Factorial Design Assisted CelecoxibEmulgel: Formulation, Optimization and Characterization

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Abstract:

Topical drug delivery has been used from centuries for the treatment of local skin disorders. Topical application offers the potential advantages for the delivery of drug at the effected site for extended period of time. Topical delivery of the drug increase the contact time and mean resident time of the drug. The aim of the work was to develop and evaluateCelecoxib loaded Emulgel by using high molecular weight water soluble polymer Carbopol-934. This polymer possesses very high viscosity, transparency, film forming properties at low concentration and these are useful in formation of gel with an objective to increase transparency and spread ability. Formulation of CelecoxibEmulgel were prepared by using carbopol-934 as gelling agent, span80, tween80 as emulsifier and light liquid paraffin as oil phase. The influence of the type of gelling agent and concentration of both oil phase and emulsifying agent on the drug release from the prepared Emulgel was investigated using 2^3 factorial designs. The formulated formulations were evaluated for their physical appearance, pH determination, spreadability, extrudability, rheological study, drug content determination and in vitro release study. The release study was determined by Franz diffusion cell and optimized batch shows better release 92.13±1.15 within 8 hours. The drug release profile follows zero order plot and KorsmeyerPeppas model.

Keywords: Emulgel, CelecoxibEmulgel, topical drug delivery, carbopl-934

Introduction:

Topical drug delivery (TDDs) can be defined as the application of a drug containing formulation to the skin to treat cutaneous disorder and these system generally applied when the other system of drug administration fails or on local infection like fungal infection[1]. The Topical drug delivery system is generally preferred when other routes (like oral, sublingual, rectal, parenteral) of drug administration fails. Drugs are administrated topically for their action at the site of application or for systemic effect[2]. Topical drug delivery (TDD) increases the contact time and mean time of drug at the applied site. The Topical preparations are applied to the skin for both cosmetic and dermatological purpose to the healthy and diseased skin[3].
Celecoxib was the first synthesized non-steroidal anti-inflammatory drug (NSAID) able to selectively inhibit COX-2 activity and exhibits anti-inflammatory, analgesic and antipyretic activities. It has been used in the treatment of rheumatoid arthritis, osteoarthritis, acute pain familial adenomatous polyposis and primary dysmenorrhea[4].

These potential side effects may be overcome by the topical administration of the drug. The reason for incorporating the drug Celecoxib into Emulgel drug delivery system include, its non-irritating to the skin, extensively bound to plasma proteins (97%), has short half-life and low molecular weight could provide

localized action at particular site. Topical application as an alternative route of administration has demonstrated better to sort-out these problems, and it was speculated that topical administration of NSAIDs may increase the patient compliance and continuous absorption of drug in controlled manner[5,6].

Within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetic and in pharmaceutical preparations. Polymer can function as emulsifier 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[7-9].

Materials and Methods

Celecoxib sample was obtained from Balaji Chemicals, Surat, and Tween80 from S.D. Fine Chem Limited, Mumbai and Light liquid paraffin from Arora Pharmaceutical, Delhi.

Formulation of CelecoxibEmulgel:

CelecoxibEmulgel were prepared by dissolving accurate quantity of weighed carbopol-934 in water at temperature 60°C with constant stirring at moderate speed and and pH are adjusted to 6 to 6.5 using Triethanolamine (TEA). The aqueous phase was prepared by dissolving tween80 in purified water and in another beaker methyl paraben was dissolved in propylene glycol whereas Celecoxib was dissolve in sufficient quantity of ethanol separately. Afterword both solutions were mixed. The oily phase was prepared by dissolving span80 in light liquid paraffin. The emulsion was prepared by mixing oily phase in aqueous phase at a temperature of 60-70°C with constant stirring. Incorporation of gelling phase into the emulsion gave rise to Emulgel[10]. Compositions of all batches are given in table 1.

Table 1: Composition for Emulgel Formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Celecoxib (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Carbopol-934 (gm)	0.5	1	0.5	1	0.5	1	0.5	1
Light Liquid Paraffin (ml)	0.5	0.5	1	1	0.5	0.5	1	1
Tween-80 (ml)	0.5	0.5	0.5	0.5	7.5	7.5	7.5	7.5
Span-80 (ml)	0.5	0.5	0.5	0.5	7.5	7.5	7.5	7.5
Propylene Glycol (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol (ml)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methyl Paraben (gm)	0.015	0.015	0.015	0.015	0.015	0.015	0.015	0.015
Menthol (gm)	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
Purified Water (q.s. uptogm)	50	50	50	50	50	50	50	50

Factorial design study

In the present study 2^3 full factorial design was applied with three factors as Polymer (Caopol-934) (X1=A), Emulsifier (Light Liquid Paraffin) (X2=B) and Surfactant (i.e. Tween-80 and Span-80) (X3=C)

at two levels (+) and (-). It was performed with the aim of determining the importance of selected factors that influence the drug release.

Evaluation of Celecoxib Emulgel:

Physical appearance:

The prepared Celecoxib Emulgel was inspected visually for their colour, consistency, and homogeneity and phase separation[11].

pH determination:

The pH values of prepared Emulgel formulation were determined by using 1% w/v aqueous solutions of the prepared Emulgel by digital meter. One gram of Emulgel was dissolved in 100 ml was dissolved in 100 ml of distilled water and it was placed for two hours. The measurement of pH of each formulation was done in triplicate and average value was calculated[12].

Spreadability study:

Spreadability coefficient was to be determined by apparatus suggested by Mutimer. The apparatus consists of wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of prepared Emulgel. A ground glass slide having same dimension as that of the fixed ground slide was provided with the hook. Weight of 20 gm was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of Emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (seconds) required by the top slide to separate from ground slide was noted[13]. The spreadability is calculated by using the Formula.

$$S = \frac{M.L}{T}$$

Where M= Weight tied to upper slide.

L= Length of glass slide.

T= Time taken to separate the slides.

Extrudability:

A 15 gm of Emulgel was filled in aluminum tube. The plunger was adjusted to hold the tube properly. The weight of 1 kg/cm^2 was applied for 30 seconds the quantity of Emulgel extruded was weighed[14].

Rheological study:

Viscosity of the prepared Emulgel was determined using digital viscometer (Labman LMDV-60 Digital Rotational Viscometer L2415) at the temperature of 37°C. The formulation was added to the beaker, Spindle number III was lowered perpendicular in to the centre of Emulgel taking care that spindle does not touch bottom to the jar and rotated at a 10 (minimum) and 100 (maximum) rotations per minute, the viscosity was noted down[15].

Drug content determination:

Drug concentration in Emulgel was calculated by spectrophotometric method. Celecoxib content in Emulgel was estimated by dissolving 1 gm of Emulgel in 100 ml solvent (methanol) by sonication

(Ultrasonic Probe Sonicator). Aliquots of different concentrations were prepared by suitable dilution after sonication and filtering the stock solution and absorbance was measured 254 nm in UV-VIS spectrophotometer (Systronic PC Based Double Beam Spectrophotometer 2202). Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve[16].

***In vitro* Drug Release:**

The *in vitro* drug release studied of the Emulgel was carried out on Franz diffusion cell using egg membrane. Take a fresh egg and put into the concentrated HCL for 15 min. and then remove into the HCL and put into the fresh water for 5 min. and then remove the egg membrane. This egg membrane was clamped carefully between donor and receptor compartment. Emulgel (1 gm) was applied on to the surface of egg membrane. The receptor chamber was filled with freshly prepared Phosphate buffer solution (5.5) to solubilize the drug the drug. The receptor chamber was stirred by magnetic stirrer. 5 ml aliquots were withdraw at zero time, 30 min, 1hr, 2 hr, 4 hr, 6hr and 8 hr. The samples after filtrations were assayed spectrophotometrically at 254 nm. Each determination was carried out in triplicate. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time[17].

Result and Discussion:

Physical Appearance:

All the prepared formulation was evaluated for their colour, homogeneity and phase separation. The physical appearance of all the formulations was found to be creamy, homogenous without phase separation. The results for all batches are shown in Table2.

Table 2: Physical examination of Celecoxib Emulgel

Sr. No.	**Formulation code**	**Colour**	**Phase Separation**	**Homogeneity**
1.	F1	Creamy white	None	Homogeneous
2.	F2	Creamy white	None	Homogenous
3.	F3	Creamy white	None	Homogenous
4.	F4	Creamy white	None	Homogenous
5.	F5	Creamy white	None	Homogenous
6.	F6	Creamy white	None	Homogenous
7.	F7	Creamy white	None	Homogenous
8.	F8	Creamy white	None	Homogenous

pH Determination:

pH value of the Emulgel formulations were in range of 5.4-5.8, which lies in the normal pH range of the skin and would not produce any types of skin irritation. The pH values of all the formulations are shown in Table3.

Table 3: pH value of Emulgel Formulations

Sr. No.	Formulation code	pH Value
1.	F1	5.47 ± 0.04
2.	F2	5.42 ± 0.06
3.	F3	5.44 ± 0.03
4.	F4	5.52 ± 0.05
5.	F5	5.49 ± 0.08
6.	F6	5.53 ± 0.06
7.	F7	5.56 ± 0.07
8.	F8	5.63 ± 0.02

5.6.3 Spreadability Study:

Spreadability test was carried out for all the formulations and the results indicate that the Emulgel is easily spreadable from the tube by small amount of shear. Spreadability of F5 batch was found to be better as compared to the other batches. It was found 25.3g.cm/sec due to low level of light liquid paraffin. The values for all formulation are shown in Table4.

Table 4: Spreadability coefficient of Emulgel Formulations

Sr. No.	Formulation code	M (gm)	L (cm)	T (sec.)	S=M*L/T
1.	F1	15	7.1	5.2	19.7
2.	F2	15	7.1	11.2	22.4
3.	F3	15	7.1	15.4	20.5
4.	F4	15	7.1	3.2	17.3

5.	F5	15	7.1	18.5	25.3
6.	F6	15	7.1	6.8	23.5
7.	F7	15	7.1	12.1	15.8
8.	F8	15	7.1	4.1	19.95

Extrudability Study:

Extrudability study of all formulations was carried out and it was observed that all formulations were easily and uniformly extrudable from the collapsible tube. Extrudability of F5 was found to be good due to low concentration of emulsifying agent. The Extrudability values of different formulations are shown in Table5.

Table 5: Extrudability of Emulgel Formulations

Sr. No.	Formulation code	Wt Extruded from the tube (gm)
1.	F1	2.31 ± 0.11
2.	F2	2.48 ± 0.09
3.	F3	12.01 ± 0.12
4.	F4	7.21 ± 0.15
5.	F5	15.9 ± 0.08
6.	F6	11.9 ± 0.13
7.	F7	13.12 ± 0.07
8.	F8	2.70 ± 0.05

Rheological Study:

The rheological behaviour for all formulations was measured by using Digital viscometer (Labman DV-III viscometer). The highest viscosity was found in formulation F5 due to low level concentrations of Carbopol-934 and Light liquid paraffin concentration. The values of viscosities in all formulation are shown in Table6.

Table 6:Viscosities of Formulations

Sr. No.	Formulation code	Viscosity in Centipoise
1.	F1	3600
2.	F2	3650
3.	F3	4200
4.	F4	3900
5.	F5	4800
6.	F6	3200
7.	F7	4300
8.	F8	3550

Drug Content Determination:

The drug content was calculated to determine the quantity of drug present in formulation. The drug content in the prepared formulation was found in the range 80.5% to 94.7%. The higher drug content was found in F5 i.e. 94.7% and the lowest drug content in F8 i.e. 80.5%. The drug content data for all formulations is shown in Table7.

Table 7: Drug Content of Formulations

Sr. No.	Formulation code	Drug Content (%)
1.	F1	81.6 ± 1.53
2.	F2	83.3 ± 1.21
3.	F3	86.3 ± 1.45
4.	F4	85.8 ± 1.37
5.	F5	94.7 ± 1.89
6.	F6	84.5 ± 1.43
7.	F7	86.3 ± 1.51
8.	F8	80.5 ± 1.21

***In vitro* Drug Release Study:**

The *in vitro* drug release profiles of Celecoxib from its all the prepared formulation of Emulgel are shown in Figure. The release of the drug from all Emulgel formulations was observed and shown the following order: F5 > F7 > F3 > F4 > F6 > F2 > F1 > F8. The higher drug release was observed in formulation F5. This finding may be due to the presence of liquid paraffin in low concentration and emulsifying agent in higher concentration. The higher concentration of emulsifying agent increased the hydrophobicity of the Emulgel which facilitate the penetration of dissolution medium into the Emulgel and then increased the amount of drug release. The lower drug release was found in F8 due to the presence of higher

concentration of Carbopol-934 which leads to higher viscosity in the formulation. The *in vitro* release study data is shown in Table8 and Figure1.

Table 8: *In vitro* drug release study data of Emulgel formulation

Time/ Batch	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1/2 hr	10.75	11.47	10.33	11.79	13.96	9.31	8.21	9.29
1 hr	20.93	19.25	13.41	16.97	25.94	15.82	16.24	18.75
2 hr	34.25	35.61	22.61	32.13	41.13	35.45	37.49	36.57
4 hr	55.69	59.48	42.21	52.34	65.32	53.48	52.21	54.09
6 hr	69.65	70.98	62.67	65.96	82.89	69.67	71.67	68.08
8 hr	80.78	87.34	73.17	76.32	92.13	79.09	89.66	77.89

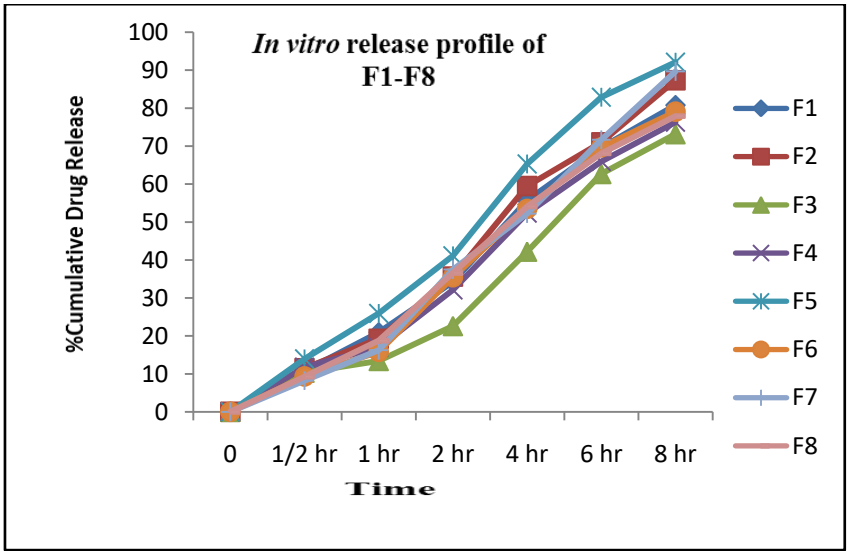

Figure 1: Drug release profile of Celecoxib Emulgel formulations

ANOVA on percentage cumulative drug release from various formulations

On the basis of cumulative drug release (%CDR) and all the evaluation parameters, batch F5 was selected as the optimized batch due to 80.13± 1.15% cumulative drug release.

ANOVA was applied on %CDR to study the fitting and significance of model. The model developed from multiple linear regression to estimate effect (Y) can be presented mathematically as:

Y = 82.90 + 0.3447A + 1.67B + 1.59C – 4.75AB +1.99AC+ 4.36 BC

Where, Y is % CDR, A is concentration of Carbapol-934,B is concentration of Liquid Paraffin and C is concentration Surfactant (Tween and Span).

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design

is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings.

The estimated model, therefore, may be used as response surface for the %CDR as shown by three-dimensional surface model graph and contour plots employing Design Expert software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN). The developed model can further be utilized to determine the desired %CDR. Figures 2 and Figure 3 display the 3D surface and contour plot of cumulative percent of drug release. The release profile of the optimized batch F5, fitted best to the Korsemeyer Peppas model (0.9685). Thus, it may be concluded that drug release from Celecoxib Emugel is best explained by the Korsemeyer Peppas model.

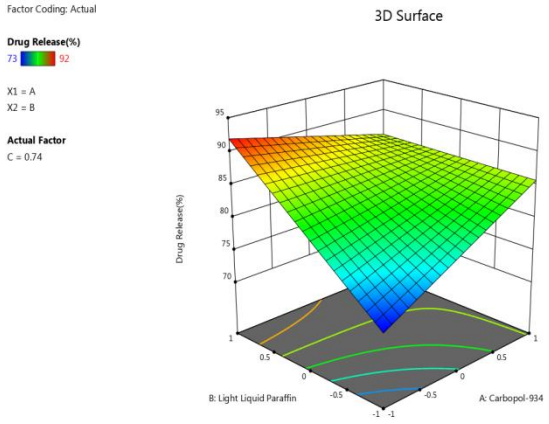

Figure 2: Three Dimensional (3D) Surface of % Cumulative Drug Release

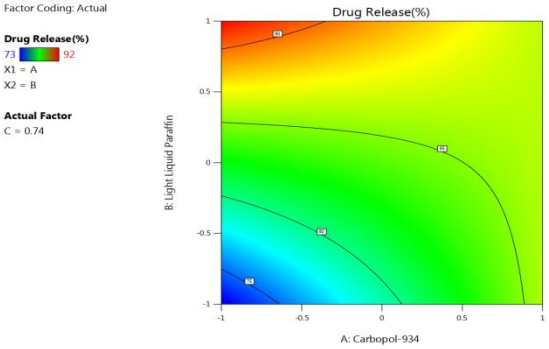

Figure 3: Contour Plot for % Cumulative Drug Release

The result showed that the in vitro drug release was found to be varying from 73% to 92%. The percent release was maximum at low value of Carbapol-934, low value of Liquid Paraffin and high value of Surfactant (Tween and Span).

Conclusion:

In this present research work all the formulations were selected using 2^3 factorial designs. The optimized batch (F5) was selected on the basis of spreadability, drug content and cumulative drug release.pH of all the formulation was in the range of pH of the skin i.e. 5.5. High drug content release and cumulative drug release was 94.7% and 92.13% respectively. On the basis of drug release kinetics the Emulgel formulation followedHiguchi model release kinetics.

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