Research Paper

Formulation Optimization of Topical Simvastatin Emulgel by Box Behnken Method

SURBHI GUPTA AND A. ANAND*

Department of Pharmaceutics, Hygia Institute of Pharmaceutical Education and Research, Prabandh Nagar, Lucknow, Uttar Pradesh 226020, India

Simvastatin is classified as a biopharmaceutics classification system class II drug. Emulgel is a superior alternative for biopharmaceutics classification system class II drugs with low solubility and high permeability. For emulgel preparation, the solubility of simvastatin was assessed in sesame, groundnut and olive oil. The maximum solubility of simvastatin is found in sesame oil (21.06 mg/ml). Simvastatin emulgel was prepared and optimized using a three-factor, three-level Box-Behnken design. For optimization, concentrations of carbopol 934, sesame oil and surfactant (Tween 80) were selected as independent variable and viscosity, spreadability and *in vitro* drug release was selected as dependent variables, which are critical components of any semisolid formulation, as well as patient compliance. The optimized formulation was evaluated for viscosity, spreadability, pH, drug content and *ex vivo* release. The optimized formulation had 6875±531.21 mPas of viscosity, spreadability of 10.1446±0.31 gcm/s and *in vitro* drug release of 40.75±0.42 %, respectively. *Ex vivo* release investigations revealed that 42.15±0.32 % of simvastatin was released in 24 h. The study results demonstrated that the simvastatin emulgel might be an alternative the conventional topical administration form.

Key words: Emulgel, simvastatin, Box-Behnken design, hydrophobic drug, sesame oil

Gels are the three Dimensional (3D) polymeric matrix in which large volumes of aqueous or hydroalcoholic liquids are entrapped[1]. Gel formulations often allow for faster pharmaceutical release than traditional ointments and lotions. Despite the numerous advantages of gels, one major disadvantage is the difficulty in administering hydrophobic drugs[2-4]. Emulgels were designed to help people get over these limitations. Emulgels are dosage forms made up of a mixture of gels and emulsions[5]. Emulgel is a superior alternative for Biopharmaceutics Classification System (BCS) class II drugs with low solubility and high permeability[6,7]. Emulgel is thixotropic, greaseless, easily spreadable, removable, emollient, non-staining, water-soluble, biofriendly and pleasing in appearance, all of which contribute to patient adequacy[8].

Simvastatin ([(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]2,2-dimethylbutanoate) has also been proven to have antibacterial activity and the ability to reduce Gram-positive bacteria[9-11], making it a viable alternative to some of the more well-known antibiotics[12,13]. The study's objective was to develop a topical simvastatin emulgel to improve drug loading and sustained release. A response surface approach (Box-Behnken design) was employed in this study to construct an optimal emulgel system and to investigate the impact of formulation factors on the properties of the developed emulgel system.

MATERIALS AND METHODS

Materials:

Simvastatin was obtained as a gift sample from Biodeal Pharmaceuticals Pvt. Ltd., Carbopol 934 was obtained from Central drug house Pvt. Ltd. All other substances were of analytical grade and had not been modified in any way.

***Address for correspondence**
E-mail: anubhavanand2000@gmail.com

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Methods:

Solubility study: The solubility of simvastatin in oils (sesame, arachis and olive) was determined by the shake flask method. The oils (5 ml) were kept in the vials and an excess of simvastatin was added to the vials. The vials were capped, shaken on a vortex shaker and kept for 48 h[14]. Mixtures were then centrifuged at 5000 rpm for 15 min at 25° to remove the undissolved simvastatin. The supernatant thus obtained was separated and adequately diluted with ethanol and estimated for the drug by a Ultraviolet (UV) spectrophotometer at 238 nm[15].

Preperation of emulgel:

The formula of the emulgel is shown in Table 1. The aqueous and oily phase was prepared separately. The oil phase was prepared by dissolving Tween 80 and drug in sesame oil, while methylparaben, propylparaben and glycerine were dissolved in distilled water to make the aqueous phase. Both the phases were heated individually at 70°-80° for 20 min; then oily phase was added to the aqueous phase[16] by stirring on a magnetic stirrer and allowed to cool down to room temperature to get an emulsion. The emulsion was dispersed in the gel base, prepared separately by dispersing the carbopol 934 in purified water and stirred continuously by magnetic stirrer to establish the gel phase of the formulations[17]. A 10 % Triethanolamine (TEA) solution was added dropwise to adjust pH 6.8 and produce an emulgel[18].

Optimization of emulgel formulation:

Box-Behnken design was employed to evaluate the impact of independent factors on the responses to establish the optimal emulgel formulation. Carbopol 934 (Polymer), sesame oil (Oil), and Tween 80 (surfactant) concentrations were the independent variables. Viscosity (Y1), Spreadability (Y2), and *in vitro* drug release (Y3) were the dependent responses. The concentrations of the independent variables are shown in Table 2. The emulgel formulation was optimized using a three-factor, three-level (33) design[19]. The software predicted a design with 15 experimental runs, three of which are central values as shown in Table 3.

TABLE 1: FORMULATION OF SIMVASTATIN EMULGEL

S. no	Carbopol 934 (% w/v)	Sesame oil (% w/v)	Tween 80 (% w/v)	Glycerine (ml)	Methyl paraben (g)	Propyl paraben (g)	TEA	Distilled water q.s. (ml)
1	1.5	5	2	0.6	0.05	0.05	q.s.	100
2	1	5	3	0.6	0.05	0.05	q.s.	100
3	0.5	5	2	0.6	0.05	0.05	q.s.	100
4	0.5	10	1	0.6	0.05	0.05	q.s.	100
5	1	10	2	0.6	0.05	0.05	q.s.	100
6	1	10	2	0.6	0.05	0.05	q.s.	100
7	1.5	10	3	0.6	0.05	0.05	q.s.	100
8	0.5	15	2	0.6	0.05	0.05	q.s.	100
9	0.5	10	3	0.6	0.05	0.05	q.s.	100
10	1	15	1	0.6	0.05	0.05	q.s.	100
11	1	15	3	0.6	0.05	0.05	q.s.	100
12	1.5	15	2	0.6	0.05	0.05	q.s.	100
13	1	10	2	0.6	0.05	0.05	q.s.	100
14	1.5	10	1	0.6	0.05	0.05	q.s.	100
15	1	5	1	0.6	0.05	0.05	q.s.	100

Note: q.s.: Quantity sufficient

TABLE 2: INDEPENDENT VARIABLES AND THEIR LEVELS FOR BOX- BEHNKEN DESIGN OF EMULGEL

Independent variables	Levels		
	-1	0	1
Carbopol 934 % w/v (A)	0.5	1	1.5
Oil % w/v (B)	5	10	15
Surfactant % w/v (C)	1	2	3

TABLE 3: THREE FACTOR THREE LEVEL BOX BEHNKEN DESIGN IN CODED VALUE

Run	Carbopol 934 (% w/v)	Oil (% w/v)	Surfactant (% w/v)
1	1	-1	0
2	0	-1	1
3	-1	-1	0
4	-1	0	-1
5	0	0	0
6	0	0	0
7	1	0	1
8	-1	1	0
9	-1	0	1
10	0	1	-1
11	0	1	1
12	1	1	0
13	0	0	0
14	1	0	-1
15	0	-1	-1

Evaluation parameters of emulgel:

Organoleptic character: Organoleptic properties such as colour, appearance and homogeneity of the prepared emulgel were visually evaluated.

Viscosity: The viscosity of the formulations was determined using a Brookfield Viscometer (RV viscometer)[20]. The spindle (#5) was placed in the emulgel's centre, ensuring it did not touch the bottom of the beaker and revolved for 10 min at 10 rpm. The viscosity was calculated and reported. An average of three readings was used to determine the viscosity of the emulgel.

Spreadability test: Khullar *et al.*[21] provided a method for determining the spreading coefficient. It has built out of a wooden block with a pulley on one end. The spreading coefficient was calculated using the emulgel's 'Slip and Drag' features. A glass slide was mounted on the wooden block. An excess amount of emulgel (about 2 g) was placed on the ground slide. Another slide, attached with thread, was placed over the fixed one. The thread was passed over the pulley and another end of the thread held a pan. A 2 g weight was placed initially over the two slides to form a uniform film between the slides. After 5 min, the weight was removed and was put on the pan to move the upper slide, and the time (in s) needed by the top slide to traverse a maximum distance of 5 cm was noted[22]. The spreading coefficient was calculated by using the formula:

$S=M\times L/T$

Where M, is a weight put on the pan attached to the upper slide, L is for the length covered by the glass slides, T is the time taken by the slide to cover the distance L.

pH determination: At room temperature, the pH of the sample was determined using a digital pH metre (Thermo Scientific). The emulgel was suitably diluted with purified water and allowed to sit for 2 h. The pH was checked directly by dipping the electrode into the gel and allowed to equilibrate[23], and then the pH was measured by calibrated pH meter.

Extrudability test (tube test)[24]: The weight needed to extrude a 0.5 cm emulgel ribbon from a lacquered collapsible aluminium tube in 10 s is the basis for the extrudability test. A collapsible aluminium tube was filled with the optimum emulgel mixture and the end was crimped shut to seal it. The substance was forced through the tubes and the emulgel's extrudability was verified. The following formula was then used to determine the extrudability.

Extrudability=Weight applied to extrude emulgel from tube (g)/area (cm^2)

Swelling index[25]: It is determined by taking 1 g of emulgel in a porous aluminum foil and mixed with 0.1 N NaOH kept in a 50 ml beaker. Then samples are withdrawn at different time intervals and kept for drying and it is reweighed.

$\text{Swelling index}=W_t-W_0/W_t\times 100$

Where, W_t=Weight of swollen emulgel after time 't'; W_0= Weight of emulgel at zero time.

Microscopy of emulgel: The emulgel was placed on the glass slide and the droplet size and morphology of the emulgel was studied by microscope with the camera (Radical [RXL-4T]) at a magnification of 10X[26].

Drug content: Drug content was determined by dissolving a 1 g of emulgel in 10 ml of ethanol, stirring with a magnetic stirrer until the emulgel was dissolved entirely. The solution was centrifuged at 5000 rpm for 10 min and the clear supernatant was taken and diluted suitably. The absorbance was recorded at λ_{max} 238 nm with a double beam UV spectrophotometer (Labindia).

Percentage drug content=Drug content (mg)/Label claim×100

***In vitro* release test:**

In vitro drug release studies were carried out using a Franz Diffusion (FD) cell with a dialysis membrane (HIMEDIA LA 395-10MT). The phosphate buffer pH 7.4 solution containing 0.5 % w/v of sodium dodecyl sulphate was used as a dissolution media. This buffer solution was placed into the receptor compartment of the diffusion cell. The membrane previously soaked in phosphate buffer pH 7.4 for 24 h was carefully clamped on between the donor and receiver chamber of the diffusion cell. The entire assembly was placed on a magnetic stirrer. The solution on the receptor side was continually stirred while the temperature was preserved at 37°. To maintain sink condition, an aliquot was withdrawn at different intervals and replaced with equal amounts of fresh dissolution media. The sample was diluted with phosphate buffer. These samples were analyzed on UV visible spectrophotometer (Labindia) at 238 nm and the cumulative percent drug release was calculated.

***Ex vivo* release test:**

Ex vivo drug release was studied by FD cell, using excised rat skin. The skin was fastened amid the donor and receptor chambers of the Franz cell. 1 g of emulgel was spread over to the rat skin. Phosphate buffer pH 7.4 solution containing 0.5 % w/v of sodium dodecyl sulphate was used as a dissolution media. This buffer solution was filled up in the receptor compartment, kept at 37° and stirred at 50 rpm. 3 ml of aliquot was withdrawn from the receptor compartment with the help of an extra-long needle syringe *via* sampling port at pre-specified time intervals. For maintaining the sink condition, an equal amount of phosphate buffer was introduced back to the receptor compartment. Samples were analyzed at 238 nm for simvastatin using a UV-visible spectrophotometer[27].

Stability test:

Emulgel was supplied in aluminium tubes that could be folded up (5 g). 3 samples in a set were stored under different settings and subjected to tests for a month at three different temperatures; 5°/60 % RH, 25°/60 % RH and 30°/65 % RH. Every 10 d, samples are collected in accordance with International Council for Harmonisation (ICH) requirements and their colour, viscosity, spreadability, pH and medication concentration are assessed.

RESULTS AND DISCUSSION

The solubility data obtained for simvastatin in various oil media was used to select oil for emulgel. The solubility of simvastatin in different oil was shown in Table 4 and the maximum solubility was found in sesame oil. Oil with a maximum solubility of simvastatin was used in the emulgel preparation because it enhances the drug loading in the emulgel.

All the responses (dependent variables) observed for the 15 runs were simultaneously fitted to the quadratic response surface model using the trial version of Design-expert® 13 (StatEase®) software. The observed responses/dependent variables for the emulgel formulation are shown in Table 5. The physicochemical character of the emulgel is a crucial issue to consider before starting the fabrication process, especially when it comes to topical drug delivery.

The viscosity is the most critical factor in emulgel formulation. The viscosity prevents the coalescence and formation of the large droplet (instability in the emulsion) in the case of emulsion. The prepared emulgels have a viscosity of 4165 to 16753 mPas. The model F value of 6.16 indicates that the model is significant in this case. The parameter substantially affects the design if the model p value is less than 0.05. The model p value was found to be 0.0296 (<0.05), indicating that the parameter has a significant impact on the experimental design. Additionally, there is only a 2.96 percent probability that an F value will become significant due to noise.

Viscosity=8183+5185.875A+2632.87B-

$1888.25C+3720.25AB-789AC+15BC+801.875A^2+1601.375B^2+685.125C^2$

The p value less than 0.05 indicates the significance of model terms. A, B and AB were significant model terms (Table 6) because the p value was 0.0023, 0.0343 and 0.0344. Carbopol 934 (A) and oil (B) have a significant effect on viscosity in the current design (fig. 1). In emulgel formulation, carbopol is utilized as a gelling agent and any change in carbopol concentration reflects in the viscosity of the emulgel. Oils are also viscous liquids, so if there is an increase in oil percentage, it increases viscosity. Carbopol and oil have also shown a positive interaction effect on viscosity, i.e., the viscosity is further increased due to the interaction of carbopol and oil. The positive terms indicate that the viscosity increases on increasing carbopol concentration and oil percentage.

The spreadability test demonstrated how easily the emulgel could be spread on the affected area with just a little shear. The spreadability of the emulgel formulation was ranged from 0.335-14.59 gcm/s indicating that the formulation is non-greasy and smooth. A quadratic model of polynomial analysis was used to analyze spreadability values.

$Spreadability=3.44667+1.41175A-2.60362B-0.544375C-2.4365AB+0.52AC+0.03625BC+0.524292A^2+1.23054B^2-2.48596C^2$

The specified model terms are significant when the p values are less than 0.05. There are no significant model terms in the case of spreadability (Table 7), and it implies that there is no factor that significantly affects the spreadability. The 3D surface diagram of the spreadbility was shown in fig. 2.

The drug release is the extensive parameter that could differentiate emulgel. The drug release of the developed emulgels was in range of 20.12 and 41.67 % (fig. 3). This formulation showed the sustained type of drug release over an extended period. The 3D surface plot of *in vitro* drug release was shown in fig. 4.

TABLE 4: SOLUBILITY OF SIMVASTATIN IN OIL

S. no	Oil	Solubility (mg/ml)
1	Sesame oil	21.06±0.99
2	Arachis oil	20.92±0.41
3	Olive oil	17.53±0.79

TABLE 5: INDEPENDENT VARIABLE AND THEIR RESPONSES

Run	Carbopol 934 (% w/v)	Oil (% w/v)	Surfactant (% w/v)	Viscosity (mPas)	Spredability (gcm/s)	Drug release (%)
1	1.5	5	2	10069	14.59	40.23
2	1.0	5	3	4998	2.07	41.67
3	0.5	5	2	6643	4.42	38.92
4	0.5	10	1	5298	1.93	36.32
5	1.0	10	2	7554	7.3	35.72
6	1.0	10	2	12281	1.86	32.81
7	1.5	10	3	12464	2.08	30.23
8	0.5	15	2	3663	0.686	27.12
9	0.5	10	3	4165	0.69	28.67
10	1.0	15	1	15911	2.24	26.01
11	1.0	15	3	11099	0.335	21.32
12	1.5	15	2	21970	1.11	20.12
13	1.0	10	2	4714	1.18	23.43
14	1.5	10	1	16753	1.24	21.43
15	1.0	5	1	9870	4.12	30.14

TABLE 6: COEFFICIENTS TABLE FOR VISCOSITY

	Viscosity	p value
Intercept	8183	0
A	5185.87	0.0023
B	2632.87	0.0343
C	-1888.3	0.0932
AB	3720.25	0.0344
AC	-789	0.5675
BC	15	0.9912
A^2	801.875	0.5764
B^2	1601.38	0.2865
C^2	685.125	0.6316

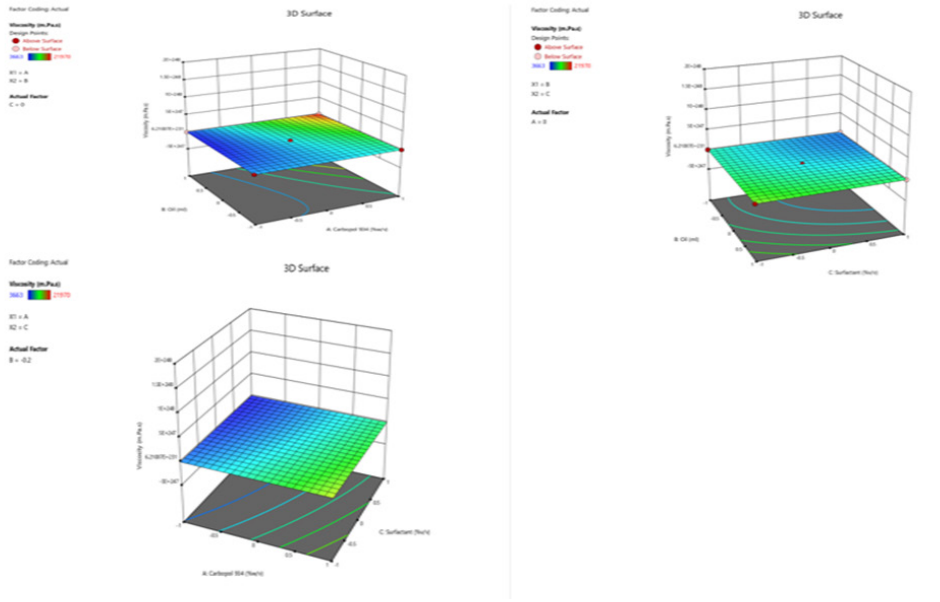

Fig. 1: 3D response surface diagram of viscosity

TABLE 7: p VALUE FOR THE COEFFICIENT IN SPREADABILITY

	Spreadability	p value
Intercept	3.44667	0
A	1.41175	0.2991
B	-2.60362	0.0858
C	-0.544375	0.6739
AB	-2.4365	0.2167
AC	0.52	0.7751
BC	0.036525	0.984
A^2	0.524292	0.7819
B^2	1.23054	0.5233
C^2	-2.48596	0.2245

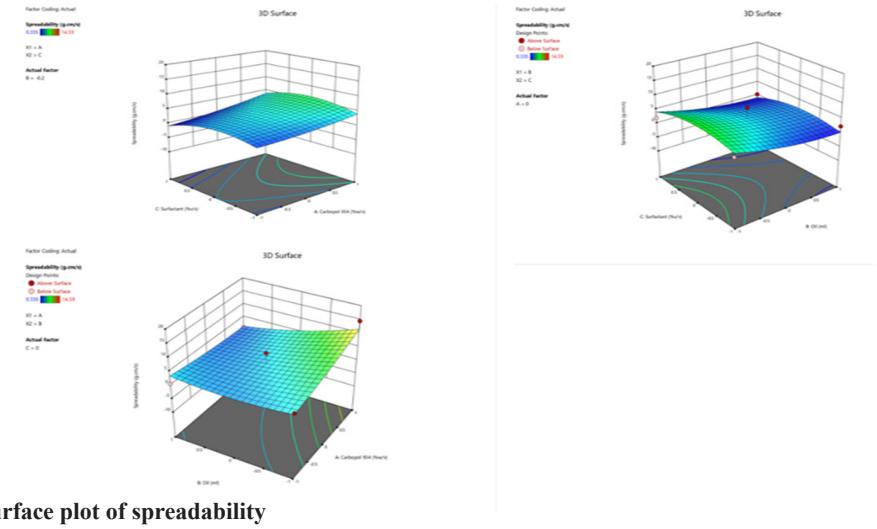

Fig. 2: 3D response surface plot of spreadability

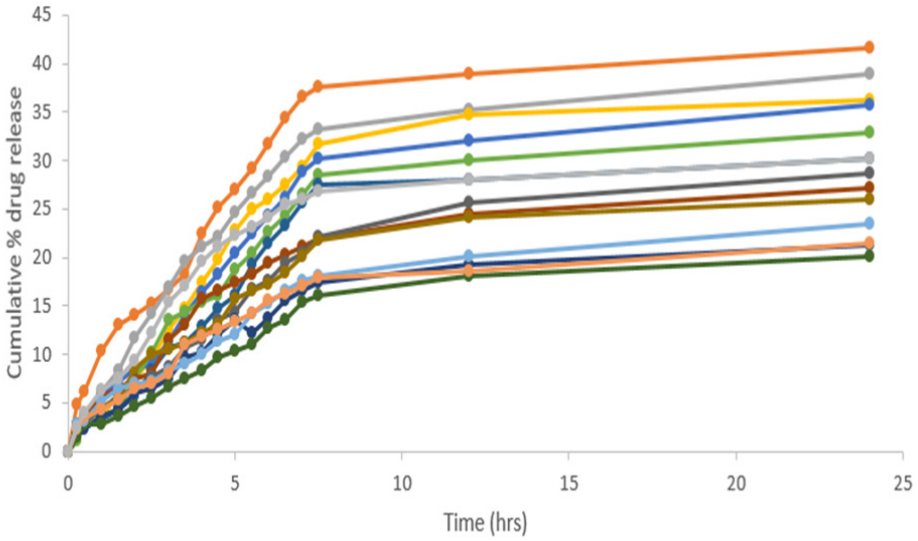

Fig. 3: *In vitro* cumulative percentage drug release profile of formulations
Note: Solvent Evaporation (SE); ( ): SE 2; ( ): SE 3; ( ): SE 4; ( ): SE 5; ( ): SE 6; ( ): SE 7; ( ): SE 8; ( ): SE 9; ( ): SE 10; ( ): SE 11; ( ): SE 12; ( ): SE 13; ( ): SE 14 and ( ): SE 15

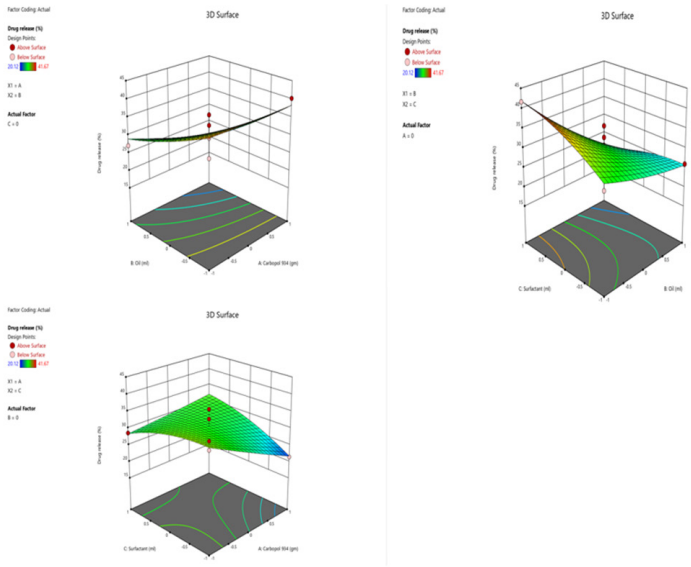

Fig. 4: 3D response surface plot of drug release

Drug release=30.65-2.38A–7.05B+0.9988C–2.08AB+4.11AC–4.05BC+0.1608A^2+0.7833B^2–1.65C^2

Table 8, depicting the coefficient value shown that the oil percentage significantly affected the drug release, by the p value of 0.0068 (<0.05). As per the equation, the value of oil (B) preceded the negative sign, which indicates that an increase in oil percentage causes a decrease in the drug release. It can be attributed to the lipophilic character of the drug. Because the drug is lipophilic; therefore, it has an affinity towards the oil phase, and it slowly partitions into the aqueous phase of emulsion and gel phase of emulgel.

Optimization of emulgel formulation:

Following the completion of the experiments, the data was entered into design expert software, along with the desirability of the responses (dependent variable). Based on the run's replies, the software projected the values of the independent variable indicated in Table 9. The software predicted the values of dependent variables depending on the response values (fig. 5). The optimized formulation with predicted values of independent variables was prepared and evaluated. The response/dependent variables value was shown in Table 10. The resulting optimum formulation had an average of those three runs found for viscosity 6875±531.21 mPas, spreadability of 10.1446±0.31 gcm/s and drug release of 40.75±0.42 %, showing that the ideal formula was reasonably stable.

The organoleptic properties of emulgels are shown in Table 10. The formulations were homogeneous, white in colour, non-greasy, pleasant to the touch and had no phase separation. The extrudability of a pharmaceutical formulation is a critical parameter because it can influence the manufacturing process and quality of finished product. The formulation should have right rheological properties to be successfully extruded. The extrudability of the formulations are shown in Table 10 and were ranged from 10.1±0.05 to 16.4±0.06 g/cm^2. The higher extrudability was found in formulation containing higher percentage of polymer. The optimized formulation exhibited the 12.7±0.07 g/cm^2.

TABLE 8: COEFFICIENT TABLES FOR DRUG RELEASE

Source	Sum of squares	Df	Mean square	F value	p value
Model	614.7	9	68.3	3.39	0.0961^{ns}
A-carbopol 934	45.22	1	45.22	2.24	0.1944
B-oil	397.48	1	397.48	19.73	0.0068
C-surfactant	7.98	1	7.98	0.3961	0.5568
AB	17.26	1	17.26	0.8568	0.3971
AC	67.65	1	67.65	3.36	0.1264
BC	65.77	1	65.77	3.26	0.1306
A^2	0.0955	1	0.0955	0.0047	0.9478
B^2	2.27	1	2.27	0.1124	0.751
C^2	10.07	1	10.07	0.4999	0.5111
Residual	100.74	5	20.15		
Lack of fit	18.24	3	6.08	0.1474	0.9229^{ns}
Pure error	82.5	2	41.25		
Cor total	715.44	14			

Note: ns: Not significant

TABLE 9: PREDICTED CODED VALUE OF INDEPENDENT VARIABLE

Factor	Name	Level	Low level	High level	Standard deviation	Coding
A	Carbopol 934	1	-1	1	0	Actual
B	Oil	-1	-1	1	0	Actual
C	Surfactant	0.39	-1	1	0	Actual

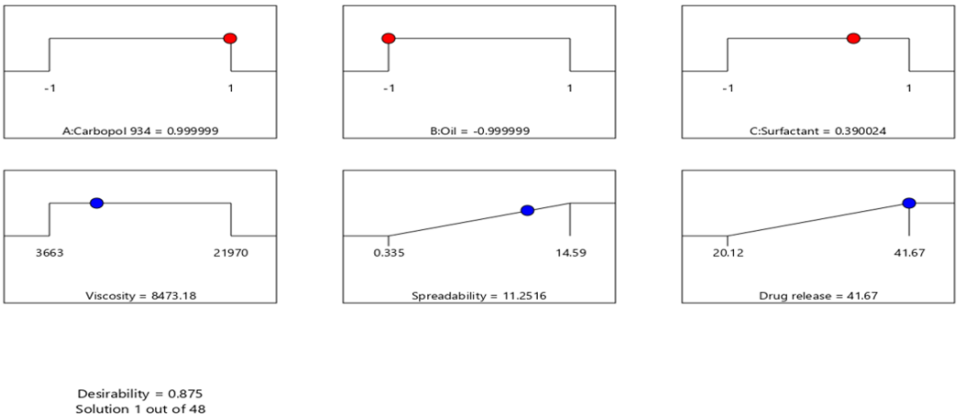

Fig. 5: Desirability ramp shows the levels for independent variables and predicted

TABLE 10: EXTRUDABILITY DATA OF TEST FORMULATION AND OPTIMIZED FORMULATION

Formulation	Colour	Appearance	Extrudability (g/cm^2)
F1	White	Homogenous	15.1±0.02
F2	White	Homogenous	14.1±0.07
F3	White	Homogenous	10.2±0.01
F4	White	Homogenous	12.6±0.07
F5	White	Homogenous	11.4±0.04
F6	White	Homogenous	12.2±0.06
F7	White	Homogenous	15.8±0.05
F8	White	Homogenous	10.5±0.02
F9	White	Homogenous	11.1±0.01
F10	White	Homogenous	10.1±0.05
F11	White	Homogenous	11.3±0.02
F12	White	Homogenous	16.4±0.06
F13	White	Homogenous	10.3±0.01
F14	White	Homogenous	16.1±0.06
F15	White	Homogenous	10.2±0.02
OF	White	Homogenous	12.5±0.07

Note: OF: Optimized Formulation

The swelling index is a critical parameter in formulations involving polymers that may undergo swelling. The drug release from the formulations can be controlled through the swelling of the polymer materials. Fig. 6, shows the percentage swelling in the formulation. The maximum swelling was observed in the formulation F1 (39.2 %) followed by F7 (38.4 %). Both formulations contain high polymer concentration (1.5 % w/v). With spindle 05, the emulgel was rotated at 10 rpm for 10 min. The optimized formulation's viscosity was found to be 6875±29 mPas which was in desired range.

Spreadability reveals how easily the emulgel can be dispersed with a modest amount of shear[28]. The spreadability of the emulgel is highly requisite since it reveals how it behaves when it gets out of the tube[20]. The improved formulation's spreadability was found to be 10.15±0.30 gcm/s. Tiny oil globules dispersed in the polymer matrix were visible in the microscopic image (fig. 7) of the emulgel formulation. The globules are all the same size and are dispersed equally throughout the matrix. The average droplet size of the emulsion is about 3±0.16 µm. A digital pH metre was used to determine the pH of the optimized formulation. The formulation had a pH of 6.85±0.01. The drug content of the prepared emulgel was estimated. The drug content in optimized emulgel was realized to be 98.26±0.31 %.

Ex vivo release studies were performed to understand the drug release behaviour through the skin. The release of the drug from the emulgel formulation was 40.75±0.42 % over 24 h (fig. 8). The initially slightly high drug release was observed due to the drug partitioned in the gel phase. After that, the drug release was slowed down due to the slow partitioning of lipophilic drugs from the oil phase of the emulsion to the gel phase (Table 11).

In conclusion, Box-Behnken design was used to optimize a carbopol 934, oil, surfactant loaded with simvastatin intended for the topical treatment of wounds in the current investigation. The improved formulation was obtained and put through a series of physicochemical tests, including rheological tests, spreading coefficient tests, drug content tests, and an *ex vivo* release study on rat skin. The prepared emulgel revealed a maximum release of 40.75±0.42 % in 24 h in an *ex vivo* investigation. Furthermore, the microscope image reveals that the globules in the matrix are consistent in size and equally dispersed. As a result, simvastatin emulgel can be employed as a topical drug delivery system.

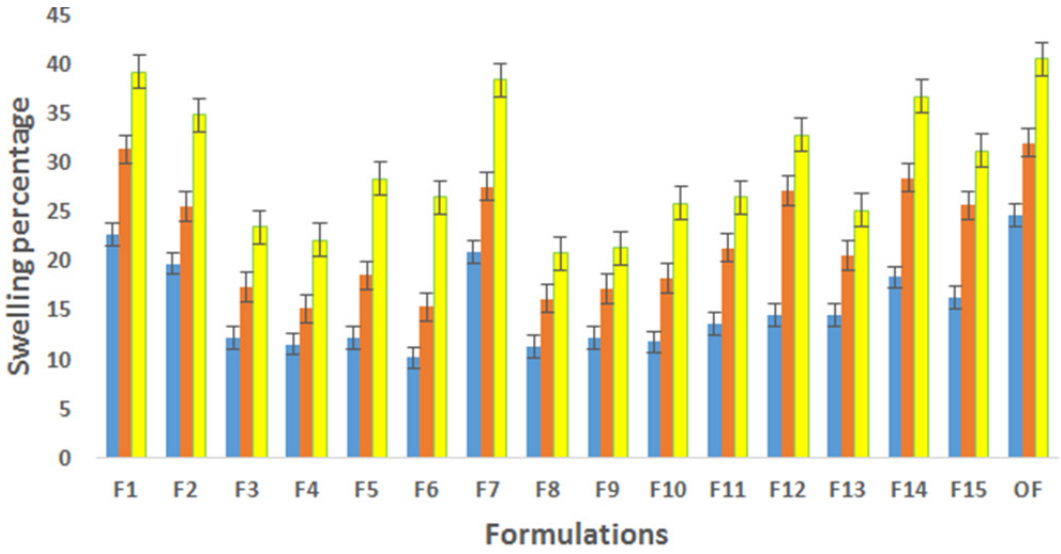

Fig. 6: Swelling index of formulations and optimized formulation
Note: ( ): 1 h; ( ): 2 h and ( ): 3 h

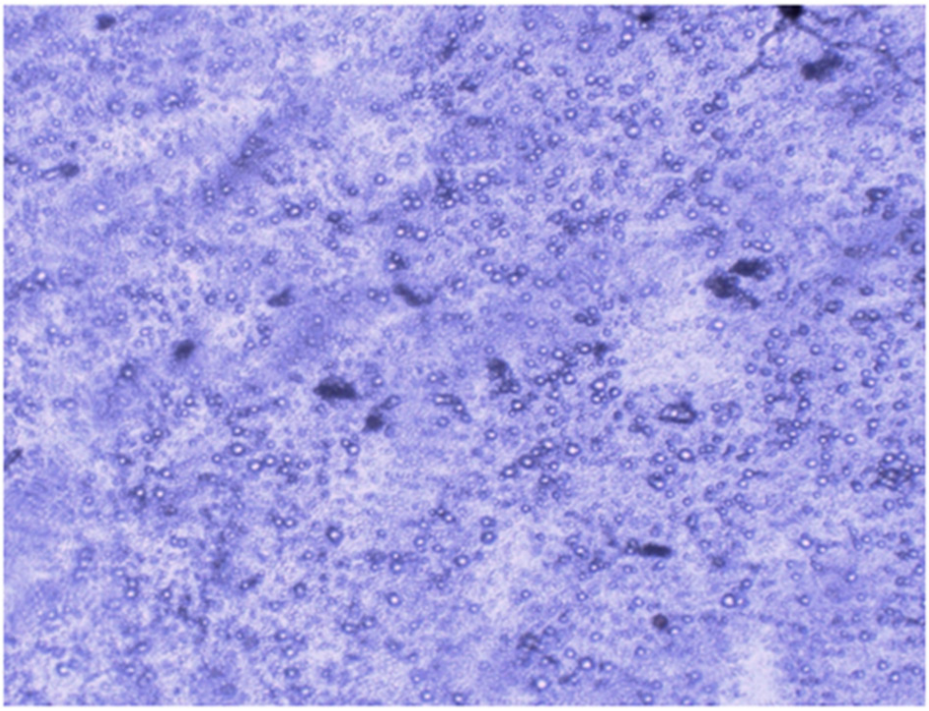

Fig. 7: Microscopic image of optimized emulgel formulation at 10X

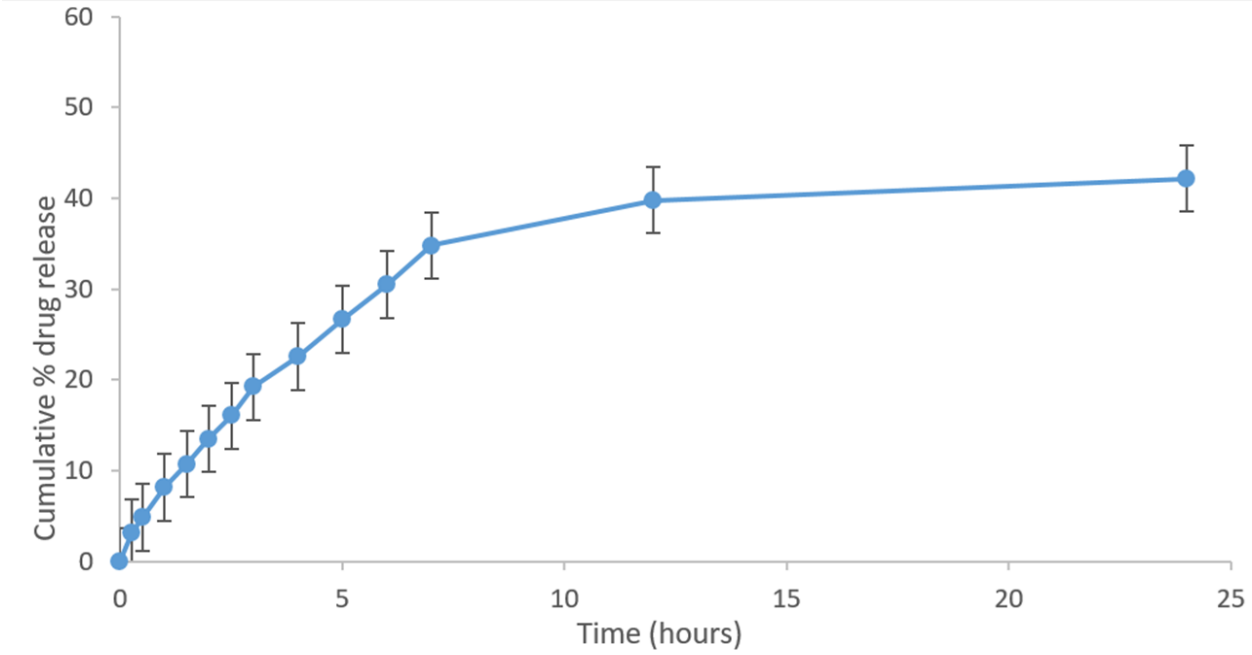

Fig. 8: *Ex vivo* cumulative percentage drug release profile of optimized formulation

TABLE 11: RESPONSE DATA OF OPTIMIZED FORMULATION

Parameters	Values
Viscosity	6875±531 mPaS
Spreadability	10.14±0.30 gcm/s
Percentage drug release	40.75±0.42
pH	6.85±0.01

Conflict of interest:

The authors declare no conflict of interest.

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