Section: Research Paper

OPTIMIZATION OF FORMULATION BY BOX BEHNKEN AND IN-VITRO STUDIES OF EMULSIFIED GEL CONTAINING ZALTOPROFEN FOR THE MANAGEMENT OF ARTHRITIS

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Abstract:

Zaltoprofen, which is a non-selective COX inhibitor, is very beneficial in arthritis especially rheumatoid arthritis. It has a very short half-life of 4.96± 2.96 hr. The drug has different side effects like ulceration, nausea, vomiting, constipation, loss of appetite, and urinary disturbance when taken orally. The Transdermal Emulsified gel of Zaltoprofen was formulated by using varying concentrations of Light Liquid Paraffin and Carbopol934p. The Emulgel was characterized for physical appearance (Colour, Phase separation, Homogeneity, Consistency), pH, Spreadability, Viscosity, Extrudability, Drug content, *In-vitro* drug release study, Stability study. A 3^2 factorial design was used to determine the effect of the Carbopol 934P and Light Liquid Paraffin on various parameters such as Spreadability, Viscosity, % CDR at 12 hr. The responses were analyzed using ANOVA & by the predictive equation by design expert. From study It was established that Light Liquid Paraffin and Carbopol934p significantly affect all the parameters. The developed formulation F7 shown very satisfactorily results of Spreadablity25 ± 0.53mg*cm/sec, Viscosity 3817 ± 0.62 cps and percentage cumulative drug release at 12^{th}hour was 96.62±0.76%. The most appropriate formulation was found to be stable for one month during stability study.

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Key Words: Zaltoprofen, Emulgel, Rheumatoid Arthritis, Light liquid paraffin, Carbopol934p

Introduction:

The term arthritis has been used to describe mild to severe changes or pain in the joints which may be either inflammatory or degenerative in the character. It is imperative for all adults to have at least a basic understanding of arthritis since most adults face some form of Arthritis.[1] It is an extremely common and is among the oldest known disease among men and women. Rheumatoid arthritis is a chronic inflammatory disease which is characterized by symmetrical inflammation of joints, yet may involve other organ systems. Rheumatoid arthritis is a form of chronic arthritis.[2] This disease affects chiefly young adults, mainly women and one or many joints may be involved; it also occurs in children (Still's Disease).[3, 21-35] The drugs which is most frequently used for the management of rheumatoid arthritis are the didisease-modifyingntirheumatic drugs (DMARDs) and Non - steroidal anti-inflammatory drug (NSAID).[4] Some immunosuppressant (e.g. – azathioprine, cyclosporine) are also used. Newer agents, with more specific agent the disease processes of rheumatoid, are the ant cytokine drugs. Zaltoprofen, a non-steroidal anti- inflammatory agent is widely used for the management of rheumatoid arthritis.[5] The bioavailability of zaltoprofen is relatively low after oral route of administration due to its limited solubility in water.[6] Zaltoprofen, having a very common adverse effects of ulceration, nausea, vomiting, constipation, loss of appetite, numbness, dizziness, drowsiness, urinary disturbance which all can be eliminated by applying with topical route.[7] The dose of zaltoprofen can be minimized as the drug is given with topical route due to localized action, so there is no loss of drug due to first pass metabolism. [8] As in the arthritis and rheumatoid arthritis frequent dosing is needed as the continue pain is there.[9] Conventional dosage form of zaltoprofen has a relatively poor pharmacokinetic profile. [10] The short half-life (4-5hr) necessitates 2-3 times daily dosing, which may reduce patient compliance. Hence the present work (Zaltoprofen emulsified gel) to provide a better patient compliance as the oral dosage form is sustained release.[11]

Materials and Methods:

Zaltoprofen was obtained as a gift sample from ZCL chemical Ltd. Ankeleshwar, Gujarat, India. Ethanol, span 20, Tween 20, Carbopol 934, HPMC were obtained from ACS chemicals (Ahmedabad, Gujarat). Light liquid paraffin, Isopropyl myristate, propylene glycol was obtained from sulab laboratories (Vadodara, Gujarat). Triethanolamine was obtained from Loba chemicals (Mumbai, Maharashtra).

METHOD OF PREPARATION OF EMULSIFIED GEL

GEL FORMATION: -

The gel was prepared by dispersing gelling agent in purified water with the help of magnetic stirrer and continues the stirring till the uniform solution was obtained. This uniform solution was neutralized at pH 7 with tri ethanolamine to form gel.[12]

EMULSION FORMATION: -

Oil phase: The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin.

Aqueous phase: The aqueous phase was prepared by dissolving Tween 20 in purified water. Propyl paraben was dissolved in propylene glycol whereas Zaltoprofen was dissolved in ethanol, and both solutions were mixed with the aqueous phase. Both the aqueous phase and oily phases were heated separately to 70 to 80°C then the oily phase of emulsion was added to the aqueous phase with stirring continue for 15-20 minutes and cooled to room temperature. The obtained emulsion was mixed appropriately with the gel in 1:1 ratio with gentle stirring to obtain the emulgel.[13]

Table-3: Composition of Zaltoprofen Emulsified gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zaltoprofen	1	1	1	1	1	1	1	1	1
Light liq paraffin	8	8	8	10	10	10	12	12	12
Span 20	2	2	2	2.5	2.5	2.5	3	3	3
Tween 20	1.5	1.5	1.5	2	2	2	2.5	2.5	2.5
Propylene glycol	5	5	5	5	5	5	5	5	5
Ethanol	5	5	5	5	5	5	5	5	5
Propyl Paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Carbopol	1.3	1.5	1.7	1.3	1.5	1.7	1.3	1.5	1.7
Water upto(ml)	100	100	100	100	100	100	100	100	100
Triethanolamine	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7	Adjust Ph 6 to 7

1. Phase Separation:[14]

The prepared emulsion is set aside without disturbance. The time required for the separation of oil phase from continuous water phase is noted.

2*. Oil globule size*:

The eosin red is added to prepared emulsion and the emulsion is examined under the microscope. The continuous water phase is observed pink coloured and colourless oil globules are measured. The structure and size of oil globules is measured with stage micrometre.

***3*. Milkiness:**

The milkiness is compared in different emulsion batches.

Different Characterizations of Emulsified gel:

1. Fourier Transformed Infrared (FT-IR) Spectroscopy

IR spectroscopy will be conducted using a Shimadzu FTIR 8400 Spectrophotometer (Shimadzu) and the spectrum will be recorded in the wavelength region of 4000-400 cm^{1}The procedure consisted of dispersing a sample in KBr and compressing into discs by applying pressure. The pellet will be placed in the light path and the spectrum will be recorded.

***2*. Physical appearance:**

The prepared Emulsified formulations were inspected visually for their colour, homogeneity, consistency and grittiness.

3. Measurement of pH:

The pH of Emulsified gel formulations was obtained by using a digital pH meter. One gram of gel was dissolved in 100ml of distilled water and it was placed for two hours. The measurement of pH is done using a Digital pH meter.

4. Microscopical examination:

The size of globules of emulsified gel is measured under the microscope.

5. Spreadability:

Spreadability is determined by apparatus 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 based on the 'Slip' and 'Drag' characteristics of the emulsified gel. A ground glass slide is fixed on this block. An excess of emulsified gel (about 2 gm) under study is placed on this ground slide. The emulsified gel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulsified gel between the slides. Excess of the emulsified gel 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 7 cm be noted. A shorter interval indicates better spread ability. 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.

6. Rheological Study:

The viscosity of the different emulsified gel formulations is determined at 25°C using a cone and plate viscometer with spindle 62 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

7. 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 emulsified gel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulsified gel 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)

8. Drug content:

Drug concentration in emulgel was measured by spectrophotometer. Drug content in emulsified gel was measured by dissolving known quantity of Jellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS'S spectrophotometer.

9. *In*- vitro drug release study:

Modified Franz diffusion cell was used for the drug release studies. Emulsified 1 gm was applied onto the surface of semi permeable membrane evenly. The semi permeable membrane (cellophane paper) was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly

prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the semi permeable membrane was determined as a function of time.

10. Stability Study

A study is carried out to assess the stability of Zaltoprofen emulsified gel. The optimized formulation was subjected to the accelerated stability studies according to ICH guidelines 45ºC and 75±5% RH for a period of 30 days in a stability chamber. Samples were evaluated at 1^{st} and 30^{th} day for different parameter such as spreadability, Viscosity, Drug Content, Extrudability and *in vitro* drug release.

Result and Discussion:

The aim of this research work was formulation and *In-vitro* evaluation of topical emulgel of anti-inflammatory drug in view to improve bioavailability & patient compliance as well as to remove of side effect of conventional dose. In present study, an attempt was made to formulate emulsified gel formulation of Zaltoprofen using various gelling agent like carbopol 934p and HPMC K4M. Zaltoprofen is a non-steroidal anti-inflammatory drug which is widely used in rheumatoid arthritis. Emulsified gel was prepared by mixing emulsion and gel. The emulsion was prepared by using light liquid paraffin as oil phase and Span 20 and Tween 20 as emulsifying agent. The gel was prepared by using carbopol 934p and HPMC K4M for comparison. The concentration of emulsifying agent and carbopol 934p was optimized in preliminary studies. The emulsion was first evaluated for its milkiness, oil globule size and its distribution and phase separation time. The emulsified was evaluated for its physical appearance for its color, homogeneity, consistency, and grittiness. The emulsified gel was also evaluated for its pH, Microscopical examination, spread ability, Rheological Study, Extrudability study, Drug content, *In- vitro* drug release study, short term accelerated stability Studies. The 3^2 full factorial design is used in that concentration light liquid paraffin (X1) and concentration of Carbopol 934p (X2) were selected as independent variables and Spreadability, Viscosity and % Cumulative drug release at 12 hr were selected as dependent variables. The all batches were analyzed for physical appearance, Spreadability, Viscosity, and % CDR at 12 hr. Optimum concentration of these variables was used to formulate optimized formulation which was evaluated. The optimized formulation was found to be satisfactory having percentage cumulative drug release at 12 hours of 96.62 ± 0.76%., spread ability 25 ± 0.53 mg*cm/sec, viscosity 3817 ± 0.62 cps, Drug content 95.72 ± 0.61. The release mechanism of all formulation was found to be Zero order.

Optimization of Emulsified gel Formulation:

The formulation was optimized using a Box-Behnken design expert, which is a response surface type of design of experiment wherein responses of 3 factors were studied at 3 levels. A total no. of 9 experiments were designed. Two check point batch has been developed for most appropriate formulations to choose the best model among the linear, analysis of variance (ANOVA), F-value has been developed by using design expert software. The responses were recorded & analysis of the data was carried out using ANOVA in DESIGN-EXPERT 8.0.7.0 demo version software (STAT-EASE). The individual parameters were evaluated using F test.

Table-4: Primary evaluation of emulsion

Formulation	Milkiness	Phase separation time	Oil globule size	D Mode	D Median
F1	+++	Not upto 5hrs	25.9± 1.10	4.5	2.5
F2	+++	Not upto 5hrs	23.04± 0.85	0.5	1.5
F3	+++	Not upto 5hrs	24.7± 0.67	0.5	3.4

F4	+++	Not upto 5hrs	**22.56 ± 0.94**	**2.5**	**2.4**
F5	+++	Not upto 5hrs	23.94 ± 0.70	4.5	2.6
F6	+++	Not upto 5hrs	24.52 ± 0.67	0.5	3.3
F7	+++	Not upto 5hrs	**22.34± 0.81**	**2.5**	**2.4**
F8	+++	Not upto 5hrs	24.93 ± 1.09	4.5	2.7
F9	+++	Not upto 5hrs	23.7 ± 0.68	0.5	1.9

Table-5 Physicochemical characteristics of Emulgel formulation

Formulation	Colour	Phase Separation	Grittiness	Homogeneity	Consistency
F1	White	None	-	+++	*
F2	White	None	-	+++	**
F3	White	None	-	+++	**
F4	White	None	-	+++	***
F5	White	None	-	+++	**
F6	White	None	-	+++	***
F7	White	None	-	+++	***
F8	White	None	-	+++	***
F9	White	None	-	+++	**

+++ Excellent ++Good +Satisfactory

*** Excellent **Good *Poor

Among all Batches F7 Batch Showed Better Colour, Phase Separation, Grittiness, Homogeneity, Consistency.

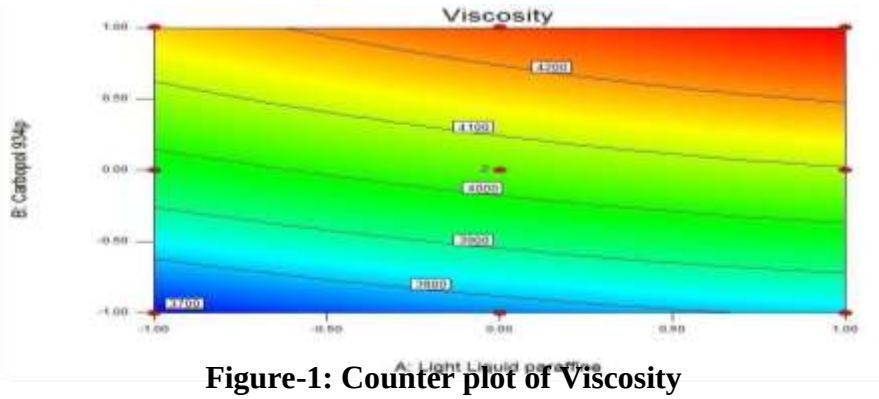

Figure-1: Counter plot of Viscosity

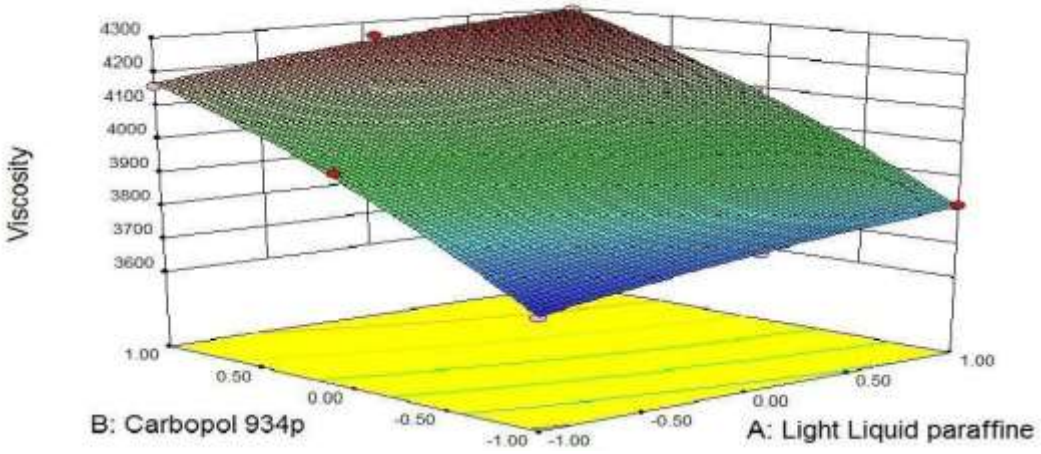

Figure-2: 3D-Surface plot of viscosity

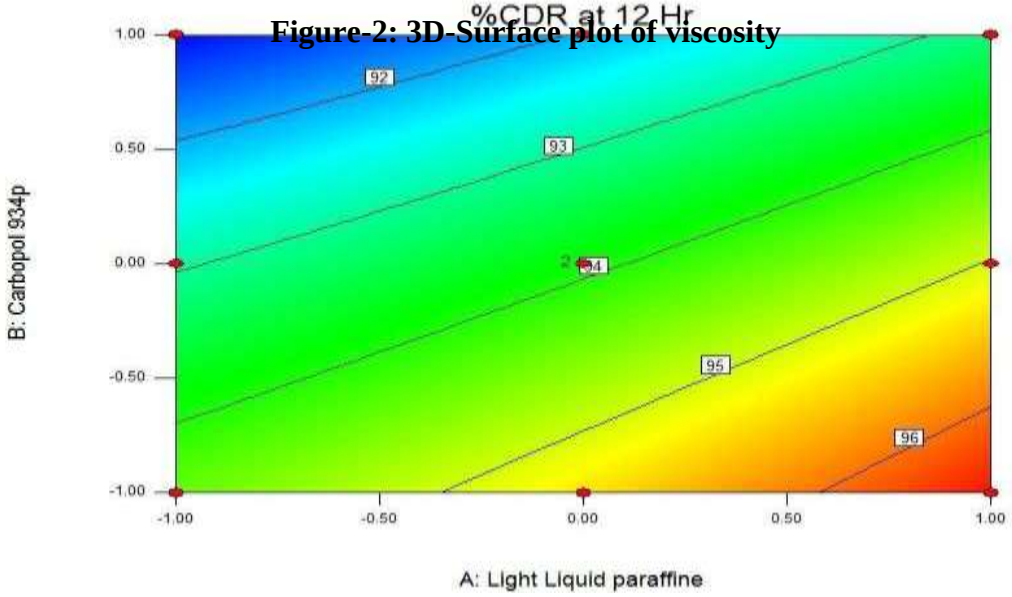

Figure-3: Counter plot of % CDR at 12 hr

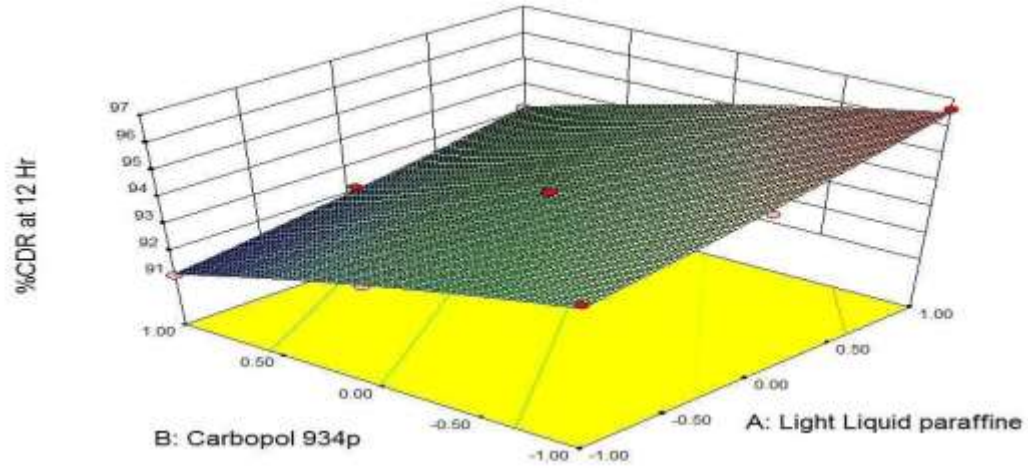

Figure-4 3D surface plot of % CDR at 12

Comparison between experimental and predicted result of check point batch:

As shown in table Experimental value of dependent variables (i.e. Spreadability, Viscosity and % CDR at 12 hour) obtained were compared with predicted value obtained from Box Behnken Design Expert 8.0.7.0 trial version® software.

Table-6: Comparison of predicted value & Experimental value of check point batch

Formulation	Parameters	Predicted Value	Experimental Value	% Error
F4	Viscosity	3991.761	3978	0.345
	% CDR at 12 hour	94.129	93.26	0.931
F7	Viscosity	3907.360	3886	0.549
	% CDR at 12 hr	95.024	94.31	0.757

Experimental values were found to be closer to predicted values obtained from the check point batch. It was found that there was no significant difference between Experimental Value and predicted value.
Hence it is concluded that level of independent factors is suitable to prepare optimized formulation.

Stability Study of Optimized Batch- (F7):

Optimized formulation (F7) was subjected to stability study for 1 month and evaluated for physical appearance (Colour, Phase separation), pH, Viscosity, Drug content, *In-vitro* drug release study, then compared with the previous results obtained for optimized formulation F7. The result after the stability period is given in the table.

Table-7 Stability study of optimized formulation (F7)

Evaluation Parameter	1 Day	After 30 Day
Colour	White	White
Phase Separation	None	None
pH	6.30 ± 0.2	6.68 ± 0.06
Spreadability	25 ± 0.53	23.00 ± 0.46
Viscosity	3817 ± 0.62	3875 ± 0.20
Drug Content	95.72 ± 0.61	95.28 ± 0.36
In-vitro Drug release	96.62 ± 0.76	96.16 ± 0.55

Conclusion:

Zaltoprofen was formulated as emulsified gel formulations to give sustain release effect. Prepared emulsified gel is topical preparation so it eliminates the side effect of drug like ulceration, nausea, vomiting, constipation, loss of appetite, urinary disturbance when taken orally as well as removal of first pass metabolism so lower dose is required. It was found that concentration of gelling agent Carbopol 934p & concentration of oil phase Light liquid paraffin played an important role in spreadability Viscosity & percentage cumulative drug release of formulated emulsified gel. Hence optimum concentration of Carbopol 934p and Light liquid paraffin were required to formulate emulsified gel of required properties to increase spreadability as well as viscosity and cumulative percentage drug release. The application of experimental design & optimization technique was helpful in obtaining optimum formulation with a smaller number of experiments. The optimized formulation when undergo stability study, showing stable nature which conclude that emulsified gel is acceptable formulation which provide many advantages over conventional dosage form as mention earlier. It is also possible to formulate nano-emulsion and nano-gel to formulate emulsified gel.

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