ORIGINAL ARTICLE

Microemulsion based Transdermal Gels of Isradipine to Enhance Bioavailability: *In vitro* and *In vivo* Evaluation

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Abstract

Aim: The main objective of the current investigation was to develop and evaluate the microemulsion based transdermal gel for isradipine, poorly water soluble and low bioavailable drug. **Materials and Methods:** Saturation solubility studies of the drug were conducted in various solvents and oils. Oleic acid, Tween 80 and Transcutol P were selected as oil phase, surfactant and cosurfactants, respectively, as the drug was having highest solubility in these solvents. The pseudo-ternary phase diagrams were constructed using water titration method by varying surfactant to the co-surfactant (S_{mix}) ratio as 1:1, 1:2, 1:3, 2:1, and 3:1. Microemulsion formulations ratios were selected from the constructed pseudo-ternary phase diagrams. **Results and Discussion:** Microemulsion prepared with oil to S_{mix} ratio of 1:9 (F9) was found to be stable with the globule size of 50.4 ± 3.54, and has more % of drug diffusion of 88.4 ± 1.9% within 6 h and has been selected for the preparation of microemulsion based gel (MEBG) using carbopol 934 as gelling agent. The prepared gel has shown 96.74 ± 2.8% drug releases in 8 h which was higher than control gel. *In vivo* pharmacokinetic studies conducted in rabbits revealed that the bioavailability of MEBG was increased 5.4 times compared to oral suspension. **Conclusion:** This demonstrates avoidance of first pass metabolism and oral degradation and indicates the effective management of plasma profile of isradipine when it is administered as MEBG through transdermal route.

Key words: Carbopol, gel, isradipine, microemulsion, transdermal

INTRODUCTION

Transdermal drug delivery system has several advantages such as ability to deliver the drug into systemic circulation by avoiding first pass metabolism, avoids drug degradation in gastrointestinal tract, and improves bioavailability.[1] Moreover, sustained drug release can be achieved by the transdermal route. A remarkably broad range of transdermal formulations are available, ranging from simple solutions and lotions, through commonly used creams, ointments, gels and patches. While selecting a suitable dosage form drug physicochemical properties such as solubility, pKa, and lipophilicity must be taken into consideration.[2-4]

Microemulsion based gels (MEBGs) possess gained much popularity because in the recent era, as they offers the advantages of both emulsions and gels while having good patient acceptability. Because of its non-greasy nature, it can be easily applied to the skin as compared to other topical formulations such as creams, ointments which are very much thick, greasy and require excess rubbing.[5-7]

The majority of the drugs entering into market are suffering from bioavailability as they belong to low soluble, high permeable BCS Class II. Moreover, the drugs having less biological half-life are needed to be administered as sustained release dosage forms. Therefore, when one is concerned with the topical delivery of poorly water-soluble drug, MEBGs may serve as a better option. Emulsified gel has proven a stable one and better vehicle for hydrophobic or poorly water-soluble drugs.[8,9]

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Isradipine is one of the most promising antihypertensive drugs belonging to BCS Class II. Thus, there is a need to enhance solubility and bioavailability of drug and it has less half-life of 1-2 h, needs to be administered as sustained release dosage form. Hence, in the current research work an attempt was to made to prepare MEBGs of isradipine for transdermal delivery.[10-12]

MATERIALS AND METHODS

Materials

Isradipine was obtained as gift sample from Shasun Pharmaceuticals Limited, Cuddalore, Tamil Nadu, India. Labrafil 1944 CS and Trancutol-P were received as gift samples from Gattefosse, India. Remaining all the excipients were purchased from Finar Chemicals India.

Methods

Saturation solubility studies

The saturation solubility studies of isradipine was carried out in different oils and solvents such as distilled water, myglyol, ethanol, labrafil M 1944 CS, oleic acid, Transcutol P, poly ethylene glycol 400, propylene glycol, span 80, Tween 80, soyabean oil, glycerol, pH 1.2 phosphate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer. Saturated solutions of drugs were prepared by adding excess amount of drug to 2 mL of each selected vehicle and were agitated on the mechanical shaker for 48 h at 25°C. After reaching equilibrium, samples were collected and centrifuged at 10,000 rpm for 15 min. Further 100 µL of supernatant was collected and suitably diluted with methanol and amount of drug dissolved was quantified by using UV-visible spectrophotometry.[13]

Construction of pseudo-ternary phase diagram

Oleic acid, Tween 80 and Transcutol P were selected as oil phase, surfactant and cosurfactants, respectively, based on the results obtained from saturation solubility studies, as the drug was having highest solubility in these solvents. Pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature. For each pseudo-ternary phase diagram oil, and surfactant to co-surfactant (S_{mix}) mixtures were prepared at weight ratios (w/w) of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. Double distilled water was added drop by drop to each oily-surfactant mixture under magnetic stirring until the mixture became clear at a certain point. The concentrations of the components were recorded to complete the pseudo-ternary phase diagrams, and the contents of oil, surfactant, co-surfactant and water at appropriate weight ratios were selected based on the transparency and stability of formed microemulsions.[14]

Formulation development of isradipine loaded microemulsions

The microemulsion formulations were prepared using oleic acid as oil phase, Tween 80 as surfactant and Transcutol P as co- surfactant. Microemulsion formulations ratios were selected from the constructed pseudo-ternary phase diagrams. Compositions of isradipine loaded microemulsions are given in Table 1. Microemulsions were prepared by mixing the oil phase and water phase at constant stirring rate. The surfactant mixture and drug were added to the oil phase, followed by dropwise addition of aqueous phase to oil phase at constant stirring rate until turbidity was observed. Thus, formed microemulsions were checked for physical appearance after 24 h and categorized as clear/transparent/translucent if stable and as milky if there is precipitation.[12]

Characterization of drug loaded microemulsions

Measurement of droplet size and zeta potential

The mean droplet size and zeta potential were determined by photon correlation spectroscopy using Zetasizer (Malvern Instruments, UK). Each sample was diluted to a suitable concentration with filtered double distilled water. Globule size analysis was performed at 25°C with an angle of detection of 90°C. Size and polydispersity index of microemulsions were obtained directly from the instrument.[7]

Measurement of pH

The pH values of the microemulsion samples were measured by pH meter (Remi equipment Pvt Ltd). The pH meter was calibrated before each use with buffer solution of pH 4.0, 7.0, and 9.0. The measurement of pH of the formulation was done in triplicate and mean values were calculated.[7]

Measurement of viscosity

The viscosities of microemulsions were measured with a Brookfield viscometer DV–II+PRO, equipped with spindle no. LV1 has spindle code as 61. The spindle was dipped in the

Table 1: Composition of micro emulsion formulations

Formulation code	S_{mix} (1:2) (% w/w)	Oil (% w/w)	Water (% w/w)	Drug (mg)
F1	9.7	87.3	3	5
F2	19.4	77.6	3	5
F3	28.5	66.7	4.8	5
F4	37	55.6	7.4	5
F5	45.7	45.7	8.6	5
F6	53.6	35.7	10.7	5
F7	58.3	25	16.7	5
F8	47.1	11.7	41.2	5
F9	41	4.5	54.5	5

preparation and rotated at ambient temperature at 100 rpm for 5 min. It was measured in triplicate and mean values were calculated.[11]

Thermodynamic stability studies of emulsion

Prepared microemulsion formulations were evaluated for physical thermodynamic stability tests by the following process:

1. Heating cooling cycle: 6 cycles between refrigerator temperature 4°C and 45°C with storage at each temperature of not less than 48 h were studied. Those emulsions which were stable at these temperatures were subjected to centrifugation test
2. Centrifugation: Emulsions of respective formulations which passed heating and cooling cycle were centrifuged at 3500 rpm for 15 min. Those emulsions that did not show any phase separation were taken for freeze thaw stress test.
3. Freeze thaw cycle: Three freeze thaw cycles between −21°C and +25°C with storage at each temperature for not less than 48 h was done for the emulsions.

In vitro drug diffusion studies

In vitro drug diffusion studies were conducted for thermodynamically stable microemulsions by using Franz-diffusion cells fitted with a modified dialysis membrane. Initially, the dialysis membrane was soaked in a pH 7.4 phosphate buffer solution for 12 h at room temperature before initiation of the experiment. The receptor compartment was filled with 18 mL of phosphate buffer (pH 7.4) a small bar magnet was used to stir the elution medium at a speed of 600 rpm with the help of magnetic stirrer. The temperature of the elution medium was maintained and controlled at 37°C ± 1°C by a thermo static arrangement to mimic *in vivo* condition. An aliquot of 1 mL was withdrawn at a predetermined time interval replaced by an equal volume of elution medium to maintain sink conditions, diffusion studies were carried out for a period of 6 h. The drug concentration in the aliquot was determined by UV-visible spectrophotometer using the standard curve. The amount of drug diffused at various time intervals was calculated and plotted against time for all the developed formulations.[16]

Formulation development of MEBG

The best microemulsion was selected based on the results of *in vitro* characterization of microemulsions. The selected best formulation of microemulsion was incorporated into gel base and further research was done. Carbopol 934 was selected as gelling agent. About 1 g of carbopol 934 was soaked in the 100 mL of distilled water overnight. The formed carbopol 934 gel base was neutralized by dropwise addition using triethanolamine until the pH was adjusted to 6.8. To the gel base, the best microemulsion formulation equivalent to 5 mg dose for isradipine was dispersed slowly with the help of overhead stirrer.[15]

Characterization of MEBG

Physical appearance of gel

The prepared MEBG and drug solution were inspected visually for their color, appearance and consistency.

Rheological study

The rheological analysis of the MEG was performed using a Brookfield viscometer DV–II+PRO, equipped with standard spindle LV3 with spindle code 63. Viscosity was done in triplicates and the mean value was calculated at 100 rpm.

Drug content

For determination of drug content, about 1 g of the MEBG which was equivalent to 5 mg in case of isradipine was weighed and dissolved in methanol and the volume was made up to 100 mL. The above solution was diluted appropriately and drug content was determined spectrophotometrically.

Spreadability

Two glass slides were taken and onto one slide an excess of 3 g of gel was placed. Then, another glass slide was placed such that gel sandwiched between two glass slides. The top slide was subjected to a stress of 50 g by putting weight on it. Then, the time (in seconds) required by the gel to travel a distance of 10 cm was noted. A shorter time interval indicates better spreadability.

In vitro drug diffusion study from dialysis membrane

An *in vitro* drug release study was performed using Franz diffusion cell. The release of drug of optimal formulation was compared with the control gel and marketed gel. Dialysis Membrane (Hi Media, molecular weight 5000 Daltons) was placed between receptor and donor compartments. MEBG equivalent to 1 g was placed in the donor compartment and the receptor compartment was filled with pH 7.4 phosphate buffer (18 mL). The diffusion cells were maintained at 37°C ± 0.5°C with stirring at 600 rpm (Remi, India) throughout the experiment. At fixed time interval, 1 mL of aliquots were withdrawn for every 1, 2, 3, 4, 6, and 8 h from receiver compartment through side tube and equal aliquots were replaced. The samples were analyzed by UV-visible spectrophotometry.

In vivo pharmacokinetic study

In vivo studies were conducted in accordance with the approval of the Institutional Animal Ethical Committee. The *in vivo* pharmacokinetic study was conducted in white New Zealand rabbits weighing 3.10-3.50 kg. Comparative pharmacokinetic evaluation was made between optimized MEBG (equivalent to 5 mg of isradipine) and oral suspension

with the same dose. The oral suspension was prepared by suspending the weight equivalent drug in 0.5% w/v sodium carboxymethyl cellulose. Rabbits involved in the study were acclimatized to the study environment 1 day before the study. They were allowed to take standard diet and water until the night before beginning the study. The rabbits were fasted for 10 h. Latin square two ways cross over design was followed in the study. Total animals were divided into two groups, each group consisting of three rabbits. The rabbits used for MEBG were shaved carefully with the help of electrical shaver before applying the formulation and then cleaned with distilled water. In first study period, one group was administered with oral suspension through oral feeding tube followed by rinsing with distilled water and other group was applied with 1 g equivalent MEBG onto the skin to cover the 4 sq.cm surface area and covered with water impermeable back up membrane, further fixed with adhesive membrane. In the second study period, formulations were administered vice versa. Wash-out period of 15-day was maintained between each study period to eliminate the complete drug from the body. Blood samples of about 2-3 mL were collected from ear marginal vein at predetermined time intervals such as 0, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 h, respectively, after administration/application of formulation. Plasma was separated and analyzed for amount of drug present by reversed-phase high-performance liquid chromatography (RP-HPLC) method.[17]

Estimation of pharmacokinetic parameters

Pharmacokinetic parameters of both the drugs were calculated in each rabbit using software KINETICA 2000 (Version 3.0). Various pharmacokinetic parameters such as C_{max}, T_{max}, area under the curve (AUC). The relative bioavailability was calculated using the formula given below.

The relative bioavailability = AUC of MEBG/AUC of oral suspension

RESULTS AND DISCUSSION

Saturation solubility studies

The solubility of isradipine in various solvents and buffers was analyzed to select components for microemulsions. The amount of drug solubilized in the respective vehicle was calculated from the standard graph. The bar graph of solubility in various solvents is shown in Figure 1.

From the solubility studies, oleic acid was selected as oil phases based on the drug solubility and natural penetrating action. Tween 80 and Transcutol P were selected as surfactant and co-surfactant, respectively. Tween 80 was chosen as surfactant because of its high hydrophilic nature (Hydrophilic-lipophilic balance = 15) and good emulsion forming capacity. However, the drug is also having good solubility in Tween 80 and Transcutol P.

Construction of pseudo-ternary phase diagram

Figure 2 represents the pseudo-ternary phase diagrams of oleic acid with various ratios of Tween 80 and Transcutol P. The transparent microemulsion region is presented in phase diagrams. The rest of the region of the phase diagram represents the turbid and conventional emulsions based on visual observation. It was found that the area of microemulsion became enlarged as the S_{mix} reached 1:2 ratio.

Development of microemulsion formulations

Formulations were developed based on the microemulsion zone of pseudo-ternary phase diagrams. 4.5-87.3% of oil and 9.7-58.3% S_{mix} concentration was selected and formulations were developed. All the developed formulations were found to be clear/transparent, but at higher amounts of oil (F1 and F2 which contains more than 70% w/v of oil) precipitation was observed on overnight storage at ambient conditions.

Characterization of microemulsion

Measurement of pH and viscosity

The pH of all the nine formulations was measured using pH meter (Remi Equipment Pvt. Ltd), which was nearer to skin pH and the results found to be in the range of 5.1 ± 0.2 to 6.6 ± 0.2 and viscosity of all the formulations was carried out using brookfield viscometer and the results of viscosity are in the range of 7.4 ± 1.2 to 14.8 ± 0.3.

Determination of drug content

Drug content of all the microemulsion formulations was determined and found to be within the limits. The drug

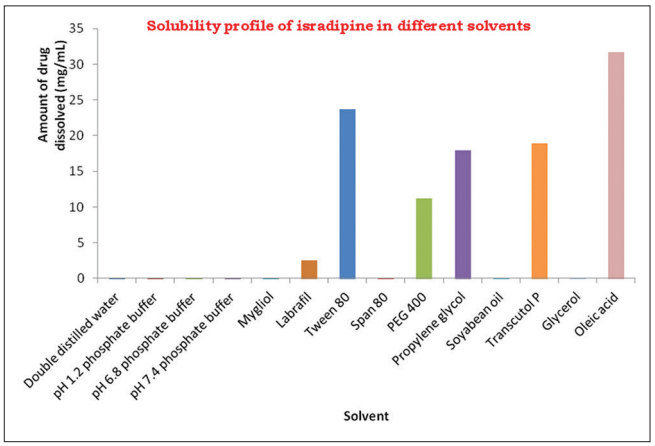

Figure 1: Saturation solubility studies of isradipine in various solvents

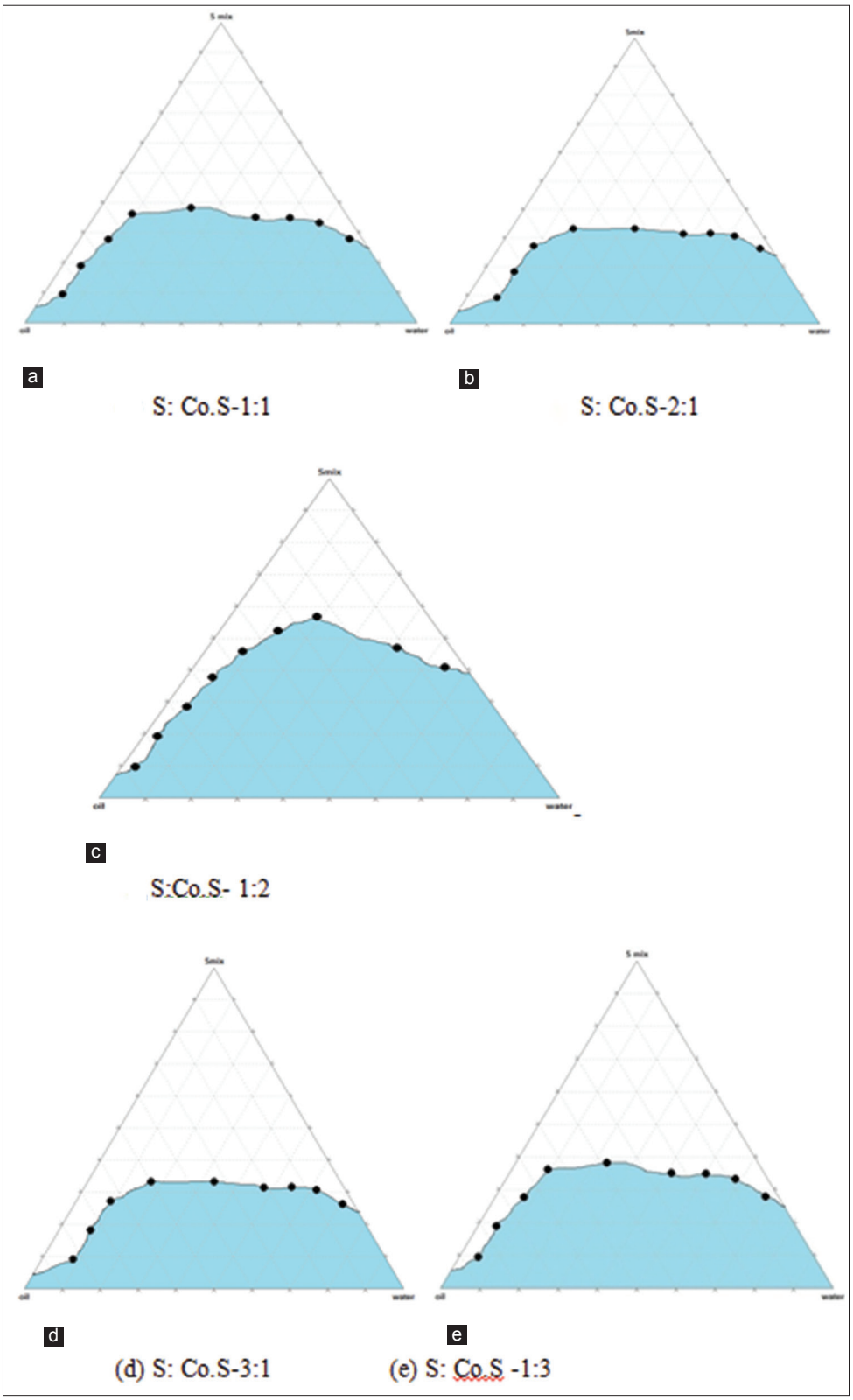

Figure 2: (a-e) Pseudo-ternary phase diagrams microemulsion formulations

content of all the formulations was found to be in the range of 4.98 ± 0.1 to 5.01 ± 0.14 and the highest amount of drug content was observed in F9 formulation.

Thermodynamic stability studies

During heating and cooling cycles formulations F1 and F2 have shown precipitation and hence these were excluded and

remaining formulations were found stable and hence they were further evaluated by centrifugation at 3500 rpm. All the formulations (F3-F9) were centrifuged at 3500 rpm. During centrifugation F3 has shown instability, so it was eliminated and remaining formulations were evaluated for further studies. Pseudo-ternary phase diagram of stable formulations is shown in Figure 3.

Measurement of droplet size and zeta potential

The globule size plays a significant role in the microemulsion. The size of the globules found to be in the range of 50.4 ± 3.54 to 75.3 ± 4.6 nm and as the concentration of surfactant mixture increased the globule size decreased. Polydispersity indicates the uniformity of droplet size within the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation. The polydisersity index (PDI) was within the acceptable limits for all the microemulsion formulations. The F9 formulation has shown the low PDI (0.102 ± 0.17), low globule size (50.4 ± 3.54) and high zeta potential (−35 ± 1.7) compared to other formulations.

In vitro drug diffusion studies

In vitro release studies were performed for microemulsions (F4 to F9), using dialysis method. The study was carried up to 6 h. The results are graphically represented in Figure 4. It can be observed that optimal formulations F9 have shown 88.4 ± 1.9% in 6 h. This indicates that the diffusion was increased by the use of surfactant mixture at highest ratio (oil: Surfactant mixture-1:9). Hence, it has selected as best formulation.

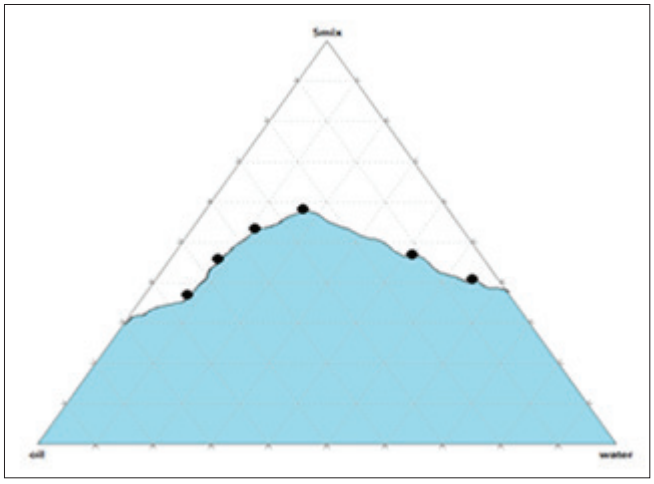

Figure 3: Pseudo-ternary phase diagrams stable microemulsion formulations

Formulation development MEBG

The optimal microemulsion formulations F9 was incorporated into gel base by continuous stirring until a homogenous MEBG is formed. The pure drug solution (control) was also incorporated into gel base to form control gel for comparative analysis with the optimal formulation.

Characterization of MEBG

Physical appearance

The prepared gels were inspected for their color; appearance and consistency and were having smooth homogenous texture and glossy appearance [Table 2].

Rheological study

Rheological behavior of the MEBG systems were indicated in Table 2. Brookfield viscometer was used to measure the viscosity using LV3 spindle at 100 rpm.

Determination of drug content

Drug content was determined in the optimal formulation and found to be 4.8 ± 0.3 for MEBG and it was 4.7 ± 0.6 for control gel and is shown in Table 2.

Spreadability coefficient

Spreadability of the optimal formulation was determined. The results were shown in Table 2, indicating that the optimal gel formulations have shown good spreadability in less than 1 min.

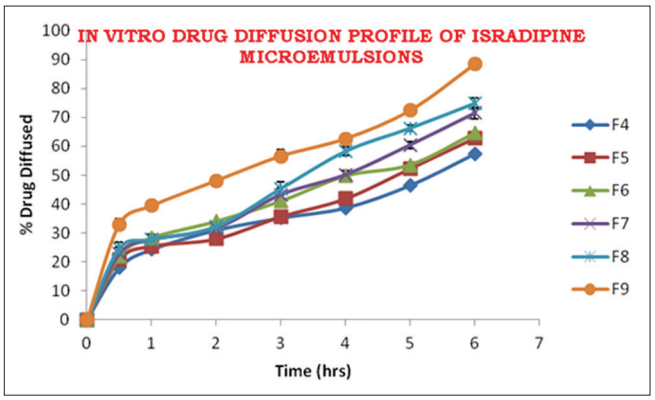

Figure 4: *In vitro* diffusion profiles of microemulsions

Table 2: Characterization of microemulsion gel

Formulation*	Physical appearance	Viscosity (cps)	Drug content (mg)	Spreadability (s)
F9 – Carbopol gel	Translucent	37.467±4.5	4.8±0.3	35 s
Control gel	White	45.678±1.4	4.7±0.6	54 s

Average of *n*=3 ± SD F9 indicates micro emulsion based gel. SD: Standard deviation

In vitro drug diffusion study from dialysis membrane

Isradipine drug diffusion studies were carried through dialysis membrane and the cumulative amount of drug permeated was calculated. The release of drug from gel formulations has been prolonged to 8 h which was 6 h in case of microemulsion. This delay was due the effect of the carbopol 934 (gelling agent). The release of drug of optimal formulation was compared with the control gel. It was observed that optimal gel showed 96.74 ± 2.8% drug release in 8 h and the percent of drug release for control gel was 62.6 ± 1.4%. Results of drug diffusion study of gels are shown in Figure 5. Steady state flux was calculated for the optimal formulation and the permeability coefficient was determined. The flux and permeability coefficient of the optimal formulation was compared with control gel. Flux of the optimized gel through dialysis membrane was 9.64 ± 1.6 µg/h/cm^2, which was significantly higher than control gel whose flux was found to be 4.845 ± 1.4.

In vivo pharmacokinetic study

The *in vivo* pharmacokinetic study was conducted in white New Zealand rabbits. Comparative pharmacokinetic evaluation was made between optimized MEBG (equivalent to 5 mg) and oral suspension with the same dose. Latin square two ways cross over design was followed in the study. Blood samples of about 2-3 mL were collected from ear marginal vein at predetermined time intervals such as 0, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 h, respectively, after administration/ application of formulation. Plasma was separated and analyzed for amount of drug present by RP-HPLC method. Plasma concentrations time profile is given in Figure 6. Different pharmacokinetic parameters were calculated in each rabbit by using software KINETICA 2000 (Version 3.0) and are given in Table 3. Various pharmacokinetic parameters include C_{max}, T_{max}, AUC and relative bioavailability.

The results from *in vivo* pharmacokinetic study reveal that the isradipine is released well from and permeated well from MEBG through transdermal route when compared to oral suspension. C_{max} value of microemulsion based formulation (1554.7 ± 41.3 ng/mL) was found to be higher than the oral suspension (1451.3 ± 15.7 ng/mL). Whereas Tmax values were higher in the case of MEBG formulation (11.5 ± 2.5 h) compared to oral suspension (1.5 ± 1.7 h), which indicates the drug diffusion through transdermal route is sustained. This might be due to the reason that the corneum could delay the permeation of drug from MEBG, in contrast, oral suspension is administered orally and is immediate release dosage form. The average AUC value was found to be significantly increased in the case of MEBG (34357.8 ±112.5 ng/h/mL) when compared to oral suspension (6340.2 ± 11.8 ng/h/mL). Bioavailability of MEBG was found to be increased 5.4 times demonstrating avoidance of first pass metabolism and oral degradation. This indicates the effective management of plasma profile of isradipine when it is administered as MEBG through transdermal route.

Table 3: Pharmacokinetic parameters of isradipine formulations

Pharmacokinetic parameter	Value	
	MEBG	Oral suspension
C_{max} (ng/mL)	1554.7±41.3	1451.3±15.7
T_{max} (H)	11.5±2.5	1.5±1.7
AUC (ng/h/mL)	34357.8±112.5	6340.2±11.8
Relative bioavailability	5.419±1.25	

CONCLUSION

The study demonstrated that the MEBG formulation can be employed to improve the solubility and skin permeability of isradipine. Microemulsions were prepared successfully using oleic acid as oil, Tween 80 as surfactant and Transcutol P as cosurfactant. Microemulsion-based gel was successfully prepared with carbopol 934 (1%) as a gelling agent to impart viscosity to the preparation as well as to sustain the action of the drug by increasing residence time. It can be concluded

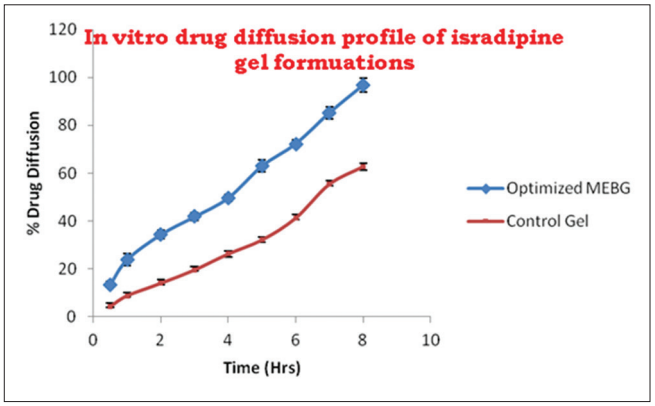

Figure 5: *In vitro* diffusion studies of gel formulations. OG: Optimal gel, CG: Control gel

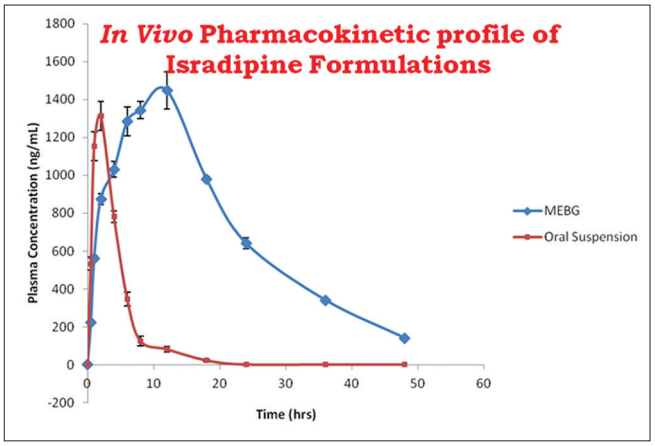

Figure 6: *In vivo* pharmacokinetic profile of isradipine formulations

that microemulsion-based gel can be formulated successfully for isradipine with improved bioavailability and sustained action.

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REFERENCES

1. Shingade GM, Aamer Q, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, *et al*. Review on: Recent trend on transdermal drug delivery system. J Drug Deliv Ther 2012;2:66-75.
2. Loyd V, Allen JR, Popovich NG, Ansel HC. Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th ed. Philadelphia: Lippincott-Williams & Wilkins; 2005. p. 298-9.
3. Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation via the skin. Trop J Pharm Res 2007;6:633-44.
4. Rizwan M, Aqil M, Talegoankar S, Azeem A, Sultana Y, Ali A. Enhanced transdermal drug delivery techniques: An extensive review on patents. Recent Pat Drug Deliv Formul 2009;3:105-24.
5. Parag P, Mansi AM, Mandal SN, Nikita P, Rajesh KS. Formulation and evaluation of microemulsion based gel of itraconazole. Pharmagene 2013;1:32-6.
6. Patel VA, Makwana SB, Patel BA, Parmar SJ. Formulation and characterization of micro-emulsion based gel of curcumin for the management of plaque psoriasis. Int J Adv Pharm Res 2014;5:1-6.
7. Wani RR, Patil MP, Dhurjad P, Chaudhari CA, Kshirsagar SJ. Microemulsion based gel: A novel approach in delivery of hydrophobic drugs. Int J Pharm Res Sch 2015;4:398-410.
8. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 2000;45:89-121.
9. Sarisozen C, Vural I, Levchenko T, Hincal AA, Torchilin VP. PEG-PE-based micelles co-loaded with paclitaxel and cyclosporine A or loaded with paclitaxel and targeted by anticancer antibody overcome drug resistance in cancer cells. Drug Deliv 2012;19:169-76.
10. Hitesh K, Jagruti P. Development and validation of UV spectrophotometric method for determination of isradipine loaded into solid lipid nanoparticles. Int J Pharm Rev Res 2013;20:162-6.
11. Tirunagari M, Jangala VR, Khagga M, Gannu R. Transdermal therapeutic system of isradipine: effect of hydrophilic and hydrophobic matrix on *in vitro* and *ex vivo* characteristics. Arch Pharm Res 2010;33:1025-33.
12. Veerareddy PR, Bobbala SK. Enhanced oral bioavailability of isradipine via proniosomal systems. Drug Dev Ind Pharm 2013;39:909-17.
13. Jakki R, Afzal Syed M, Kandadi P, Veerabrahma K. Development of a self-microemulsifying drug delivery system of domperidone: *In vitro* and *in vivo* characterization. Acta Pharm 2013;63:241-51.
14. Bhagwat DA, DSouza JI. Development of solid self micro emulsifying formulation to improve oral bioavailability. Int J Ther Appl 2012;1:38-41.
15. Vasanthavada M, Serajuddin AT. Lipid based self emulsifying solid dispersions. In: Oral Lipid Based Formulations: Enhancing Bioavailability of Poorly Water Soluble Drugs. New Jersey: Princeton; 2007. p. 149-84.
16. Sintov AC, Shapiro L. New microemulsion vehicle facilitates percutaneous penetration *in vitro* and cutaneous drug bioavailability *in vivo*. J Control Release 2004;95:173-83.
17. Gannu R, Palem CR, Yamsani VV, Yamsani SK, Yamsani MR. Enhanced bioavailability of lacidipine via microemulsion based transdermal gels: formulation optimization, *ex vivo* and *in vivo* characterization. Int J Pharm 2010;388:231-41.

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