Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2019; 9(1); 65-75
doi: 10.25258/ijddt.9.1.11
ISSN: 0975 4415

Research Article

Optimization of Sumatriptan Succinate Transdermal Emulgel For Treatment of Migraine

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Received: 11th Dec, 18; Revised: 15th Jan, 19, Accepted: 15th Feb, 19; Available Online: 25th Mar, 2019

ABSTRACT

Purpose: Sumatriptan succinate is a BCS class III drug. Oral administration of drug suffers from poor bioavailability problem due to pre-systemic metabolism. Bioavailability for oral route is 15%, for nasal route is 17% and for parenteral route is 97%. Substantial proportion of patients suffers from severe nausea or vomiting during their migraine attack, which make oral treatment unsatisfactory. Transdermal delivery will overcome the problems of the drug giving better results to patients suffering from migraine. Methods: Oleic acid, labrafil M 1994 and transcutol P was used as oil, surfactant and cosurfactant respectively. Both the oily and aqueous phases were heated separately. Oily phase were added to the aqueous phase. Mixing of gel and emulsion in ratio of 1:1 gave emulgel. Emulsion was evaluated for globule size, zeta potential, drug content, stability etc. Carbopol 934 and Xanthan gum was used as a gelling agent. Optimization was carried by factorial design. Emulgel was evaluated for physical parameters, viscosity, drug content, bioadhesive strength, spreadability, *in-vitro* and *ex-vivo* diffusion study. Results: FE-SEM image shown spherical globules in shape with size 51.40 µm. Zeta potential showed good stability of the emulsion. FTIR and DSC studies revealed that drug and all excipients were compatible. Factorial design gave batch F7 as optimized one. ANOVA results shown that drug release and gel viscosity values are strongly dependent on concentration of carbopol 934 and xanthan gum respectively. *Ex-vivo* diffusion study for batch F7 through goat skin indicated 88.68±2.52 % drug release. Statistical studies showed that drug release from the optimized formulation (F7) followed First order release kinetics. Conclusion: Sumatriptan succinate emulgel act as depot of drug which releases drug in controlled manner overcoming oral route side effects.

Keywords: Sumatriptan, Transdermal, Emulsion, Factorial, Xanthan, Delivery.

INTRODUCTION

Skin is one of the most readily accessible organs on human body for transdermal drug delivery system. Dermatological products applied to skin are various in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. When a systemic effect is sought, transdermal delivery can offer many advantages over oral and parenteral administration[1-2]. Ointments, creams and lotions which are mostly used have stick texture causing uneasiness to the patient. Emulgels are emulsions of oil in water or water in oil which are mixed with gelling agent. Emulsion itself is considered as a controlled delivery system. In this drug present in internal phase pass through external continuous phase to the skin and then get absorbed. Internal phases of emulsion act as reservoir of drug from which drug slowly releases through external phase in controlled manner to the skin. Gel forms cross linked network where it captures small drug particles and provides its release in a controlled manner. Both oil-in-water and water-in-oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in emulgel formulation. Emulgel is helpful in enhancing spreadability, adhesion, viscosity and extrusion of the formulation[3-5]. Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. First line agents useful in treatment include NSAID'S and triptan. In recent years, most of the triptans have been designed to deliver the drug in the form of topical gels to avoid gastrointestinal irritation, to overcome first pass effect and to maximize the drug concentration at the site of action[6]. ZECUITI is a disposable, single use system designed to deliver sumatriptan through the skin using iontophoresis. It is indicated for the acute treatment of migraine with or without aura in adults. Sumatriptan succinate is a 5-hydroxy tryptamine 1D (5-HT1D) receptor agonist. It was the first triptan available to use in the treatment of migraine. It is metabolized primarily by monoamine oxidase-A and excreted in the urine and bile. Sumatriptan succinate is BCS class III drug with low permeability and high solubility. It has plasma half-life of 2.5 hrs. Oral administration suffers from poor bioavailability problem. Bioavailability for oral is 15% only due to pre-systemic metabolism. Substantial proportion of patients suffers from severe nausea or vomiting during their migraine attack, which may make oral treatment unsatisfactory[7-8].

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Table 1: Preliminary trial batches Emulsion.

Formulation Batch	Volume of Oleic acid (ml)	Volume of Water (ml)	Volume of Labrafil M 1994 (ml)	Volume of Transcutol P (ml)
A1	1	2	4	3
A2	2	1.8	3.6	2.7
A3	3	1.5	3.3	2.4
A4	4	1	3	2
A5	5	0.8	2.6	1.7
A6	6	0.6	2.3	1.4
A7	7	0.5	2	0.5

Table 2: Preliminary trial batches of gel.

Formulation Batch	Carbopol 934 (%)	HPMC K100M (%)	Guar gum (%)	Xanthan gum (%)
C1	-	1	-	3
C2	-	0.5	-	2
C3	-	2	2	-
C4	-	2.5	2	-
C5	1	-	2	-
C6	2	-	-	1
C7	3	-	-	2
C8	4	-	-	3
C9	5	-	-	4
C10	6	-	-	5
C11	7	-	-	6

Table 3A: Selection of variables.

Independent variables	Variables (levels)		
	High (+2)	Medium (0)	Low (-2)
Carbopol 934 (%)	7%	5%	3%
Xanthan gum (%)	6%	4%	2%

Transdermal delivery of sumatriptan succinate will be helpful for migraine. Hence the aim of the study is to enhance the bioavailability of sumatriptan succinate, to decrease the oral side effects and to give a controlled drug release via transdermal delivery for treatment of migraine.

MATERIALS AND METHOD

Sumatriptan succinate was a gift sample from Sun Pharmaceuticals Industries Ltd, Silvassa, India. Labrafil M 1994, Transcutol P was a gift sample from Gattefosse India Pvt. Ltd, Mumbai. Other chemicals used are as xanthan gum (M/s. Ranbaxy Laboratories Ltd., Mumbai), oleic acid (Merck Specialities Private Ltd, Worli, Mumbai) and carbopol 934 (Analab fine chemicals, Mumabi)

Drug Characterization

Drug sample was analyzed by checking its physical appearance, powder nature and characteristics. Melting point was determined by melting point apparatus. Sumatriptan succinate was analyzed using UV spectrophotometer (Varian, Carry 100) to identify the λmax in range of 200 to 400 nm and spectrum was recorded. FTIR spectra of the drug were recorded on FTIR (Jasco, FTIR model 6100, Japan) using a potassium bromide pressed disc method. Drug was mixed with previously dried IR grade KBr in a ratio of 2:200 and triturated to form a homogenous mixture which is then pressed into a pellet with the help of the KBr press. Scanning range was 400-4000 cm^{-1}. DSC thermogram for drug was recorded using differential scanning calorimeter (Hitachi 9020). Approximately 2-5 mg of sample was heated in a pierced aluminium pan up to 300°C at a heating rate 10°C/min under a stream of nitrogen at flow rate of 50 ml/min. Thermal data analyses was then done by DSC thermogram.

Solubility Study

For selecting solvents with good solubilizing capacity for sumatriptan succinate, the saturation solubility of sumatriptan succinate in various oils such as oleic acid, vegetable oil, light liquid paraffin, olive oil, castor oil, linseed oil, surfactants such as labrafil M 1994, span 80, tween 80, span 20, tween 20 and co-surfactants such as transcutol P, propylene glycol, and propylene glycol 400 were determined. Excess of sumatriptan succinate was added to 5 ml of each oil, surfactant and co-surfactant in rubber capped vials and stirred for 24 hrs on magnetic stirrer at 200 rpm at ambient temperature. After completion of stirring, the suspension was centrifuged at 5000 rpm and clear supernatant liquid was separated and filtered through Whatman filter paper. The solubility of sumatriptan succinate was estimated by UV spectrophotometer at 227 nm[9]. Various concentrations of oil, surfactant and co-surfactant were tried for preparation of emulsion (Table 1).

Selection of gelling agent

For preparation of gel phase polymers carbopol 934, HPMC K100M, xanthan gum and guar gum were tried (Table 2). Gel was prepared by dispersing carbopol 934 and xanthan gum separately in sufficient amount of warm water (40-50°C) with constant stirring. After that both gels were mixed in ratio of 1:1 and pH to 6-7 was adjusted with triethanolamine.

Preparation of Emulgel

Oleic acid and Labrafil M 1994 were mixed with stirring on magnetic stirrer at 400-500 rpm. Sumatriptan succinate (2%) was dissolved in the required quantity of distilled water and transcutol P were dissolved in an aqueous phase with stirring on magnetic stirrer at 400-500 rpm. Both oil and aqueous phase were heated separately to 70-80°C and then oil phase were mixed with aqueous phase with continuous stirring. Carbopol 934 gel was prepared by dispersing it in sufficient amount of purified water with constant stirring. In case of xanthan gum gel, it was prepared by dispersing required quantity of xanthan gum in warm distilled water (40°C), the dispersion was cooled and kept overnight. The emulsion was mixed with gel in 1:1 ratio with homogenizer to get an emulgel[10-11].

Experimental design

3^2 level factorial design was applied to study the effect of independent variables i.e. concentration of carbopol 934 and concentration of xanthan gum on dependent variables i.e. % cumulative drug release at 8 hrs and viscosity[12]. Independent variables are listed in table 3A while all the

Table 3B: Composition of emulgel.

Ingredients (%w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sumatriptan succinate	2	2	2	2	2	2	2	2	2
Oleic acid	40	40	40	40	40	40	40	40	40
Labrafil M 1994	30	30	30	30	30	30	30	30	30
Transcutol P	20	20	20	20	20	20	20	20	20
Carbopol 934	3	3	3	5	5	5	7	7	7
Xanthan gum	2	4	6	2	4	6	2	4	6
Triethanolamine	q. s. to adjust pH to 6-7								
Water	q. s.								

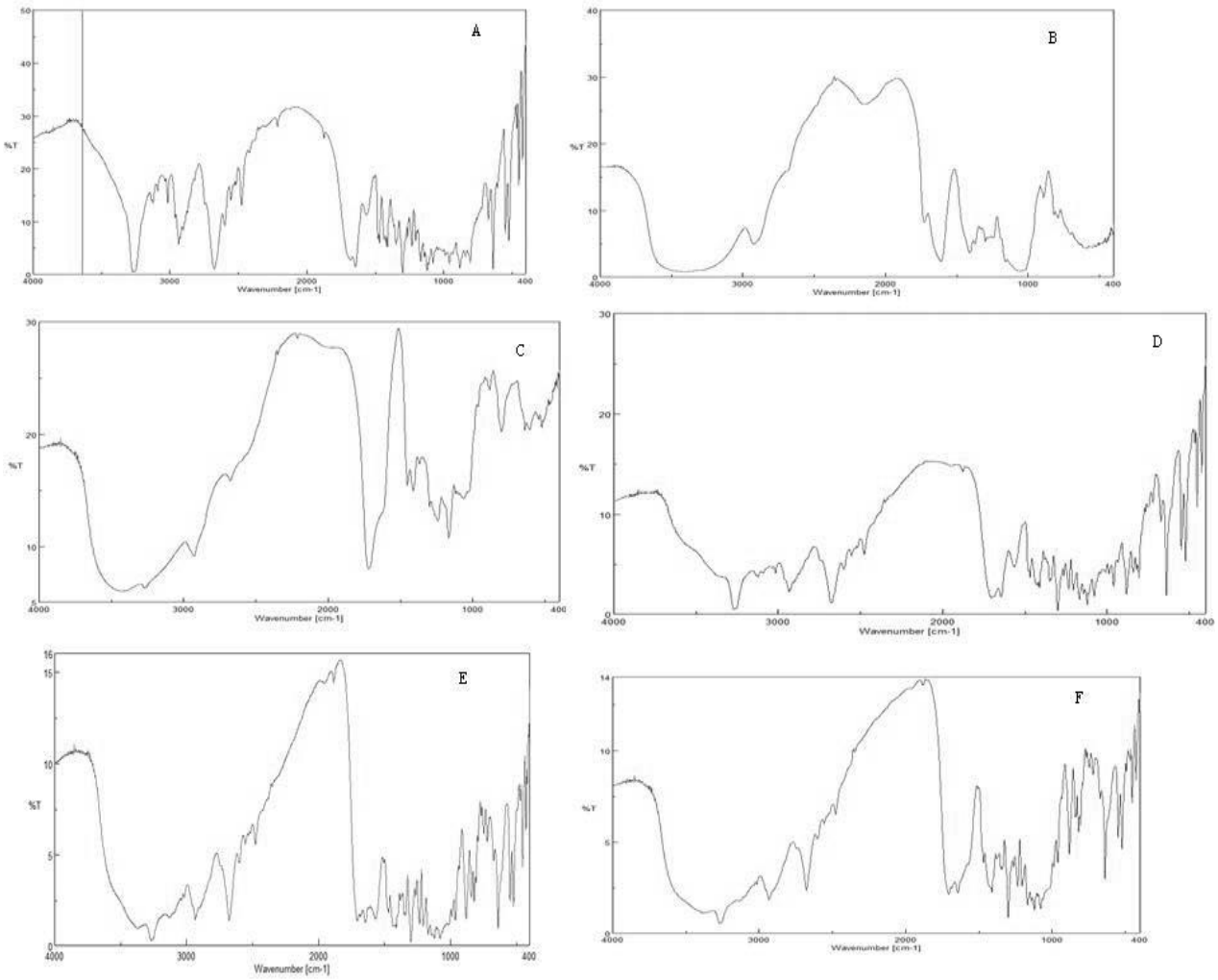

Figure 1: FTIR Spectrum of A- Sumatriptan succinate ; B- Xanthan gum ; C- Carbopol 934, D- Drug + Carbopol 934; E- Drug +Xanthan gum ; F- Drug + Carbopol 934 + Xanthan gum.

batches were prepared according to the experimental design as shown in table 3B.

Evaluation of Emulsion[10,13]

Droplet size measurements

Optical Microscopy (MOTIC microscope)- Size analysis of A4 batch of emulsion was carried out by MOTIC microscope. The drop of emulsion was placed on glass slide and then cover slip was placed on it and the globule size was observed under microscope with the use of 10X object lenses.

FE-SEM (Field Emission-Scanning Electron Microscopy) - The globule size of A4 batch emulsion was measured by using FE-SEM (FEI-NOVO, NANOSEM 450). The sample prepared by drop casting method with dilution of emulsion. 1 ml of emulsion was diluted with 10 ml of distilled water, then drop of emulsion taken in micropipette and placed it on aluminium foil in petri dish. Petri dish was dried at room temperature for 24 hrs. Then the sample placed in sample holder of the FE-SEM and the images were captured at different parts[8].

Zetasizer- The globule size of A4 batch emulsion was measured by zetasizer (Malvern zetasizer, 90) with use of disposable sizing cuvette at 25°C. 1 ml emulsion sample was diluted with 10 ml water and result was recorded.

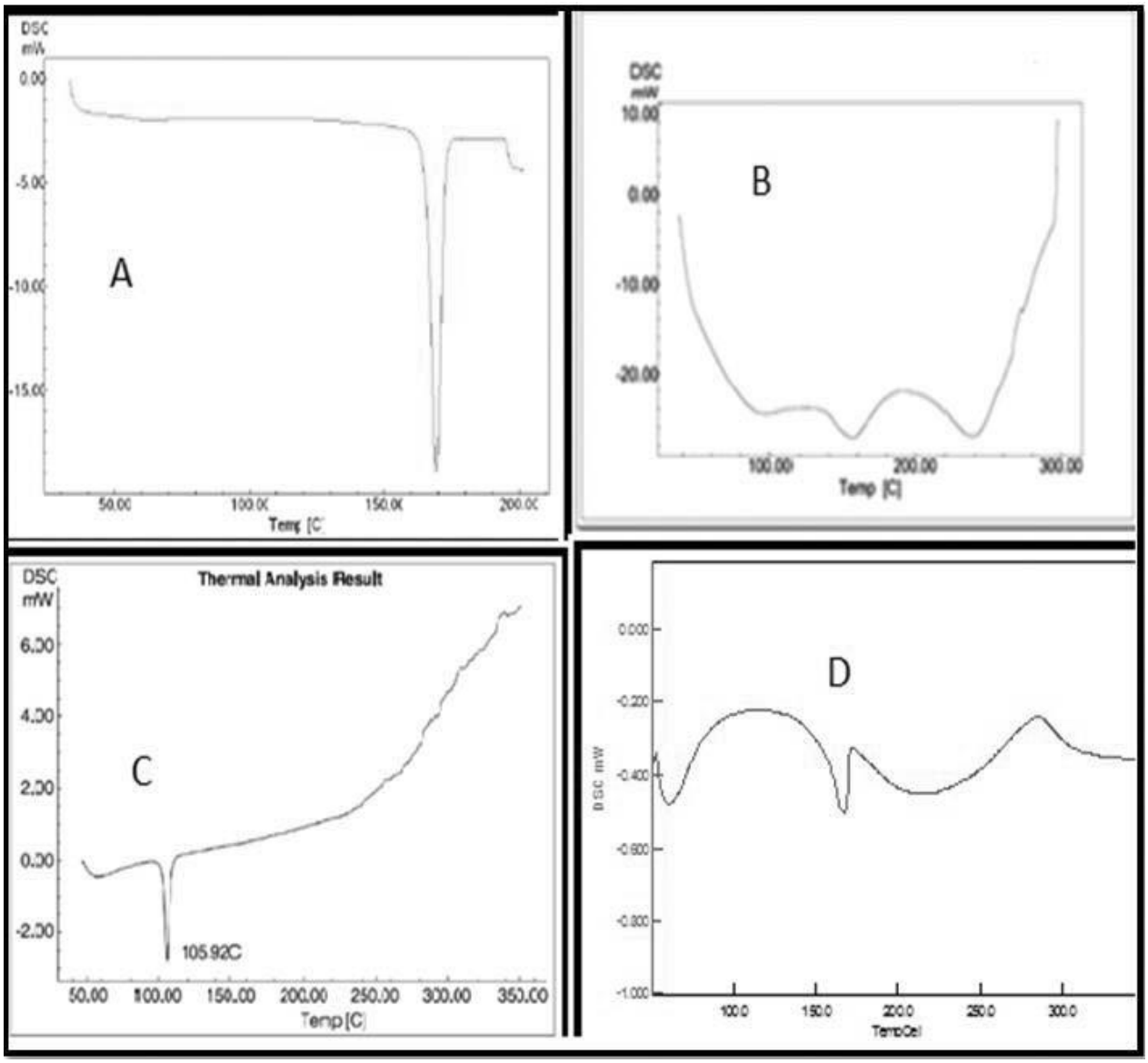

Figure 2: A- Sumatriptan succinate; B- Carbopol 934; C- Xanthan gum, D -Sumatriptan succinate + Xanthan gum+ Carbopol934.

Table 4: Solubility Study.

Oils/surfactant/co surfactant	Solubility (mg/ml)
Oleic acid	30.95±0.24
Olive oil	27.25±1.45
Castor oil	8.53±0.25
Liquid paraffin	14.56±0.55
Vegetable oil	22.79±0.89
Labrafil M 1994	31.18±1.37
Transcutol P	26.69±1.25
Tween 20	25.59±1.78
Labrasol	28.56±2.38
Tween 80	25.59±1.43
PEG 400	14.67±2.10

Zeta potential measurement

Zeta potential of the emulsion was determined by Zetasizer (Malvern zetasizer). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvette were washed with methanol and rinsed using the sample to be measured before each experiment.

Dilution test

To know type of emulsion was formed, this test carried out. Prepared emulsion was diluted with water which is external /continuous phase[9].

pH and Drug content

pH of the emulsions was measured by digital pH meter. Drug content was measured by dissolving known quantity of emulsion in methanol and it was stirred for 4 hrs. Absorbance was measured after suitable dilution at 227 nm in UV/VIS spectrophotometer[9].

Centrifugation

This parameter was measured to evaluate physical stability of the emulsion. The prepared emulsion was centrifuged at ambient temperature and at 5000 rpm for 10 min to evaluate the system for creaming or phase separation. Emulsion was observed visually for appearance.

Evaluation of Emulgel[14-17]

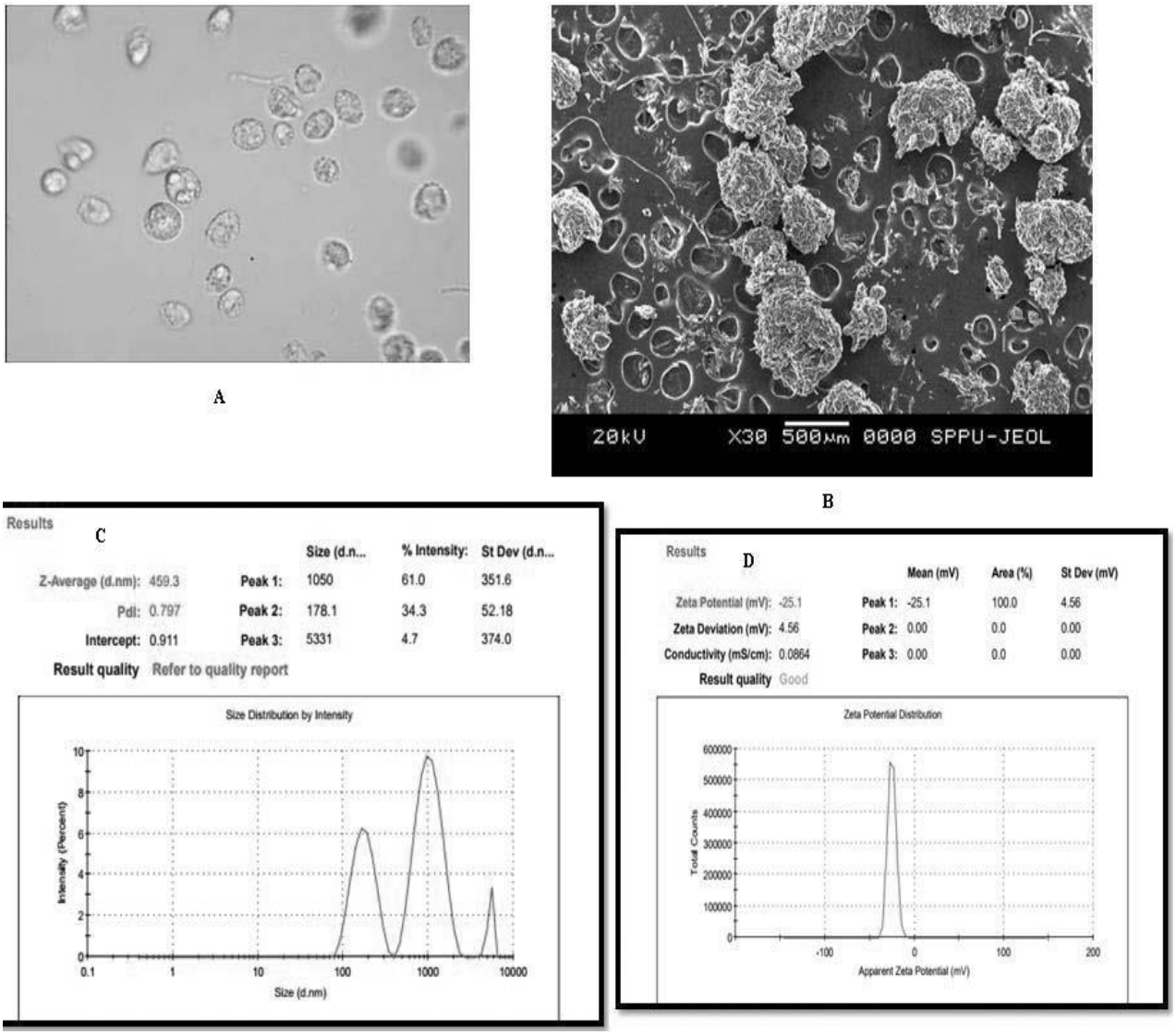

Figure 3: A- Motic Image; B- FESEM image ; C- Zeta size measurement; D- Zeta potential measurement.

Physical Evaluation

Emulgels were evaluated for clarity, colour, homogeneity, drug content, presence of particles and fibres.

Determination of pH

pH of the optimized gel formulation was determined with a digital pH meter at room temperature.

Viscosity

Viscosity of gel was determined by using Brookfield's viscometer.

Drug Content

Drug content uniformity of the dosage form is an important parameter determining its *in-vivo* performance. If drug distribution is non-uniform in the formulation, it may lead to availability of drug in sub-therapeutic dose or toxic dose. Drug content uniformity ensures minimum batch to batch variation. This characterization is an important step in scaling up formulation for larger batches. The quality control and quality assurance are entirely based on this parameter, once the product is manufactured in large batches. Sumatriptan succinate content in emulgel was measured by dissolving accurately weighed emulgel equivalent to 10 mg in methanol by stirring for 4 hrs. Absorbance was measured after suitable dilution at 227 nm in UV/VIS spectrophotometer.

Bio-adhesive strength measurement

Bioadhesion measurement was performed using a modified balance method. Two pans of physical balance were removed. Right side pan was replaced with a 100 ml beaker and on the left side, a glass slide was hanged. For balancing the assembly, a weight of 20 g was hanged on the left side. Another glass slide was placed below the hanged slide. Portions of egg membrane were attached with both slides. One gram of gel was placed between two egg membrane faces. Little pressure was applied to form bioadhesion bond, and then slowly water was added on right side beaker, till the gel was separated from one face of egg membrane attached. Volume of water added was converted to mass. The bioadhesive strength of gel in grams calculated as follows:

$$\text{Bioadhesive strength} = \frac{mg}{A} \quad \text{..... Eqn.1}$$

Where, m = weight required to detached the slides

A = Area of rat skin attached to slides

g = Acceleration due to gravity (980 cm/s^2)

Spreadability

Table 5: Evaluation of emulgel.

Sr. No.	Formulation Batch	pH	Viscosity (cps)	Drug content %	Spreadability (gm.cm/s)	Bioadhesive force (dynes/cm^2)
1	F1	6.44±0.25	22000	100.29±0.37	29.49±1.24	2360.20 ± 0.15
2	F2	6.21±1.25	40000	92.78±0.88	22.42±1.56	2193.51 ± 0.11
3	F3	6.81±1.30	48000	85.72±0.55	28.02±2.2	2338.77 ± 0.16
4	F4	6.42±0.80	28000	89.2±0.61	29.6±1.24	2525.36 ± 0.13
5	F5	6.21±0.75	24000	92.29±0.45	24.51±1.4	1568.87 ± 0.15
6	F6	6.71±1.10	36000	95.25±0.36	26.4±1.85	1922.44 ± 0.11
7	F7	6.70±2.20	26000	98.10±0.82	28.4±1.5	2703.06 ± 0.12
8	F8	6.6±0.62	40000	95.27±1.24	22.85±2.3	1833.67 ± 0.16
9	F9	6.5±0.21	30000	92.51±1.56	21.74±1.6	1311.73 ± 0.14

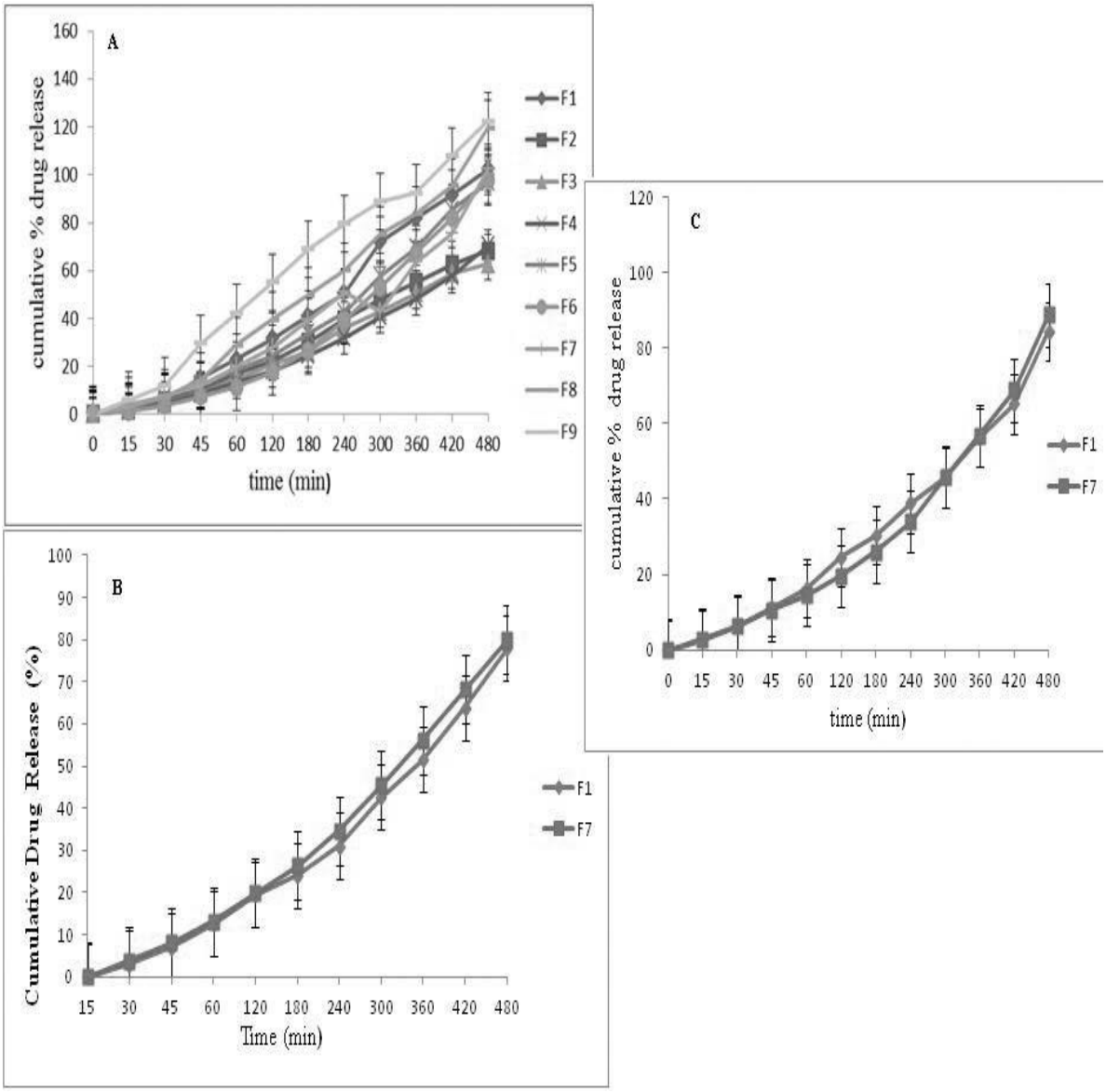

Figure 4: *In-vitro* drug release through A- Cellophane membrane; B- Egg membrane; *Ex-vivo* drug release C- Goat Skin.

A semisolid formulation should possess good spreadability. The spreadability denotes the extent of area on which the semisolid formulation spreads on application. The therapeutic efficacy of a formulation depends upon its spreading value. Therefore, spreadability determination is important. Spreadability of the formulation was determined by an apparatus suggested by Mutimer et al, which was suitably modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass

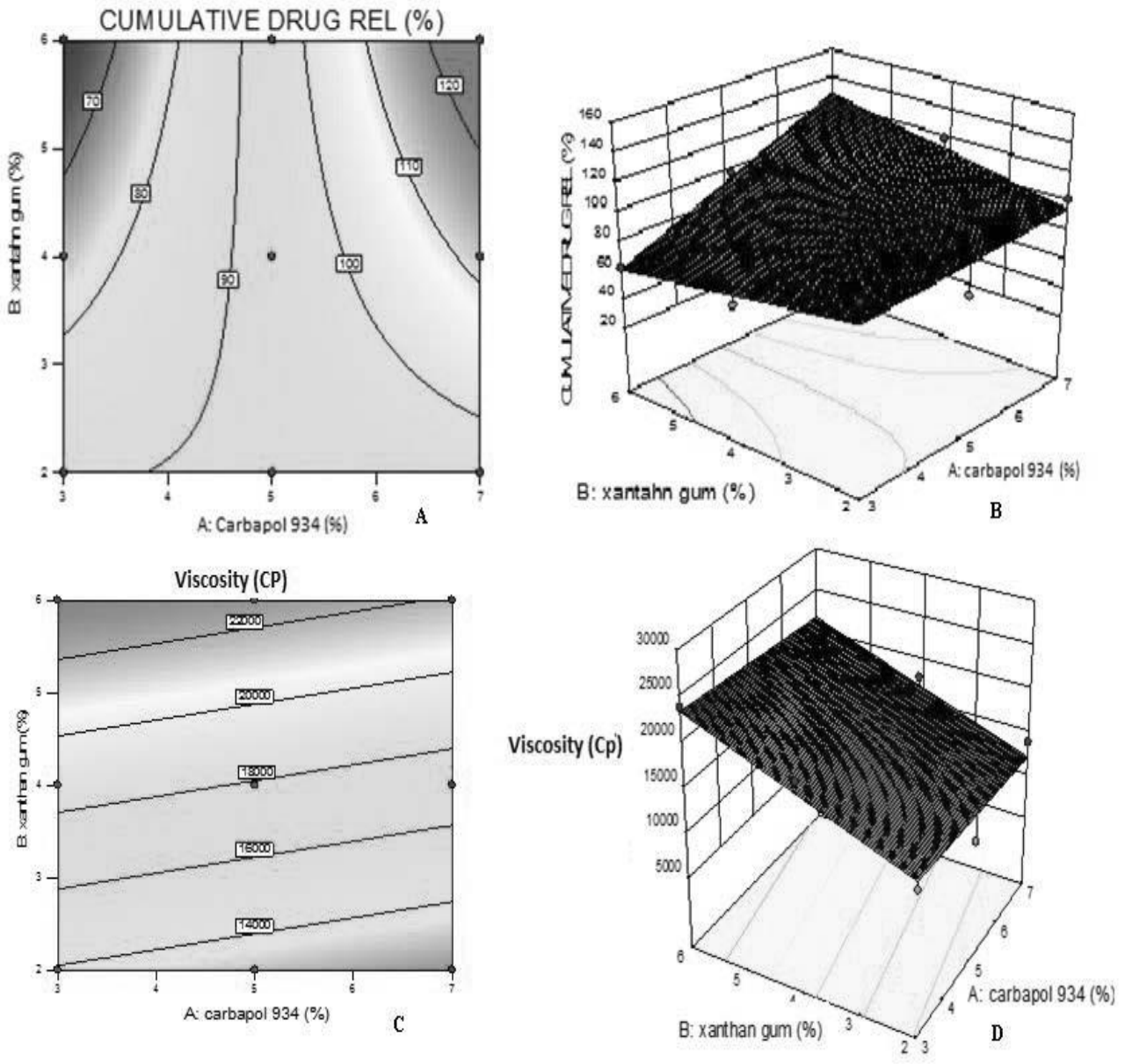

Figure 5: (A,C) Contour plot and (B,D) response surface plot showing relationship in between % drug release at 8 hrs and polymer concentration and in between viscosity and polymer concentration.

plate was fixed on the block. An excess of gel (about 2 gm) under study was placed on the lower plate. The gel was then sandwiched between lower glass plate and another upper glass plate having the same dimensions, provided with the hook. A weight of 500 mg was placed on the top of the two plates for 5 minutes to expel air and to provide a uniform film of the gel between the plates. Excess of gel was scrapped off from the edges. The upper plate was then subjected to a pull of 50 gm. With the help of a string attached to the hook and the time (in sec.) required by the upper plate to cover a distance of 10 cm was noted. A shorter the time interval better the spreadability. The spreadability was calculated as follows.

$S = M \times L / T$……. Eqn.2

Where, S = Spreadability, M = weight tied to upper slide, L = length of the glass slide,

T = time taken for plates to slide the entire length (sec.)

In-vitro diffusion study

Cellophane membrane

A modified Franz diffusion cell was used. Cellophane membrane 12, having an average pore size of 2.4 nm, mol. wt. approx. 12,000 Dalton and capacity of approx. of 1.61 mL/cm was utilized. Cellophane membrane was placed in between the donor and the receptor compartment. Accurately weighed gel equivalent to 1gm was taken and transferred to the donor compartment. Entire surface of membrane was in contact with receptor compartment containing 25 ml of phosphate buffer pH 6.8. The cell was agitated by a magnetic stirrer at 50 rpm and maintained at 37±1°C. Aliquots of 2ml were withdrawn at intervals of 15, 30, 45, 60, 120, 180, 240, 300, 360, 420 and 480 mins and each time was replaced with equal volume of fresh phosphate buffer pH 6.8, previously heated to 37±1°C. The samples were diluted suitably and the absorbance was

Table 6: Analysis of Variance.

Sr. No.	Response Model	Sum of Squares	D.f.	Mean Square	F value	P value	R^2	Adequate Precision
1	Drug Release (480 min)	2959.52	3	986.51	5.74	0.0448	0.7751	7.652
2	Viscosity	1.443E+008	2	7.217E+007	17.63	0.0031	0.8546	9.703

measured at 227 nm.

Egg membrane

The same procedure as that of used for the *in-vitro* drug release study was followed. Instead of cellophane membrane egg membrane was used. Raw egg was taken and a small hole was made at the bottom to remove all its contents. Then the egg shell was dipped into 0.1 N HCl for 3 hrs. The egg shell was dissolved and the membrane was collected.

Ex-vivo diffusion study: Goat skin

Male goat skin free from any visible sign of disease was selected. The goat dorsal skin was brought from the slaughter house and store in a physiological salt solution at 37±0.5°C. The dorsal hair was removed from the skin and the cleared area was washed thoroughly with distilled water. Dorsal skin of full thickness was excised from the goat. Adhering subcutaneous fat was carefully removed with scissor. This it was mounted on the donor compartment with the epidermis facing the donor compartment and same procedure as that of cellophane membrane was carried out.

Release Experiment

In order to insight of the drug release mechanism from emulgel, drug release data were examined according to the zero order, first order, and Higuchi's model, Hixson and Crowell, Korsmeyer and Peppas model[18]

Flux

PCP Disso V3 software was used to study the average flux of sumatriptan succinate from the emulgels through cellophane membrane for F1 to F9 batches.

Stability study

Stability studies were carried out as per the ICH guidelines for the optimized the batch F7. Short term accelerated stability for gel was done for one month where as long term stability was carried out for 3 months at 40°C ± 2°C/75% ± 5% RH and 30°C±2°C/ 65% ± 5% RH. After storage, the samples were tested for their physical appearance, consistence, viscosity, drug content and drug release.

RESULTS AND DISCUSSION

Drug Characterization

Sumatriptan Succinate was white to pale yellow colored powder. Melting point of Sumatriptan Succinate was 169–171°C within the reported range (169-171°C). The λ max of sumatriptan succinate, in a phosphate buffer pH 6.8 solution was observed at 227 nm . FTIR spectra of pure sumatriptan succinate displayed band at 3094 cm^{-1}due to C-H stretch, at 1702 cm^{-1} due to C=O stretching, at 964 cm^{-1}due to heterocyclic C=C stretching. The spectra also showed bands at 1266 cm^{-1}due to C-N stretching, at 3275 cm^{-1} due to N-H stretching, at 1081 cm-1due to S=O stretching, due to C-S stretching at 634 cm^{1} as shown in figure 1A.

DSC spectrum of pure drug indicated melting point of sumatriptan succinate sharp at 167.31°C (Figure 2A).

Solubility Study

Sumatriptan succinate showed higher solubility in oleic acid among various oils, among various surfactants & co-surfactants labrafil M 1994 and transcutol P (26.69±1.25) led to the highest solubility (Table 4). From these solubility results oleic acid, labrafil M 1994 and transcutol P were selected for the formulation of emulsion

Evaluation of emulsion

Motic microscope image showed spherical shape globules of size range between 0.2-0.5µ (Figure 3A). FE-SEM image indicated that the oil globules of optimized emulsion were spherical in shape and size was 51.40 µm (Figure 3B). Globule size of optimized emulsion was found to be 459.3 nm. PDI of optimized emulsion was found to be 0.797; hence it indicates prepared emulsion is monodisperse which remains stable and has not converted to micro-emulsion (Figure 3C).

Zeta potential

The zeta potential of optimized batch was found to be -25.1mV which showed good stability of the emulsion (Figure 3D).

Dilution test

Upon dilution with water no phase separation was observed. So, it means that optimized batch of emulsion (B4) was w/o type.

pH, drug content and Centrifugation

pH, drug content and viscosity of A4 batch emulsion was found as 7.2 and 96.71±1.70 %.

After centrifugation, no phase separation was observed which indicates that emulsion was stable.

Drug excipient compatibility study

The major peaks of sumatriptan succinate (figure 1 A) at 3275 cm^{-1}(NH), 3123cm^{-1}(OH), 3094 cm^{-1}(CH), 1775 cm^{-1}(C=O), 1266cm^{-1}(CN)and 1081 cm^{-1}(S=0) were observed. Figure 1B spectrum showed major IR peaks at 339.22cm^{-1}(O-H), 2880.45 cm^{-1} (C-H) and 1743cm^{-1}(C=O) for Xanthan gum. Figure 1C spectrum showed prominent peaks of carbopol 934 in between 605.78 (C=C-H) cm^{-1}, 803.20 (C-H) cm^{-1}, 1242.9 (C-O) cm^{-1}, 1719cm^{-} (C=O) ^{1}, and 2927.41cm^{-1}(O-H). The spectrum of drug + Carbopol 934 peaks of mixture at 3275 $cm^{-1,}$ 1775 cm^{-1}, 1266 cm^{-1} and 1081 cm^{-1} (figure 1 D). The spectrum of drug + Xanthan gum showed in the figure 1 E indicate peaks of mixture 3275 cm^{-1}, 964 cm^{-1}, 3123 cm^{-1}, 667 cm^{-1}, 1081cm^{-1} and 1266 .The spectrum of drug + Xantham gum + Carbopol 934 showed in the figure 1 F showed peaks at 3274 cm^{-1}, 1775 $cm^{-1,}$ 1266 cm^{-1}, 1081 cm^{-1}, 639 $cm^{-1,}$ cm^{-1}, and 3120 cm^{-1}. The spectrum of mixtures of drug and

Table 7: Validation Data.

Polymers	Coded levels	Actual levels	Response	% drug release at 8 hrs	Viscosity
			Predicted value	95.8433	12222.2
			Observed value	102.25	26000
Carbopol 934	7	7	Standard deviation	13.1063	2023.02
Xanthan gum	2	2	Standard error mean	10.92	1348.68

excipients does not show any major change in the peaks of the drug so it was concluded that there was no chemical reaction in between drug and excipients. DSC spectrum of pure drug as shown in figure 2A indicated melting point of sumatriptan succinate sharp at 167.31ºC. Sharp peak indicates that the drug sumatriptan succinate is in crystalline form. Carbopol 934 showed melting point at 242.6°C (figure 2B). Xanthan gum showed melting point at 105.92°C (figure 2 C). The mixture of plain drug, xanthan gum and carbopol 934 showed melting point at 167.3°C, 286.5°C and 59.9°C (figure 2 D) respectively. The drug and excipients does not show any change in melting point of drug. This showed that a polymer does not show any interference with the sumatriptan succinate.

Evaluation of emulgel

Emulgels were found to be yellowish, white viscous creamy having good appearance, spreadability and viscosity. pH of all the formulations was found to be within the range of 6 to 7. pH of the skin is in the range of 5.5 to 7. So it was concluded that all the formulations are compatible to the skin pH.

Batch F2 and F3 showed higher viscosity compare to all batches. As the concentration of carbopol 934 increase, the viscosity of formulation was also increased (Table 5). The viscosity of the emulgels indicated the shear-thinning property.

Drug content

Batches F1, F6 and F7 showed higher drug content. The drug content for all the formulations were found to be within the range of 70-100%. The results indicated that the drug dispensed uniformly throughout the emulgel (Table 5).

Bio-adhesive strength

The bio-adhesive strength was determined in terms of detachment stress i.e. force required to detach the formulation from membrane. Results indicated that the change in concentration of carbopol 934 and xanthan gum showed changes in bio-adhesive strength. The gradual increase was observed in bio-adhesive strength as the level of carbopol 934 increased, due to availability of carboxyl group. Carbopol has very high percentage of (58-68 %) of carboxyl group that undergo hydrogen bonding with sugar residues in oligosaccharide chain in membrane. Batch F1 and F7 were showed higher bio-adhesive strength (Table 5).

Spreadability

Spreadability of emulgel is an important parameter. It was found that spreadability increases with decrease in viscosity. Batch F1 and F4 were showed highest spreadability. As compare to optimized batch the marketed formulation showed more spreadability (Table 5).

In-vitro diffusion study

Cellophane membrane

The results of *in-vitro* drug release study showed that batch F1 and F7 release drug faster than the other formulation due to the lower concentration of xanthan gum and higher concentration of carbopol 934 (Figure 4A).

Egg membrane

Batch F1 and F7 at 15 min and 30 min showed less drug release compare to release through cellophane membrane because of thickness of the egg membrane. After 1hr formulations showed increase in drug release compare to release through cellophane membrane. Formulations showed less drug release as compared to the drug release through cellophane membrane after 8hrs. This may be due to complexity of the egg membrane (Figure 4B).

Ex-vivo drug diffusion study

Ex-vivo study of F1 and F7 formulations at 15 min and 30 min showed less drug release as compare to release through cellophane membrane and egg membrane. After 1hr formulations showed increase in drug release compare to release through cellophane membrane and egg membrane. It was found that *ex-vivo* releases of all formulations were less than *in-vitro* release through cellophane membrane and egg membrane after 8 hrs. This decrease in drug release may be due to the fat content and thickness of goat skin. F7 showed better release than F1, this may be due to the high viscosity of F1 (Figure 4C)

Kinetic study and mechanism of drug release

The release kinetics data indicated that the release of drug of batch F1, F3, F4, and F5 followed Zero order kinetics. Batch F2, F6 and F9 followed Korsmeyer Peppas kinetics and F7, F8 showed First order kinetics.

Experimental design

ANOVA Study

The data obtained was treated using Design Expert 10.0.2 software and analyzed statistically using analysis of variance (ANOVA- Table 6). The data was also subjected to the 3-D response surface methodology to study the interaction of X_1 and X_2 on dependent variables[20].

Effect of Formulation Variables on Drug Release at 480 min

Drug Release (at 480 min) =+93.59 +18.53 *A+1.37*B+14.90* AB… Eqn.3

Where, A: Carbopol 934 conc. B: Xanthan gum conc.

The model terms for the drug release at 480 min were found to be significant with high value of R^2 0.7751 with adequate fitting to a linear model. Values of "Prob F" less than 0.05 confirmed that the model terms were significant. Also, the "Pred R-Squared" value-0.0390 F was in reasonable agreement with the "Adj R-Squared" value of. 0.6401. Overall both the variables have positive effect on the % drug release. As it can be seen from the equation 3, the concentration of Carbopol 934 and concentrate xanthan gum both has positive effect on release of drug.

The "Adequate precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. In our case the ratio was 7.652 which indicated an adequate signal. This inferred that the model can be used to navigate the design space (Figure 5A, B)

Effect of Formulation Variables on Gel Viscosity

The regression equation obtained for the emulgel viscosity is as follows:

Gel Viscosity = +17888.89-833.33*A+4833.33* B….. Eqn.4

Where, A: Carbopol 934 concentration

B: Xanthan gum concentration

The model terms for the gel viscosity was found to be significant with high value of R^2 0.9284 which indicates the adequate fitting to a linear model. Values of "Prob F" less than 0.05 indicated that the model terms were significant. The "Pred R-Squared" of 0.7712 is in reasonable agreement with the "Adj R-Squared" of 0.8126; i.e. the difference is less than 0.2 A ratio greater than 4 is desirable.

The "Adequate precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. In our case the ratio was 11.373 which indicated an adequate signal.

In design, as the concentration of carbopol 934 was increased, the gel viscosity increased. It was observed that higher concentration of carbopol 934 while lower the concentration of Xanthan gum produced a gel of higher viscosity (Figure 5C,D).

ANOVA for the independent variables i.e. conc. of Carbopol 934 (X1) and conc. of Xanthan gum (X2) respectively. The coefficients of X_1 and X_2 were found to be significant at $p \leq 0.05$, hence confirmed the significant effect of both the variables on the selected responses.

Carbopol 934 showed greater linear effect on release of drug while xanthan gum showed greater linear effect on viscosity of formulations as it having high degree of gelling capacity. Values of "Prob> F"(p value) less than 0.0500 indicate model terms were significant

Validation of statistical model

After statistical analysis by the Design expert software, optimized batch was found to be F7. The experimental values for the % cumulative drug release at 480 min and viscosity were found very close to the applied predicted values as indicated in (Table7), hence the model was successfully validated.

Flux

The flux of emulgel through cellophane membranes with an area of 7 cm^2. The flux of batch F7 was found to be more than batch F4.

Stability Study

From the stability studies it was observed that there was no significant change on evaluation parameters before and after the study. In stability study it is indicated that appearance of formulation of batch F6 was white and viscous with smooth consistency. % drug content was 97.45% for first month, 96.58% for second month and 96.18% for third month for long term stability study and 95.49% drug content accelerated stability study.

CONCLUSION

Sumatriptan succinate has plasma half-life of 2.5 hrs. The aim of this work was to develop and optimize a transdermal emulgel formulation of sumatriptan succinate for antimigraine activity. Preformulation study carried out with formulation of emulsion with different oil, surfactants and co-surfactants as well as for emulgel with different polymer. *In-vitro* diffusion study through egg membrane showed 91.94±1.82 % drug release for F7 batch. Carbopol 934 has greater linear effect on drug release and viscosity of formulations as it has high degree of gelling capacity. It is concluded that the emulgel formulation will enhance the patient compliance by enhancing bioavailability, avoiding first pass metabolism and overcoming oral route side effects.

ETHICAL ISSUES

Not applicable.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Authors are sincerely thankful to Gattefosse India Pvt. Ltd, Mumbai and Colorcon Asia Pvt. Ltd., Mumbai, India for providing gift sample Authors are highly grateful to Dr. B. S. Kuchekar, Principal and management of MAEER's Maharashtra Institute of Pharmacy, Pune, India for moral support and providing necessary infrastructure to carry out research work.

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