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Formulation and Evaluation of Spironolactone Loaded Emulgel for Topical Application

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ABSTRACT:

Emulgel is one of the recent technologies in NDDS used for dual control release of emulsion and gel for topical use. Gel formulations generally provide faster drug release compared with conventional ointments and creams. Spironolactone is a well-known therapeutic agent that is used mainly for its diuretic ability. Recently, it gained a lot of attention for treating alopecia due to its potent anti-androgenic properties. The aim and objective of the study is to formulate spironolactone loaded emulgel for topical application. Emulgel of spironolactone, consist of carbopol-947 or carbopol-974 or HPMCk15 or xanthan gum as a gelling agents for gel formulation and tween 20, span 20, light, PEG-400, light liquid paraffin for emulsion formulation. Emulgel was formulated by emulsion incorporated in gel. Spironolactone loaded emulgel was formulated by using o/w emulsion because of lower solubility in water. Mentha oil was used as a penetration enhancer in emulgel formulation. Optimization of spironolactone loaded emulgel by 32 full factorial design. Optimized formulation evaluated for was evaluated for physical examination, swelling index, skin irritation study, extrudability study, drug content determination,spreadability, globule size determination and in-vivo drug release, rheological study. Optimized formulation give drug release 78.47% and viscosity 1610 cps.

KEYWORDS: Spironolactone, Emulgel, Alopecia, Topical gel.

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INTRODUCTION[1-3]:

When gels and emulsions are used in combined form the dosage forms are known as emulgels. As the name suggest they are the mixture of emulsion and gel. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to transport various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water- soluble, longer shelf life, bio-friendly, transparent& pleasing appearance. Use of topical agents requires an appreciation of thefactors that influence percutaneous absorption. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through the sebaceous follicle.

The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outermost layer is therate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin; release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, water-soluble ions and polar molecules do not enter intact stratum corneum. Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and antibacterial help a damaged barrier to ward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer. Emulgel emerges as one of the important and better way of delivering the drug; it is because of its better control and reliability over the other topical dosage forms. The various kinds of hydrophobic drugs cannot be incorporated directly into the gels base because of their low solubility. Thereby the emulgels helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. This emulsion thereafter can be mixed into gel base. Thus, the emulgels preparations are much more stable than that of the other types of the topical preparations like powder may be hygroscopic that may absorb environmental humidity during its direct exposure to the surroundings, creams shows phase inversion and the ointments shows rancidity due to oil base. The emulgels also have the better loading capacity as compared to those of the niosomes and liposomes. The other disadvantage of using niosomes and liposomes is that due to vesicular structures it may cause leakage and thus result in lesser entrapment efficiency. The emulgels can be easily formulated from the gels, the material used are easily available and cheaper so the preparation cost of the emulgels is very low. Its formulation also involves the simpler steps. Emulgels have one important advantage that it can be used to in formulating the controlled release drug delivery system to prolong the effect of the drugs having shorter half-life ($t_{1/2}$). Spironolactone is BCS class-II drug with high permeability and lower solubility. Spironolactone is an antagonist of the androgen receptor (AR) as well as an inhibitor of androgen production. Due to the antiandrogenic effects, it is used to treat a variety of dermatological conditions in which androgens, such as testosterone and dihydrotestosterone (DHT), play a role. So, Spironolactone used in treatment of alopecia.

MATERIALS AND METHOD

Table 1: List of materials and reagents

Sr. No	Material	Supplier
1	Spironolactone	Indoco remedies Pvt. Ltd. - USP
2	Xanthan gum	Balaji drugs
3	Carbopol 947 & 974	Balaji drugs
4	HPMC K15	Balaji drugs
5	Liquid paraffin	Aaturinstru. chem.
6	Span 20	Qualikems fine chempvt.ltd
7	Tween 20	Suvidhinath lab.(Sulab)
8	PEG 400	Chiti-chem corporation
9	Methyl paraben	Oxford lab.
10	Propyl paraben	Chiti-chem corporation
11	Chloroform	Aaturinstru. chem.
12	Mentha oil	Aaturinstru. chem.

METHOD[4-9]

The gel was prepared by dispersing gelling agent in water under mechanical stirrer, and the dispersion was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben& propyl paraben was dissolved in polyethylene glycol (PEG) whereas drug was dissolved in methanol, and both solutions were mixed with the oil phase. Both the oily and aqueous phases were separately heated to 70° to 80°C then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was incorporated into the gel in 1:1 ratio with gentle stirring to obtain the emulgel.

CHARACTERIZATION OF EMULGEL[10-17]

FTIR study

The identity of the pure spironolactone drug sample was studied by scanning the sample in the wave number

range 400-4000 cm^{-1} using FTIR spectroscopy by KBr pellet method. The finger print obtained was compared with the reference standard.

Drug excipients compatibility study

Excipients are integral component of almost all pharmaceutical dosage forms. The successful formulation of a stable and effectual dosage form depends on the cautious selection of the excipients, which are added to make easy administration, promote the steady release and bioavailability of the drug and to protect it from degradation.

The drug and polymer interactions were studied by Fourier transform infrared spectroscopy by potassium bromide (KBr)disc method. In this method, a small amount of drug was mixed with the spectroscopic grade of KBr and triturated for uniform mixing. A thin and transparent pellet was prepared by applying 2000 psi pressure. The prepared pellet was exposed to the IR beam and spectra were recorded at the scanning range of 400-4000 cm^{-1} by using FTIR spectrophotometer.

Physical appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared gellified emulsion were measured by a pH meter (Digital pH meter).

Globule size measurement

Globule size of emulgel formulation was measured by using optical microscope.

Drug Content Determination

Drug concentration in gellified emulsion was measured by spectrophotometer. Drug content in gellified emulsion was measured by dissolving known quantity of gellifiedemulsion in solvent (methanol) by sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV -1700 CE, Shimadzu Corporation, Japan).

Spreadability

Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm.) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula,

$$S=M*L/T$$

Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides completely from each other.

Rheological Study

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 64 (Brookfield viscometer).

Swelling Index

To determine the swelling index of prepared topical emulgel, 1 gm. of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows: Swelling Index (SW) % = [(Wt. – Wo) / Wo] × 100. Where, (SW) % = Equilibrium percent swelling, Wo = Original weight of emulgel at zero time, Wt. = Weight of swollen emulgel after time t.

***In-Vitro* Release Study**

This study was carried out by modified membrane bag method. The in vitro release was quantified as a function of time. An dialysis membrane was attached to the lower portion of glass cylinder tube. One gm of spironolactone emulgel formulation was placed in the modified membrane bag and this was coupled to diffusion cell containing receptor compartment filled with phosphate buffer saline (PBS, pH 5.5). The entire system was

maintained at 37±0.5oC with continuous stirring at 200 rpm. Samples were withdrawn from receptor compartment at predetermined intervals of time and replaced by fresh medium. The amount of drug release was quantified by UV spectrophotometer at 242 nm.

Kinetic modeling of *in vitro* drug release data [18-23]

To analyze the mechanism of drug release from all the floating tablet formulations, *in vitro* drug release data of all formulations were subjected to the kinetic analysis. The dissolution profiles of all batches were fitted to various models such as zero order, first order, Higuchi and Korsemeyer and Peppas. The model for best fit was predicted from the value of R^2. The value which was closer to 1 was selected as the best fit model for the drug release.

Comparison with various models

Zero order kinetics

A zero order release would be predicated by the following equation

$$At = A_0 - K_0t$$

Where, At = Drug released at time t
A_0 = Initial drug concentration
K_0 = Zero order rate constant (h -1)

When the data was plotted as cumulative percent drug release versus time it yields astraight line indicating that the release obeys zero order kinetics, with a slope equal toK_0.

First order kinetics

A first order release would be predicated by the following equation

$$Log\ C = Log\ C_0 - kt/2.303$$

Where,
C = Amount of drug remained at time t
C_0 = Initial amount of drug
K = First order rate constant (h -1)

When the data was plotted as cumulative percent drug remaining versus time it yieldsa straight line, indicating that the release follows first order kinetics. The constant 'k'can be obtained by multiplying 2.303 with slope values.

Higuchi's model

Drug release from the matrix devices by diffusion has been described by Higuchi'sclassical diffusion equation

$$Q = kt_{1/2}$$

Where,
Q = Amount of drug released at time't'
t = Time (h)

When the data is plotted according to equation i.e. cumulative drug released versussquare root of time yields a straight line, indicating that the drug was released bydiffusion mechanism. The slope is equal to 'k'

Korsmeyer Peppas model

In order to understand the mode of release of drug from swellable matrices, the datawere fitted to the following equation

$$M_t/ M_\infty = kt^n$$

Where,
Mt/ M∞ =Fraction of drug released
k = Kinetic constant
n = Diffusional exponent for drug release

The equation can be simplified by applying log on both sides, we get

$$Log\ M_t/ M_\infty = Log\ k + n\ Log\ t$$

When the data plotted as log percentage drug released versus log time, yields astraight line with a slope equal to 'n' and the 'k' can be obtained from y-intercept.The value of 'n' gives an indication of the release mechanism. When n = 1, the releaserate is independent of time (zero order case II transport); n = 0.5 for fickian diffusionand when 0.5 < n <1, diffusion and non-fickian transport are implicated. When n > 1.0super case II transport is apparent.

***Ex–vivo* release study**

This study was carried out by modified membrane bag method. The in vitro release was quantified as a function of time. An rat sacrifice skin was attached to the lower portion of glass cylinder tube. One gm of spironolactone emulgel formulation was placed in the tube and this was coupled to diffusion cell containing receptor compartment filled with phosphate buffer saline (PBS, pH

5.5). The entire system was maintained at 37±0.5°C with continuous stirring at 200 rpm. Samples were withdrawn from receptor compartment at predetermined intervals of time and replaced by fresh medium. The amount of drug release was quantified by UV spectrophotometer at 242 nm.

Extrudability study

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm.) / Area (in cm 2).

Skin irritation test

The emulgel preparation was applied on the properly shaven skin of Albino rabbit (Either sex) and changes in color, change in skin morphology, erythema, edema should be checked up to 24, 48 and 72 hours.

Table 2 : Animal study on albino rabbit

Animal	Weight	Sex	Treatment	
Albino rabbit	1.5 – 2.5 kg	Either sex	Without treatment Emulgel on one site	Blank emulgel on second site

Stability study

Stability study of selected formulation was done at room temperature for 1 month and formulation was finally evaluated for appearance, drug content and pH.

RESULT AND DISCUSSION

Fourier transforms infrared spectroscopy (FTIR)

The peak of Spironolactone is shown below Figure 1 which confirms the identification of drug with its functional group. FTIR spectrum is due to presence of FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of Spironolactone indicating purity of drug.

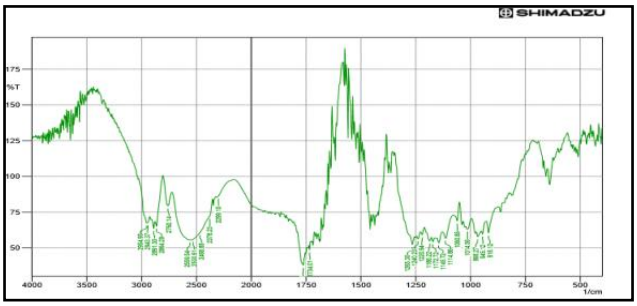


Figure 1: FTIR spectra of Spironolacton

Drug Excipient Compatibility Study

FTIR (Fourier transform infrared spectrophotometer) of Carbopol 947P

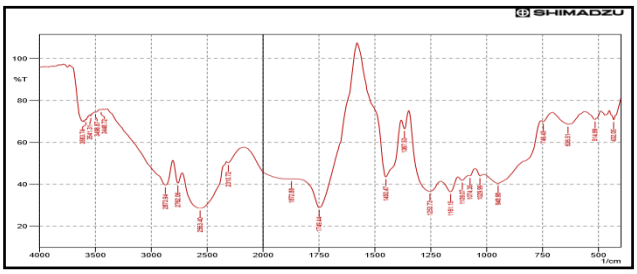


Figure 1 : FTIR spectra of Carbopol 947P

FTIR of Physical mixture (Spironolactone with Carbopol 947P)

FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of spironolactone and if confirms the absence of chemical interaction between drug and polymer. The disappearance of the characteristic peaks of the drug in the formulation indicated that the drug is dispersed at a molecular level in the polymer matrix.

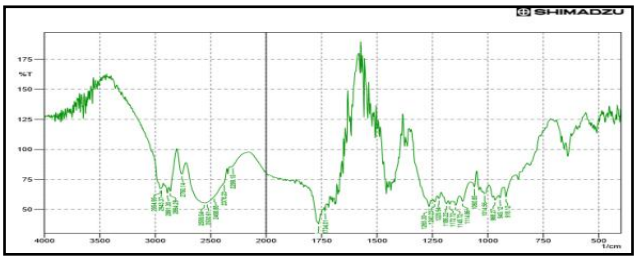


Figure 2: FTIR spectra of Spironolactone + Carbopol 947P

Composition of factorial formulation

Table 3: Composition of optimized formulation

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Spironolactone (gm)	5	5	5	5	5	5	5	5	5
Carbopol 947P (gm)	5	5	5	7.5	7.5	7.5	10	10	10
Liquid paraffin (ml)	1	1.5	2	1	1.5	2	1	1.5	2
Span 20 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Tween 20 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
PEG 400 (ml)	5	5	5	5	5	5	5	5	5
Methyl paraben (ml)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben (ml)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mentha oil (ml)	4	4	4	4	4	4	4	4	4
Chloroform (ml)	10	10	10	10	10	10	10	10	10
Water (ml) (up to 100)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Viscosity of formulation (F1 to F9)

All the formulations were evaluated for viscosity

Table 4 : Viscosity of optimized formulations

RPM	Viscosity (cps)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	977	1336	1482	1110	1582	1758	1249	1695	1840
5	972	1328	1472	1094	1574	1749	1239	1689	1834
10	967	1324	1468	1089	1567	1742	1232	1682	1828
20	964	1319	1459	1084	1556	1736	1226	1676	1821
50	960	1310	1450	1080	1550	1730	1220	1670	1810
100	946	1291	1437	1068	1539	1721	1209	1659	1798

***In vitro* drug release study of formulations (F1 to F9)**

All the formulations were evaluated for drug release study. The data and curve obtained from *in vitro* release test are as follows.

Table 5 : Drug release data of F1 to F9 formulation

Time (hr)	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	34.7	28.4	24.1	31.5	26.4	23.7	27.5	26.1	21.1
1	42.5	38.3	36.2	37.9	34.1	32.5	36.3	33.9	30.7
2	51.9	46.5	44.2	48.6	43.3	41.3	48.7	40.3	39.1
3	58.6	55.1	53.1	56.8	51.8	52.6	57.4	49.1	47.2
4	64.2	61.3	59.2	63.9	59.2	58.4	62.8	56.7	54.1
5	69.9	65.8	62.4	66.2	63.8	61.7	67.3	62.5	59.2
6	78.4	74.1	73.5	76.1	72.1	67.9	75.5	70.4	65.8

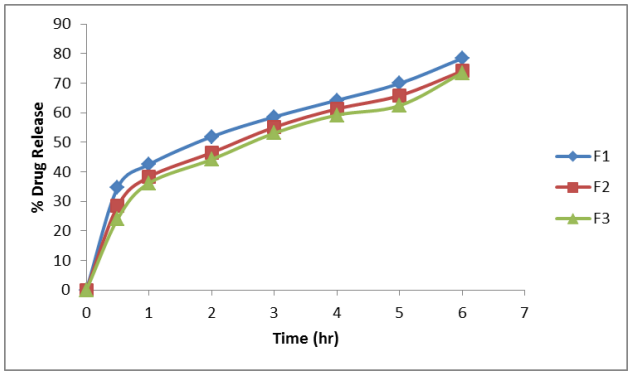


Figure 3 : Drug release curveof F1 to F3

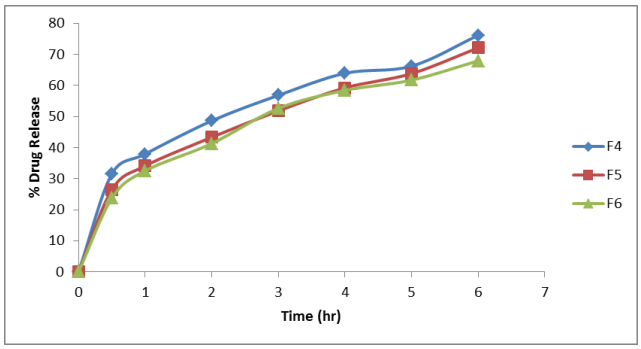


Figure 4 : Drug release curve of F4 to F6

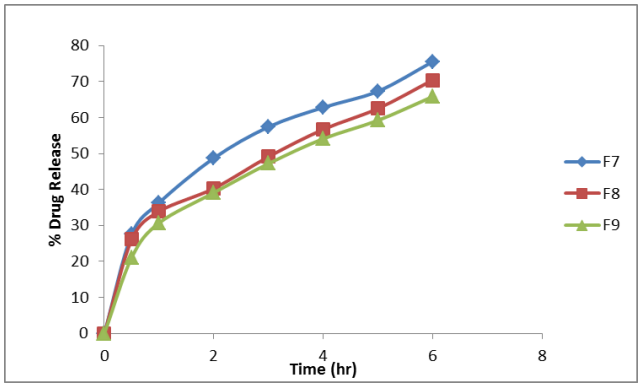


Figure 5 : Drug release curveof F7 to F9

Optimization of Emulgel By 3^2 Factorial Designs

Methodology

Optimization using factorial design method

Optimization has been done by 3^2 factorial designs for the evaluation of the combined effect of the selected dependent variables [Table 7] viscosity and % drug release. In the present investigation, concentration of Liquid paraffin and Carbopol 947P were chosen as independent variables.

Table 6 : Factors (independent variables), factor levels and responses (dependent variables) used in 3^2factorial experimental design

Factors	Type of factor	Factor level used			Response
		-1	**0**	**1**	
X_1=Concentration of Liquid paraffin (%)	Numeric	5	7.5	10	Y1=Viscosity (cps)
X_2=Concentration of Carbopol 947 (%)	Numeric	1	1.5	2	Y2=Drug release (%)

Table 7: Formulation code for preparation of various emulgel compositions by 3^2 design and summary of response data

Formulation Code	Independent variable				Dependent variable	
	Coded		**Uncoded**		**Y1**	**Y2**
	X_1	**X_2**	**X_1**	**X_2**		
F1	-1	-1	5	1	960	78.4
F2	-1	0	5	1.5	1310	74.1
F3	-1	1	5	2	1450	73.5
F4	0	-1	7.5	1	1080	76.1
F5	0	0	7.5	1.5	1550	72.1
F6	0	1	7.5	2	1730	67.9
F7	1	-1	10	1	1220	75.5
F8	1	0	10	1.5	1670	70.4
F9	1	1	10	2	1810	65.8
Broad Range			(5-10)	(1-2)	(960-1810)	(65.8-784)

Contour Plots

Contour plots are diagrammatic representation of the values of the response. They are helpful in explaining the relationship between independent and dependent variables. The reduced models were used to plot two dimension contour plots using DESIGN EXPERT® software.

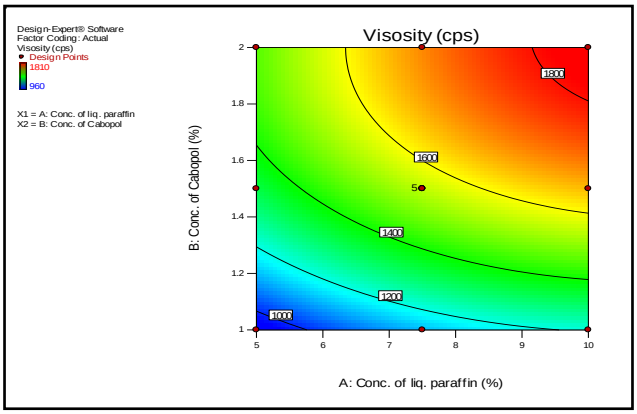


Figure 6 : Contour plot showing the effect of Liquid paraffin (X_1) and Carbopol947P (X_2) on response Y_1 (Viscosity)

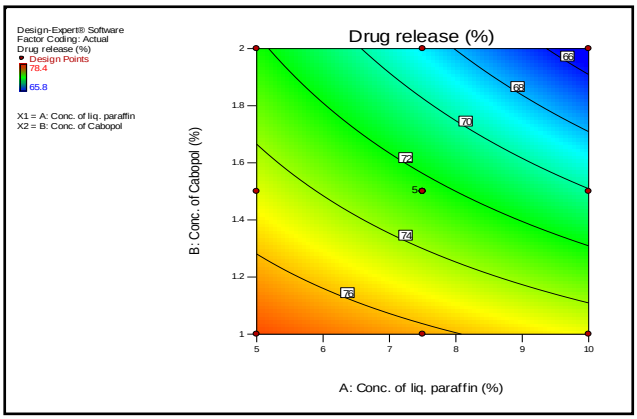


Figure 7 : Contour plot showing the effect of Liquid paraffin (X_1) and Carbopol 947P (X_2) on response Y_2(% Drug release)

Two dimensional contour plots were established for all the responses as shown in (Figure 7 & 8). The contour plots were found to be non-linear for all the responses. So the relationship between independent variables and all the responses are not linear.

Response Surface Plots

Response surface plots are more helpful in understanding both the main and the interaction effects of variables. The effects of different levels of independent variables on the response parameters can also be predicted from the respective response surface plots depicted in Figure 9 and 10

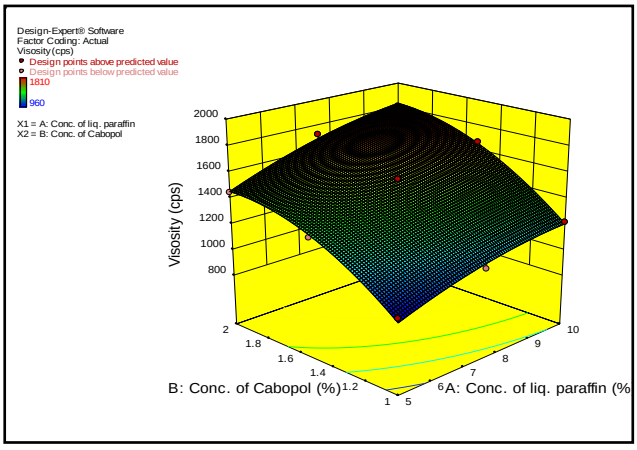


Figure 8 : Response surface plot showing the effect of Liquid paraffin (X_1) and Carbopol 947P (X_2) on response Y_1 (Viscosity)

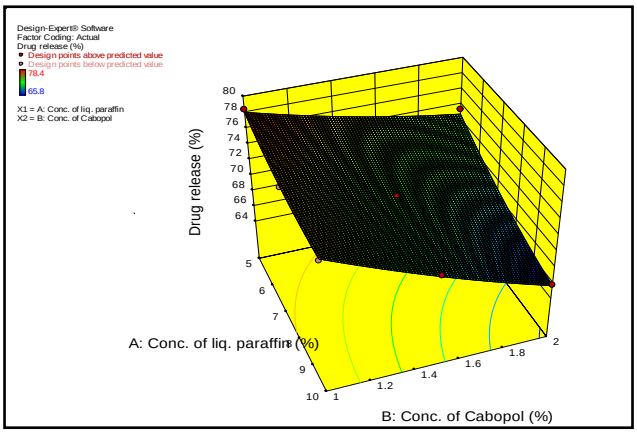


Figure 9 : Response surface plot showing the effect of Liquid paraffin (X_1) and Carbopol 947P (X_2) on response Y_2 (% Drug release)

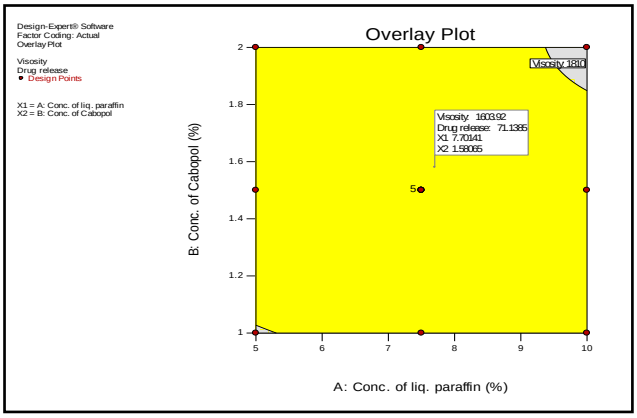


Figure 10 : Overlay plot of Liquid paraffinand Carbopol 947P

Table 8 : Composition of optimized formulation

Ingredients	Quantity
Spironolactone	5 %w/v
Carbopol 947P	1.581 %w/v
Liquid paraffin	7.701 %v/v
Span 20	0.5 %v/v
Tween 20	0.5 %v/v
PEG 400	5 %v/v
Methyl paraben	0.03 %w/v
Propyl paraben	0.03 %w/v
Chloroform	10 %v/v
Mentha oil	4 %v/v
Water	100 ml

Evaluation of Optimized Formulation

Evaluation parameters

Table 9 : Evaluation parameters of optimized formulation

Sr. No.	Evaluation test for optimized batch
1	Physical examination and pH of emulgel
2	Globule size measurement
3	Drug content determination
4	Spreadability
5	Rheological study
6	Swelling index
7	*In-vitro* drug release
8	*Ex-vivo* drug release
9	Extrudability study (Tube test)
10	Skin irritation test(Histopathology study)
11	Stability study

Physical examination and pH of Emulgel

Optimized batch of emulgel formulation were white viscous creamy preparation with a smooth homogeneous glossy appearance.

Table 10 : Physical examination of optimized formulation

Physical examination	Color	Homogeneity	Consistency	Phase separation
	White	Excellent	Excellent	None

pH of Emulgel

The pH values of optimized formulations was 6.7, which is considered acceptable to avoid the risk of irritation upon application to the skin.

Globule Size Measurement

Globule size measurement by optical microscopy

Calibration of eye piece micrometer

81 division of eye piece μm = 100 division of stage μm

1 division of eye piece μm = 1.23 division of stage μm

Calibration of stage micrometer

100 division of stage μm = 1 mm

1 division of stage μm = 0.01 mm = 10 μm

Avg. globule size = 1.35 μm

Globule size = 1.35*12.3 = 16.605 μm

Drug content determination

The drug content of optimized formulation was found to 98.2%.

Spreadability

Spreadability of optimized formulation was calculated by following equation,

S=M*L/T

Where, S=Spreading coefficient

M=Weight to be taken

L=Spreading emulgel length of the slide

T=Time taken for spreading on slide

Table 11: Spreadability of optimized formulation

M=Weight	**45 gm**	Spreadability (S)=20.16
L=Length	11.2 cm	
T=time	25 sec.	

Rheological study

Rheological parameter of optimized formulation

Table 12 : Viscosity of optimized formulation

Viscosity of formulation	**Spindle No.**	**RPM**	**Viscosity**
	64	50	1610 cps

Swelling index

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100

Where, (SW) % = Equilibrium percent swelling, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time.

Table 13 : Swelling index of optimized formulation

Time	**Initial weight of emulgel solution**	**Final weight of emulgel**	**Avg. weight Increased**
0	2.95	2.95	11.18%
15	2.95	3.24	
30	2.95	3.32	

In-vitro drug release

Table 14 : *In-vitro* drug release of optimized formulation

Time (hrs)	**Abs**	**Conc.(mcg/ml)**	**Conc. *D.F**	**Conc. (mg/ml)**	**Conc. (mg/80 ml)**	**% drug release**
0.5	0.144	1.70	85.10	0.08	6.808	13.62

1	0.233	3.59	179.78	0.17	14.383	28.737
2	0.311	5.25	262.76	0.26	21.021	42.044
3	0.394	7.02	351.06	0.35	28.085	56.167
4	0.432	7.82	391.48	0.39	31.319	62.644
5	0.498	9.23	461.70	0.46	36.936	73.867
6	0.525	9.80	490.42	0.49	39.234	78.467

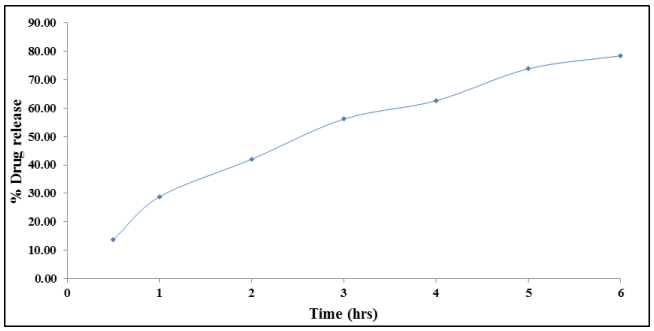


Figure 11: *In-vitro* drug release plot of optimized formulation

Release kinetic of *in-vitro* drug release

Table 15 : Release kinetic of *in-vitro* drug release

Optimized formulation	Higuchi (R^2)	Zero order (R^2)	First order (R^2)	Korsmeyer-peppas (R^2)
PD1	0.9881	0.9443	**0.9949**	0.4569

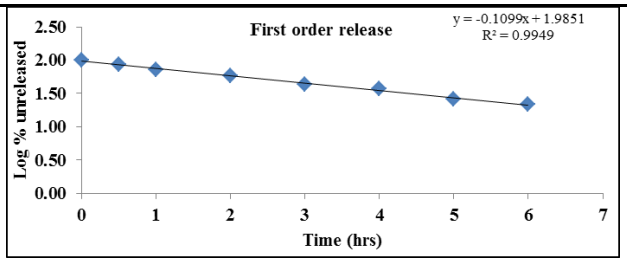


Figure 12 : Release kinetic of *In-vitro* drug release plot of optimized formulation

***Ex-vivo* drug release**

Ex-vivo drug release by using rat sacrifice skin

Table 16 : *Ex-vivo* drug release of optimized formulation

Time (hrs)	Abs	Conc.(mcg/ml)	Conc. *D.F	Conc. (mg/ml)	Conc. (mg/80 ml)	% drug release
0.5	0.133	1.46	73.40	0.073	5.872	11.74
1	0.224	3.40	170.21	0.17	13.617	27.23
2	0.305	5.12	256.38	0.25	20.510	41.02
3	0.388	6.89	344.68	0.34	27.574	55.15
4	0.426	7.70	385.10	0.38	30.808	61.62
5	0.491	9.08	454.25	0.45	36.340	72.68
6	0.515	9.59	479.78	0.47	38.383	76.767

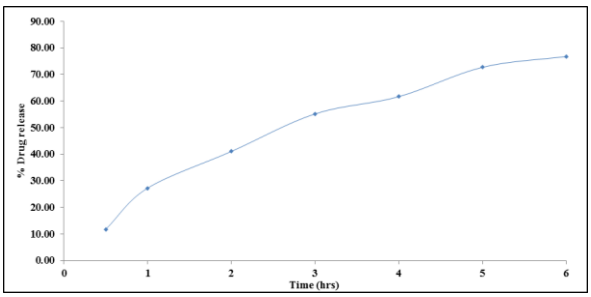


Figure 13 : *In-Ex-vivo* drug release plot of optimized formulation

Extrudability study (Tube test)

During the test, Optimized batch 15.4 ±0.5 gm/cm weight requiered to extrude 0.5 or 1 cm ribbon of emulgel in 10 sec from aluminium collapsible tube , From the result consider that more quantity of emulsion based gel extrude at little applied pressure on tube which shows better patient compliance and indicat that emulgel have a good extrudability.

Skin irritation study

The emulgel preparation was applied on the properly shaven skin of Albino rabbit (Either sex) and changes in color, change in skin morphology, erythema, edema should be checked up to 24, 48 and 72 hours.

Dose Calculation For Rabbit

For rabbit:-Human dose × Factor

50 × 0.07 = 3.5 mg/kg = 5.25 mg/1.5 kg

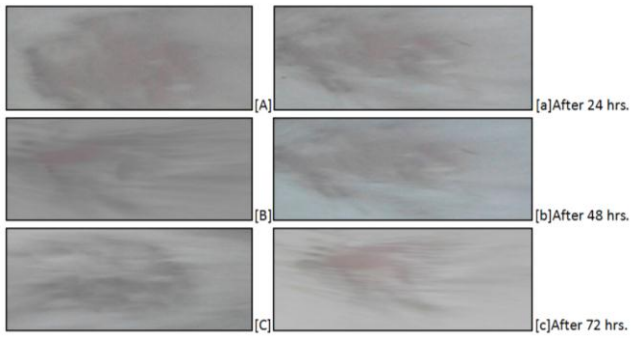
Dose for rabbit-5.25 mg/105 mg Emulgel

Table 17 : Animal study

Animal	Weight	Sex	Treatment	
Albino rabbit	1.5 – 2.5 kg	Either sex	Without treatment	
			Emulgel on one site	Blank emulgel on second site

A-Normal controlled area
B-Applied Spironolactone loaded emulgel formulation
C-Applied gel base(without drug)

The result of skin irritation studies indicated that the formulation was non-irritant to the skin. No signs of erythema or edema were observed.



[A], [B], [C]-Applied spironolactone loaded emulgel on skin
[a], [b], [c]-Applied gel base (without drug) on skin

Figure 14 : Skin irritation study of optimized formulation

Stability study

Table 18 : Stability study

PARAMETER	Optimized Spironolactone loaded emulgel Room Temperature			
	0 Day	10 Day	20 Day	30 Day
Color	White	White	White	White
Odour	Odourless	Odourless	Odourless	Odourless
pH	6.75	6.72	6.64	6.5
Spreadability	20.16 gm.cm/sec	20.18 gm.cm/sec	20.19 gm.cm/sec	20.22 gm.cm/sec
Viscosity(cps)	1610	1614	1616	1619
% Drug content	98.2%	97.04%	95.89%	93.87%

Optimized Spironolactone emulgel formulation was selected for stability studies from each concentration and each polymer based on their release characteristics. At fixed time interval drug content determination of these formulations shows no significant changes when compared to the initial formulations.

SUMMARY

Spironolactone is BCS class-II drug with high permeability and lower solubility. Spironolactone is an antagonist of the androgen receptor (AR) as well as an inhibitor of androgen production. Due to the antiandrogenic effects, it is used to treat a variety of dermatological conditions in which androgens, such as testosterone and dihydrotestosterone (DHT), play a role. So, Spironolactone used in treatment of alopecia. Emulgel is more effective than any other topical preparation. The emulgels also have the better loading capacity as compared to those of the niosomes and liposomes. Emulgel is easily removable from skin.Emulgel give controlled release of hydrophobic drug through skin. For the preparation of spironolactone emulgel liquid paraffin, span 20, tween 20, peg 400 used as a emulsifier and methyl paraben, propyl paraben used for preservatives. The emulsion incorporated into gel base in 1:1 ratio to prepare emulgel. Optimized batch evaluated for physical examination, rheological study, swelling index, in-vitro drug release, ex-vivo drug release, drug content determination, globule size measurement, skin irritation study and spreadability. Optimized emulgel give drug release, viscosity, spreadability, drug content, pH were found to be 78.47%, 1610 cps, 20.16gm*cm/sec., 98.2% and 6.3 respectively. Optimized Spironolactone emulgel formulation was selected for stability studies from each concentration and each polymer based on their release characteristics. At fixed time interval drug content determination of these formulations shows no significant changes when compared to the initial formulations. Spironolactone loaded emulgel used for female pattern hair loss or alopecia and give controlled release of drug from the formulation.

CONCLUSION

The present work shows that emulgel is promising transdermal drug delivery vehicle and enhance the solubility of spironolactone drug was done by using this approach . Spironolactone containing emulgel was formulated for topical application. Emulgel appear better & effective drug delivery system as compared to other conventional topical drug delivery system. Many ingredients used in the formulations are highly stable and safe for the topical delivery and that pharmaceutical ingredient into emulgels is used in treatment of various diseases like fungal infection, as topical anti-inflammatory infection, psoriasis etc. Emulgel have advantages in term of better spreadilbility, adhesion, viscosity and extrusion, this type of drug delivery system will become a popular drug delivery system. Regarding various advantages of emulgel offer a wide utility in derma care.

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