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Advances in Bioresearch

ORIGINAL ARTICLE

Evaluation of Anti- Inflammatory and Analgesic Activity of Diclofenac Sodium Bigel

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ABSTRACT
The research is in concern with the formulation and evaluation of transdermal bigel of Diclofenac sodium for anti-inflammatory activity. This bigel is formulated to escape first pass effect, dosing frequency and improve bioavailability of drug. Pre- formulation studies of diclofenac sodium were done and from FTIR studies it is proved that there is no interaction between drug and polymers. DSC thermogram of diclofenac sodium shows the melting point of the drug which is according to British pharmacopoeia. Absorption maxima of Diclofenac sodium was found at 276 nm by using U.v spectroscopy. Total eight formulations were developed by varying the polymer concentration of carbopol 934, HPMC K100 and span 60. Linseed oil used as organogelator. These bigels were evaluated for appearance, homogeneity, spreadability, extrudabiity, surface PH, viscosity measurement, drug content, In-vitro diffusion studies and ex-vivo permeation studies. Animal study is also carried out for evaluating anti-inflammatory activity of optimized bigel (DL8) as compare to marketed formulation. The optimized DL8 bigel shows desirable In-vitro drug release ie. 99.14%. Ex-vivo permeation studies of DL8 formulation was done, which shows 98.6% drug permeation using rat's abdominal skin. Anti-inflammatory studies were also carried out using albino wistar rats. Encorporation of vasodilators and vasoconstrictors to the formulation was done to increase the activity and efficacy of optimized bigel. The bigel with vasodilator increases the activity of the formulation as compare to bigel with vasoconstrictor. Vasodilators dilate or prevent constriction of blood vessels, which allow greater blood flow and increases drug release of the bigel. Treatment of the rat's paw with the optimized DL8 bigel with vasodilator and vasoconstrictor after inducing inflammation using 1 % carrageenan. The results show significant reduction in the paw volume was achieved by application of DL8 bigel with vasodilator. This bigel can also be used in the management of arthritis.
KEYWORDS: Bigel, mucoadhesion, organogel, apodization, vasodilator, spectrophotometrically.

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INTRODUCTION

For local and systemic effect of drug transdermal drug delivery is promising system which is available. The drug has to pass through stratum corneum, intercellular, transcellular and may be appendageal route. For permeation through the skin mostly drug follow intercellular pathway. Bigels are systems that generally result from mixing a hydrogel and an organogel: the aqueous phase is usually formed by a hydrophilic biopolymer, however the organic phase consists of a gelled vegetable oil because of the presence of an organogelator. The amount of the corresponding gelling agent in each phase, the organogel/ hydrogel ratio, and the mixing temperature and speed all need to be taken into consideration for bigel manufacturing. Bigels, which are principally useful drug delivery systems, which have been formulated for transdermal, buccal, and vaginal routes. The bigel composition and distinctive structure confer promising drug delivery attributes, such as mucoadhesion, the ability to control release of drug, and the possibility of including both hydrophilic and lipophilic drugs in the same system. The prepared bigel of Diclofenac sodium has been used for its anti-inflammatory and analgesic effect and it may also be used for its anti- arthritic activity. GIT related problems like irritation and ulceration caused by Oral route. This Diclofenac sodium bigel gives enhanced anti-inflammatory and analgesic effect. The study is

conducted to formulate and evaluate bigel of Diclofenac sodium which provides Prolonged drug release, increase residence time of drug on skin which ultimately increases bioavailability of drug.

MATERIAL AND METHODS

Diclofenac sodium was gifted with a warm hearted from Ajanta pharma limited, Mumbai, India. Carbopol 934, HPMC K100 tri-ethanolamine and menthol was purchased from Swaroop pharmaceutical pvt. Limited, Aurangabad, India. Linseed oil was purchased from local market, Aurangabad, India. All the reagents and chemicals was used are of analytical grade.

Pre- formulation studies

Characterization of Diclofenac sodium:

Appearance

The sample of Diclofenac sodium was tested for its colour, odour and taste.

Melting point

The melting point of the drug sample (Diclofenac sodium) was determined by using thiele's tube apparatus.

Drug-Excipient compatibility studies

The drug polymer and polymer-polymer interaction were studied by the FTIR spectrometer using Shimadzu 8400-S, Japan. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was grind into a fine powder using an agate mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 1000psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm-1 using cosine apodization. The characteristic peaks were recorded.

The FTIR spectrum of pure Diclofenac sodium and excipient mixture + diclofenac sodium is shown in a figure no.3, 4.

Differential scanning colorimetery of Diclofenac sodium

The thermogram of diclofenac sodium is shown in figure no. (6). DSC studies depict a sharp endothermic peak at 282 °C which corresponds to melting point of the drug sample which matches with the melting point of diclofenac sodium that indicates purity of drug sample (Diclofenac sodium).

UV Spectroscopy

Different concentrations of drug (Diclofenac sodium) solutions were prepared and they were diluted with suitable solvent and scanned under U.V spectrophotometer. Maximum absorption of the solution was found at 276 nm. So, 276 nm was considered as λmax of Diclofenac sodium. The calibration curve and absorption maxima is given in a figure no.1 & 2.

Method

Formulation of Diclofenac sodium bigel

Bigel is formulated by addition of hydrogel in oleogel. For the preparation of oleogel weighed amount of carbopol 934 is dissolved in sufficient quantity of water and kept it on a magnetic stirrer at 500 rpm for about 1 hour. After complete dispersion of polymer solution, tri-ethanolamine is added to this solution to form a transparent gel. In another beaker weighed quantity of span 60 is taken and heated on a water bath. When span 60 is completely dissolved then required amount of linseed oil was added and dissolved it completely, to this above gel was added by continuous stirring on a water bath to form oleogel.

For the hydrogel preparation weighed quantity of HPMC K100 was taken and dissolved it in a sufficient quantity of water and kept it on a magnetic stirrer at 500 rpm for about 1 hour. Into the required amount of ethanol Diclofenac sodium and minoxidil (vasodilator) was dissolved, menthol is also added to this and mixed it with the polymer solution to form a hydrogel. The formed hydrogel was added to the oleogel by continuous stirring under mechanical stirrer at 1000 rpm to form a bigel. Different batches DL1, DL2, DL3, DL4, DL5, DL6, DL7, DL8 was prepared with variation in quantities of polymers. As shown in table no. (1).

Evaluation parameters

Appearance: The formulated bigel was inspected visually for colour and texture.

Homogeneity: Prepared bigel was visually inspected for their appearance and presence of aggregates after they have been set into the containers. The results are shown in table no.2

PH measurement: Measurement of PH of all the formulations was done with the help of calibrated digital PH meter by dipping the glass electrode completely into the bigel. The PH of all the formulations were in the range of 6.9 – 7.5 which comes within the limits of skin's PH. So it was concluded that the bigel does not causes skin irritation. The results are given in table no.2

Spreadability: The spreadability was evaluated by the apparatus which was suggested by Mutimer. It consists of wooden block which is provided with a pulley at one end. This method is also called as slip and

drag method by which spreadability is evaluated. For the determination of spreadability, excess amount of bigel was applied in between two glass slides and then was compressed to uniform thickness. 50 gram of weight was added to pan, and the time was notes when two glass slides separated i.e., the time taken by upper glass slide to move over lower glass slide was taken as a measure of spreadability (S). The formula for calculating spreadability is given below:

S = M. L / T

Where M = wt. tied to upper slide L = length of glass slides T = time taken to separate the slides

The results are shown in table no. 02

Extrudability: Extrudability test was carried out by using Pfizer hardness tester. The method adopted for evaluating bigel formulation for extrudability is depends on the percentage quantity of bigel and pressure applied on aluminium collapsible tube to extrude the bigel at least 0.5cm ribbon of bigel in 30 sec. 15gm of gel was filled in collapsible aluminium tube. The plunger was adjusted to hold the tube properly the pressure of 1kg/cm2 was applied for 30 sec. The quantity of the bigel extruded was weighed. This method was repeated at three equidistance places of the aluminium collapsible tube. The test was carried out in triplicates. The results are given in table no.2

Viscosity: Evaluation of bigel for viscosity was done by Brookfield viscometer (Brookfield Engineering Laboratories, Inc. USA). The measurement of viscosity was done at a temperature (25- 27°C). The results are given in table no.3

Drug content: A required quantity (100 mg) of formulated bigel is taken and dissolved in 100 ml of phosphate buffer PH 6.8. The volumetric flask containing bigel solution was shaken on a mechanical shaker for a period of 2 hours in order to get absolute solubility of drug. The solution was filtered through membrane filter of pore size 0.45 µm filter paper. 2 ml of this solution is pipetted out and diluted upto 10 ml with phosphate buffer. The absorbance of this solution was determined at 276 nm spectrophotometrically using phosphate buffer as blank. The concentration of the Diclofenac sodium was evaluated from calibration curve. The results are given in table no.3

In-vitro Release Studies: The drug release from the prepared formulation was evaluated by using apparatus called Franz diffusion cell. The assembly consist of a cylindrical glass tube which was opened at both the ends. For receptor medium Phosphate buffer (PH 6.8) was used. Cellophane membrane was used in franz diffusion cell. 1 gm of bigel was applied on the surface of cellophane membrane and fixed between donor and receiver compartment of franz diffusion cell in such a way that the bigel was just touches 2mm surface of the diffusion medium. For controlling the temperature of diffusion medium thermostatically at 37 ± 0.5ºC the diffusion medium was continuously stirred at a speed of 500 rpm by surrounding water in jacket.The sample at predetermined intervals were withdrawn and replaced by equal volume of freshly prepared phosphate buffer. The samples withdrawn were spectrophotometrically determined at 276nm. The results are shown in table no.3 and fig no.9

Ex-vivo permeation studies

Isolation of tissue

Albino Wister rat weighing between 250-300 gm was used to obtain the skin. The rat was sacrificed by spinal dislocation. Hairs from abdominal regions was removed by means of surgical and razor taking care not to damage the epidermal surface, Subcutaneous fats was removed carefully without damaging to the skin.

Drug release through rat's abdominal skin

Franz diffusion cell was used to study release of diclofenac sodium through rat's abdominal skin membrane. The rats skin was mounted between donor and receiver compartment of Franz diffusion cell with a diffusion area of 2.1 cm^2 and the receiver compartment's volume of 21ml.The two chambers were tied with the help of springs so that the skin membrane did not move from its place. The phosphate buffer pH 6.8 in the receiver compartment was continuously stirred at 500 rpm using a magnetic stirrer. The entire setup was placed over a magnetic stirrer and the temperature was maintained at 37˚±0.5°C. The optimized bigel containing 1 mg of Diclofenac sodium was spread over rat's skin in a donor compartment. The amount of drug permeated through the skin membrane was determined by taking 67liquots from receiver compartment and replacing the same volume with the phosphate buffer PH 6.8 and determined spectrophotometrically at 276 nm. The results are given in a table no.5.figure no.8.

Anti-inflammatory study of bigel by addition of some vasoconstrictor and vasodilators

The albino Wistar rats of either sex weighing between 250-300 gm was selected for study and divided into five groups of 5 animal each and marked with picric acid and was treated with the vehicle, 0.1 ml of 1% carrageenan in to the sub plantar tissue to group II, standard diclofenac sodium gel containing 1 gm of 1% was applied to the subplantar tissue of left hind paw by gently rubbing 50 times with the index finger, 1 hour after receiving the above mentioned treatments all the rats in the group II,III,IV except group I ,

was injected with 0.1 ml of 1% carrageenan into the subplantar tissue of left hind paw . Swelling of carrageenan injected foot was measured at 0, 2, 4, and 6 hours by using vernier calliper (Laboratory enterprises). 0.1 ml of the vehicle (bigel base without drug) was applied to right hind paw of the rat.
Group I- Control group (Bigel base without drug) applied on left and right hind paw
Group II- Negative control group (0.1 ml of 1% carrageenan was injected into subplantar tissue of rat's left hind paw
Group III- Inflammation treated with marketed gel preparation (containing 1% Diclofenac sodium)
Group IV- Inflammation treated with optimized formulation (10 mg Diclofenac sodium/ gm 1 hour before 0.1 ml of 1 % carrageenan) along with vasoconstrictor (oxymetazoline hydrochloride)
Group V- Inflammation treated with optimized formulation (10 mg Diclofenac sodium/ gm 1 hour before 0.1 ml of 1 % carrageenan) along with vasodilators (minoxidil)
The results are given in a table no. 6.

Stability studies: Stability study was carried out for the period of 3 months. Stability studies of the optimized formulation was done as per ICH guidelines, at a temperature of 25˚±2°C with relative humidity RH= 60±5% for initial 30 days and 40º ± 2°C with relative humidity RH= 75±5% upto 90 days. The optimized formulation was analysed for changes in appearance, colours, homogeneity, extrudability, PH, viscosity, drug content, In-vitro drug release studies as the procedure stated above. The results are shown in table no. 5.

RESULTS AND DISCUSSION

The objective of this study is to prepare bigel for transdermal delivery of drug Diclofenac sodium. Total 8 different formulations were prepared by varying amount of polymer ratios. All the formulations were evaluated for by various characterization test for bigel and optimized formulation was selected based on the results of characterization tests.
The optimized formulation was further studied for anti-inflammatory, skin irritation and ex- vivo permeation study of drug through rat's abdominal skin.

Pre-formulation study

Diclofenac sodium characterization tests

The tests were performed according to British pharmacopoeia.
Description: White powder
Solubility: Freely soluble in Methanol and Ethanol
Melting Point: 285˚C from these tests it was confirmed that the sample complies with the monograph.

Compatibility Studies

The drug and excipients were studied for incompatibility which was studied by FTIR spectroscopy. From the FTIR spectrum it is proved that there is no chemical in-compatability between drug and excipients used in the bigel preparation. The results are shown in figure no.3,4,5.

Evaluation tests of Transdermal bigel

Appearance: The bigels were found to be smooth milky white in colour. All bigels are free from grittiness and particles. The results are shown in table no. 2.

Homogeneity: All the formulated bigels shows homogeneity and absence of aggregates or lumps. The results are shown in a table no. 2.

Spreadability: The values of spreadability shows that the bigel is easily spreadable when small shear is applied. The formulations DL1 to DL8 were shows the spreadability values in the range 19.57-26.54 g.cm/sec. The optimized formulation DL8 shows good spreadability ie. 26.54. The results are shown in table no. 2.

Extrudability: The extrusion of bigel is important characteristic to remove the bigel from its tube it should have optimum viscosity and hence suitable consistency is required to extrude the bigel from its tube and for patient compliance. Extrudability of DL8 formulation was found to be excellent as compared to the other formulations. The results are given in a table no. 2.

Surface PH: The surface PH of the bigels were in the range 6.90 to 7.52 which comes under the limit of skin's PH. From this it can be concluded that all the formulations could not produce any skin irritation. The results are shown in table no. 2.

Viscosity measurement: The viscosity of all the bigels DL1 to DL8 were in the range from 18600-44000 cps. The viscosity of optimized bigel was 20400cps. The results are shown in table no.3

Drug content: The % drug content of all the bigels DL1 TO DL8 were found to be in the range of 96.68-99.82. The percentage drug content of all the bigels was within the I.P limits, that's why the methods adopted for bigels preparation was found suitable. The results are shown in Table 03.

In-vitro drug diffusion study: In-vitro drug release of all the bigels were evaluated by using cellophane membrane in Franz Diffusion cell. The % drug release of all the bigels were in the range of 70.12 -99.14% in four hours. Among all the bigels DL8 bigel shows high % drug release ie 99.14%. The results are shown in table no.3. Figure no.9.

Ex-vivo permeation studies: The DL8 formulation shows required viscosity, good spreadability, in-vitro drug release, extrudability. On the basis of above results it can be concluded that the DL8 formulation is best and hence ex- vivo study of the optimized bigel formulation is carried out using rats abdominal skin for a period of about 6 hours. The release was analysed by Uv spectroscopy. The graph was shown in table no.4. figure no.8.

The results indicate that Diclofenac sodium can release from the optimized formulation and permeate through rat's abdominal skin. It could possibly be permeating through human's skin membrane.

Anti-inflammatory studies: Treatment of the rat's paw with the optimized DL8 bigel formulation with vasodilator significantly inhibited carrageenan induced rat paw oedema as compare to control group. Maximum inhibition of oedema was observed after 4 hours when compared to control group. The results are given in table no.6. Figure no. 10,11,12,13,14,15 & 16.

$P < 0.0001$, $P < 0.0001$ values are Mean ± SEM, n=5 when compared with control group by using one-way ANOVA followed by Dunnette's multiple comparison test.

Stability studies: The optimize formulation DL8 was studied for stability studies as per ICH guidelines. The formulation DL8 was kept at 25˚±2˚C/60±5%RH for first 30 days and at later on at 40˚±2˚C/75±5%RH upto 90 days.

The results indicate that DL8 formulation deos not show change in colour, PH, viscosity, spreadability, extrudability, drug release. The results are shown in table no.5

Table 1: Different ratios of the polymer used in formulation of bigel

Formulation code	Carbopol 934 (gm)	HPMC K100 (gm)	Span 60 (gm)	Linseed oil (organogelator) (ml)
DL1	0.08	0.08	2	1
DL2	0.08	0.08	1	1
DL3	0.06	0.08	1	1
DL4	0.08	0.06	1	1
DL5	0.06	0.06	1	1
DL6	0.08	0.06	2	1
DL7	0.06	0.08	2	1
DL8	0.06	0.06	2	1

Table 2: Colour, Homogeneity, Spreadability, Extrudability Parameters, PH

Formulation code	Colour and texture	Homogeneity	Spreadability	Extrudability	PH
DL1	White colour smooth texture	Good	19.57	+ +	7.22
DL2	White colour smooth texture	Good	20.11	+ +	7.01
DL3	White colour smooth texture	Good	21.73	+ +	7.11
DL4	White colour smooth texture	Good	21.46	+ +	7.16
DL5	White colour smooth texture	Satisfactory	22.11	+	6.90
DL6	White colour smooth texture	Excellent	24.32	+ + +	7.32
DL7	White colour smooth texture	Good	20.54	+ +	7.34
DL8	White colour smooth texture	Excellent	26.54	+ + +	7.52

Table 3: Viscosity (cps), % Drug content, In- vitro drug release (%)

Formulation code	Viscosity (cps)	Drug content (%)	In-vitro drug release (%)
DL1	44000	96.68±0.18	70.12
DL2	37400	96.14±0.22	70.89
DL3	24600	98.67±0.28	77.64
DL4	25400	97.46±0.26	82.93
DL5	18600	98.20±0.14	86.69
DL6	26100	98.67±0.37	90.19
DL7	25800	99.35±0.20	94.00
DL8	20400	99.82±0.11	99.14

Table 4: Ex-vivo permeation of optimized bigel (DL8) through rat's skin

Sr.no	Time	Avg % release
1	0	0
2	0.5	57.2
3	1	63.7
4	2	68.6
5	3	75.9
6	4	84.1
7	5	90.9
8	6	98.6

Table 5: Stability studies of the optimized bigel (DL8)

Formulation	Days	Temperature and Relative humidity	Colour and texture	PH	Drug content	% Drug release
DL8	0	25˚±2˚C/60±5%RH	White colour smooth texture	7.50	99.82	97.84
DL8	15	25˚±2˚C/60±5%RH	White colour smooth texture	7.52	99.80	97.83
DL8	30	25˚±2˚C/60±5%RH	White colour smooth texture	7.52	99.80	97.82
DL8	60	40˚±2˚C/75±5%RH	White colour smooth texture	7.49	99.79	97.80
DL8	90	40˚±2˚C/75±5%RH	White colour smooth texture	7.48	99.78	97.78

Table no. 6. Anti-inflammatory activity using carrageenan induced paw oedema in rats

Sr.no.	Groups (n=5)	Paw oedema volume (mm) at different hours			
		0	2	4	6
1	Control	3.20±0.30	3.28±0.54	3.28±0.55	3.4±0.34
2	Negative control	3.20±0.30	11.2±0.54	11.2±0.55	10.4±0.34
3	Std Diclofenac gel	3.20±0.30	9.4±0.54	7.0±0.55	8.4±0.34
4	Bigel with vasoconstrictor (oxymetazoline hydrochloride)	3.40±0.30	13.2±0.54	9.8±0.55	10.4±0.34
5	Bigel with vasodilator (Minoxidil)	3.6±0.30	8.4±0.54	5.2±0.55	4.6±0.34

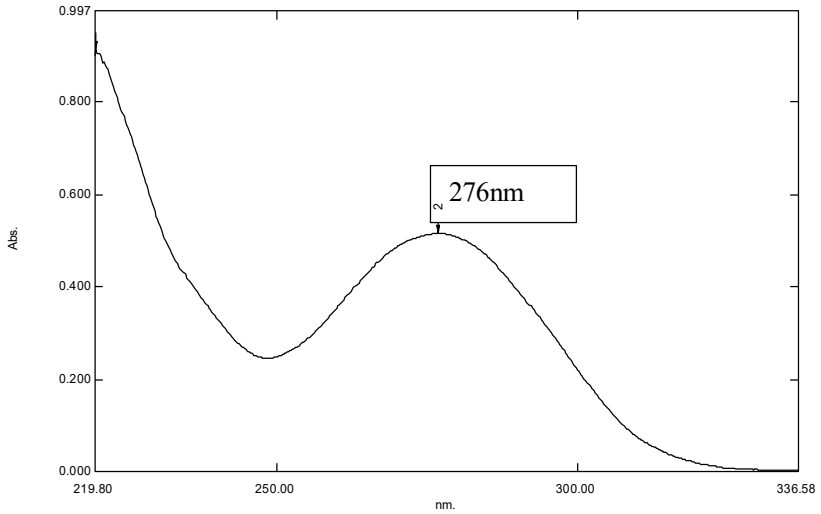

Figure 1: Absorption maxima of Diclofenac sodium

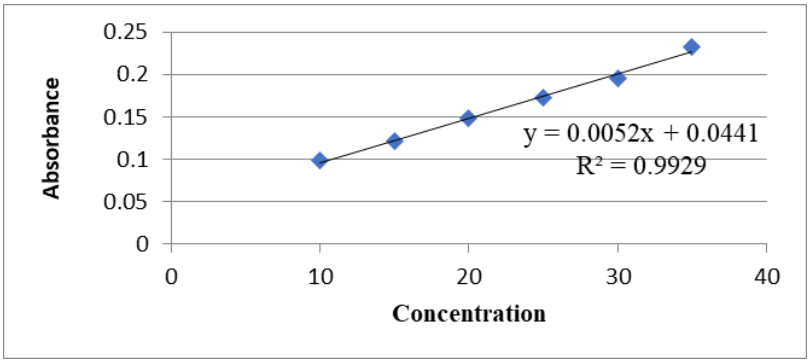

Figure 2: Calibration curve and linear regression equation of diclofenac sodium at 276 nm

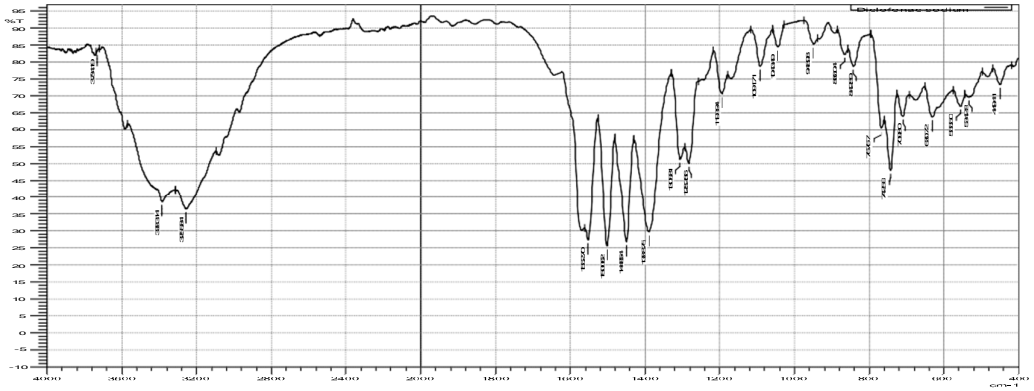

Figure 3: FT-IR Spectrum of Diclofenac sodium

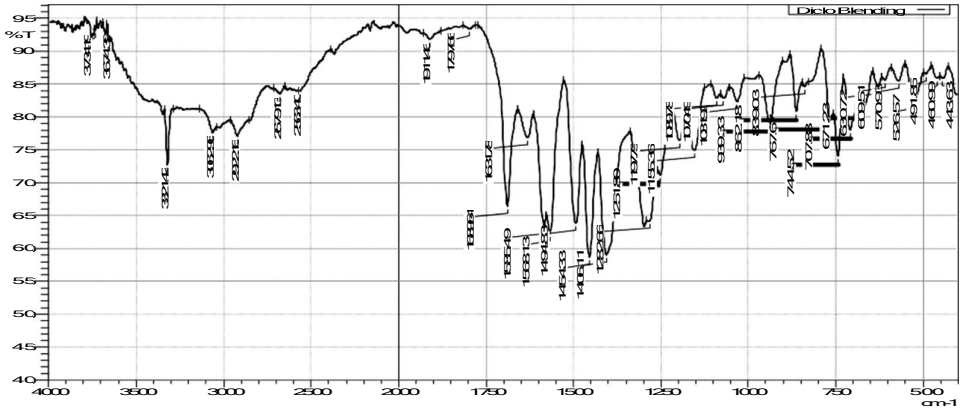

Figure 4: FT-IR spectrum of Diclofenac sodium with blend of excipients

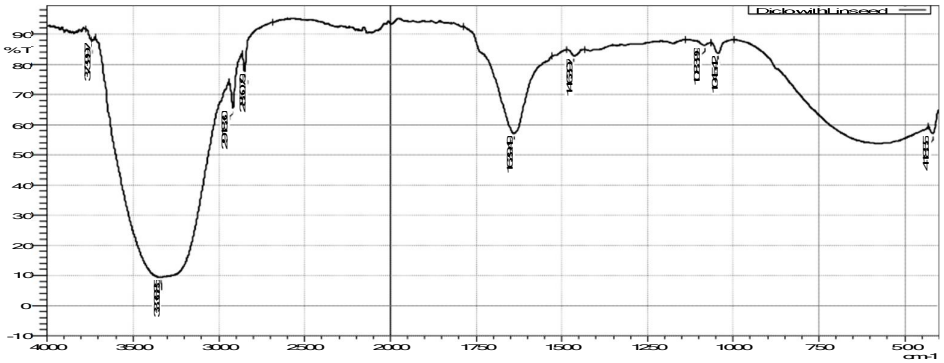

Figure 5: FT-IR spectrum of optimized bigel (DL8) formulation

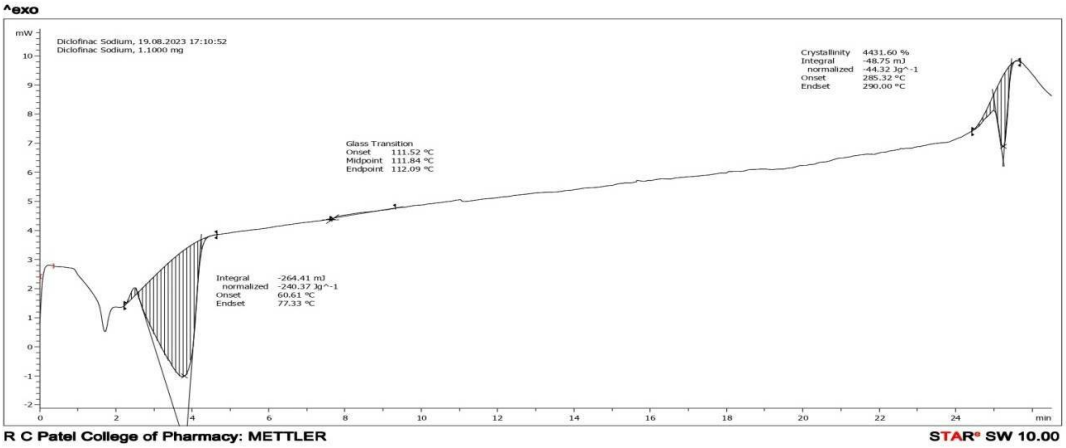

Figure 6: DSC thermogram of Diclofenac sodium

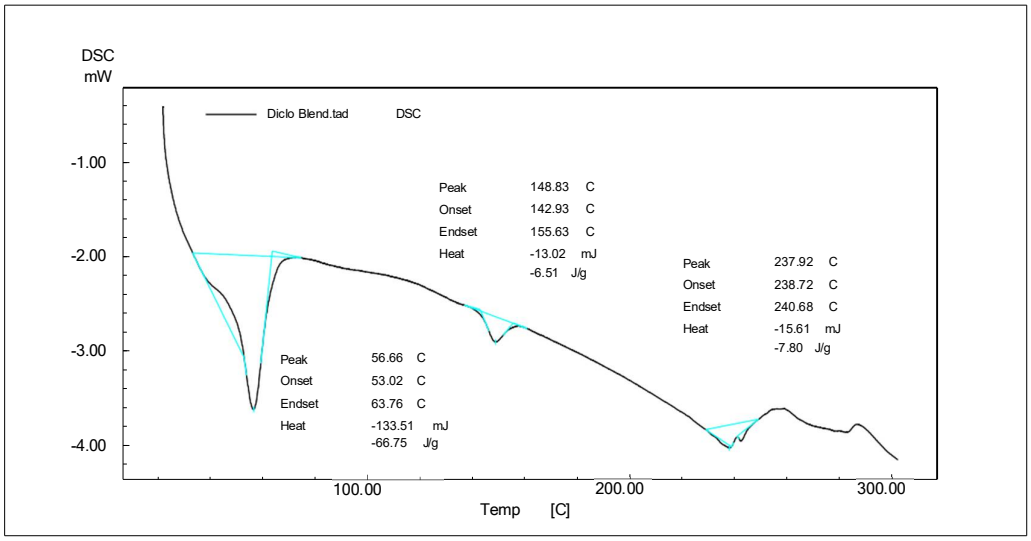

Figure 7: DSC thermogram of Diclofenac sodium with blend of excipients

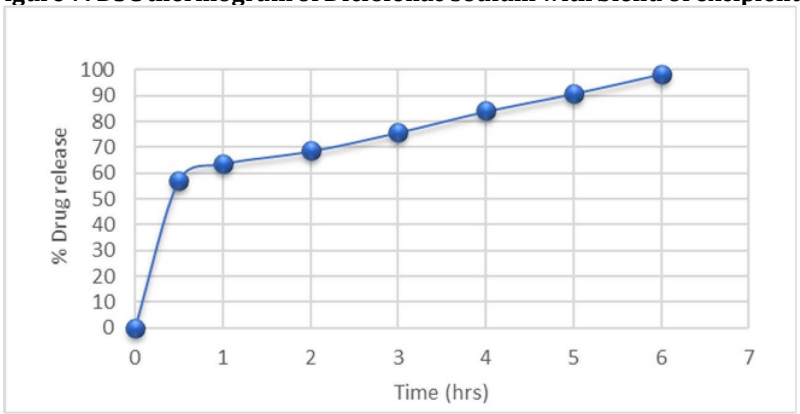

Figure 8: Ex-vivo % drug release of optimized bigel (DL8)

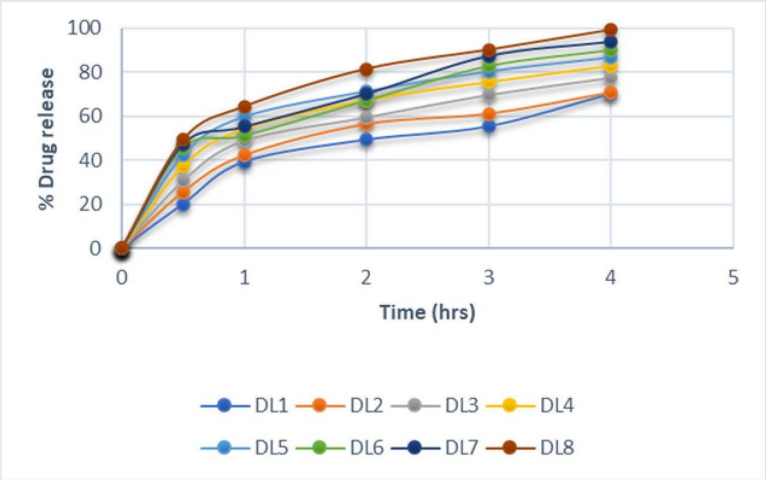

Figure 9: In- vitro % drug release of DL1 TO DL8 bigels

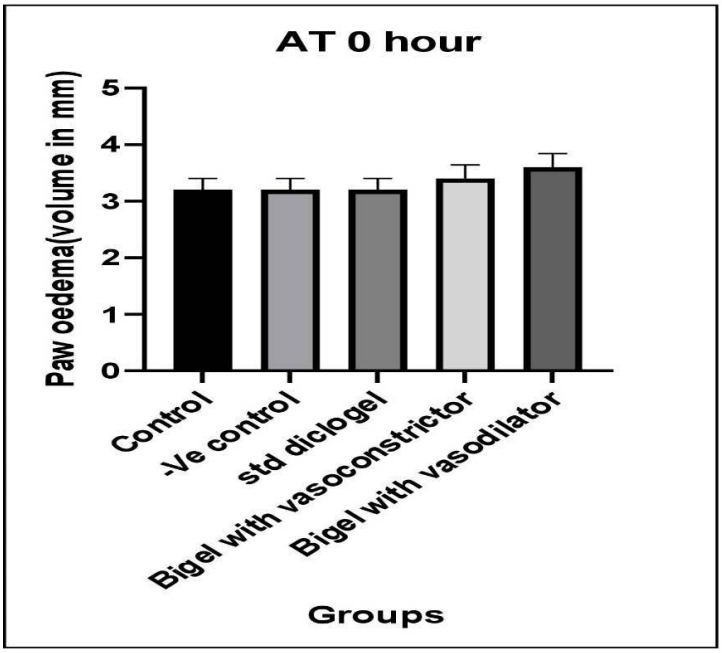

Figure 10: Comparison of Anti-inflammatory activity of control group with DL8 bigel vasodilator and DL8 bigel vasoconstrictor after inducing 0.1% carrageenan into subplantar region of rat.

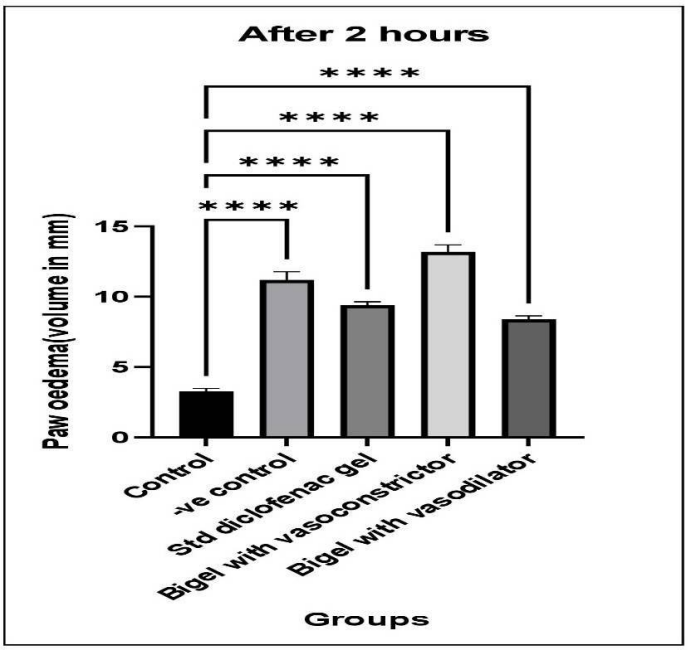

Figure 11: Comparison of analgesic activity of DL8 bigel with vasoconstrictor & Vasodilators. The results are expressed as mean± SD: p<0.0001 vs control and p<0.0001 vs Bige DL8 with vasodilator.

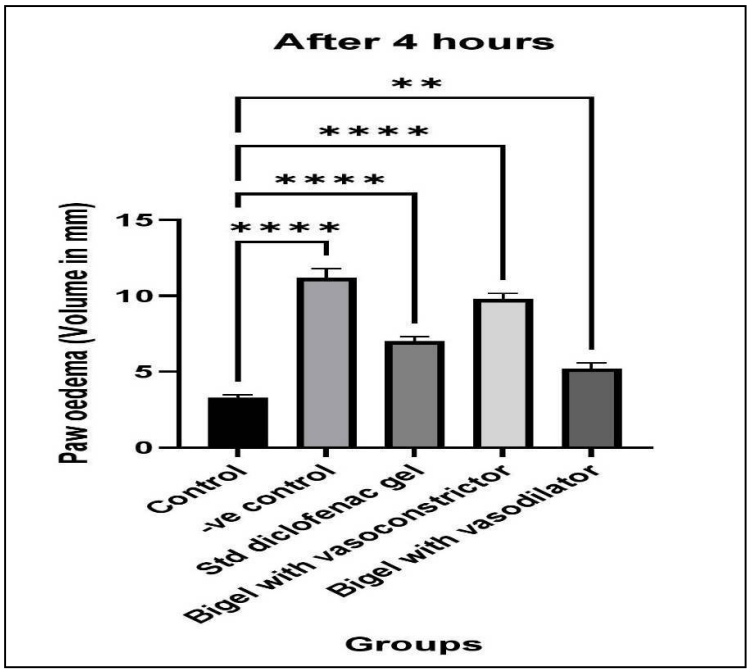

Figure 12: Significant reduction of paw oedema of DL8 with vasodilator as compare to control and DL8 with vasoconstrictor after 4 hours of treatment. Results are expressed as mean ± SD p< 0.0001 vs control.

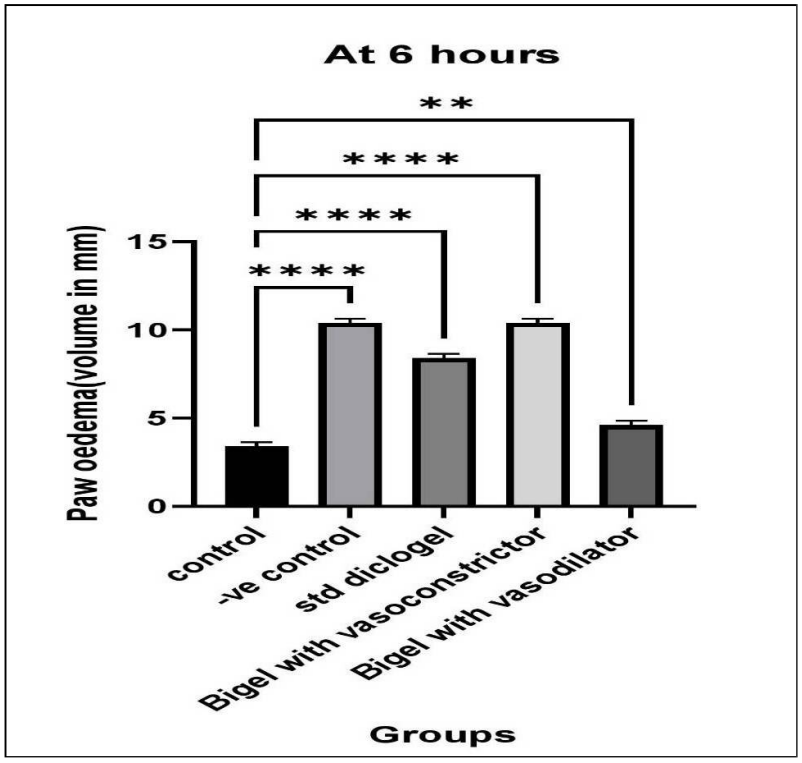

Figure 13: Maximum paw reduction in paw volume was observed of DL8 formulation with vasodilator as compare to control and DL8 with vasoconstrictor. The results are expressed as mean ± SD p<0.0001 vs control; p<0.0001 vs DL8 with vasoconstrictor.

Figure 14: Measurement of paw oedema using vernier calliper

Figure 15: Oedematous paw after inducing 1 % carrageenan

Figure 16: Rats paw after treatment

CONCLUSION

From all the evaluation tests it has been observed that DL8 bigel which contain carbopol 934 (0.06 gm) and HPMC K100 (0.06 gm) showed good homogeneity, spreadability, drug content and suitable PH 7.52 which deos not produce skin irritation or redness. The maximum in-vitro % drug release was found to be 99.14 % after 4 hours. From the ex-vivo studies the % drug release was found to be 98.6%. From ex-vivo studies it can be concluded that this bigel DL8 could permeate through human skin membrane also. This bigel is non-sticky, water washable hence can increase patient compliance. From animal studies it can be concluded that DL8 bigel have good anti-inflammatory and analgesic properties. This bigel could also be used in arthritis as it can reduce swelling or oedema.

REFERENCES

1. V.K. Singh, I. Banerjee, T. Agarwal, K. Pramanik, M.K. Bhattacharya, K. Pal, (2014). Guar gum and sesame oil based novel bigels for controlled drug delivery, Colloids Surf B Biointerfaces. 123. 582–592.
2. V.K. Singh, A. Anis, I. Banerjee, K. Pramanik, M.K. Bhattacharya, K. Pal, (2014). Preparation and characterization of novel carbopol based bigels for topical delivery of metronidazole for the treatment of bacterial vaginosis, Mater Sci Eng C. 44. 151–158.
3. H. Alsaab, S.P. Bonam, D. Bahl, P. Chowdhury, K. Alexander, S.H. Boddu, (2016) Organogels in drug delivery: a special emphasis on pluronic lecithin organogels, J Pharm Pharm Sci. 19 (2) 252.
4. A. Vintiloiu, J.-C. Leroux, (2008). Organogels and their use in drug delivery — a review, J.-Control Release. 125. 179–192.
5. M.M. Ibrahim, S.A. Hafez, M.M. Mahdy, (2013) Organogels, hydrogels and bigels as transdermal delivery systems for diltiazem hydrochloride, Asian J Pharm Sci. 8 (1) .48–57.

6. Satyabrata Bhanja*, P. Kishore Kumar, Muvvala Sudhakar, Arun Kumar Das. 2013 Formulation and Evaluation of Diclofenac Transdermal Gel; J. Adv. Pharm. Edu. & Res. 3(3): 248-259.
7. Fre´de´rique Bariguian Revel. Marina Fayet. Martina Hagen. (2020) Topical Diclofenac an efficacious treatment for osteoarthritis a narrative review; Rheumatol Ther.7:217–236.
8. Babasaheb V. Bhagat, Punit R. Rachh, Anil R. Pawar. Evaluation of anti-inflammatory and analgesic activity of optimized lipid based non-aqueous nanoemulsion of naproxen in experimental animals. International Journal of Health Sciences, 6(S1), 5963–5972.
9. Obanewa Opeyemi Adegbenro1, Oyeniran Taiwo Opeyemi. (2019) Development and estimation of anti-inflammatory activity of topical etoricoxib emulgel by carrageenan induced paw oedema method. Universal Journal of Pharmaceutical Research. Volume 4, (3).
10. Saifullahi U, Onyekachi MK, (2017) Development and evaluation of transdermal gel of lornoxicam. Univ J pharm res. 2(1):17-20.
11. Mohamed MI. (2004) Topical emulsion gel composition comprising Diclofenac sodium. AAPS J; 6(3):12.
12. Syed Nisar Hussain Shah, Mehboob-E-Rabbani , Yasser Shahzad , Amir Badshah , Victor M. Meidan And Ghulam Murtaza.(2012), Developing an Efficacious Diclofenac Diethylamine Transdermal Formulation. Journal of Food and Drug Analysis, Vol. 20, No. 2, Pages 464-470.
13. P Rajalakshmi, M Sakthivel , S Mohammed Halith , R Saranya Devi , R Rasiga , P suriya , C Sundharapandian , K Sathish Kumar. (2022) Formulation and Evaluation of Diclofenac Sodium Gel – Using Carbopol 934 And 940. International Journal of Pharmaceutical Research and Applications. 7(2), pp: 1051-1058.
14. Swati Talele, Preetam Nikam , Braja Ghosh , Chaitali Deore , Ashwini Jaybhave , Anil Jadhav.(2017) A Research Article on Nanogel as Topical Promising Drug Delivery for Diclofenac sodium. Indian Journal of Pharmaceutical Education and Research .51 (4)
15. Rajesekaran A, Arulkumaran G, Arivukkarasu R. (2016) Formulation and evaluation of topical herbal gel for the treatment of arthritis in animal model. Brazilian journal of pharmaceutical sciences. Vol. 52.
16. S.K. Gupta, P. Bansal, R.K. Bhardwaj, J. Jaiswal, T. (2002) Velpandian. Comparison of analgesic and anti-inflammatory activity of Meloxicam gel with Diclofenac and Piroxicam gels in animal models: Pharmacokinetic parameters after topical application. Skin pharmacology applied skin physiology (15);105-111
17. Anca Zanfirescu & et al. Evaluation of Topical Anti-inflammatory effects of a gel formulation with Plantago Lanceolata, Achillea Millefolium, Aesculus Hippocastanum and taxodium Distichum. Scientia Pharmaceutica (88)26, 2020.1-13
18. Balasubramanian, et al. (2012). Oleogel: A promising base for transdermal formulations. Asian Journal of Pharmaceutics. 6(1). 1-9.
19. Zanfirescu, Anca Nitulescu, & et al. (2020) Evaluation of topical anti-inflammatory effects of a gel formulation with plantago lanceolata, achillea millefolium, aesculus hippocastanum and taxodium distichum. Scientia Pharmaceutica, 88 (26).1-13
20. Md, S., Alhakamy, N. A., Aldawsari, H. M., Kotta, S., Ahmad, J., Akhter, S., Alam, M. S., Khan, M. A., Awan, Z., & Sivakumar, P. M. (2020). Improved analgesic and anti-inflammatory effect of diclofenac sodium by topical nanoemulgel: Formulation development—in vitro and in vivo studies. Journal of Chemistry, 2020. 1-10.