUC→24 h (µg.h/ml)	55.40 ±0.26	71.30 ±0.32	25.44 ±0.28

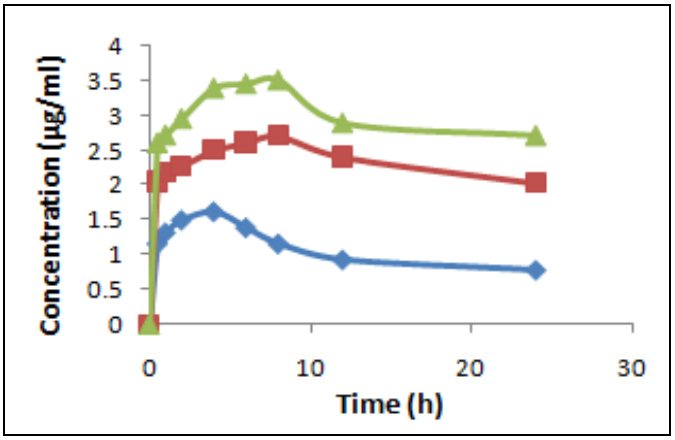

FIG. 5: THE PLOT OF IRBESARTAN PLASMA CONCENTRATION VERSUS TIME

◊ ----- ◊ - Aqueous suspension of irbesartan

□----- □ - Oil in water microemulsion-based gel (MGa)

Δ -----Δ - Oil in water microemulsion-based gel (MGb)

DISCUSSION:

Calibration Graph of Irbesartan: The calibration curve was linear within the concentration range of 2.0 – 10.0 µg/ml, suggesting that Beer's law was obeyed. Regression equation defining the observed linearity is

$$A = 0.0496C-0.0461 \ (r = 0.9944)$$

Pseudoternary Phase Diagrams: Pseudoternary phase diagrams with large microemulsion areas evidenced the efficiency of polyethylene glycol 400 as a cosurfactant in increasing the flexibility of the interfacial film. The phase behavior of the pseudoternary phase diagram was not changed when irbesartan was incorporated into micro-emulsion, suggesting that the formation and stability of the microemulsion were never influenced by the physicochemical properties of the drug.

Thermodynamic Study: The results in the thermodynamic study might have arisen from low interfacial tension between oil and water at the weight ratio of surfactant with respect to the co-surfactant as well as the position of the droplet size.

Characterization Studies: Characterization results suggest that the droplet size obtained could provide larger surface area available for transdermal irbesartan absorption. Previous studies have reported that microemulsion with a droplet size of less than 100 nm would enhance the bioavailability of drugs [21, 22]. Intrinsic properties of the drug might have caused any slight changes in the physicochemical properties (for example, pH) of irbesartan-loaded microemulsion gel. It was also observed that there was no significant change in globule size when microemulsion was formulated in gel form. Lack of any significant change in the polydispersity index suggested the absence of globule aggregation when the gelling agent was incorporated into micro-emulsion. These apparent similarities go to suggest that the constituents (oil, water and surfactant/co-surfactant, gelling agent) of the microemulsion gels which control the physico-chemical properties will have similar effects on the permeation of irbesartan through the excised rat skin.

Drug Content Analysis: The results suggest that irbesartan is completely solubilized in the micro-emulsion gel.

Determination of Activation Energy: Route of diffusion and physicochemical properties of a drug very often being control activation energy (Ea) for the diffusion of a drug molecule across the skin. The activation energy for transdermal permeation of irbesartan was found to be lower for the microemulsion gel formulations when compared to an aqueous suspension of irbesartan, indicating the existence of a lower energy barrier for the microemulsion gel formulations. The results suggest a significant change in stratum corneum (SC) lipid bilayer's morphological characteristics by the formulations, thereby creating pathways in the bilayers that allowed transdermal permeation of irbesartan to be enhanced. Previous reports have shown that colloidal dispersions can change Ea value to a greater extent by their action on SC lipids [23, 24].

Pharmacokinetic Studies: Interferences that might occur in this study while using spectrophotometric method in the pharmacokinetic measurement was

not considered, because previous report [15], has shown that the only metabolite of irbesartan (irbesaran glucuronide)) that could be found in plasma is at very low concentration. The polar metabolite (not observed in the UV spectrum), when compared to irbesartan, is expected to show maximum absorption of an ultraviolet photon at a longer wavelength than irbesartan. Furthermore, it has been shown that acetonitrile: methanol ratio (4:1) is very effective in precipitating plasma proteins. A non-compartmental pharmacokinetic analysis was used to evaluate the rate and extent irbesartan permeation through the rat skin into the systemic circulation. The maximum plasma concentration of irbesartan (C_{max}) and the time to reach C_{max} (T_{max}) were obtained from the plot of plasma drug concentration against time. The T_{max} of the microemulsion gel formulations was found to be twice that of irbesartan tablet suspension, suggesting control release of the drug by the formulations. The area under the drug concentration-time curve and mean residence time (MRT) were calculated based on the trapezoidal rule. Total clearance (CL_{total}) was estimated as dose (30mg/kg)/$AUC_{0\rightarrow\infty}$ while volume of distribution at a steady state (Vss) as CLtotal × MRT. The elimination half-life ($t½$) was calculated from the division of 0.693 by the elimination-rate constant Ke (CL_{total}/Vss) respectively. Increase in irbesartan solubility and enhanced skin permeation could be responsible for the observed bioavailability increase from microemulsion gel formulations.

CONCLUSION: Transdermal delivery route avoids drawbacks encountered with oral and parenteral routes of drug administration. The characterization data confirmed the suitability of the microemulsion gel formulation method. Stability data indicated stable formulations. Activation energy determination results suggest that permeation might have occurred by the SC lipids disruption. The pharmacokinetic studies showed significantly greater absorption of irbesartan with microemulsion gel formulations than the oral tablet formulation ($p<0.05$). However, when compared to microemulsion formulation [16], there was no significant difference between area under curve of irbesatan. The *in-vitro* and *in-vivo* results of the present study therefore suggest that microemulsion gel could also be used successfully for enhancement of skin permeation as well as bioavailability of irbesartan and, therefore a potential transdermal delivery system for irbesartan.

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CONFLICTS OF INTEREST: None

REFERENCES:

1. Tanwar H and Sachdeva R: Transdermal Drug Delivery System: A Review. Int J Phar Sci Res 2016; 7(6): 2274-90.
2. Pandey S, Badola A, Bhatt GK and Kothiyal P: An overview on transdermal drug delivery system. Int J Pharm and Chem Sci 2013; 2 (3): 1172-80.
3. Jepps OG, Dancik Y, Anissimov YG and Roberts MS: Modeling the human skin barrier-towards a better understanding of dermal absorption. Adv Drug Deliv Rev 2013; 65: 152-68.
4. Petrilli R and Lopez RFV: Physical methods of topical skin drug delivery: concepts and application. Braz J Pharm Sci 2018; 54.
5. Chaudhary A, Gaur P, Barman M and Mishira R: A review on microemulsion: A promising technique used as a novel drug delivery system. Int Res J Pharm 2018; 9(7): 47-52.
6. Mehta DP, Rathod H, Shah DP and Shah CN: A review on microemulsion based gel: A recent approach for topical drug delivery system. Research J Pharm and Tech 2015; 8(2): 118.
7. Saroha K, Singh S, Aggarwal A and Nanda S: Transdermal gels - an alternative vehicle for drug delivery. Int J Pharm Chem and Bio Sci 2013; 3(3): 495-503.
8. Deboroh E, Chuah CW, Sokkalingam AD and Jaya RK: Development and evaluation of microemulsion based gel (MBGs) containing econazole nitrate for nail fungal infection. J Pharm Res 2012; 5(4): 2385-90.
9. Shinde U, Pokharkar S and Modani S: Design and evaluation of microemulsion gel system of nadifloxacin. Ind J Pharm Sci 2012; 74(3): 237-47.
10. Chhatrani BM and Shah DP: A review on microemulsion based gel: a novel approach for enhancing topical delivery of hydrophobic drug. Int J Pha Phar Res 2017; 8(4): 19-35.
11. HSDB Irebesartan. http://pubchem.ncbi.nim.nih.gov/ source/hsdb/8215.
12. British National Formulary: BNF 76 (76 ed) Pharmaceutical Press 2018; P175.
13. Nasr1 AM, Gardouh AR, Ghonaim HM and Ghorab MM: Design, formulation and *in-vitro* characterization of irbesartan solid self-nanoemulsifying drug delivery system (S-SNEDDS) prepared using spray drying technique. J Chem Pharm Res 2016; 8(2): 159-83.
14. Dezsi CA: The different therapeutic choices of ARBs. Which one to give? When? Why? Am J Cardiovasc Drugs 2016; 16: 255-66.
15. Brunner HR: The New Angiotensin II Receptor Antagonist, Irbesartan. Pharmacokinetic and Pharmaco-dynamic Considerations. Am J Hyp 1997; 10: 311S-317S.
16. CM Onah, CJ Mbah and AA Attama: Studies on transdermal delivery of irbesartan: microemulsion as a delivery system. IJPSR 2018; 9(12): 5463-73

17. Bachhav YG and Patravale VB: Microemulsion based vaginal gel of fluconazole: Formulation, *in-vitro* and *in-vivo* evaluation. Int J Pharm 2009; 365: 175-9.
18. Chen M, Alexander KS and Baki G: Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application 2016; https://doi. org/10.1155/2016/5754349.
19. Krishnaiah YSR, Satyanavayana V and Karthikeyan RS: Effect of solvent system on the *in-vitro* permeability of nicardipine hydrochloride through excised rat epidermis. Journal of Pharm & Pharm Sci 2002; 5: 123-30.
20. Niazy EM: Differences in penetration-enhancing effect of Azone through excised rabbit, rat, hairless mouse, guinea pig and human skins. Int J Pharm 1996; 130: 225-30.
21. Dahan A and Miller JM: The solubility-permeability interplay and its implications in formulation design and development for poorly soluble drugs. AAPS J 2012; 14: 244-51.
22. Miller JM, Beig A, Carr RA, Webster GK and Dahan A: The solubility-permeability interplay when using cosolvents for solubilization: revising the way we use solubility-enabling formulations. Mol Pha 2012; 9: 581-90.
23. Pagano R and Thompson TE: Spherical bilayer membranes: electrical and isotopic studies of ion permeability. J Mol Biol 1968; 38: 41-57.
24. Monti D, Saettone MF, Giannaccini B and Galli-Angeli D: Enhancement of transdermal penetration of dapiprazole through hairless mouse skin. J Cont Rel 1995; 33: 71-77.

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