World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Preparation and evaluation of Diclofenac & Aceclofenac pain relieving gel

Prabhat Ekka, Nisha Dewangan *, Devid Patel, Kamlesh Kushwaha, Chandrashekhar Sao, Rishabh Yadav and Girdhar Prasad Chakradhari

Rungta Institute of Pharmaceutical Sciences and Research, Kohka, Kurud, Bhilai, CG. 490024

World Journal of Biology Pharmacy and Health Sciences, 2024, 18(02), 227–238

Publication history: Received on 31 March 2024; revised on 08 May 2024; accepted on 11 May 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.18.2.0277

Abstract

It is phenyl acetic acid derivative developed as anti-inflammatory agent. It has analgesic anti-inflammatory antipyretic like actions like other NSAIDS. . It is recommended in long term treatment of rheumatoid arthritis, osteoarthritis and enclosing spondylitis. It is also useful acute miscue skeletal disorder post operative pain and dysmenorrhoea Diclofenac sodium gel were developed in seven different formulations) by employing different grades of polymers such as Hpmck4m and Crbopol940. There the various Diclofenac gels are available in market. But the propose gel is formulated with two key ingredients oleoresin, and l linseed oil contribute to anti-inflammatory effect. The formulations were evaluated for various physical parameters, pH spredability, drug release excludability studies drug released mechanisms. Formulation showed maximum drug release of 8 hours and maximum drug. Finally the gel formulations found to be economical and may overcome the draw backs associated with the drug during its absorption. The purpose of the study is to prepare the combination of diclofenac and aceclofenac pain relieving gel. This gel combined form of gel is multifunctional and getting rapid onset of action. And that is to get instant relieve from pain as comparison of plain aceclofenac tablet and plain Diclofenac gel. This formulation is also beneficial for diabetic patient to get cure fast of skin injury and buildup of skin irritation and growth or new epidermis layer of skin in the body. Out of various semisolid dosage forms, gels are becoming more popular due to ease of application and better percutaneous absorption

Keywords: Diclofenac; Aceclofenac; Combine gel; Diabetic patient

1. Introduction

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominates the system for topical delivery. There have been concerns related to the conventional topical dosage

forms such as lotions, creams, ointment and powder in terms of drug diffusion or release from the vehicle and delivery through the skin. Creams and lotions often provide poor bioavailability of the drug because they are rapidly cleared from the skin and poorly release the drug from the base. Non-hydrophilic ointments are oleaginous, greasy and are not convenient to patients, and also medicated powders for topical application have short residence time on the skin. Gels are

semisolid systems in which the movement of the dispersion medium is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed phase. The transdermal drug delivery systems are self contained, discrete dosage forms which when applied to intact skin deliver the drug through the skin at a controlled rate to the systemic circulation. At present, the most common form of delivery of drugs is the oral routemolecule. The stratum corneum provides the greatest resistance to penetration and it is the rate The increased viscosity caused by

* Corresponding author: Nisha Dewangan

interlacing and consequential internal friction is responsible for the semisolid state. Also, a gel may consist of twisted matted strands often tied together by stronger types of Vander Waals Forces to form crystalline and amorphous regions throughout the system.

1.1. Pain

Inflammatory disorders may include arthritis, rheumatoid arthritis, polymyositis, dermatomyositis, osteoarthritis, dental pain, temporomandibular joint (TMJ) pain, spondylarthritis, ankylosing spondylitis, gout attacks, and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines.

2. Selection of herbal drugs and drug profile

2.1. Diclofenac-Sodium

Diclofenac, sold under the brand name Voltaren, among others, is a nonsteroidal anti inflammatory drug (NSAID) used to treat pain and inflammatory diseases such as gout.[6] It is taken by mouth or rectally in a suppository, used by injection, or applied to the skin. Improvements in pain last for as much as eight hours. It is also available in combination with misoprostol in an effort to decrease stomach problems. Common side effects include abdominal pain, gastrointestinal bleeding, nausea, dizziness, headache, and swelling. Serious side effects may include heart disease, stroke, kidney problems, and stomach ulceration. Use is not recommended in the third trimester of pregnancy. It is likely safe during breastfeeding. Diclofenac is believed to work by decreasing the production of prostaglandins, like other drugs class.

Figure 1 Diclofenac

2.2. Aceclofenac

Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) analog of diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and anky losing spondylitis. It was patented in 1983 and approved for medical use in 1992. Aceclofenac (C16H13Cl2NO4), chemically [(2-{2, 6-dichlorophenyl) amino} phenyl aceto oxyacetic acid], is a crystalline powder with a molecular weight of 354.19. It is practically insoluble in water with good permeability. It is metabolized in human hepatocytes and human microsomes to form [2-(2',6'-dichloro-4'-hydroxy-phenylamino) phenyl] acetoxyacetic acid as the major metabolite, which is then further conjugated. According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability. Aceclofenac falls under the BCS Class II, poorly soluble and highly permeable drug. Aceclofenac works by inhibiting the action of cyclooxygenase (COX) that is involved in the production of prostaglandins (PG) which is accountable for pain, swelling, inflammation and fever. The incidence of gastric ulcerogenicity of aceclofenac has been reported to be significantly lower than that of the other frequently prescribed NSAIDs, for instance, 2-folds lesser than naproxen, 4-folds lesser than diclofenac, and 7-folds lesser than indomethacin.

Figure 2 Aceclofenac

2.3. Carbopol

Carbopol polymers are easy-to-use liquid thickeners designed to thicken and improve the flow properties in a broad range of product types for household, industrial and institutional applications. These polymers are especially effective for use in surfactant-containing applications.

Figure 3 Carbopol

2.4. HPMC

Hydroxypropyl methylcellulose (HPMC) or hypromellose refers to soluble methylcellulose ethers. HPMC is used as a thickening agent, binder, film former, and hydrophilic matrix material. HPMC polymers for fabricating hydrophilic atrix systems are available in various viscosity grades ranging from 4000–100,000 mPas.

Figure 4 HPMC

2.5. Sodium CMC

Sodium carboxymethyl cellulose is intended for use as a technological additive (functional groups: emulsifier, stabilizer, thickener, gelling agent and binder) in premixtures and feeding stuffs for all animal species with no minimum and maximum content.

Figure 5 Sodium CMC

2.6. Triethanolamine

Triethanolamine is a tertiary amino compound that is ammonia in which each of the hydrogen is substituted by a 2-hydroxyethyl group. It has a role as a buffer and a surfactant. It is a tertiary amino compound, a triol and an amino alcohol. It is functionally related to a triethylamine.

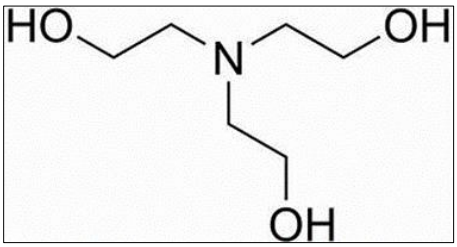

Figure 6 Triethanolamine

2.7. Ethanol

Ethanol (also called ethyl alcohol, grain alcohol, drinking alcohol, or simply alcohol) is an organic compound with the chemical formula CH3CH2OH. It is an alcohol, with its formula also written as C2H5OH, C2H6O or EtOH, where Et stands for ethy[1]

Figure 7 Ethanol

2.8. Propyleneglycol

Propylene glycol (IUPAC name: propane-1,2-diol) is a viscous, colorless liquid, which is nearly odorless but possesses a faintly sweet taste. Its chemical formula is CH3CH(OH)CH2OH. As it contains two alcohol groups, it is classed as a diol. It is miscible with a broad range of solvents, including water, acetone, and chloroform. In general, glycols are non-irritating and have very low volatility. It is produced on a large scale primarily for the production of polymers. In the European Union, it has E-number E1520 for food applications. For cosmetics and pharmacology, the number isE490. Propylene glycol is also present in propylene glycol alginate, which is known as E405

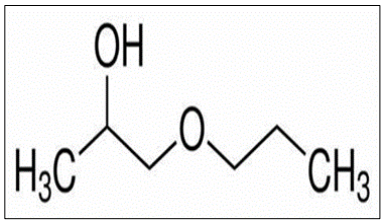

Figure 8 Propyleneglycol

2.9. PEG400-

PEG 400 (polyethylene glycol 400) is a low-molecular-weight grade of polyethylene glycol. It is a clear, colorless, viscous liquid. Due in part to its low toxicity, PEG 400 is widely used in a variety of pharmaceutical formulations.

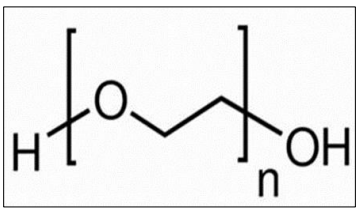

Figure 9 PEG400

3. Material & Methods

All the chemical components and active pharmaceutical ingredients that are used in the preparation of diclofenac and acclefenac pain relieving gel has been collected.

3.1. Ingredient Table

Table 1 Quantity table

S. no	Name of Ingredients	Amount
1.	Diclofenac Sodium	1
2.	Aceclofenac	1
3.	Carbopol 934	0.5
4.	HPMC K4M	2.5
5.	Sodium CMC	1
6.	Triethanolamine	0.4
7.	Ethanol	20
8.	Propylene glycol	10
9.	PEG400	07
10.	Distilled Water	Q.S.

3.2. Preformulation-studies

- •Characterization of Diclofenac sodium: Description The sample of Diclofenac sodium was analysed for its nature, colour and type and organoleptic properties of the drug and its taste.
- •Melting Point The melting point was determined by using thiesel's tube apparatus method. Drug Excipient were very complex to did its formality and its compatibility studies:
- •The drug polymer and polymer-polymer interaction was 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 properly allowing the formulation and at last 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 scanned16times at 2 mm/sec at a resolution of 4 cm-1 using cosine apodization. The characteristic peaks were recorded.

3.3. Procedure

Various batches of gels were prepared with the help of different ethanol and water proportions taken as vehicle in carbopol 940 base. Hpmc k4MOut of this formulation batch. All the formulations were evaluated for the post formulation Organoleptic characteristic, homogeneity, drug content, pH, viscosity, spreadability, *In vitro* diffusion stud stability study, It was found that, all the formulation were smooth in touch and showed no clogging which indicate good texture of formulation. All the formulations were evaluated spectrophotometrically for the drug content, the results were found in the acceptable range, indicating the no drug and excipient interaction and also form the uniformity of content. It was found that the pH of all the formulations is in the range of 6.84 to 7.41 that suits the skin pH (pH 4.5 to 7.2), indicating skin compatibility. This is the primary requirement for a good topical formulation.

3.4. Method to preparation of formulation

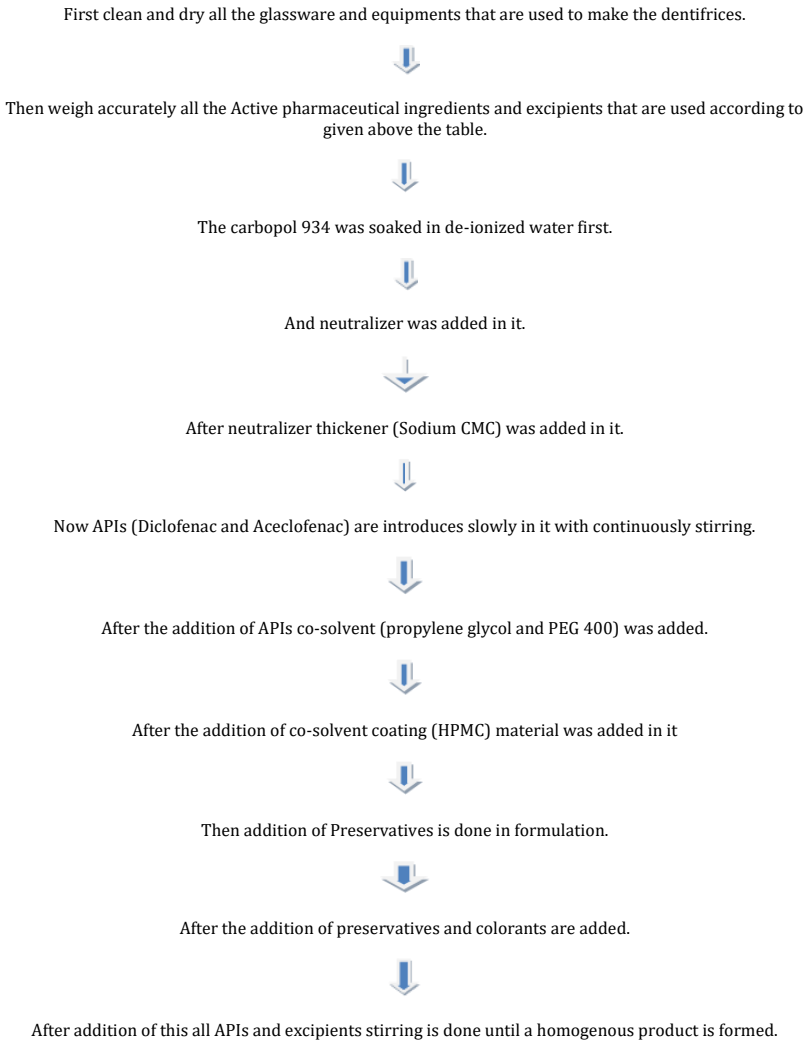

Figure 10 Prepared Diclofenac & Aceclofenac gel

3.5. Evaluation tests of diclofenacand aceclofenac gel

- **Homogeneity**: The formulation were tested for homogeneity by visual appearance and by touch.
- **Appearance**: The appearance of the Diclofenac and Aceclofenac gel was very clear.
- **Acid Value**: Take 10gm of substance dissolve in accurately weighed in 50ml mixture of equal volume of alcohol and solvent ether. The flask was connected reflux condenser and slowly heated, until sample was dissolved completely. To this 1ml of phenolphthalein added and titrated with 0.1N NaOH, until faintly pink colour appeares after shaking for 30sec.Acid Value=n x 5.61/wn= number of ml of NaOH required w= weight of substance
- **pH measurement**: The pH meter was calibrated using standard buffer solution. About 0.5gm of Diclofenac and Aceclofenac Pain relieving gel was weighed and dissolved in 50ml of distilled water and its pH was measured using digital pH meter with dipping the electrode in this.
- **Irritancy test**: Mark an area (1 sq. cm) on the left hand dorsal surface. The Diclofenac and Aceclofenac pain relieving gel was applied to the specified area and time was noted. Irritancy, erythema, edema, was checked if any for regular intervals upto 24hrs and reported.
- **Viscosity**: Viscosity of the formulation was determined was brookfield or ostwald viscometer at 100 RPM, using spindle no. 7 at temp 25℃. The determinations of Diclofenac and Aceclofenac pain relieving gel were carried out in triplicate and the average of three reading was recorded.
- **Accelarated stability testing**: Accelarated stability testing of prepared gel was conducted for 2 most stable formulations at room temp, studied for 7 days. The formulations were placed at 40oC + 1oC for 20 days. Both formulations were kept at room temp and elevated temp and observed on both, 5th, 10th, 15th and 20th day for any change in color, phase separation etc.
- **Subjective Properties**: Consistency, feel on application and irritation parameters are determined.
- **Spreadability**: Two glass slides of standard dimensions (20 × 5cm) were selected. The formulation was over one of the slide. The other slide placed on the top of the lotion such a that the formulation sandwiched between the two slides in an area occupied by a distance of 7.5 cm, alongside 100 gm weight was placed uniformly to form a thin layer. The weight was removed and the excess of lotion adhering to the slides was scrapped off. The two slides in a position were fixed to stand (45° angle) without slightest disturbance and in such a way that only the lower slide held firmly by the opposite fangs of the clamps allowing the upper slide to slip off freely by the force of weight tied to it. 60 gm of weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 5 cm and separate away from the lower slide under the direction of weight was noted. The experiment repeated for 3 times and the mean taken for three such dimensions was calculated. The results were recorded. The Spread ability is calculated by using formula:

$$S = M \times L/T$$

Where, S= Spread ability, L= Length of glass slide, M= Weight tied to the upper slide and T= Time.

- **Type of emulsion test**: Dye solubility and dilution test was conducted to determine the type of emulsion formed. A portion of lotion was applied on the forearms of 6 volunteers and left for 20 minutes. After 20 minutes any kind of irritation if occurred was noted.

- **Washability Test**: A portion of Diclofenac and Aceclofenac pain relieving gel was applied over the skin of hand and allowed to flow under the force of flowing tap water for 10 minutes. The time when the Diclofenac and Aceclofenac pain relieving gel completely removed was noted.
- **In vitro permeation studies**: In vitro permeation studies of TRA gel across rabbit skin were carried out using two-chambered Franz-type diffusion cells (manufactured "in house") having a receptor phase of ~5 ml, 2 and a diffusional area of ~0.788 cm .Adult rabbit skin was used for permeation studies at 37 ± 0.5 C. Abdominal full thickness skin of male White New Zealand rabbit (3 - 4 kg weight) was carefully excised after sacrificing the rabbit. Subcutaneous fats and other extraneous tissues adhering to the dermis were completely removed and trimmed with forceps and scissor. The skin was cleaned with phosphate buffered saline (PBS) at pH 7.4 and stored in 500 ml normal salinein a o refrigerator (18 – 20 C) The skin was used within one week of excision. Sheets of the skin were cut to appropriate sizes 2 (~ 1 cm in diameter) and soaked overnight in the receptor solution (PBS). The membrane was then placed between the two compartments of the diffusion cells with epidermis side facing the donor compartment while the dermal side was bathed with PBS at pH 7.4 (receptor fluid). The donor compartment was filled with PBS at pH 7.4 ± 0.1.This pH is close to that of human skin. The receptor fluid was stirred with a magnetic stirring bar at 500 rpm, keeping the temperature at 37 ± o 0.5 C by means of a water jacket. Care was exercised to remove any bubbles between the underside of the skin and the solution in the receiver compartment. Vacuum grease was used to produce a leak-proof seal between the membrane and the two compartments of the diffusion cell, i.e., donor and receptor. Ultrasonic bath. To avoid evaporation from the compartments, the cell arm and donor compartment were covered with a para film. Constant mixing of the receptor phase was obtained with a magnetic stirrer placed in the receptor compartment. The diffusion cells were placed on a stirring-bed immersed in a water o bath at 37 ± 0.05 C, to maintain the temperature of membrane surface. After 24 hours, both chambers were cleared of PBS and the receptor compartment was immediately refilled with pre- thermo stated PBS, while the skin remained intact. The donor compartment was charged with 1 ml of the lotion (test formulation). At time intervals of 5,15, 30, 60, 90, 120, 180, 240, 360 and 480 min, 0.2 ml sample was drawn, using a micro-pipette, from receptor solution followed by addition of same volume of pre-thermostated receptor solution to maintain sink conditions. The samples were analyzed spectrophotometrically at 271 nm using UV/Vis spectrophotometer to obtain the amount of TRA permeated through rabbit skin after diluting with 1.8 ml PBS. Since skin shows great sampleto-sample permeability variations, each of these analyses was conducted in pentaplicate (n = 5). To construct a calibration curve, 500 mg of TRA was dissolved in PBS (10 ml) in 100 ml volumetric flask and the final volume made up to 100 ml by adding PBS to prepare stock solution. From this solution, dilutions of 10, 20, 30, 40, 50, 60, 70, and 80 µg/ml were prepared. The resultant dilutions were analyzed spectrophotometrically for UV absorbance' maximum UV absorbance of TRA was found at 271 nm. The linear equation of the constructed calibration curve was y = 0.022x – 2 0.021 and correlation coefficient (R) of 0.998. Steady-state flux was determined from the slope of the linear portion of the cumulative amount of permeation (Q) versus time (t) plot. The input rate of TRA permeating across rabbit skin was determined as in EqInput rate = K p × C × A.....Where, K p is permeability coefficient, C is donor amount (µg), i.e., amount of drug in the donor compartment and A is the Franz cell area of 2 permeation (~0.788 cm).Enhancement ratio (ER) was calculated by dividing the flux of the test formulation by the flux of control formulation.
- **Statistical analysis**: The receptor and donor compartments were filled with PBS at pH 7.4 ± 0.1. To remove air bubbles and preclude the development of air pockets in the receptor phase, PBS was degassed in Diclofenac and Aceclofenac pain relieving gel The results are expressed as mean ± standard deviation (SD, n = 5). Statistically significant differences between various permeation data were determined using F-test, Fisher's least significant difference (LSD), analysis of variance (ANOVA) and multiple range tests at 95% confidence level.
- **Preference Test:** The parameters of preference tests based on sensory evaluation were a scent, color, and sensation on the skin. The level of preference was assessed using a numerical scale, i.e. 5 = like extremely, 4 = like, 3 = neutral, 2 = dislike, 1 = dislike extremely.8
- **Test for thermal stability** Thermal stability of the formulation Diclofenac and Aceclofenac pain relieving gel was determined by the humidity chamber controlled at 60- 70% RH and 37 ± 1oC.
- **Patch test**: About 1-3gm of material to be tested was placed on a piece of fabric or funnel and applied to the sensitive part of the skin e.g. skin behind ears. The cosmetic to be tested was applied to an area of 1sq.m.of the skin. Control patches (of similar cosmetic of known brand) were also applied. The site of patch is inspected after 24 hrs. As there was no reaction the test was repeated three times. As no reaction was observed on third application, the person may be taken as not hypersensitive.
- **Analgesic activity:** the method described by Khan et al. was adopted for the study. In brief, animals were grouped into four groups, with four rats in each group. Group I was taken as control and was treated with vehicle base while groups 2, 3, and 4 were treated with test formulations; DF&A gel formulation respectively. In different treated groups, 300mg of respective formulations was applied on the dorsal surface of the right

hind paw with gentle rubbing. After 30 minutes, 20µl of 5% formalin was subcutaneously injected into the plantar aponeurosis of the right hind paw. The time spent in licking and biting responses of the injected paw was considered as an indicator of pain response. All the measurements were done for 5 min after formalin injections.

4. Result and discussion

The objective of the present study was to formulate Transdermal gels of Diclofenac sodium. Total twelve different Diclofenac sodium and aceclofenac pain relieving gel with different polymer ratios were prepared. In order to select the optimized formulation, various evaluation parameters were checked and subjected to in-vitro diffusion study and their release kinetic study were observed. The optimized formulation was further studied for ex-vivo permeation using ratabdominal skin. The project was undertaken with the aim to design gel formulation for topical delivery of Diclofenac, Aceclofenac pain relieving gel . Preliminary studies indicates that Carbopo940, and HPMC, can be used as a gelling agents and methanol as solvent. Different formulations were screened at preliminary level on the basis of drug solubility, drug release, spreadability, excrutability, Rheological behaviour, etc. The formulations have satisfactory Spreadability, Rheological behaviour and their diffusion profile was comparable to marketed gel formulation.

The formulations have shown stability over 45 days period at 37ºC + 20and 45ºC + 20ºC The procured sample of Diclofenac was tested for its identification. The quality of Diclofenac was confirmed by physical characterization, melting point, chemical test and UV-absorption maximain methanol. The results of these entire tests were in compliance with specification of Indian Pharmacopoeia. The IR- spectrum obtained for identification of Diclofenac. The different formulations using various water and ethanol Proportion were developed. Ethanol, propylene glycol has become recognized as a possible permeation enhancer in the topical drug delivery of drugs and to produce proper viscosity Carbopol 940 and h was used in combination.

Table 2 Evaluation Parameter and their result

S. no.	Parameters	Result
1	Molecular formula	$C_{14}H_{11}Cl_2NO_2$
2	Chemical name	2-(2,6-dichlorophenyl)amino benzene acetic acid
3	Molecular weight	318.13 g/mol
4	Wavelength of maximum absorbance	277nm
5	Melting point	275-277 °C
6	Solubility	Water: 50.0 mg/ml
7	pKa	4.15
8	pH	5.92
9	Viscosity	3045.31±1.12
10	Spreadability	23.05
11	Physical appearance	Clear
12	Skin irritation	No irritation

Figure 11 pH measurement

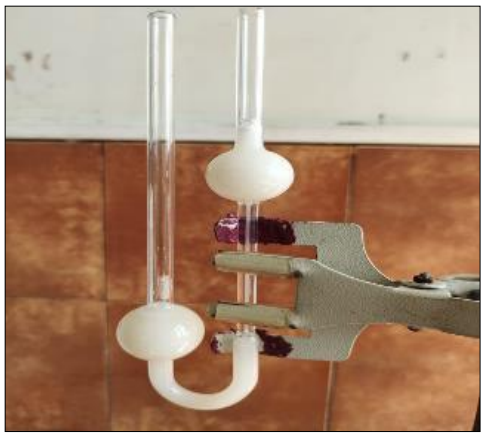

Figure 12 Viscosity measurement

Figure 13 Spreadability measurement

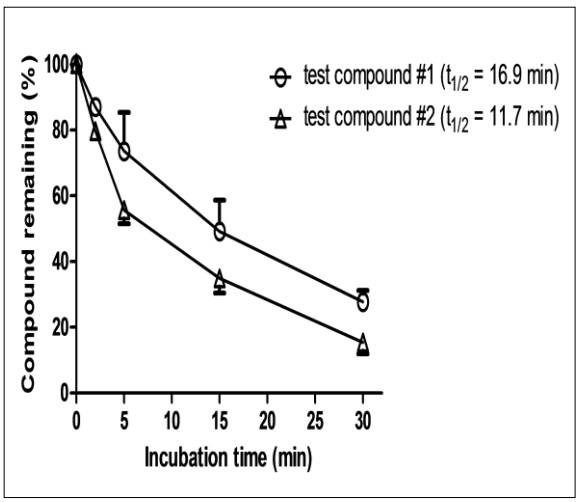

Figure 14 Thermal Stability Measurement

Figure 15 Consistency measurement

5. Conclusions

It was observed that Carbopol 934P gel containing Diclofenac sodium and aceclofenac in 1:2 ratio (produced better spreadability and consistency as compared to other formulations. The developed F4 gel showed good homogeneity, suitable pH, no skin irritation and good stability. The maximum percentage of drug release was found to be 98.68% in 6 hours in formulation. The drug permeation from optimized formulation i.e. this was slow and steady and 0.89 gm of Diclofenac sodium could permeated through rat abdominal skin membrane with a flux 0.071 gm hr-1 cm-2 and could

possibly permeate through human abdominal membrane. The Carbopol 934P forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system. Formulation batch (2% Diclofenac, Aceclofenac 10% PG, 0.15% Methylparaben, 0.05% PropylParaben,1.5% Carbopol 940, 67.44% ethanol,16.86% water) had shown higher amount of percent cumulative release as compared to marketed gel. Spreadiability of formulation was good to cover the painful area. In formulation the ethanol in following concentration had shown the higher penetration enhancer activity which result in higher drug release, flux and permeatability value. On the basis of organoleptic characteristic the improved patient acceptability was achieved through formulation. The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations. The release penetration enhancer and other materials are cheap, readily available, safe, having wide regulatory acceptance and easy to handle for economic point of view. It may beneficial to adopt such simple technology for the commercial production of Diclofenac Aceclofenac pain relieving gel. The future scope of this study is that formulation should be subjected for long-terms tability and in-vivo performance study.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Priya P. Munshi, D.S. Mohale, R. Akkalwar, A.V. Chandewar. Formulation and Evaluation of Diclofenac gel. Research J. Pharm. and Tech. 4(9): Sept. 2011; Page 1394- 1399.

[2] Kartin Moser,Katrin Kriwet, Aarti Naik, Yogeshwar N.Kalia, Richard H.Guy 2001,"Passive skin penetration enhancement and its qualification in vitro" European Journal of Pharmaceutics and Biopharmaceutics 52,103-112.

[3] Kumar, R., Katare O. P., 2005. Lecithin organogel as a potential phospholipid-structured system for topical drug delivery: A review, AAPS PharmSciTech. 40, 6 (2), E298-E310.

[4] Flynn, L. G., 1996. Cutaneous and Transdermal Delivery: Processes and systems of delivery. In: G. S., Banker, C.T., Rhodes, (Ed.), Modern Pharmaceutics, 3rd edition.Marcel Dekker Inc. New York, 239-298.

[5] Indian Pharmacopoeia 2007;"Government of India ministry of health and family welfare, volume 2,1ssu2, 1020-1021.

[6] Garg Alka, Aggarwal Deepika, Garg Sanjay, and Singla Anil K. ,SEP-2002, "Spreading of Semisolid Formulation update", Pharmaceutical Technology,(www.Pharmtech.com), 84-102.

[7] Magdy I. Mohamed, 2004 "Optimization of Chlorphenesin Emulgel Formulation", The AAPS Journal 6 (3) Article 26,1-7.

[8] Indian Pharmacopoeia, 1996. Volume II, Appendix 13.2, Controller of publications, Ministry of Health and Welfare, Govt. of India, Delhi, A-1

[9] Shrikhande B. K., and Goupale D. C.: Devlopment and evaluation of anti-inflammatory oleogels of Bosewella serrata (gugul) and Curcuma longa (turmeric), Indian Drugs, 2001, 38 (12), 613 – 616.

[10] Indian paharmacopoeia2007.Volume II, Appendix , Controller of publications, Ministry of Health and Welfare, Govt. of India, Delhi, A- ,1021

[11] Bidkar sanjay, jain devendra, padsalg amol, patel kishna and mokale vinod,Apriljun2007, " Formulation evelopment and evaluation of fluconazole in various polymer Based formulation development evaluation of fluconazole gel in various polymer bases," Asian journal of pharmaceutics,volume1,issue1, 63-68

[12] Hsieh D.,Drug Permeation Enhancement-Theory and Applications. In Drug and the Pharmaceutical Sciences, New York, Marcel Dekker, 1987; 11-13

[13] Langer R., Transdermal Drug Delivery: Past progress, current status and future prospects. Adv Drug Deliv Rev. 2004; 56: 557-558.

[14] Barry B., Transdermal Drug Delivery. In: Aulton ME, Pharmaceutics. The science of dosage form design. 2nd ed. Churchill, Livingstone, 2002; 499-543.

[15] Idson B.,Jack L.,Semisolids. In: Lachmann L, Liebermann HA and Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd ed. Bombay: Varghese Publishing House, 1990; 534-563.

[16] Pena LE., Gel dosage form: Theory, Formulation and Processing. In: Osborne DW, Amann AH. Topical drug delivery formulation. New York, Marcel Dekker; 1990; 381- 388.

[17] Alberto B., Clinical pharmacokinetics and metabolism of Nimesulide in flammopharmacology. 2001; 9: 81-89.

[18] Sankar S V.,Chandrasekharan AK.,Durga S., Prasanth KG., Nilani P., Formulation and stability evaluation of diclofenac sodium ophthalmic gels. Ind. J. Pharm. Sci. 2005; 67(4): 473-476.

[19] Lakshmi P K.,Marka K K.,Aishwarya S., Shyamala B., Formulation and evaluation of Ibuprofen Topical gel: A Novel approach for penetration enhancement. Int.J. Applied Pharm. 2011; 3 (3): 25-30.

[20] Swamy N.G.N., Mazhar P., Zaheer A., Formulation and evaluation of Diclofenac sodium gels using Sodium carboxymethyl Hydroxypropyl Guar and Hydroxypropyl methylcellulose. Indian J. Pharm. Educ. Res. 2010; 44 (4): 310-314.

[21] P.B.Patil, S.K.Datir, R.B.Saudagar. Journal Of Drug Delivery And Therapeutics.2019; 9 (3-S),989-994.

[22] Poonam Madhukar Kasar, Kalyanisundarrao Kale, Dipti Ganesh Phadtare International Journal Of Current harmaceutical Research- 2018 ;10(4),71-74.