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Investigations in Transdermal Delivery of Lacidipine

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ABSTRACT: Lacidipine is a calcium channel blocker which exhibits limited oral bioavailability. This study sought to formulate and assess lacidipine-loaded bigels for hypertension management by transdermal administration, resulting in lower doses, controlled drug delivery and improved patient compliance. Box-Behnken design was employed to optimize bigels by studying the effect of independent variables i.e. organogelator concentration, hydrogelator concentration, mixing proportion of Hydrogel:Organogel on dependent variables viscosity, time for 80% drug release. Bigels were characterized for physical appearance, pH, spreadability, extrudability, gel sol transition temperature, drug content, in vitro and ex vivo skin permeation, stability. Compatibility studies showed drug's compatibility with excipients. Carbopol 940, Span 60 were used as hydrogelator, organogelator respectively and mixing proportion of hydrogel:organogel was 1:1. Statistical model indicated that higher amount of hydrogelator and organogelator increased viscosity is increased. The higher proportion of hydrogel in bigel reduced the time for 80% drug release decreased. Optimized formula was found to show 86% drug release in 8 hours and stable in the accelerated stability study. Thus the novel formulation can be a commercially viable dosage form for efficient management of hypertension.

Keywords: lacidipine, bigel, hydrogel, organogel, transdermal, hypertension.

INTRODUCTION

High blood pressure, often known as hypertension, is a common and significant illness that can cause a number of health issues. It has a direct impact on mortality and the risk of cardiovascular illnesses. High blood pressure is linked to a number of conditions, including stroke, heart attack, angina, heart failure, kidney failure, and early mortality from cardiovascular causes (Dhyaneshwar *et al.*, 2019; Kearney *et al.*, 2004). The prevalence of hypertension rises with age. Prolonged high arterial pressure leads to significant pathological changes in the heart and blood vessels (Addo *et al.*, 2007).

Hypertension is a significant worldwide public health concern. Around 1.3 billion people globally, mostly in low- and middle-income nations, suffer from hypertension, according to the World Health Organisation. A survey conducted in 2015 revealed that one in four women and one in five men suffer from hypertension. Surprisingly, only about one in every five patients with hypertension has their condition under control, and hypertension is responsible for about 9 million deaths globally (Beaglehole *et al.*, 2014; Kumar *et al.*, 2022).

The current paradigm of treating hypertension involves using therapeutic agents such as ACE inhibitors (e.g., captopril, lisinopril, enalapril), angiotensin receptor blockers (e.g., valsartan, losartan, candesartan), beta blockers (e.g., metoprolol, esmolol), calcium channel blockers (e.g., amlodipine, felodipine, nicardipine, lacidipine), diuretics (e.g., furosemide, chlorthiazide, hydrochlorothiazide, spironolactone), and other medications (e.g., hydralazine, enalaprilat). Lifestyle modifications, including weight loss, reduced dietary sodium intake, potassium supplementation, adopting a healthy diet, engaging in physical activity, and limiting alcohol consumption, are also recommended (Carey *et al.*, 2022; Kitt *et al.*, 2019; Goit and Yang 2019; Hunter *et al.*, 2021).

Calcium channel blockers (CCBs) are medications that inhibit the flow of extracellular calcium through particular ion channels, leading to relaxation of vascular smooth muscle cells and lowering blood pressure. They

also reduce contractility in cardiac muscle and slow down the heart's electrical conduction (Abernethy and Schwartz 1999; Elliott and Ram 2011). Lacidipine, a lipophilic dihydropyridine calcium antagonist, is a type of CCB that acts slowly and has a long duration of action. It inhibits the contractile function of vascular smooth muscle, thereby reducing blood pressure. According to several research investigations, lacidipine binds and accumulates in the cell membrane first before diffusing to the calcium channel receptor in order to reach its target receptor. The calcium channel in its inactivated form is selectively blocked by lacidipine. When taken orally at a dose of 2-6mg once daily, lacidipine has equivalent antihypertensive activity as compared to other dihydropyridine calcium antagonists, thiazide diuretics, atenolol (a beta-blocker), and enalapril (an ACE inhibitor). However, lacidipine has a very low oral bioavailability (10%) (McCormack and Wagstaff 2003).

Researchers have looked into numerous drug delivery methods to increase the oral bioavailability of lacidipine (Lee and Bryson 1994; Van Amsterdam *et al.*, 1992; Kardile *et al.*, 2023). These include lacidipine self-nanoemulsifying drug delivery systems (SNEDDS), lacidipine-loaded spanlastic orally dissolving films, and liposomes designed to enhance the solubility and lymphatic uptake of lacidipine (Subramanian *et al.*, 2016; Naguib *et al.*, 2020; Gannu *et al.*, 2010; Kassem *et al.*, 2017; Qumbar *et al.*, 2017; Soliman *et al.*, 2016; Chandra *et al.*, 2018). However, the low bioavailability of lacidipine remains a challenge in the treatment of hypertension (DCruz *et al.*, 2022; Elkasabgy *et al.*, 2014).

Transdermal drug delivery through the skin has emerged as a promising alternative for improving the bioavailability of lacidipine. By bypassing the gastrointestinal tract and avoiding first-pass hepatic metabolism, transdermal delivery can ensure drug absorption. Equivalent therapeutic effects can be elicited with a smaller dose if given as a transdermal patch as compared to same dose if given orally. Drugs can be delivered through the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period of time (Keleb *et al.*, 2010; Shakeel *et al.*, 2019).

Bigels area useful dosage form for transdermal drug delivery. Bigels are biphasic systems comprising hydrogels and organogels with improved mechanical and controlled delivery features. They were initially explored for food applications but have demonstrated potential in cosmetics and pharmaceuticals. In comparison to other multiphase systems (such as emulsions, emulgels, or filled gels), the key distinguishing feature is that both phases (internal and external) are semisolid in nature. They are generally made by mixing an organogel and a hydrogel at high shear rates, which results in complex matrices (Shakeel *et al.*, 2018; Sreekumar *et al.*, 2020). Bigels help in enhanced hydration of the stratum corneum. Bigels can be used for loading both lipophilic and hydrophilic drugs and can provide controlled drug delivery. Further, bigels have a good moisturizing effect on the skin, hydrating it and facilitating drug diffusion. Bigels offer advantages like ease of application, good spreadability, and wash ability (Sreekumar *et al.*, 2020).

The present study was conceived with the hypothesis that transdermal delivery of lacidipine through thebigel system will minimize the first pass hepatic metabolism and exhibit controlled drug delivery for effective hypertension management.

MATERIALS AND METHODS

Materials. Lacidipine, a generous gift sample, was provided by BLD Pharma. Methanol was obtained from Loba Chemie. Soybean oil, Sunflower oil, Sorbitan Monostearate (Span 60) (Span 40), Cetyl Alcohol, HPMC K4M, HPMC K100M were procured from Chemdyes Corporation Rajkot. Tween 80, Beeswax, Carbopol were sourced from Suvidhinath Laboratories. All other chemicals and solvents utilized in the study were of analytical reagent (AR) grade.

Bigel Preparation. The preparation of bigel involves a three-step process: the preparation of organogel, the preparation of hydrogel, and the mixing of hydrogel and organogel to form the bigel (Sreekumar *et al.*, 2020). For the preparation of organogels, the organogelator and drug were dissolved in oil in wide-mouth vials or a beaker. Surfactant may or may not be added to the mixture. The vial or beaker containing the mixture was placed in a water bath maintained at 60° until the solution was homogeneous and clear. This solution was then kept aside to cool to ambient conditions, promoting the formation of organogel. Preliminary batches of organogels were prepared to determine the optimal composition of the organogel. To prepare the hydrogels, predetermined amounts of hydrogelator were soaked in distilled water for 24 hours until complete hydration. The mixture was gently mixed to ensure uniform gels. Similar to the organogels, preliminary batches of hydrogels were prepared to select the appropriate hydrogel composition. The bigels were formulated by adding the organogel to the hydrogel while continuously stirring at a slow speed using a mechanical stirrer (Fig. 1, 2).

Process Variable Optimization: The key variables that significantly impact the formulation of bigels are the mixing speed and RPM (rotations per minute). The optimization of these variables is detailed in Table 1. Consistently maintaining a ratio of 1:1 between hydrogel and organogel in all batches, the optimization process focused on assessing factors such as consistency, phase separation, and microscopic examination.

Formulation Optimization using Box-Behnken Design. A Box-Behnken design was utilized to create a design for bigels, aiming to investigate the impact of independent variables on dependent variables. The independent variables included organogelator concentration (X1), hydrogelator concentration (X2), and the ratio of hydrogel: organogel (X3), while the dependent variables were viscosity (Y1) and the time for 80% drug release (Y2) (Table 2). To evaluate the responses, a statistical model incorporating interactive and polynomial terms was employed. The response

surface methodology, implemented through Design Expert ver. 13 software, facilitated the optimization process (Peng *et al.*, 2020; Ibrahim *et al.*, 2020; Ismail *et al.*, 2018; Alkhalidi *et al.*, 2020; Lardy *et al.*, 2000).

Validation of Experimental Model: To verify the accuracy of the equations that described the impact of factors on efficiency and the time required for 80% drug release, an additional experimental batch was conducted as a checkpoint. The percentage relative error between the predicted values from the equations and the actual observed values was calculated employing the below mentioned formula.

$$\%\text{Relative error} = \frac{\text{Predicted value} - \text{observed value}}{\text{Predicted value}} \times 100 \quad (1)$$

Optimization by Numerical and Graphical Method. The primary objective of the formulation development was to explore the optimal levels of variables to achieve the desired characteristics in the final product. To accomplish this, the desirability function was utilized for optimization. Criteria were set for different dependent factors, and based on these criteria, the optimized formulation was selected. The selection was made by considering the desirability function (D) value closest to 1, indicating the highest level of desirability. The overlay plot, obtained through graphical analysis, provided the necessary design space for the optimization process.

Characterization of Bigels

pH. The pH values of all the formulations were measured by immersing a digital pH meter electrode into the prepared gel and allowing it to stabilize before recording the observations. Prior to usage, the pH meter was calibrated to ensure accurate measurements (Soni *et al.*, 2021).

Viscosity. The viscosity of the developed gels was evaluated using a Brookfield viscometer (Brookfield DV-II+ Pro). The viscosity measurements were performed using spindle number 96 at a temperature of 25° and an angular velocity of 10 rpm. Each measurement was conducted in triplicate, and the mean value was computed (Soni *et al.*, 2021).

Spreadability. The spreadability of the formulated gels was assessed by placing 0.5g of the gel onto a premarked glass plate with a 1cm diameter circle. Another glass plate of similar size was placed on top, and a 100g weight was applied for 5 minutes. The increase in diameter resulting from the gel spreading was measured (Soni *et al.*, 2021).

$$Ei = d^2 \frac{\pi}{4} \quad (2)$$

Where, Ei = spreadability of the sample, d= diameter (mm).

Extrudability. The extrudability test is used to measure the force needed to extrude bigel from a collapsible tube within a 10-second timeframe. Approximately 20g of the formulation was filled into a standard capped collapsible aluminium tube, and the end was crimped to seal. The tube was positioned between two slides and securely fastened. A 10g sample of the bigel was placed on top of the slides, and the cap was subsequently removed. The weight of the extruded bigel within 10 seconds was then measured and recorded (Soni *et al.*, 2021).

Gel-sol transition temperature. The gel-sol transition temperature of the formulated gels was assessed by placing them in a temperature-controlled bath with a range of 25°C to 60°C. The temperature at which the gel began to flow when the container was inverted was recorded. The temperature was increased gradually at a rate of 5°C in 5 minutes (Sreekumar *et al.*, 2020).

Drug content. The drug content of the formulations was analyzed using high-performance liquid chromatography (HPLC). The HPLC analysis was conducted using a Shimadzu HPLC system (Model LC-10 ATVP, Shimadzu, Japan) fitted with a binary pump and UV detection system (SPD-10A). Chromatographic separation was achieved using a Lichrospher-100 C18 column (average particle size 5 µm, 250 mm × 4.6 mm I.D., Merck). The mobile phase comprised of acetonitrile and 2-mM ammonium acetate, and the flow rate was set at 1.0 ml/min. For each run, a 20 µL sample was injected using an injection pump, and detection was performed at a wavelength of 240 nm with a total run time of 10.0 minutes (Qumbar *et al.*, 2014; Khullar *et al.*, 2012).

In vitro drug release. The in vitro release of the drug from the bigel formulation was evaluated using a modified Franz diffusion cell in which a pre-activated cellulose acetate membrane with a molecular weight cut-off of 12 kDa was mounted. A measured amount of the bigel formulation (1 g) was placed and spread on the cellulose acetate membrane on the donor side of the diffusion cell. The receptor section of the cell was filled with 50 ml of phosphate buffer solution (pH 5.5) as the receptor medium. The entire assembly was placed on a magnetic stirrer, and continuous stirring of the receptor solution was achieved using a magnetic bead. The cell was maintained at 37 ± 1˚C throughout the experiment. At specified time intervals (every hour), a 5 ml aliquot of the receptor solution was withdrawn, and the study was conducted for a total of 8 hours. The withdrawn samples were analyzed using HPLC, and the cumulative percentage of drug release was computed based on the measured drug concentrations (Salamanca *et al.*, 2018; Lulekal *et al.*, 2019).

Ex-vivo skin permeation study. Ex-vivo permeation studies were carried out on hairless abdominal rat skin to assess the permeability of the bigel formulation. The excised skin was carefully mounted onto Franz diffusion cells, with the dermal side of the skin exposed to a receptor fluid of phosphate buffer with a pH of 7.4. The stratum corneum, the outermost layer of the skin, was positioned on donor compartment side, where the bigel formulation was applied. The temperature was maintained at 32 ± 1ºC to simulate physiological conditions. A quantity of the bigel formulation equivalent to 5 mg of the drug was applied to the stratum corneum side of the skin. To maintain a sink condition, sampling was performed at specific time intervals by withdrawing the contents of the receptor compartment and replacing them with fresh receptor fluid. The collected samples were then analyzed using

HPLC to determine the drug concentration (Mazurkeviciute *et al.*, 2018).

Stability studies. Stability studies were conducted in accordance with the guidelines provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The purpose of these studies was to evaluate how the active pharmaceutical ingredient in the formulation changes over time when exposed to different environmental conditions such as humidity, temperature, and light. The stability study was conducted at two specific conditions: 25ºC±2ºC with a relative humidity (RH) of 60% and 45ºC±2ºC with a RH of 75%. All the prepared formulations were filled into aluminium collapsible tubes and sealed. These packed gels were then subjected to the specified temperature and climatic conditions. After the completion of the study, the gels were analyzed for various parameters including the percentage of drug content, percentage of drug release, viscosity, and pH to assess their stability (Lalan *et al.*, 2017).

RESULT AND DISCUSSION

Preliminary study on organogels. To determine the suitable organogel components and their versatile applications, initial batches of organogels were prepared (as shown in Table 3). It was noted that when soyabean oil was combined with Tween 80 and Span 60, the resulting organogel exhibited a desirable texture and consistency. Considering these positive attributes, the combination of soyabean oil, Tween 80, and Span 60 was selected for subsequent optimization steps (Misra *et al*., 2010).

Preliminary study on hydrogels. Initial batches of hydrogels were formulated (as shown in Table 4) to evaluate different hydrogel components and their wide range of applications. Among them, carbopol 940 demonstrated promising performance as a hydrogelator, even at low concentrations. The hydrogels formulated with carbopol 940 exhibited desirable consistency and excellent texture. As a result, Carbopol 940 was chosen as the preferred hydrogelator for further product development (Lalan *et al.*, 2017).

Process Variable Optimization. The ratio of organogel to hydrogel was maintained at a constant 1:1, while the process variables of mixing time and mixing rpm were optimized. The mixing time varied from 2 to 6 minutes. It was observed that increasing the mixing time from 2 to 4 minutes resulted in improved mixing efficiency, as confirmed by optical microscopy. However, extending the mixing time to 6 minutes did not provide any additional benefits. Insufficient mixing times led to phase separations between the organogel and hydrogel. Therefore, the optimal mixing time was determined to be 4 minutes.

The mixing rpm (revolutions per minute) varied from 400 to 800. It was observed that increasing the mixing speed decreased the globule size of the bigel formulation. The optimal mixing speed was found to be 600 rpm, as further increases in speed resulted in excessive air entrapment in the formulation (Table 5). The optimized batches exhibited bicontinuous structures composed of both organogel and hydrogel (Fig. 3). The distribution of organogel and hydrogel within the formulation was influenced by the interfacial forces between emulsifying agents, the cross-linked network structure of the gelator molecules, and the proportion of hydrogel to organogel (Lalan *et al.*, 2017; Misra *et al.*, 2010).

Evaluation of Box-Behnken Design Batches. The response surface methodology was applied using Design Expert ver. 13 software to investigate bigels. A Box-Behnken design was utilized to determine the impact of independent variables, namely organogelator concentration % (X_1), hydrogelator concentration % (X_2), and the ratio of hydrogel to organogel (X_3), on dependent variables: viscosity (Y_1) and T80% drug release (Y_2). A statistical model incorporating interactive and polynomial terms was used to analyze the responses. The model can be represented as:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

The main effects(X_1, X_2, X_3) illustrate the mean outcome when changing one factor at a time, ranging from low to high level. The interaction terms (X_1X_2, X_1X_3, X_2X_3) indicate the change in response when two factors are simultaneously varied. Fifteen batches of the formulation were prepared according to the design matrix specified in Table 6.

The response surface plots (Fig. 4) generated from the design demonstrated that increasing the concentrations of hydrogelator and organogelator resulted in an increase in viscosity. Conversely, an increase in the proportion of hydrogel in the bigel formulation led to a decrease in viscosity. The software-generated polynomial equation for viscosity is provided as follows:

$$\text{Viscosity} = +4846.67 + 438.75 * X_1 + 185 * X_2 - 258.75 * X_3 + 117.5 * X_1X_3 - 194.583 * X_1^2$$

The analysis of variance (ANOVA) for the model, presented in Table 7, revealed that the viscosity of the bigel formulation was primarily dependent on the concentration of the organogelator. Both the organogelator concentration and the ratio of hydrogel to organogel significantly influenced the viscosity. The concentration of the hydrogelator also had a noticeable impact on viscosity, although it was relatively less significant compared to the organogelator concentration. The increased cohesiveness resulting from a higher organogelator concentration could potentially affect the spreadability of the formulation.

The response variable plot (Fig. 5) indicated that as the amount of hydrogelator and organogelator increased, the time required for 80% drug release also increased. Conversely, when the proportion of hydrogel in the bigel formulation was increased, the time for 80% drug release decreased. These trends were reflected in the coefficients associated with the amount of hydrogelator, organogelator, and the ratio of hydrogel to organogel.

$$\text{Time for 80\% drug release} = 3.33958 + 0.15 * A + 1.125 * B - 0.33125 * C$$

The statistical parameters of the model were examined to validate its reliability. For the dependent variable viscosity, the predicted R-squared value of 0.9373

reasonably matched the adjusted R-squared value of 0.9883. The adequate precision value of 39.1812 indicated a satisfactory signal, suggesting that this model could effectively guide the design process. Similarly, for the time taken for 80% drug release, the predicted R-squared value of 0.8505 was reasonably consistent with the adjusted R-squared value of 0.9081. The adequate precision value of 20.3086, indicating a satisfactory signal, further supported the usability of this model for navigating the design space (Table 8) (Patel *et al.*, 2023; Lalan *et al*., 2020).

Optimization of Bigel formulation by Numerical Method. The key objective of the formulation development was to investigate the variables influencing the process and formulation design and determine their optimal levels to achieve the best possible characteristics in the finished product. The desirability function was applied to predict the optimal levels for the independent variables. Constraints were imposed on the dependent variables to obtain an optimized formulation composition. The goal was to maximize viscosity with a minimum target value of 5000 cps and to maximize the time for 80% drug release with a minimum target value of 7 hours. A value of "D"close to 1 indicated an optimal combination of different criteria, where the response values were in proximity to the target values. The aim was to target these two responses in order to achieve the desired characteristics. The partial desirability function (di) for each response and the calculated geometric means as the maximum global desirability function (D=1) were depicted in Fig. 6, with D varying between 0 and 1 depending on the proximity of the response to its target. The software generated solutions were analysed for D values and the solution with D closest to 1 was selected (Patel *et al*., 2023; Lalan *et al.*, 2020). The composition of the optimized lacidipine bigel is shown in Table 9.

Characterization of the optimized batch. The organogel in its optimized form underwent characterization for various parameters. The visual appearance of the formulation holds importance in topical delivery as it influences patient compliance. Therefore, transparency, color, and uniformity were assessed for the optimized batch (Table 10). The optimized batch exhibited a non-transparent, white color with a smooth and creamy consistency. This can be attributed to the uniform mixing of hydrogel and organogel phases facilitated by the presence of surfactants(Span 60 and Tween 20). The stability of the formulation was confirmed by successfully inverting the organogel beaker without any dripping. The pH of the prepared bigel formulation was measured to be 6.9±0.3, which closely aligns with the pH range of the skin (4.5-6.5). Such pH compatibility suggests that the formulations are expected to be non-irritating during application.

Viscosity, an important parameter, was measured using a Brookfield viscometer. The viscosity of the optimized batch was determined to be 5620 cps, and it depended on the concentration of organogel added to the formulation. Spreadability, which affects ease of application, accurate dosing, and patient compliance, was influenced by the polymer concentration. The mean spreadability value of the formulation was measured to be 1.73±0.08. Based on the spreadability coefficient (Φ), the formulation fell under the "stiff gel" class, displaying a pseudoplastic nature. Extrudability, measured by the force required to extrude the formulation from the packaging material, indicated excellent extrudability as more than 90% of the formulation was extruded within 10 seconds. The gel sol transition temperature of the optimized formulation was determined to be 48±0.01 ºC, representing the critical temperature at which the three-dimensional networked structures of the semi-solid preparation undergo deformation and disruption. This transition temperature was found to be directly dependent on the amount of organogel added to the formulation and provided thermal stability to the formulation through increased gelator molecule entanglement (Soni *et al.*, 2021; Lalan *et al.*, 2017; Patel *et al*., 2023; Lalan *et al.*, 2020).

The average drug content of the bigel formulations was 96.01±0.02%, indicating that the processing did not negatively affect the drug content. In-vitro drug release studies showed that 80% of the drug was released over a period of 7.82 hours. The drug release was influenced by the intertwined network formed by the hydrogelator molecules, with self-association or assembly of fatty acid based surfactants (such as Span 60) acting as a limiting factor for drug diffusion across the gel matrix. This suggests that bigel formulations have the potential to provide controlled drug delivery through their biphasic matrix structure.

The optimized bigel formulation was further evaluated for its potential in transmembrane drug delivery through ex-vivo skin permeation studies. The results demonstrated slow and sustained drug release over a period of 8 hours (Fig. 7). The balanced hydrophilic and lipophilic characteristics of the formulation contribute to skin hydration, pore opening, and enhanced drug penetration (Soni *et al.*, 2021; Lalan *et al*., 2017).

Stability Study. The optimized formulation of Lacidipine loaded bigel underwent stability studies under accelerated temperature conditions (25ºC±2ºC, 60%RH) for a duration of 30 days. The drug diffusion was evaluated using the similarity factor (f2), where two curves are considered statistically similar if the f2 value exceeds 50. In this case, the f2 value was determined to be 51.55. The stability studies revealed that there were no notable changes in pH, drug content, viscosity, and in-vitro drug diffusion when the formulation was stored at both room temperature and the accelerated condition for a period of one month (Table 11).

Table 1: Process variable optimization.

Formulation	Process Variable	
Bigel (Hydrogel : Organogel :: 1:1)	Mixing Impeller Speed (rpm)	400
		600
		800
	Time for mixing (min)	2
		4
		6

Table 2: Optimization Studies using Box-Behnken design.

Independent Factor	Factor levels		
	Low level (-1)	Central Level (0)	High Level (+1)
% Organogelator (X_1)	10	15	20
% Hyrogelator (X_2)	0.50	0.75	1
Hydrogel:Organogel	50:50	60:40	70:30
Response Variable	Viscosity (Y1), Time for 80% drug release (t80) (Y2)		

Table 3: Preliminary batches of Organogel.

Ingredient/ Batch No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Soyabean oil (%w/w)	68	70	70	70	70	83	**80.5**	78	88
Span 60 (%w/w)	10	-	-	10	-	15	**17.5**	20	10
Tween 80 (%w/w)	2	-	-	-	2	2	**2**	2	2
Cetyl alcohol (%w/w)	-	10	10	-	10	-	-	-	-
Water (%w/w)	20	20	-	-	-	-	-	-	-
Texture	Non Uniform	Non Uniform	Smooth Uniform	Smooth Uniform	Non Uniform	Non Uniform	Smooth Uniform	Smooth Uniform	Non Uniform
Consistency	Low	Very low	Good	Good	Phase Separation	Medium	**Very Good**	Very High	Very low

Table 4: Preliminary batches of hydrogel.

Ingredient/Batch No.	F1	F2	F3	F4	F5	F6
Carbopol 940	0.5%	**1%**	-	-	-	-
HPMC K4M	-	-	0.5%	1%	-	-
HPMC K100M	-	-	-	-	0.5%	1%
Propylene Glycol	10%	**10%**	10%	10%	10%	10%
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Consistency	Medium	Very High	Very Low	High	Low	High

Table 5: Processing Parameter Optimization (Mixing time and Mixing rpm).

	A1	A2	A3	A4	A5	A6
Hydrogel: organogel	1:1	1:1	1:1	1:1	1:1	1:1
Mixing time (Min)	2	4	6	4	4	4
Mixing Speed (rpm)	400	400	400	400	600	800
Consistency	Low	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Air entrapment
Separation	Yes	No	No	No	No	No

Table 6: Optimization batches of bigel using Box–Behnken design.

No.	Organogelator Concentration (%w/w)	Hydrogelator Concentration (%w/w)	Hydrogel: Organogel	Viscosity (cps)	$T_{80\%}$ drugrelease (h)
F1	10	1	0	4450	6
F2	10	0.75	-1	4620	6.1
F3	10	0.75	1	3840	5
F4	10	0.5	0	4010	5.3
F5	15	0.5	-1	4910	6.5
F6	15	1	-1	5340	7.1
F7	15	0.75	0	4840	6.6
F8	15	1	1	4760	6.7
F9	15	0.75	0	4870	6.4
F10	15	0.75	0	4830	6.5
F11	15	0.5	1	4510	5.9
F12	20	0.75	1	5010	6.7
F13	20	1	0	5230	7.3
F14	20	0.5	0	4870	7.15
F15	20	0.75	-1	5320	7.25

Table 7: Analysis of variance (ANOVA) for the model.

Source	Sum of Squares	Df	Mean Square	F-value	p-value
Model	25677.02	9	2853.00	132.19	< 0.0001
A-Organogelator conc	15400.12	1	15400.12	713.52	< 0.0001
B-Hydrogelator conc	2738.00	1	2738.00	126.86	< 0.0001
C-Ratio H:O	5356.13	1	5356.13	248.16	< 0.0001
AC	552.25	1	552.25	25.59	0.0039
A^2	1398.01	1	1398.01	64.77	0.0005
Residual	107.92	5	21.58		
Lack of Fit	99.25	3	33.08	7.63	0.1180
Pure Error	8.67	2	4.33		
Cor Total	25784.93	14			

Table 8: Result of statistical parameters obtained from ANOVA study

Response	Adjusted R^2	Predicted R^2	Adequate precision	C.V.(%)
Viscosity	0.9883	0.9377	39.1812	0.9759
Timefor80% Drug release	0.9081	0.8505	20.3086	3.21

Table 9: Composition of Optimized Formulation of Bigel Formulation.

Preparation	Ingredients	Quantity (% w/w)
Organogel	Span60	20
	Soyabean oil	77.80
	Tween80	2
	Lacidipine	0.4
Hydrogel	Carbopol940	1
	Propylene Glycol	10
	Water	89.50
Bigel	Hydrogel : Organogel	1:1

Table 10: Characterization of the optimized batch.

Property	Observation
Physical Appearance	White in color and smooth consistency
pH[$]	6.9 ± 0.3
GelSol transition temperature [$]	48 ± 0.01ºC
Viscosity	5620 ± 45.3 cps
Time for 80% drug release [$]	7.82 hrs
Spreadability [$]	1.73 ± 0.08 cm
Extrudability [$]	1.59 ± 0.01gm/sec

[$](n=3)

Table 11: Stability Studies for bigel.

Characterization	At0day	After 30 days (25ºC±2ºC , 60%RH)
Viscosity (Cps)	5620	5600
pH	6.9	6.8
% Drug content	94.4	88.53
Time for 80% drug release (h)	7.82	7.65

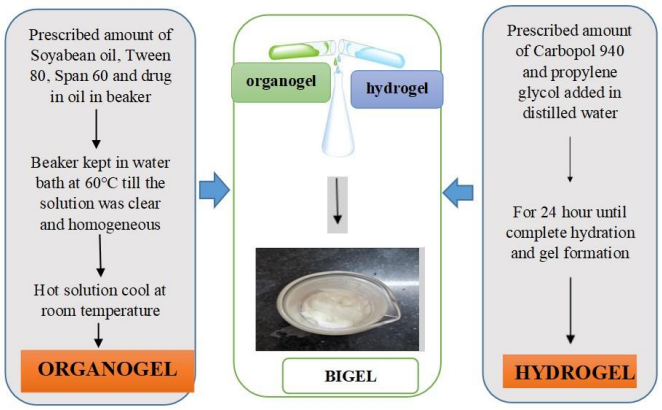

Fig. 1. Bigel formulation process.

Fig. 2. Bigel formulation of lacidipine

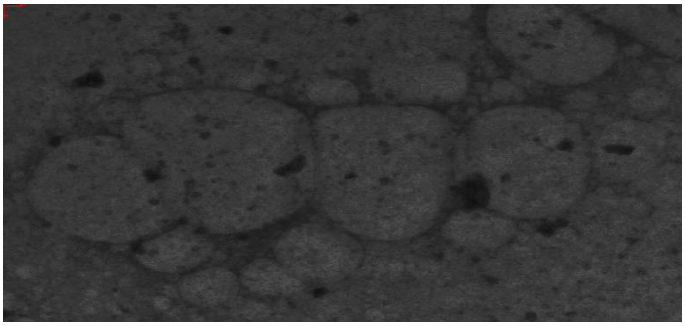

Fig. 3. High resolution microscopy of the optimized organogel.

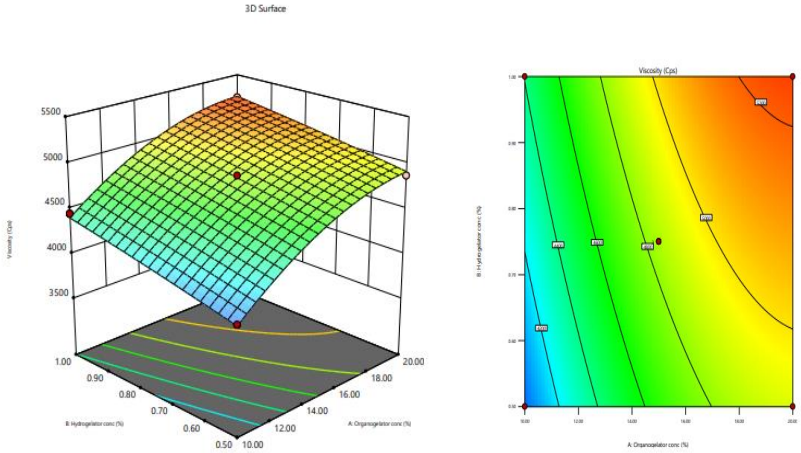

Fig. 4. Response surface plot for viscosity.

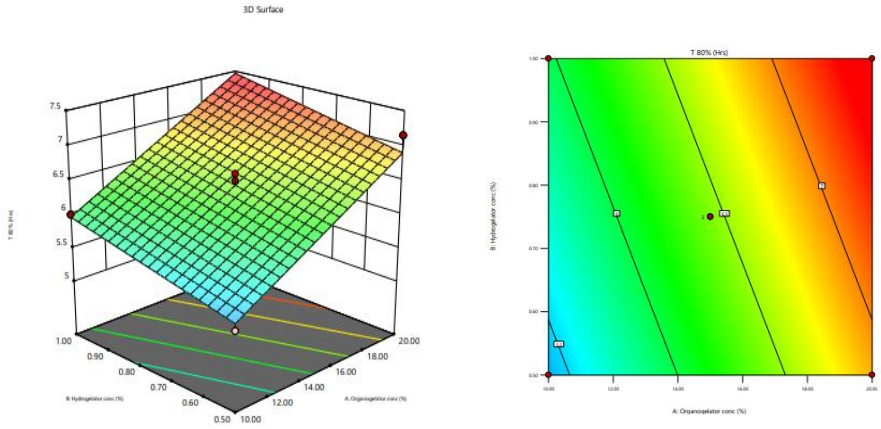

Fig. 5. Response surface plot for time for 80% drug release.

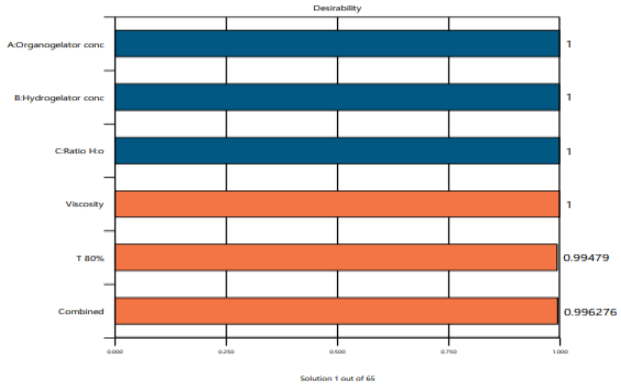

Fig. 6. Desirability value of response.

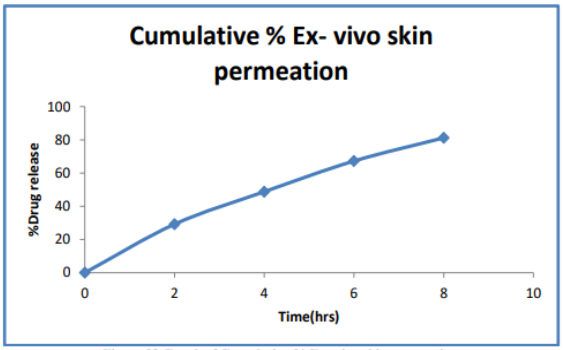

Fig. 7. Graph of Cumulative % Ex-vivo skin permeation.

CONCLUSIONS

Bigel of the antihypertensive drug lacidipine was formulated by dispersion of hydrogel and drug loaded organogel. The successful formulation was indicated by absence of phase separation and desirable consistency. The microstructure revealed uniform globular dispersion. Box Behnken design aided in optimization of the formulation's critical independent variables on the basis of desirable responses. Drug release studies through the dialysis membrane and ex vivo skin permeation suggested sustained drug release for a duration of 8 hours. The prepared formulation displayed desirable physiochemical characteristics in terms of pH, gel-sol transition, spreadability and stability in accelerated studies. The Bigel is a patient friendly dosage form for transdermal drug delivery that can be scaled up easily during large scale manufacturing.

FUTURE SCOPE

Lacidipine loaded bigels for the management of hypertension through transdermal drug delivery can translate to improved bioavailability and lower doses thus improving patient compliance. The dosage form is industrially scalable. Further non clinical studies can validate the utility of the formulation.

Author contributions. ML- Conceived and designed the analysis; RP, FP - Collected the data; PC, RG- Contributed data or analysis tools; Performed the analysis; FP, ML- Wrote the paper.

Conflict of Interest. None.

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