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Research Article

Pharmaceutical analysis for Novel drug formulation

Formulation, Optimization and Characterization of Novel Modified Release Gel Formulation of Dexibuprofen Using Full Factorial Design

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Abstract: The aim of the study is to prepare Dexibuprofen modified release gel for topical delivery to provide the drug release in a modified manner, decreasing the oral side effects of the drug and improving the stability. Dexibuprofen, an anti-inflammatory drug, was used to design Novel Modified Release Gel Formulation to avoid its first pass effect as well as to increase its bioavailability with decline in dosing rate and to reduce its adverse effects. Skin is the largest, most extensive and accessible organ for topical administration of drug on human body, compared to other organs for drug delivery. Skin is most important route of topical drug delivery system. Topical application of dosage forms offers several advantages of delivering the drug directly to the site of action and acts for an extended period of time. In this study, Dexibuprofen gel was prepared by aqueous process. Drug-Excipient compatibility study was performed for the selected excipients. A sum of 6 batches (Batch No. from F001 to F006) were arranged by means of different polymers for prototype development and these are evaluated for various parameters. Batch No. F006 was found to have better quality characteristics hence composition of this batch was taken forward for optimization. Formulation was optimized using full factorial design. Four independent factors were optimised with varying levels of Chitosan, Sepineo P 600, Lactic acid and stirrer rpm. JMP Software has given 19 trials with 3 centre points and three responses owing to quality characteristics of gel formulations namely pH, viscosity and spreadability. An Interaction between Independent factors and responses were studied. The stability studies were carried out for prepared gel formulation as per ICH guidelines. The prepared Dexibuprofen gel was evaluated for various parameters and it shows good spreadability of B.No. F006 and it is concluded that the formulation could be very promising for the topical use to relieve pain and reduce the inflammation.

Key words: Dexibuprofen gel, modified release gel, viscosity, spreadability, pH, full factorial design.

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1. INTRODUCTION

The topical drug delivery methods are self-limited, distinct dosage forms which are usually applied on skin to distribute drug directly into systemic circulation without passing through gastrointestinal tract[1]. At present, most of the drugs are delivered orally, whereas this has the remarkable advantages of simple administration, it as well has some limitations like aqueous solubility of drug, first pass metabolism, gastric enzymes and pH variability in gastric environment[2-3]. It leads to poor bioavailability of drug molecules. To prevail over these complications, there is a need for the progress of new drug delivery method; which will advance the remedial effect of products. One of the most exploited parental approaches is topical drug delivery[4]. Topical drug delivery carries therapeutic material through the skin for general effect. The accomplishment of this release depends on the capability of the drug to infuse the skin in adequate quantities to attain its required therapeutic outcome[5]. The skin is very efficient as a selective diffusion barrier. Percutaneous absorption entails the channel of the drug fragment through the Stratum corneum under the control of a concentration gradient and its successive diffusion of the fundamental epidermis through the dermis and into the blood circulation[6]. The skin acts as an inert barrier to the penetrating molecule. In percutaneous absorption, the stratum corneum offers the peak resistance to diffusion and it is the rate-limiting step. Gels are clear to opaque semi solids that have a high ratio of solvent to gelling agent fuse or entrap to form a three-dimensional colloidal complex structure. This complex limits fluid flow by entrapment and immobilization of the solvent molecules. The complex structure is also accountable for a gel resistance to deformation and so, its visco-elastic properties. Gels tend to be soft, smart, non greasy and generate cooling effects and develop better drug delivery as distinguished to other semisolid formulation[5]. Gels have enhanced potential as a vehicle to administer drugs topically in association to ointment, since they are non-sticky and need low energy during the formulations are constant and have high aesthetic rate. Dexibuprofen is well known NSAID; it is a dextrorotatory enantiomer of ibuprofen. Dexibuprofen comprises of log P value of 3.97 and biological half-life of 1.8 - 3.5 h, it possesses appropriate physicochemical and pharmacokinetic properties making it prospective contender for topical drug delivery[8-9]. The purpose of this study is to expand modified release gel formulation of Dexibuprofen by means of full factorial design. Full factorial design generates experimental points by means of all the feasible mixture of the levels of the factors in every entire trial or replication of the experiments. The trial design points in a full factorial design are the vertices of a hypercube in the n-dimensional design space identified by the least and the highest values of all the factors[7]. This delivery method will liberate the drug in a controlled mode with competent permeation to attain essential anti-inflammatory activity and excluding adverse effects linked with gastrointestinal tract [10-11].

2. MATERIALS AND METHODS

2.1 Materials

Dexibuprofen was received as gift sample from Solara Active Pharma, Sciences Limited, India, Chitosan (Chitopharm™ M) was purchased from Chitinor AS - A Company in the Sea garden Group, Kolliphor RH 40 was purchased from BASF Chemicals, Sepineo P 600 (Acrylamide/Sodium Acryloyldimethyltaurate Copolymer/Is hexadecane &Polysorbate 80) was purchased from Seppic Inc., All other reagents utilized were of analytical category

2.2 Methods

2.2.1 Drug-Excipient Physical compatibility study[12]

The drug and excipients interactions were studied for physical compatibility. Binary mixtures of drug and excipients (1:1) were taken in glass vials with punctured LDPE plugs and kept in accelerated and real time stability conditions for 1 month. Physical descriptions were observed for initial and 1 month samples. Excipient screening was done based on outcome of compatibility study.

2.2.2 Preparation of samples

The mixtures of Dexibuprofen with selected excipients were prepared in 1:1 w/w ratio by the easy incorporation of the components in a mortar with pestle at room temperature for 10 min. The drug and polymers were individually weighed in glass vials, each vial was sealed with Teflon-lined screw cap and the mixture of drug and polymers were stored in two different conditions at 25°C±2/60%±5 RH and 40°C±2/75%±5 RH for one month[13-14]. Dexibuprofen was kept alone and also kept with other excipients like Chitosan, Benzoic acid, Carbopol 971 P, Menthol, Transcutol, Triethanolamine, Chlorocresol, Sepineo P 600, Lactic acid, Kolliphor 40 & Propylene glycol.

2.2.3 Prototype development of Dexibuprofen gel

Dexibuprofen gel was formulated with aqueous base system by using different excipients. Different excipients were finalized based on compatibility studies. Chitosan and Carbopol 971 P were used as a release controlling polymer[15], Propylene glycol,Triethanolamine, Transcutol P, PEG-400 and Kolliphor RH 40 were used as mild permeability enhancers. Sepineo P 600 is a three in one polymer mainly used for thickening, emulsifying and stabilizing of gel formulation, Benzoic acid and Chlorocresol were used as preservatives. Different compositions are provided in table-01.

Table - 01.Prototype development and screening of excipient trials

Batch No.	F001	F002	F003	F004	F005	F006
Batch Size (kg)	1.00	1.00	1.00	1.00	1.00	1.00
Ingredients	Gram					
Dexibuprofen	103.14	103.14	103.14	103.14	103.14	103.14
Chitosan	-	-	-	-	-	1.00
Benzoic acid	-	2.00	2.00	-	2.00	-

Carbopol 971 P	25.00	-	-	25.00	25.00	-
Chlorocresol	1.00	-	-	1.00	-	1.00
Menthol	0.50	0.50	0.50	0.50	0.50	-
Sepineo P 600	-	30.00	40.00	-	-	40.00
Lactic acid	-	-	-	-	-	0.50
Polyethylene Glycol 400	10.00	10.00	10.00	20.00	20.00	-
Kolliphor 40	-	-	-	-	-	10.00
Propylene glycol	10.00	10.00	10.00	10.00	10.00	120.00
Transcutol HP	35.00	35.00	35.00	35.00	35.00	-
Triethanolamine	72.00	-	-	72.00	72.00	-
Purified water	743.36	809.36	799.36	733.36	732.36	724.36
Total	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**

2.2.4 Process flow

Dexibuprofen gel was manufactured by aqueous process[16-17]. Sequence of addition also played an important role in gel formulation, however it was finalized based on trial and error method hence it was not kept in the part of optimization. Finalized process scheme is provided in Figure - 01.

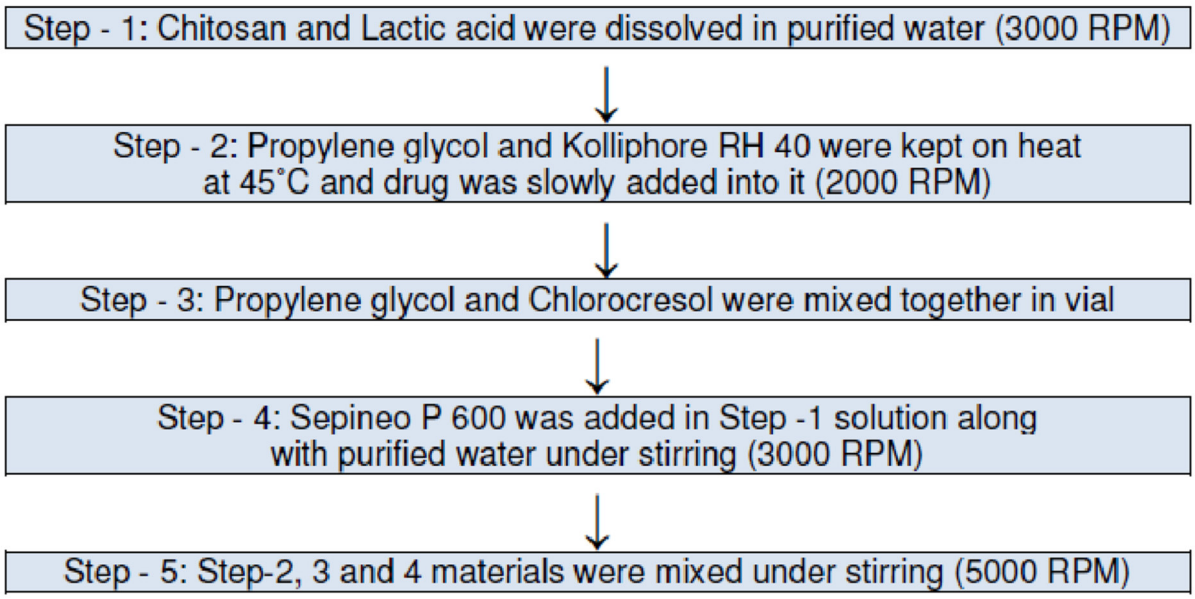

Figure - 01.Manufacturing process flowchart

2.2.5 Optimization

Dexibuprofen gel formulation was optimized using the Design of Experiment (DoE) approach. Full factorial design was employed for optimization using JMP software. Major critical quality attributes were identified. Three material attributes and three process parameters were selected based on prior knowledge and literature support. Factors and their defined levels are provided in Fig 02 and table-02 respectively. Software has given 19 trials with three centre points[18]. Trials are mentioned in table-03. Three responses like pH, viscosity and spreadability were measured during optimization trials to ensure desired quality characteristics of prepared gel formulation[19].

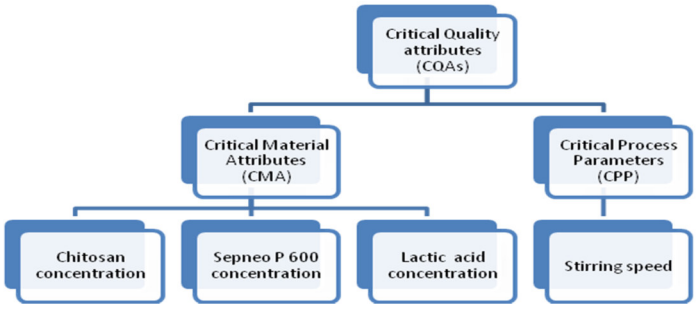

Figure 02.CMA and CPP impacts on CQAs

Table - 02. Independent factors and their levels				
S.No.	Factor	Independent factors	Level (-)	Level (+)
1	X1	Chitosan Concentration. (% w/w)	0.05	0.150
2	X2	Sepineo P 600 (% w/w)	2.0	6.0
3	X3	Lactic acid (% w/w)	0.025	0.075
4	X4	Stirrer speed (RPM)	3000	7000

Table - 03.DoE trials for optimization using full factorial design				
	Factor 1	Factor 2	Factor 3	Factor 4
	X1	X2	X3	X4
Run	A: Chitosan concentration	B: Sepineo P 600 concentration	C: Lactic acid concentration	D: Stirrer speed
	% w/w	% w/w	% w/w	RPM
1	0.15	6	0.075	7000
2	0.15	6	0.075	3000
3	0.15	6	0.025	7000
4	0.15	6	0.025	3000
5	0.15	2	0.075	7000
6	0.15	2	0.075	3000
7	0.15	2	0.025	7000
8	0.15	2	0.025	3000
9	0.05	6	0.075	7000
10	0.05	6	0.075	3000
11	0.05	6	0.025	7000
12	0.05	6	0.025	3000
13	0.05	2	0.075	7000
14	0.05	2	0.075	3000
15	0.05	2	0.025	7000
16	0.05	2	0.025	3000
17	0.1	4	0.05	5000
18	0.1	4	0.05	5000
19	0.1	4	0.05	5000

2.2.6 Characterization

2.2.6.1 Visual Inspection/Description

The formulated gels were examined for their colour, consistency, homogeneity, texture (lumps) by checking visually under a fluorescent tungsten light, viewed alongside a white and black background. This was done for six times and average values were calculated.

2.2.6.2 pH

For determination of pH, 1.0gram of gel was dispersed in distilled water (100 ml) then pH was calculated by using a digital pH meter. (pHMeter-Toledo GmbH, Switzerland). This was done for six times and average values were calculated [20-21].

2.2.6.3 Specific gravity:

The blank weight of the pycnometer was initially attained and then was tarred on an analytical weighing balance. Gel (20 gm) was placed in a pycnometer and was weighed. This was repeated with an equivalent amount of distilled water. All measurements were made at room temperature. This was repeated for 6 times and mean calculated.[22]

2.2.6.4 Viscosity

The viscosity of prepared gel formulation was measured by a Brookfield Viscometer. The gels were rotated using spindle no.4 at 10 rpm. At every speed, the subsequent dial reading was noted. This was done for six times and average values were calculated[23].

2.2.6.5 Spread ability

1 g of gel was packed in between 2 horizontal glass plates (20 X 20 cm^2) for 1 minute. The upper plate was then separated

and the diameter of the gel sticking on to it was calculated. The identical weight (125 gm) tied on the upper plate. This was done for six times and average values were calculated[24]. Spreadability was then calculated by using the formula:

$S = d \times \pi/4$

Where, S = Spread ability, d = diameter of gel, π = 3.14

2.2.6.6 Stability Evaluation

The drug product was packed in aluminium collapsible tube and laminated tubes; stability evaluated for 6 months at 40°C / 75% RH and for 6 months at 25°C / 60%RH. The product was tested for Description, pH, specific gravity and Assay of Dexibuprofen. The data is presented in Table. 12. The results revealed that the product was found to be stable.

3. STATISTICAL ANALYSIS

The data obtained for Full factorial design was employed for optimization by using JMP software. (Version 15.2.1). The data were presented for the Effect of independent factors on pH, viscosity and spreadability. Probability value of less than 0.05 was considered statistically significant.

4. RESULTS AND DISCUSSION

4.1 Drug-Excipient compatibility study

Estimation of drug–excipient interactions is an important step in pre formulation studies of formulation development to achieve consistent stability, bioavailability and manufacturability of all dosage forms[25]. It is already known that active drugs in the topical dosage form accounts only for a minor fraction in the formulation; therefore, it is important to understand how the excipients within the formulation interact with the active drug and influence the site of action and permeation[26]. Physical description was observed during compatibility study. All excipients were found to be physically compatible with Dexibuprofen at both accelerated and real time stability conditions for 1 month. Hence these excipients are taken forward for prototype development. Physical description data is provided in Table-04.

Table -04.Physical description data of compatibility study

Drug and Excipient compatibility	Initial	40°C/75% RH 1 month	25°C/60% RH 1 month	Inference
Dexibuprofen	White crystalline powder	No Change	No Change	Compatible
Dexibuprofen + Chitosan	White to off white powder	No Change	No Change	Compatible
Dexibuprofen + Benzoic acid	White to off white powder	No Change	No Change	Compatible
Dexibuprofen + Carbopol 971 P	White to off white powder	No Change	No Change	Compatible
Dexibuprofen + Menthol	White to off white crystalline powder	No Change	No Change	Compatible
Dexibuprofen + Transcutol	White to off white semi solid mass	No Change	No Change	Compatible
Dexibuprofen + Triethanolamine	White to off white semi solid mass	No Change	No Change	Compatible
Dexibuprofen + Chlorocresol	White to off white powder	No Change	No Change	Compatible
Dexibuprofen + Sepineo P 600	White to off white semi solid mass	No Change	No Change	Compatible
Dexibuprofen + Lactic acid	White to off white semi solid mass	No Change	No Change	Compatible
Dexibuprofen + Kolliphor 40	White to off white powder	No Change	No Change	Compatible
Dexibuprofen + Propylene glycol	White to off white semi solid mass	No Change	No Change	Compatible

4.2 Prototype development

Prototype development was finalized based on quality characteristics of gel products. It includes pH, viscosity and Spreadability. Six batches have been executed and data is provided in table-05. F006 batch was found to have better viscosity and spreadability; it helps to increase intimate contact time with skin[27]. It also shows acidic pH due to presence of lactic acid in composition which helps in permeation of drug through skin, hence F006 batch composition was taken forward for optimization.

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Table - 05.Evaluation data of prototype development trials

Batch No. 4						
Evaluation parameters	**F001**	**F002**	**F003**	**F004**	**F005**	**F006**
Viscosity (cps)	28360.41	31029.1	33142.8	28176	26793.1	35467.1
Spreadability (mm)	1.97	2.12	2.07	1.86	1.92	2.13
pH	5.7	4.97	4.7	5.31	5.92	3.79

Optimization trials have been executed and responses were measured. Results are provided in table- 06.

Table - 06.Optimization trials data

	Factor				Response		
	1	2	3	4	1	2	3

Run	A:Chitosan concentration	B:Sepineo P 600 concentration	C:Lactic acid concentration	D:Stirrer speed	pH	Viscosity	Spread ability
	% w/w	% w/w	% w/w	RPM	-	cps	mm
1	0.15	6	0.075	7000	3.48	37743.9	2.09
2	0.15	6	0.075	3000	3.52	35263.9	2.13
3	0.15	6	0.025	7000	3.18	35994	2.18
4	0.15	6	0.025	3000	3.2	34857.2	2.15
5	0.15	2	0.075	7000	3.39	28653.5	2.31
6	0.15	2	0.075	3000	3.61	27564.8	2.37
7	0.15	2	0.025	7000	3.83	28564.2	2.31
8	0.15	2	0.025	3000	3.49	29347.7	2.27
9	0.05	6	0.075	7000	3.51	36197.6	2.12
10	0.05	6	0.075	3000	3.57	37039.7	2.14
11	0.05	6	0.025	7000	3.73	36542.4	2.07
12	0.05	6	0.025	3000	3.84	34985.3	2.15
13	0.05	2	0.075	7000	3.29	29558.3	2.26
14	0.05	2	0.075	3000	3.36	28292.6	2.21
15	0.05	2	0.025	7000	3.68	29995.4	2.34
16	0.05	2	0.025	3000	3.37	30482.8	2.19
17	0.1	4	0.05	5000	3.75	34467.1	2.13
18	0.1	4	0.05	5000	3.77	34543.8	2.15
19	0.1	4	0.05	5000	3.75	34390.3	2.11

Table - 07 Analysis of Variance

Source	Degree of Freedom	Sum of Squares	Mean Square	F Ratio
Model	15	0.61274375	0.040850	0.7959
Error	3	0.15397204	0.051324	**Prob> F**
Total	18	0.76671579	-	0.6753

Effect of independent factors on pH:

Table - 08 Parameter Estimates		
Term	**Estimate**	**Prob>|t|**
Intercept	3.6755428	0.0007*
A:Chitosan concentration	-0.8125	0.5250
B:Sepineo P 600 concentration	0.0003125	0.9919
C:Lactic acid concentration	-1.475	0.5614
D:Stirrer speed	4.0625e-6	0.8950
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)	-1.18125	0.1283
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)	59.5	0.2805
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)	1.0625	0.4174
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)	25.75	0.3383
(A:Chitosan concentration-0.1)*(D:Stirrer speed-5000)	-6.25e-6	0.9919
(B:Sepineo P 600 concentration-4)*(D:Stirrer speed-5000)	-9.219e-6	0.5614
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (D:Stirrer speed-5000)	7.1875e-5	0.8160
(C:Lactic acid concentration-0.05)*(D:Stirrer	-0.001138	0.3893

speed-5000)		
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)* (D:Stirrer speed-5000)	-0.00625	0.8006
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)* (D:Stirrer speed-5000)	0.0006063	0.3629
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)*(D:Stirrer speed-5000)	0.001375	0.9111

Effect of independent factors on viscosity:

Table - 09 Parameter Estimates		
Term	**Estimate**	**Prob>|t|**
Intercept	25695.832	0.0009*
A:Chitosan concentration	-6381.125	0.5171
B:Sepineo P 600 concentration	1755.1469	0.0040*
C:Lactic acid concentration	-1136.75	0.9521
D:Stirrer speed	0.1692281	0.4939
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)	2058.0625	0.6689
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)	69035	0.8557
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)	10233.875	0.3250
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)	-12167.5	0.9487
(A:Chitosan concentration-0.1)*(D:Stirrer speed-5000)	1.5179375	0.7506
(B:Sepineo P 600 concentration-4)*(D:Stirrer speed-5000)	0.0507547	0.6730
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (D:Stirrer speed-5000)	1.0546563	0.6615
(C:Lactic acid concentration-0.05)*(D:Stirrer speed-5000)	3.211625	0.7370
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)* (D:Stirrer speed-5000)	96.5375	0.6183
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)* (D:Stirrer speed-5000)	-2.925812	0.5500
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)*(D:Stirrer speed-5000)	45.29125	0.6392

Effect of independent factors on Spreadability:

Table - 10 Parameter Estimates		
Term	**Estimate**	**Prob>|t|**
Intercept	2.2989967	<.0001*
A:Chitosan concentration	0.4125	0.3200
B:Sepineo P 600 concentration	-0.038438	0.0214*
C:Lactic acid concentration	-0.075	0.9208
D:Stirrer speed	2.1875e-6	0.8172
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)	-0.11875	0.5428
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)	0.5	0.9735
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)	-0.1375	0.7184
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)	-7.75	0.3455
(A:Chitosan concentration-0.1)*(D:Stirrer speed-5000)	-8.125e-5	0.6715
(B:Sepineo P 600 concentration-4)*(D:Stirrer speed-5000)	-4.531e-6	0.3729
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (D:Stirrer speed-5000)	9.6875e-5	0.3455
(C:Lactic acid concentration-0.05)*(D:Stirrer speed-5000)	-0.000263	0.5043
(A:Chitosan concentration-0.1)*(C:Lactic acid concentration-0.05)*	-0.00325	0.6715

(D:Stirrer speed-5000)		
(B:Sepineo P 600 concentration-4)*(C:Lactic acid concentration-0.05)* (D:Stirrer speed-5000)	0.0001188	0.5428
(A:Chitosan concentration-0.1)*(B:Sepineo P 600 concentration-4)* (C:Lactic acid concentration-0.05)*(D:Stirrer speed-5000)	-0.001625	0.6715

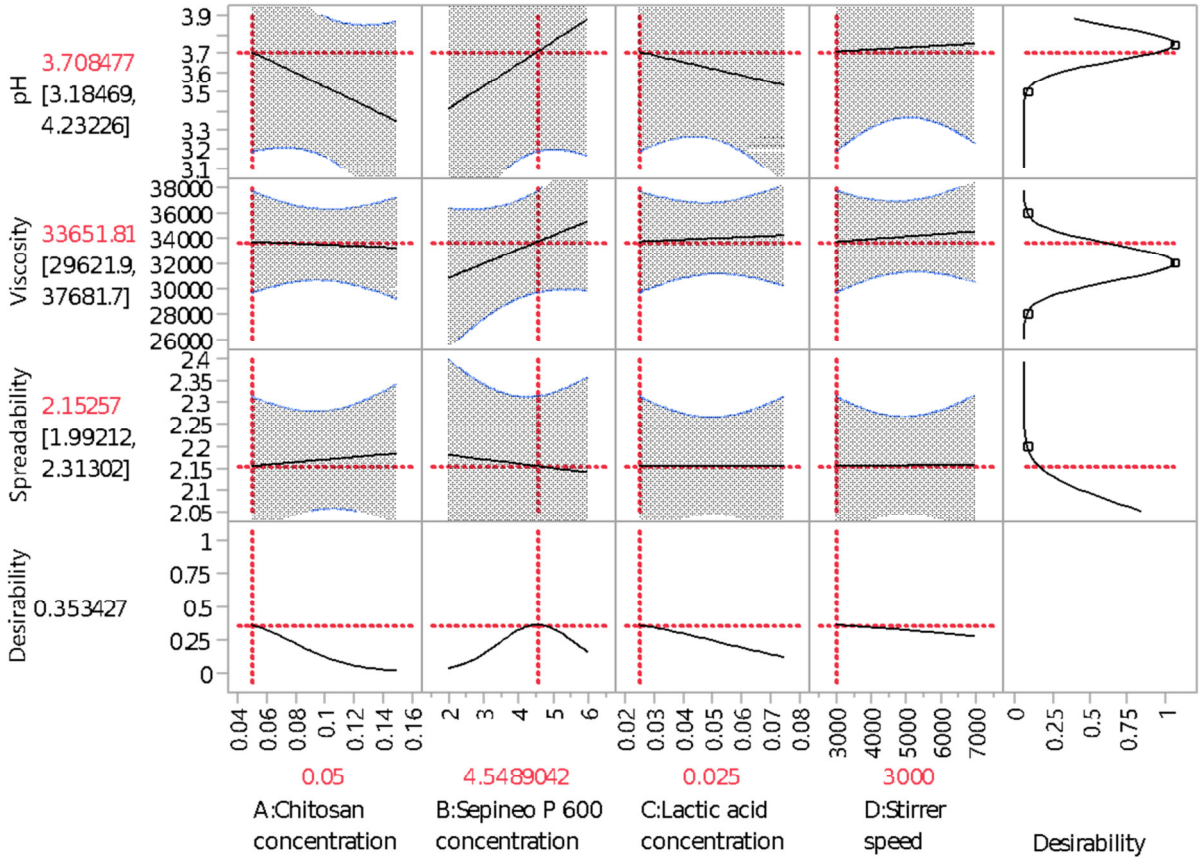

Figure - 03 Prediction Profiler

Horiz	Vert	Factor	Current X
◉	○	A:Chitosan concentration	0.05
○	◉	B:Sepineo P 600 concentration	4.549
○	○	C:Lactic acid concentration	0.025
○	○	D:Stirrer speed	3000

Response	Contour	Current Y	Lo Limit	Hi Limit
pH	3.5	3.7084878	3.5	4
Viscosity	32000	33651.922	28000	36000
Spreadability	2.225	2.1525692	1.8	2.2

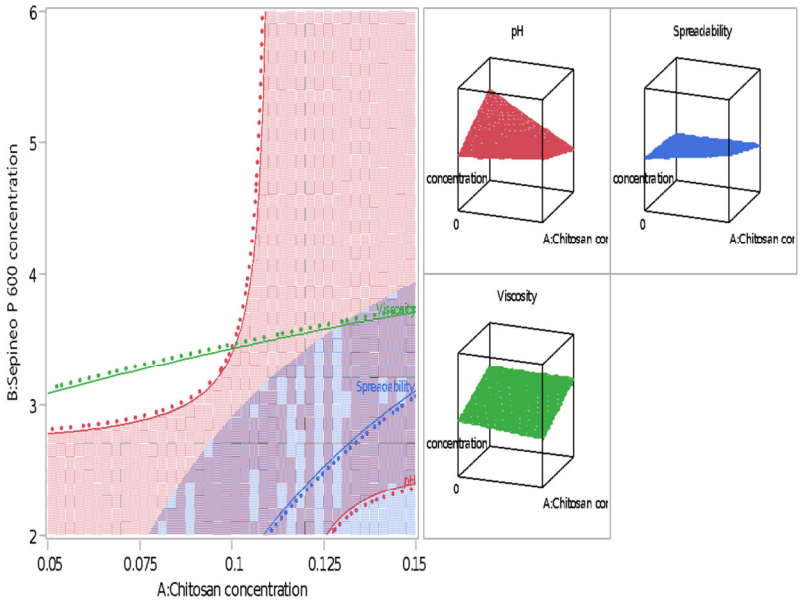

Fig - 04 Contour Profiler

Table - 11 Parameter Estimates

Response		pH	Viscosity (cps)	Spreadability (mm)
Target		3.5 - 4.0	28000 - 36000	1.8 - 2.2
Factors	A:Chitosan concentration (%w/w)	B:Sepineo P 600 concentration (%w/w)	C:Lactic acid concentration (%w/w)	D:Stirrer speed RPM
Optimum value	0.05	4.549	0.025	3000

4.3 *Design Of Experiments* (DoE):

DoE is a structured and organized method for determining the relationships between input factors (independent variables) affecting one or more output responses (dependent variables), through the establishment of mathematical models. In DoE approach, the controlled input factors are systematically varied to determine their effects on the output responses, which allows the determination of the most important input factors, the identification of input factors setting leading to optimized output responses, and the elucidation of interactions between input factors[28].

4.4 *Effect of independent factors on pH*

Inference

Regression model is insignificant for pH. No factor is significant for pH.

4.5 *Effect of independent factors on viscosity*

Inference

Regression model is insignificant for viscosity. Sepineo P 600 concentration is significant for viscosity with p value of 0.004 (p value < 0.05) on increasing Sepineo P 600 concentration viscosity increases.

4.6 *Effect of independent factors on spread ability*

Inference

Regression model is insignificant for Spreadability. Sepineo P 600 concentration is significant for viscosity with p value of 0.0214 (p value < 0.05). On increasing Sepineo P 600 concentration Spreadability decreases.

4.7 *Inference on prediction profiler and contour profiler:*

Based on the contemporary data , a representation is generated by using a prediction profiler, which is available with standard statistical software. The prediction profiler and contour profiler values (Table No. 11) proposed as optimum values to achieve target and to achieve desired quality characteristics of gel formulation.

4.8 *Stability Summary*[29]*:*

Accelerated stability studies and long term stability studies were performed on final formulation (B.No. F006) for a period of 6 months for prepared topical gel. For tests like Description, pH, Specific gravity and Assay of Dexibuprofen in pack type like Lamitubes and Aluminium collapsible tubes and the results were shown in table- 12.

Table - 12 Stability Summary					
Pack type	**Lamitubes**				
Test	**40˚C/75%RH**		**25˚C/60%RH**		**Specification**
	3 months	**6 months**	**3 months**	**6 months**	
Description	White homogenous viscous gel	White homogenous viscous gel	White homogenous viscous gel	White homogenous viscous gel	White to off white homogenous viscous gel
pH	3.8	3.9	3.85	3.88	3.5 - 4.5
Specific gravity	0.95	0.97	0.96	0.95	0.9 - 1.0
Assay of Dexibuprofen	98.2	98.0	99.5	98.8	90.0 - 110.0 % w/w
Pack type	**Aluminium collapsible tubes**				
Test	**40˚C/75%RH**		**25˚C/60%RH**		**Specification**
	3 months	**6 months**	**3 months**	**6 months**	
Description	White homogenous viscous gel	White homogenous viscous gel	White homogenous viscous gel	White homogenous viscous gel	White to off white homogenous viscous gel
pH	3.72	3.80	3.82	3.89	3.5 - 4.5
Specific gravity	0.96	0.98	0.96	0.96	0.9 - 1.0
Assay of Dexibuprofen	97.0	96.2	99.0	98.6	90.0 - 110.0 % w/w

Inference:

The selection and closures are very important and the above stability summary shows the drug product packed in laminated tubes data shows satisfactory results as compared to Aluminium collapsible tubes. It indicates the laminated tubes are more compatible for prepared Dexibuprofen gel of primary containers.

5. DISCUSSION

Formulation of a topical drug product with desirable CQA is challenging. Several factors such as physicochemical properties of the drug, formulation parameters, excipients in the formulation, and other parameters can affect the formulation stability. For successful topical product development, a thorough understanding of the impact of these factors on product performance is required. This study gives an example of a screening study approach that evaluates several excipients and formulation variables on product performance. It has been already known that the active drug which is Dexibuprofen accounts only for a considerable fraction in the dosage form and; therefore, it is necessary to recognize how the non active excipients within the formulation interact with the active drug and influence the drug release of topical dosage form. NSAID is required for Anti-inflammatory actions, Modified release Dexibuprofen was not found very much in the market to an extent. Inorder to increase the therapeutic cycle and quality of the several round was made to formulate topical preparations for adherence. Inorder to maintain the quality aspect we have considered multiple variable as specifications like viscosity, spreadability, pH. The excipient used in these standardised formulations and multiple literature is found in academic circles. From the Design of experiments we can conclude that the optimisation of formulation (figure No. 4) which shows an influence of used excipients like Chitosan concentration, Sepineo concentration, Lactic acid concentration and stirrer speed influences the viscosity; which further influences the drug release in the formulation. The topical administration of the drug provides the targeted therapy, and the active substance penetrates into the site of action and might be used by the patients which do not tolerate the nonsteroidal anti-inflammatory drugs orally. Dexibuprofen, a NSAID has been reported to possess several biological activities such as anti-inflammatory, reported that the reservoir-type transdermal patch exhibiting controlled zero-order rate of release with suitable permeation rate was prepared. The findings of in vitro studies suggest effective delivery of dexibuprofen across skin[30]. Gels were prepared by dispersing the polymers in a mixture of water and glycerol with methyl paraben as the preservative and the varying amount of ibuprofen, being kept under magnetic stirring until the homogeneous dispersion was formed. The dispersion was then neutralized and made viscous by the addition of triethanolamine. The Carbopol gels of Ibuprofen were found to be homogenous with good drug loading. Prepared formulation has better diffusion of drug through egg membrane[31]. The study investigated usage of hydrogel of an anionic polymer xanthan gum for design of ibuprofen-loaded hydrogel-thickened microemulsions (HTMs) from the nonionic oil-in-water microemulsion (M). The HTM with optimized drug release rate and spreadability (HTM1) and the polymer-free microemulsion (M) were assessed and compared with the referent hydrogel in *in vivo* studies in rats. HTM1 and M were significantly more efficacious than reference hydrogel in producing anti hyperalgesic and at lower extent anti edematous activity in prophylactic topical treatment[32].The flux of drug is independent on the viscosity of the formulae. The anti-inflammatory activity of the drug in different gel formulations was studied using carrageenan-induced rat paw edema method. The results obtained show that there is excellent anti-inflammatory activity of the gel forms on rat paw edema[33]. This study provides evidence that an anti-inflammatory reagent can be used topically to suppress pain due to IVFI and/or DRG inflammation through inhibition of

sensory neuron hyper excitability and the immune and inflammatory responses[34]. The use of the topical nonsteroidal anti-inflammatory drugs (NSAID) ibuprofen for the treatment of knee osteoarthritis. Supporting clinician decision-making in the first-line treatment of osteoarthritis. Topical NSAIDs provide good levels of pain relief in subjects with mild to moderate knee osteoarthritis. There is also evidence for the use of the topical application being a clinically effective, safe, and cost-efficient treatment.[35] Topical NSAIDs may be the preferred treatment option, especially in OA patients aged ≥75 years, and those with co-morbidities or at an increased risk of cardiovascular, gastrointestinal, or renal side effects. Furthermore, using topical NSAIDs in inflammatory rheumatic diseases leads to a 40% reduction in the need for concomitant oral NSAIDs. When selecting a topical NSAID, absorption and bioavailability are important because of heterogeneity among topical drug formulations[36]. Current evidence indicates that topical NSAIDs and capsaicin in licensed doses may be equally effective for pain relief in OA. Whether the equivalence varies between individuals remains unknown[37]. The dermato pharmacokinetic approach, using SC tape-stripping, offers a valid method to assess equivalency between topical drug formulations. *In vitro* experiments must be extrapolated cautiously to the clinic, especially when complex interactions between real formulations, which deliver both drug and excipients, and the skin occur[38]. The stratum corneum (SC) uptake and skin penetration of ibuprofen *in vitro* from the novel gels and the marketed formulations were generally comparable even though the drug loading in the TOCN-based vehicles was only 20% of that in the 'reference' products. *In vivo*, the new gels appeared to enhance drug uptake into the SC following a relatively short application time, again matching the performance of the commercial formulations[39].

6. CONCLUSION

The research methodology of the study was to make a Formulation, Optimization and Characterization of Modified Release Gel of Dexibuprofen using Full Factorial design Dexibuprofen gel is prepared by aqueous method. Drug-Excipient physical compatibility study was performed to screen the excipients for gel formulation and it was observed that Dexibuprofen was found to be physically compatible with all commonly used excipients of gel formulations. Prototype development was done by trial and error method. Six formulations were prepared and evaluated for pH, viscosity and spreadability; B.No. F006 was found to better quality characteristics of gel formulation. For this reason composition of B.No. F006 was taken forward for optimization. Optimization was performed using DoE approach and full factorial design was employed, four independent factors were taken during optimization. Chitosan concentration, lactic acid concentration, Sepineo P600 concentration and stirrer speed were selected in software and full factorial design was run; 19 trials were showed by software design with 3 centre point; these trials were executed in lab and their responses; pH, viscosity and spreadability were measured. Interactions between independent factors and responses were studied and desired ranges of responses were entered in software to meet quality characteristics of gel formulation. The progress of drug delivery methods and novel formulations would be efficient and hopeful advances for escalating the remedial index and dropping side effects. Though, it would not be ignored to balance the drug capability and functional design, as the clinical relevance would be the ultimate hub. It is essential to reinforce the research and progress of novel technologies and drug delivery methods within the pharmaceutical trade. Definitely, a new scientific design becomes a pioneering technology to be applied in drug delivery method, entailing long-term testing assessment, modification and optimization.

7. AUTHOR CONTRIBUTION STATEMENT

K.K. Janakiraman designed and performed the experimental section whereas Janakiraman Kunchithapatham assisted and supervised during the project. K.K. Janakiraman wrote a manuscript with support from R. Paramaguru.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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