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A RESEARCH ON FORMULATION AND EVALUATION OF DICLOFENAC SODIUM GEL BY USING CARBOPOL 940

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ABSTRACT

The present investigation is concerned with formulation and evaluation of Transdermal gels of Diclofenac sodium, anti-inflammatory drug, to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. Three formulations were developed with varying concentrations of polymers of Carbopol 940. The best in-vitro drug release profile was achieved with the formulation F1 containing 1 gm of Diclofenac sodium with desired therapeutic concentration which contains the drug and Carbopol 940 in the ratio of 1:2. The present research has been undertaken with the aim to develop a topical gel of diclofenac sodium gel (DS) 1%, evaluation of its physico chemical characteristics. The main objective of this research paper is to prepare and evaluate 1% polymer containing transdermal gel of Diclofenac Sodium. The gel was prepared and evaluated for pH, Spreadability, Consistancy, Homogeneity, Drug Content, Extudibility. The carbopol is high molecular weight water soluble homo polymer which posses high viscocity in low concentrations, transparency, and film Forming properties these are useful for gel formation. The percentage of drug release was 97.68%. The present study suggests that the Diclofenac sodium effectively act as in vitro anti-inflammatory activity.

KEYWORDS: Transdermal gel, Viscosity, In-vitro drug release, Topical Drug Delivery, Anti-inflammatory, Water Soluble Polymer, Carbopol940.

INTRODUCTION

Drug delivery through the skin has been a promising conception for a long time because the skin is easy to access. Diclofenac Sodium is a potent member of the non-steroidal anti-inflammatory drugs (NSAIDs), globally used because of its strong analgesic, antipyretic and

anti-inflammatory effects. Topical gel preparation is intended for skin operation and to certain mucosal surfaces for local action of percutaneous penetration of drug of or for their emollient and defensive action. The Diclofenac sodium has a short half- life in plazma (2 hrs) and only 50 of the drug reaches the circulation. NSAID's are non-steroidal medicaments having excellent anti-inflammatory and analgesic activity but NSAID produces GIT ulceration, liver and kidney.

Delivery of drugs to the skin is an effective and targeted treatment for local dermatological diseases. This route of drug delivery has gained acceptance because it avoids first pass effects, gastrointestinal irritation, and metabolic devolution associated with oral administration. Topical gel formulations give a suitable delivery system for drugs because they're thixotropic, greaseless, easily spreadable, freely removable, emollient, non staing, compatible with several excipients and water-soluble or miscible. Percutaneous concentration of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue or organ. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. An advanced Diclofenac formulation with a high degree of skin permeation could be useful in the treatment of not only locally inflamed skin tissues, but also inflammatory and painful states of supporting structures of the body bones, ligaments, joints, tendons and muscles.

The ideal of present study was conducted to develop a topical gel formulation of diclofenac sodium using carbopol 940 gelatinizing agnt for enhancing the skin penetration. Effect of penetration enhancer (propylene glycol) on the release has been studied. The gels were evaluated for physical appearance, rheological charasteristics, drug release and stability.

Hydrogels are three-dimensional structures with the capability to absorb and hold a high quantity of water without losing structural consistency. Hydrogels are very stable by nature; due to which, the solutions absorbed by hydrogels remain inside its network, even in the presence of any external force. Due to the presence of a high number of hydrophilic groups like –OH, –SO3H, –COOH, –NH2, etc. on a polymer chain, a huge quantity of water is absorbed by hydrogels. Similarly, a significant role is played by these different hydrophilic groups of polymers in the formation of non-covalent bonds of hydrogels with other numerous biological tissues like epithelial tissues andmucous membranes. Two types of crosslinking occur in hydrogels, i.e., (a) physical or (b) chemical, which restricts the hydrogels from being

dissolved even when holding a high concentration of water or other fluids. In physical hydrogels, crosslinking arises due to noncovalent bonding such as hydrogen bonding amid the polar groups on the chains of the polymer, while, in chemical hydrogels, crosslinking develops through covalent bonds among various functional groups on the chains of the polymer enabled through distinct crosslinking agents. While having distinct properties, hydrogels are considered as a potential candidate for various biomedical applications, including drug delivery and tissue engineering, due to their super-absorbency, softness, viscoelasticity, hydrophilicity, biocompatibility and biodegradability. Prominently, minor damage to the tissue or minor toxicity is caused by hydrogels. The reversible responses to various stimuli such as pH, temperature, electric field, magnetic field, biological molecules and ionic strength of a solution is another astonishing property of hydrogels that enhances their importance further, particularly for widespread biomedical applications. Stimuli-sensitive hydrogels are a special type of hydrogel that are very sensitive by nature to certain ecological changes, and responses are shown by either altering their volume or shape once visible to a specific condition. The external stimulus may be physical, chemical or biological. The physical stimuli include pressure, light, temperature, ultrasound, electric field and magnetic field, while chemical stimuli are redox, ionic strength, pH, glucose and CO2, whereas biological stimuli are antigens, glutathione, enzymes and DNA. The most-studied hydrogels amid stimuli-responsive hydrogels are pH-sensitive hydrogels. The rapid changes that are exhibited by stimuli-sensitive hydrogels are shrinkage and swelling following exposure to a particular stimulus, leading to the transition of the volume phase. The response rate of these types of hydrogels depends upon the shape, size, crosslinking bulk, composition and number of ionic groups and is enhanced via an increase in the ionic group number and pore size, as well as by reduction of their density of crosslinking and size. Carbopol polymers prepare stimuli-responsive hydrogels that bring about changes in swelling behavior when exposed to external stimuli such as temperature, pH, light or electric field. Carbopol is also known as smart gels or environmentally responsive polymers. Currently, carbopol is considered as a suitable candidate for the preparation of different types of polymeric systems, especially for controlled drug-delivery systems, and plays an important role in drug delivery to a specific area of the body. In pH-sensitive hydrogel networks, carbopol delivers the maximum drug in an alkaline medium because of its greater swelling at alkaline pH. Acrylic acid is a soluble polymer that has attracted attention because of its widespread biomedical and pharmaceutical applications. Acrylic acid is a pH-sensitive polymer used in stimuli-sensitive polymeric carrier systems, especially in pH-sensitive hydrogels like carbopol, and

has maximum swelling at alkaline pH and, hence, releases the drug in a high concentration at alkaline pH. Diclofenac sodium (DS) is prescribed mostly as a nonsteroidal anti-inflammatory drug (NSAID) for inflammation and pain, acting as a modest, competitive and irreversible inhibitor of the enzyme prostasin synthase. Inhibition of the cyclooxygenase-2 (COX-2) enzyme with a higher potency as compared to COX-1 is the one of the key benefits of diclofenac derivatives as compared to other conventional NSAIDs. Besides efficient activity, DS has some disadvantages, such as its rapid metabolism due to a short half-life, high protein binding and a very high pre-systemic metabolism. These all generate the need for frequent high doses of DS, which further causes severe side effects like cardiac, gastrointestinal, hepatic and renal adverse effects. In order to overcome all these limitations, Carbopol 940 hydrogels were prepared to prolong the release of diclofenac sodium in a controlled way. Different formulations with varying concentrations of constituents were assessed and their various parameters evaluated. The swelling behavior of the developed hydrogels was analyzed at various pH media concentrations systematically.

Preformulation studies

Diclofenac sodium: Description The sample of Diclofenac sodium was analysed for its nature, colour and taste.

- **Solubility Studies:** Determine the solubility of diclofenac sodium in various solvents such as water, organic solvents, and buffer solutions over a range of pH values. This information is crucial for selecting suitable solvents for formulation development and for predicting the drug's behavior in different physiological environments.
- **pH-Solubility Profile:** Construct a pH-solubility profile to understand the influence of pH on the solubility of diclofenac sodium. This helps in selecting the optimal pH conditions for formulation and assessing the drug's ionization behavior.
- **Melting Point:** The melting point was determined by using thiesel’s tube apparatus method. Determine the melting point of diclofenac sodium to establish its thermal stability and identify potential degradation temperature ranges.
- **Hygroscopicity:** Evaluate the hygroscopic nature of diclofenac sodium by studying its tendency to absorb moisture from the surrounding environment. This information is crucial for determining appropriate packaging requirements and storage conditions.
- **Compatibility Studies:** Conduct compatibility studies of diclofenac sodium with excipients commonly used in pharmaceutical formulations. This includes evaluating

physical, chemical, and thermal compatibility to avoid potential interactions or degradation during formulation development.

- **Stability Studies:** Assess the stability of diclofenac sodium under various storage conditions (e.g., temperature, humidity, light) to determine its shelf-life and establish suitable storage recommendations.
- **Particle Size Analysis:** Determine the particle size distribution of diclofenac sodium to optimize formulation parameters such as dissolution rate, flow properties, and bioavailability.

Characterization of Diclofenac sodium: The following tests were performed according to British Pharmacopoeia.

Description: A white or almost white powder

Solubility: Methanol and Ethanol

Melting Point: 296.149˚C

From these tests it was confirmed that the sample complies with the monograph.

METHODOLOGY

Materials

Diclofenac sodium was purchased from Yarrow Chem. Products, Mumbai, India. HPMC K100M was obtained as a gift from Colorcon, Mumbai, India. Carbopol 934P was purchased from Genuine Chemicals, Mumbai, India. All organic solvent used were of analytical grade.

Table 1: List Of Materials.

Materials	Manufacturer
Carbopol 940	Kemphasol., Mumbai.
Triethanolamine	Emplura®merck life science private Ltd
Propylene glycol	Nice ®chemicals (p) LTD.
Methanol	Changshu Hongsheng fine chemicals co., Ltd.
Diclofenac sodium	Amoli organics PVT Ltd, vapi Gujarat.
Methyl paraben sodium	BRM chemicals

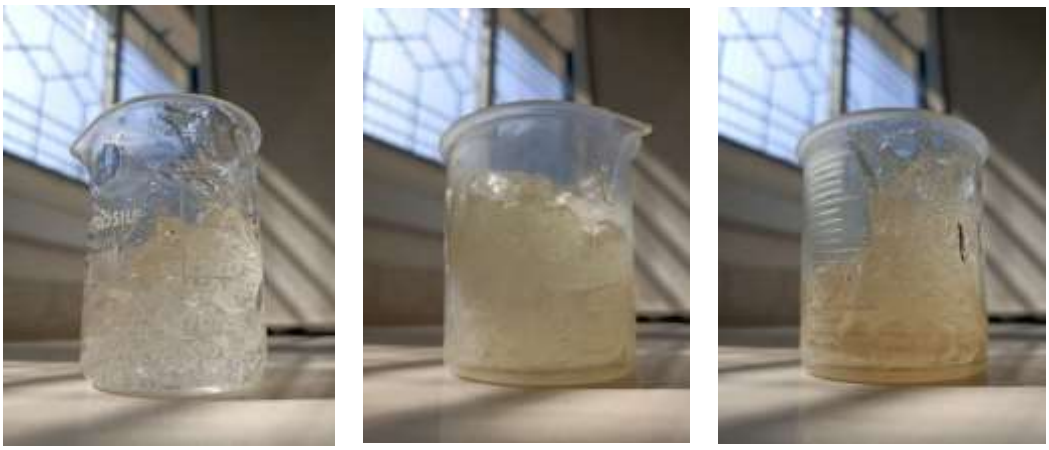
Table 2: List of Equipments.

Equipments	CompanyName
PH meter	Elico
UV spectrophotometry	Merck
Viscometer	Brook field viscometer
Electronic weighing balance	Shimadzu
Rotatory Shaker	

METHODS

Preparation of gel

Carbopol 940 gels were formulated by first preparing a stock result of the Carbopol in distilled water and propylene glycol. Independently Diclofenac sodium(1w/ w) was dissolved in preweighted quantities of propylene glycol. Then methyl paraben sodium was dissolved in a given quantity of water, heat it until it reaches 70°c. Dissolve the methanol in minimum amount of propylene glycol this was added to the formed. When it reaches 50°c dissolve the drug in propylene glycol and this was added to the formulated when it comes 40°c.when the formulation comes under 40°c. Solvent mix was transferred to carbopol vessel and agitated for fresh 20 min. The dissipation was also allowed to hydrate and swell for 60 min, eventually conditioned neutral pH by sodium hydroxide result with stir. add the triethanolamine until the clear, transparent gel was formed. also samples was allowed to equalize for at least 24 hours at room temperature previous to performing rheological measures.



F1 **F2** **F3**

Table 3: It shows gel formulations.

Sr. No	Ingredients	Formulations		
		F1	F2	F3
1	Diclofenac Sodium	1 gm	1 gm	1 gm
2	Carbopol 940	1 gm	1.5 gm	2 gm
3	Propylene Glycol	15 ml	15 ml	15 ml
4	Methyl paraben	0.1 gm	0.1 gm	0.1 gm
5	Triethanolamine	0.30 ml	0.30 ml	0.30 ml
6	Water up to	100 ml	100 ml	100 ml

Table 4: List Of Ingredients & Their Uses.

INGREDIENTS	USE
Diclofenac sodium	Osteoarthritis, Rheumatoid arthritis
Carbopol 940	Gelling Thickener
Triethanolamine	Neutralizer & PH Adjuster
Methyl paraben sodium	Anti-Microbial agent
Propylene glycol	Moisturising agent
Methanol	Provide an acidic environment

Evaluation of Carbopol 934 P gel containing diclofenac sodium gel and marketed gel

The above formulated Diclofenac Sodium gel containing polymer carbopol 940 and marketed gel were subjected to evaluation for the following parameter :

1. Homogeneity

All formulated gels were tested for homogeneity by visual examination after the gels have been set in container. They were tested for their appearance and presence of any acculumations. The results are shown in table below.

2. Grittiness

All the formulated gels were evaluated microscopically for the presence of of fragments if any no detectable particulate matter was seen under light microscope. Hence obviously the gel formulation fulfils the conditions of freedom from particulate matter and from gritiness as desired for any topical preparation. The results are shown in table below.

3. Spreadability

Sprediability of the formulations is checked manually by taking the formulation on slide and spreading it by another slide. Results are shown in table below.

4. pH

The pH of the gel formulations was determined by using digital pH meter(Systronic Instruments, India) by placing the glass electrode fully dipped into the gel system and measure the pH, which was calibrated before each use with standard buffer results at pH 4, 7, 9 and also Measured. The results are shown in table below.

5. Drug Content

A specific amount (100 mg) of developed gel and marketed gel were taken and dissolved in 100 ml of phosphate buffer of pH 6.8. The volumetric beaker containing gel result was shaken for 2 hrs on mechanical shaker in order to get complete solubility of drug. The result

was filtered and estimated spectrophotometrically at 276.0 nm using phosphate buffer pH6.8 as blank. The results are shown in table below.

6. Viscosity

The viscosity of the preparation was determined using a Brookfield digital viscometer (model DV-II, USA) and it was equipped with spindle S27. The gel sample (5 g) was placed in the sample holder of the viscometer and allowed to settle for 5 min and the viscosity measured a rotating speed of 50 rpm at room temperature (25 - 27℃). The results are shown in table below.

7. Consistency

Measurement of consistency of the gels was carried out by dropping a cone attached to a holding rod from a fix distance of 10 cm in such way that it falls in the centre of a glass cup filled with the gel. The penetration by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by the cone after 10 s was noted. The results are shown in table below.

Table 5: Evaluation Parameters.

Parameters	Formulations		
	F1	F2	F3
Homogeneity	Excellent	Good	Satisfactory
Grittiness	Absent	Persent	Present
Spreadability	27.00	19.05	20.66
PH	7.4	7.9	8.9
Physical appearance	Clear	Turbid	Clear
Viscosity(cps)	3045.31±1.12	3189.28±1.09	3369.34±1.09
Consistency	+++	++	++
Drug Content (%)	94.44	89.55	91.84

RESULT AND DISCUSSION

The goal of this study was to develop suitable topical gel formulations of diclofenac sodium gel using Carbopol 940 as a gelatinizing agent and propylene glycol as permeation enhancer. The viscosity reflects the capacity of the gel, to get ejected in constant and desired volume when the tube is squeezed. The formulated and marketed gel showed good homogeneousness with absence of lumps. It was observed that the F1 formulation produces better spreadability and thickness as compared to marketed diclofenac sodium gel. The formulated F1 gel showed good homogeneousness, good thickness and in vitro permeability was similar with marketed

gel. The carbopol 940 forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system Inhibition of egg albumin denaturation their comparison between sample and standard. From this experimental results showed significant inhibition of denaturation of egg albumin in concentration dependent manner.

CONCLUSION

Diclofenac sodium is an on-steroidal anti - inflammatory medicament (NSAID) that exhibits anti - inflammatory, analgesic, and antipyretic activities. To overcome the side effects associated with oral diclofenac sodium remedy and to have the benefits associated with topical remedy; diclofenac sodium topical gels are prepared in this study. It has been observed that the formulated F1 gel produces with good consistency, homogeneity, spreadability. Since the polymer is water soluble; consequently, it forms water washable gel and has wider prospect to be used as a topical drug delivery dosage form. Protein denaturation is a process in which protein lose their tertiary structure and secondary structure by operation of external stress as strong acid, an organic solvent or heat most biological protein lose their biological function when denaturation. Denaturation of protein is a well-proved cause of inflammation. As a part of the study on the mode of the anti- inflammatory activity, ability of diclofenac sodium to inhibit protein denaturation was studied. Other anti-inflammatory drugs have showed dose dependent ability to inhibit thermally induced protein denaturation. Denaturation of protein is a well document cause of inflammation.

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