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Formulation, Development and Physicochemical Characterization of Diclofenac Topical Emulgel

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Abstract

Emulgel is one of the convenient and promising topical drug delivery approaches especially for the hydrophobic drugs. The purpose of the study was to prepare emulgel of diclofenac sodium using polymers namely Carbopol-934, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose and studied for their drug release from the gel formulations. The 1% Carbopol-934 formulated gel was found highest drug content (101.72%) than the other formulations. The pH of the formulations ranged from 6.8 to 7.2 and viscosity is from 36,000 to 51,000 cps. Extrudability of carbopol and HPMC gels were excellent than the SodiumCMC gel. *In vitro* drug release was observed highest (64.91%) for the formulation A2 (1% Carbopol-934) and was improved further on the addition of DMSO as a permeation enhancer. In the same time, 1.0% carbopol-940 also showed a similar release pattern, but the release was lesser (51.47%) and the release of HPMC and sodium CMC gels was much lesser. The study revealed that formulation A2 with 1% Carbopol-934 was observed to be the best formulation having good *in vitro* release profile, stability and bioavailability among all prepared formulations. Hence, the study brought to a close idea that the emulgel A2 was a successful outcome as a topical anti-inflammatory and analgesic formulation among all.

*Keywords***:** Emulgel, Topical drug delivery, Diclofenac sodium, nonsteroidal anti-inflammatory drug, Carbopol-934

1. Introduction

The skin, largest organ of human body, acts as a formidable barrier which provides protection against invading pathogens. [1]. It has been accredited to the outer most layer stratum corneum acts as an effective barrier to most inorganic nanosized particles and represents a foremost challenge in clinical practices in concern to cutaneous administration of drugs [1, 2]. The major function that the skin usually accountable is to show variety of inflammatory processes to protect internal organs from bacterial disease by developing autoimmunity or immunity against microbial infection [3]. The skin has long been used as topical or parenteral route of drug delivery approaches. But the limitations allied with skin permeation now require appropriate technology for successful delivery of active substance/drugs to the target site in a sufficient quantity [4, 5]. The skin not only acts as drug release from an external reservoir but it can act as a reservoir for the slow going release of drug [4, 6]. The appraisal of percutaneous permeation is a successful technology to develop newer formulations anticipated for human use. Topical NSAIDS are frequently applied to the skin in the form of lotion, gel, ointments and creams to target tissues directly below the application site. A grafted chitosan microcapsules delivery method was developed for colon site-specific release of diclofenac sodium and studied *in vitro* drug release profile which observed effective delivery of diclofenac sodium to colon tract.[7] Drugs which are applied topically have been investigated as an alternative to intravenous or parenteral route, but transdermal delivery is frequently constrained by using negative drug permeability [6]. The general ways to improve drug penetration through skin is to facilitate the use of penetration enhancers in topical formulations. The interaction of the

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enhancers with the polar head groups of the lipids is the possible way to increase the permeation of drug molecules [8]. Permeation enhancer's increases the content of free water molecules between the bilayer, which cause to an augmentation of the cross-section for polar drug diffusion [8, 9]. There are six types of permeation enhancers which are mentioned in figure **1**.

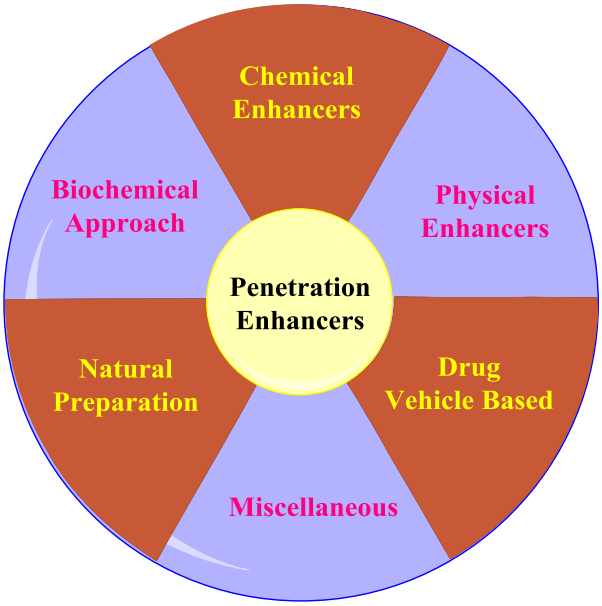


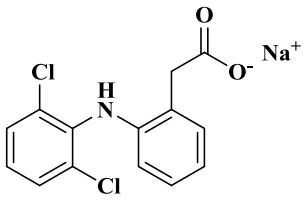
Fig. 1. Types of permeation enhancers

The certain class of penetration enhancers which can make penetration easier through skin are chemical, biochemical, physical, natural or as drug vehicle or carrier. Pyrrolidones, alcohols, alkanols, sulfoxides, glycols, surfactants and terpenes are the penetration enhancers used in nanoformulation. Physical enhancer like thermophoresis, needless injection, magnetophoresis can improve the penetration by ultrasonic, magnetic and physical separation. Chemical enhancer like pyolidones, azones, oxizolidinones, cyclodextrines are used to disturbing the ordered structure of stratum corneum interacting with the proteins to improve the drug partition [10, 11]. Terpenes (1,8-cineole, menthol, limonene, thymol) [12-14] and essentials oils (neem oil, chenopodium, basil oil) are used as skin penetration enhancers and act as promising non- toxic, non- irritating agents to improve the bio-availability of both lipophilic and hydrophilic drugs [8, 12, 15]. The effects of natural penetration enhancer could be increased with increase in diffusion coefficient, partition coefficient, solubility of drug extraction of lipids, terpenes molecular orientation with lipid bilayer [12, 14, 16]. Resveratrol, a natural antioxidant polyphenol, is useful as nanocarrier for tareted topical skin delivery[14, 17, 18] and also used for enhancement of *in vivo* human skin penetration by chitosan-coated lipid microparticles.[17, 19] Another natural bioactive sulfur containing compound Allicin upon oral administration showed a comparable anti-inflammatory effect with the standard Diclofenac sodium in rat models.[20] Miscellaneous enhancers such as phospholipids, clofibric acid reduce the diffusion resistance of the intercellular domains by inserting itself into the lipid bilayers within the intercellular channels thereby disrupting their stacking [16]. The use of polymer–drug conjugate was found to be better drug release in drug delivery system.[21-23] Saleh et al., studied the drug release of new polymeric prodrug using chitosan and levofloxacin conjugate and evaluated for its drug content and *in vitro* drug release in acidic media and evaluated the antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* species.[22]

The concentration of drug may not define the skin absorption as the absorption is not dependent upon the concentration of drug. Whereas the route of administration, poor aqueous solubility and poor permeability of drug molecule is significantly affect the absorption of a drug molecule [24]. An investigation by Pradal et al. concluded that greater in concentration of diclofenac does not effectively lead to greater skin relative to the drug with lower concentration. [25]. The Bholla et al. investigated different Ibuprofen topical semisolid preparations (Creams and gels) where the permeation through the Strat-M® membrane was found to be highest for clear gel followed by cream due to the influence of formulation parameters like physical state, formulation type and concentration etc. [26, 27] Liu Wenliet al. prepared and evaluated self-microemulsifying drug delivery system which resulted the drug release rate of SMEDDS significantly higher than that of the baicalein suspension when studied under different parameters [28]. Singh A K et al. (2009), prepared a self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of a feebly water soluble drug, Exemestane. The relative

bioavailability of Exemestane was enhanced by 287.32% [29]. In another study, diclosomes, a topical formulation was found to be a booming diclofenac gel which helped to increase drug accumulation in the *stratum corneum* and also supports its permeation across skin [30]. Further developed unani emulgel showed good outcome in physicochemical parameters and useful for topical delivery of hydrophobic drugs [31]. The formulation diphenhydramine nasal nano-emulgel was observed excellent penetrating ability for targeted control delivery to mucus membrane and found to be effective anti-inflammatory and antihistaminic effects [32]. In another study, formulated topical emulgels of mefenamic acid were observed to be well comparative analgesic and anti-inflammatory activity when compared with marketed diclofenac sodium gel [33]. A preparation with thymol loaded nanoemulsion was found to be good penetration and useful aqueous-based gel vehicle with better efficacy [34]. Our earlier discovery p-coumaric acid derivative was found to be suitable for intraperitoneal as well as oral route of administration with good absorption rate in mice plasma [35]. Later study also proved that there was shown improvement in diclofenac action in the presence of IS01957 involving MAPK pathways when associated oral administration [36]. Hence to demonstrate the important factors behind permeation of drug formulations, *in-vitro* release studies were under taken across the cellophane membrane using a diffusion cell. The percentage of drug release, the qualitative composition and physicochemical characteristics of diclofenac formulations were also assessed in order to observe better skin permeation and faster drug release from the formulation.

2. Material and Methods



Diclofenac sodium

The drug diclofenac sodium was obtained as a gift from Microlab Ltd, Ahmedabad, Gujurat. The other materials and chemicals used for the study were bought from different chemical suppliers like as Carbopol-934 and carboxymethylcellulose sodium (Kemphasol, Mumbai), hydroxypropylmethyl cellulose (Himedia Lab, Mumbai), propyl paraben (National Chemicals), triethanolamine (Reachem Labs, Chennai). All chemicals used were of analytical grade. Ethanol and hydrochloric acid was of HPLC grade and were purchased from Nanda Enterprises Mumbai, India. The equipment used used were, electronic balance (Wensar), hydraulic compression machine (Technosearch), UV/Vis spectrophotometer (Jasco V-630), hardness tester (Dr. Schleuinger Pharmaton), disintegration apparatus (Technolab), dissolution apparatus (Electrolab TDT06L), FT-IR (Jasco 4600) and XRD (Miniflex 600).

For carrying out experiment the required apparatus like glass plate, petridis, beaker, measuring cylinder and volumetric flask were purchased from Borosil. The equipment used were, digital electronic balance (S.d. fine chem. Ltd), Keshary-Chien diffusion cell (S.K. Scientific Glass Work, Siripur, BBSR), pH Meter (Labtronics, India) UV/Vis spectrophotometer (Model-2203, Systonics, Ahmedabad), screw gauge (Sterling manufacturing company), Magnetic Stirrer with Hot Plate (Macro scientific works, Delhi), Remi stirrer (Remi equipments), Viscometer (Brookfield) and centrifuge (Remi equipments).

2.1 Method for the estimation of Diclofenac sodium[37]

I. Preparation of pH 7.4 phosphate buffer: Accurately weigh 0.8 g of potassium dihydrogen phosphate and dissolve it in sufficient quantity of distilled water and make up the volume to 200 ml using a measuring cylinder.

II. Preparation of Standard graph of Diclofenac Sodium hydrochloride in 7.4 pH phosphate buffer.

Stock I: Accurately weigh amount 100 mg of Diclofenac Sodium hydrochloride into a 100 ml volumetric flask and was dissolved in 20 ml methanol the volume was made up with buffer solution.

Stock II: From stock solution-I, 10 ml is withdrawn in to volumetric flask, made the volume up to 100 ml with the buffer solution concentration of the solution is to be 100µg/ml.

Stock III: From the second stock solution (100 µ/ml), concentrations of 5, 10, 15, 20, 10, 12 µg/ml solutions were prepared and corresponding absorbance was measured at 237 nm in an UV visible spectrophotometer.

2.2 Method for Pre-formulation studies [38]

The standard solutions of diclofenac salt (sodium/ potassium/ diethylamine) in buffers (1.2, 4.0, 5.5, 6.8 and 7.4 pH) having a concentration of 10mg/ml were prepared. The solutions were scanned over the wavelength range of 250-350 nm against the respective buffer solution used as blank. The absorbance was recorded in a double beam UVspectrophotometer to determine the wavelength of maximum absorbance. The studies were conducted in triplicate to check the repeatability (n=3).

(Note: Buffer solutions for all the experimental procedures were prepared as per the standard procedure published in Indian pharmacopoeia 2010).

2.2.1 Preparation of standard curve of Diclofenac salts

Diclofenac has been quantitatively analyzed by various techniques. In the present study, diclofenac was estimated by UV spectrophotometric method.

2.2.2 Preparation of primary stock solution

About 100 mg of diclofenac salts (sodium/ potassium/ diethylamine) was weighed and dissolved in about 5ml of methanol. The volume was made up to 100ml with buffer solution (1.2, 4.0, 5.5 and 6.8pH) to get a primary stock solution of 1mg/ml.

2.2.3 Preparation of working standard solution

Working standard solutions having concentrations 5 to 25 µg/ml were prepared by suitably diluting the primary stock with buffer (1.2, 4.0, 5.5, 6.8 and 7.4 pH) respectively. The absorbance of the each working standard solution was measured and a graph of concentration of the solution was plotted against absorbance in Microsoft Excel software. The studies were conducted in triplicate (n=3) to check the reproducibility.

2.3 pH Solubility profiling of diclofenac salts [38]

Solubility of diclofenac sodium, potassium and diethylamine in buffers of varying pH was determined in order to find out the most suitable solvent for further studies. The studies were conducted in 5 different buffers of different pH as suggested by Higuchi and Connors.

An excess amount of diclofenac salt (sodium/ potassium/ diethylamine) was added to 10 ml of buffer (1.2, 4.0, 5.5, 6.8 and 7.4 pH) in a series of stoppered conical flasks. The samples were shaken for 24 hours at room temperature on a rotary flask shaker (Remi instruments, Mumbai, India). After equilibration, samples were filtered using Whatmann filter paper no. 42 (0.45µm pore size) to separate the undissolved drug, diluted suitably and assayed for diclofenac content by measuring the absorbance at 276 nm against the respective buffer as blank. The solubility experiments were carried out in triplicate to check the repeatability.

2.4 Partition coefficient

The n-octanol-water partition coefficient is a measure of the relative lipophilicity of a compound. The partition coefficient of the diclofenac sodium was determined by equilibrating the drug with equal volume of n-octanol (organic phase) and phosphate buffer pH 7.4 (aqueous phase) in a separating funnel and shaking intermittently for a time period of 24 h at room temperature. The aqueous phase was assayed before and after equilibration to obtain partition coefficient.

2.5 Preparation of emulgel [38]

A varying amount of gelling agents and penetration enhancers were used to prepare different diclofenac emulgel formulations. Diclofenac gels were formulated using different polymers like Carbopol 934, hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose.

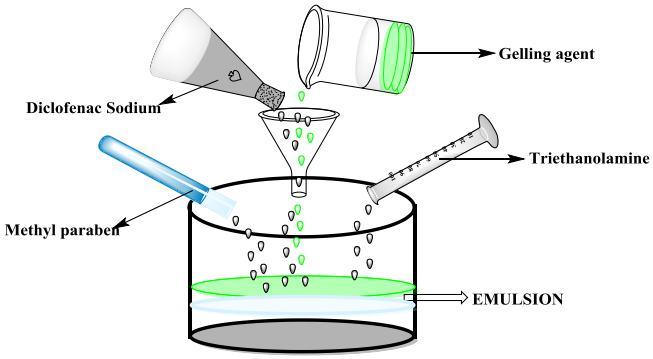


Fig. 2. Graphical presentation of preparation of verity of Emulgels

Different concentrations of polymer were used in the formulation of gels. The concentrations chose varied with the polymer used. After initial trials, the concentrations that gave products of good consistency were selected for the formulation. The concentration of drug taken in all the formulation remained constant. The methods employed for preparation in the process of making gel as mentioned here (**Fig. 2**).

2.5.1 Method for preparation of carbopol 934 gel[38]

Accurately weighed required quantity of Diclofenac was dispersed in purified water with constant stirring and the drug solution was heated to 500 °C. To this solution methyl paraben was added as a preservative. The carbopol-934 was added to the solution under stirring while temperature was maintained at 500 °C.

The dispersion of gelling agent was neutralized by addition of triethanolamine solution to attain the neutral pH. Stirred the mixture slowly till a clear gel was obtained. Three formulations **A1**, **A2** and **A3** were prepared as per the amount of carbopol-934 used to prepare 100 mg of desired formulations as presented in **Table-1**.

2.5.2 Method for preparation of hydroxy propyl methyl cellulose gels [38]

Following the method of preparation of carbopol 934 gel 2.5.1, the preparation of hydroxyl propyl methyl cellulose (HPMC) gel was carried out wherein the carbopol 934 was replaced by the use of HPMC. Three formulations B1, B2 and B3 were prepared as per the amount of HPMC used to prepare 100 mg of desired formulations (**Table-2**).

2.5.3 Method for preparation of sodium carboxy methyl cellulose gels

Following the method of preparation of carbopol 934 gel 2.5.1, the preparation of sodium carboxy methyl cellulose (sodium CMC) gel was carried out wherein the carbopol 934 was replaced by the use of sodium CMC. Three formulations C1, C2 and C3 were prepared as per the amount of sodium CMC used to prepare 100 mg of desired formulations (**Table-3**).

2.6 Method for evaluation of prepared gels

2.6.1 Method for checking stability studies

The assessment procedure for the stability of a pharmaceutical product lies in the capability of a formulation to retain its physical, chemical and therapeutic specifications. A general methodology for predicting the stability is accelerated stability analysis in which the materials are subjected to elevated temperatures [30]. This does not hold good for gels, as they melt at higher temperature conditions.

The gel formulation was stored for a period of three months. Samples were withdrawn at monthly intervals for a period of three months and assessed for the drug content. At the end of third month they were evaluated for physical parameter and integrity of the product [30, 32].

Thus the most commonly applied temperatures are refrigeration (4-5 °C), room temperature (25- 30 °C) and 37±5 °C. Then the samples were checked at the regular intervals of 1, 2 and 3 months. Different parameters considered for analysis are shown below [32].

2.6.2 Physical evaluation of gels

The physical parameters considered for the evaluation were (i) visual appearance, (ii) nature of the product, (iii) pH, (iv) viscosity, (iv) leak, (v) phase separation and (vi) extrudability [32, 38, 39].

2.6.3 Chemical evaluation

Drug content analysis of active ingredients: The drug content of the formulation was estimated by withdrawing samples from different corners of the tube. The samples were mixed together and 1g was taken for the assay. The estimation of drug content was carried out as per the procedure. The selected formulation was filled into aluminium collapsible tubes and stored at (a) room temperature, (b) 37±5 °C (c) 4-5 °C [38].

2.7 Procedure to conduct skin irritation test (patch test)

The primary skin irritation test was performed on healthy albino rabbits, weighing between 2.0 kg. The gel formulation film was prepared and used as test patches, while adhesive tape (USP) was used as control. The test was conducted on unbraided skin of the rabbits. The control and test patches were placed on the left and right dorsal surfaces of the rabbits respectively. The patches were removed after 24 hours with the help of alcohol swab and the skin was examined for erythema and edema[39, 40].

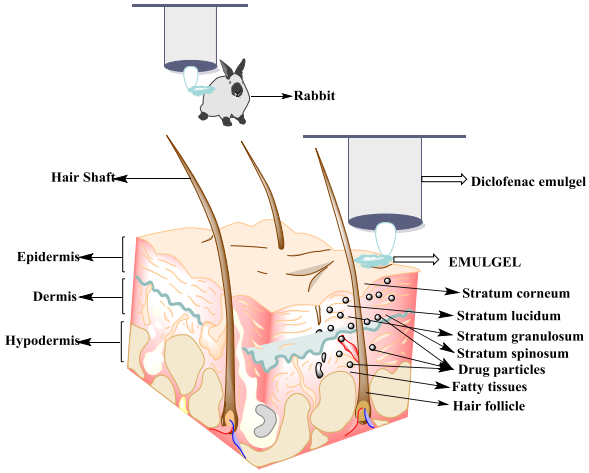


Fig. 3. Graphical presentation of application of Emulgel on skin

3. Results and Discussion

3.1 Estimation of Diclofenac Sodium

Diclofenac Sodium is a white powder, easily soluble in water, methanol and chloroform. In this study estimation of Diclofenac Sodium in dissolution fluid obtained from the purposed sustained release formulations by using UV Sepctrophotomatric method. It shows maximum UV absorbance at 237 nm. A standard graph was constructed using Phosphate buffer PH 7.4 solution of Diclofenac Sodium as detailed below to estimate its amount

either in dissolution fluids or in microsphere. Following the procedure **2.1** by using the concentration of diclofenac sodium 0 µg/ml, 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml the absorbance of the drug was found to be 0, 0.049,0.086,0.139,0.198,0.246,0.298 respectively at 273 nm. The amount of Diclofenac Sodium in either microspheres or the dissolution fluids was calculated using the linear relationship or directly from the standard graph as shown in **(Table 4, Fig. 4).**

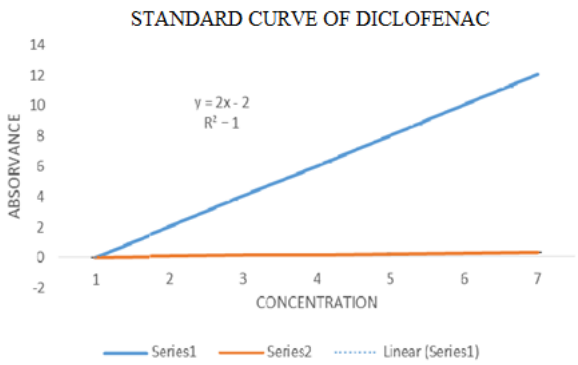


Fig 4. Standard curve of Diclofenac Sodium

3.2 Physical evaluation of diclofenac gel formulations

3.2.1 Carbopol-934 as a gelling agent

Formulations with formula A1 (0.5% Carbopol-934), A2 (1.0% Carbopol-934) and A3 (1.5% Carbopol-934) were prepared. A1 showed low consistency and A3 showed very high viscosity. The gel formulation A2 (1.0% carbopol-934) exhibited desired consistency.

3.2.2 Hydroxypropyl methyl cellulose as a gelling agent

Formulations with formula B1 (0.5% HPMC), B2 (1.0% HPMC) and B3 (1.5% HPMC) were prepared. B1 and B2 showed low consistency and B3 was highly viscous. The formulation B3 (1.5% HPMC) exhibited desired consistency.

3.3.3 Sodium Carboxy methyl cellulose as a gelling agent

Formulations with formula C1 (0.5% Sodium CMC), C2 (1.0% Sodium CMC) and C3 (1.5% Sodium CMC) were prepared. C1 showed low consistency and C3 showed very high viscosity. The gel formulation C2 (1.0% SodiumCMC) exhibited desired consistency.

3.4 Physical evaluation of formulation A2 (1% Carbopol-934)

Physical parameter of gel was evaluated by considering the Visual appearance, nature of the product, pH, viscosity, leak, phase separation, extrudability etc. Visual appearance at initial and final stage was measured a transparent result at different temperature. An excellent report was obtained during evaluation of extrudability. Additionally while conducting the phase separation and leakage test, temperature differences was noted zero. The formulated gel has a smooth nature in initial and final stage.

3.5 pH Measurements

The pH measurements of all the gel formulations were carried out by using digital pH meter. At room temperature pH value of initial and final stage measured 6.9 and 7.1 and at temperature 37±5 °C value was noted 6.9 and 7.0 whereas, at 4 -5 °C value was measured 6.9 (**Table 5**). Hence finally study was shown the pH of the formulations was in a range from 6.8 to 7.2 and the results were shown in **Table 5.**

3.6 Determination of viscosity

The viscosities of the gels were determined using Brookfield Viscometer. The viscosities of the formulations were ranged from 36,000 to 51,000 cps and the results were shown in **Table 5**.

3.7 Extrudability

This study was performed to measure the required force to extrude the gel from the tube to ensure the better extrudability of the formulation. The extrudability of the gel formulations were checked as per the procedure **2.6.2** with application of gentle finger pressure on the tube and measured the percentage quantity of gel extruded out[39]. It was observed the extrudability of carbopol and HPMC gels were excellent than sodium CMC gel.

3.8 Determination of Spreadability

The spreadability of gels was determined as per the procedure **2.6.2**. From spreadability data is observed that the formulation with 1.0% carbopol-934 showed maximum (8cm), where as the formulations with 1% carbopol-934, 3%, HPMC and Sodium CMC 3% were showed significant spreadability [32].

3.9 Chemical evaluation

The prepared formulated drug **A2** was evaluated on monthly intervals for a period of three months described in Table 6. The first month evaluation of drug **A2** was found to be consistent drug content i.e 101.72 at temperature 4-5 °C, normal temperature and 37+0.5° C storage condition. However in the second month the drug content was observed 101.54, 100.66 and 100.55 at temperature 4-5 °C, normal temperature and 37+0.5° C respectively and in the third month 100.04, 99.48 and 99.08 with same

temperature limit. At the end, the evaluation of drug content on monthly intervals was found to be steady for the prepared diclofenac gel A2. The prepared gel using 1% carbopol 934 (**A2**) showed maximum drug content (101.72%) compared to other formulations. (**Table 6**)

3.10 Compatibility Study

With reference to the IR-spectrum, the drug Diclofenac was compatible with all the polymers namely carbopol 934, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose which were used in the gel formulation.

3.11 *In vitro* drug release of gel formulation

In vitro drug release of gel formulations were carried out as per the procedure. The percentage release of drug from different gel formulations at the end of 8 h was determined. The percentage release of formulation A2 and A2 in DMSO were observed corresponding to a time interval of 1h each starting from 0h to 8h respectively as shown in **Fig. 5**. It was observed that 1.0 % carbopol-934 in DMSO shows maximum release (64.91%, **Fig. 5**) at 8h. The addition of DMSO as permeation enhancer improves the drug release from gel formulation. 1.0% carbopol-934 also showed a similar release pattern, but the release was lesser (51.47%, **Fig. 5**). The addition of DMSO as permeation enhancer improves the drug release from gel formulation. In case of HPMC and sodium CMC gels the release was much lesser than carbopol gels. The addition of DMSO as permeation enhancer drug release was improved. Based on the drug release **A2** (1.0 % carbopol-934) was the best formulation and the percentage release was found to be 64.91% (**Fig. 5**). So, stability and *in vivo* studies were carried out for **A2** formulation.

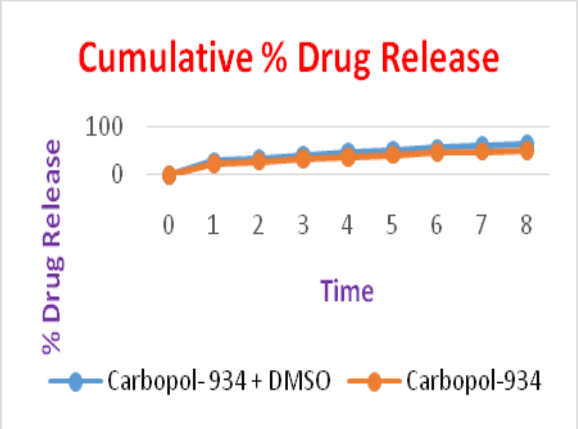


Fig. 5. Percentage Drug release of **A2** (1.0 % carbopol-934)

Table 1: Preparation of carbopol 934 gel

3.12 Stability studies for the formulation A2 (1.0 % carbopol-934)

Stability study for the best formulation was done as per the procedure **2.6.1.** The gel was both physically and chemically stable at 4-50c, Room temperature and 37±50c.

3.13 Skin irritation test

Skin irritation test was carried out as per the procedure **2.7**, there was no erythema and edema and any kind of reaction, redness or irritation appeared on rabbits. Thus the gel was found to be safer for topical use.

3.14 *In vivo* studies for the selected gel formulation

In vivo studies were carried out as per procedure **2.7**. The blood samples were drawn at different time intervals for standard and test group of animals were analyzed for the absorbance at 255 nm in UV-Spectrophotometer. The absorbance values were interpreted with standard curve the plasma drug concentration and the pharmacokinetic parameters were determined. The bioavailability of Diclofenac in test and standard were estimated by the measurement of Area Under Curve (AUC) and the relative bioavailability was estimated. The bioavailability of the drug in Test was more than the Standard. The t_{max} was 3 h for both test and standard and (peak plasma concentration) C_{max} was found to be 24.329 and 21.962 respectively (**Fig. 6**). The elimination rate constant (Ke) for Standard and Test was found to be 0.230 and 0.234 h (**Fig. 6**). The elimination half life ($t_{1/2}$) for Standard and Test was found to be 3.01 and 2.96 h (**Fig. 6**). The absorption rate constant (Ka) was determined by residual method was found to be 0.575 and 0.621 h for test and standard respectively (**Fig. 6**).

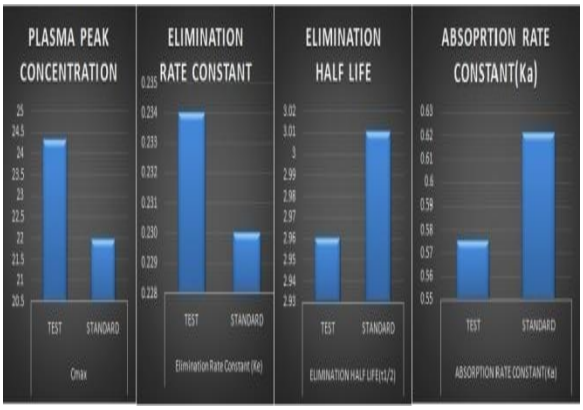


Fig. 6. Comparative bioavailability study of Diclofenac in test and standard

Ingredients	Ingredients for 100 mg		
	A1	A2	A3
Diclofenac	1	1	1
Carbopol-934	0.5	1	1.5
Triethanolamine	0.5	0.5	0.5
Purified water	98	97.5	97
Methyl paraben	0.002	0.002	0.002

Table 2: Preparation of hydroxy propyl methyl cellulose gels

Ingredients	Ingredients for 100mg		
	B1	B2	B3
Diclofenac	1	1	1
HPMC	0.5	1	1.5
Triethanolamine	0.5	0.5	0.5
Purified water	98	97.5	97
Methyl paraben	0.002	0.002	0.002

Table 3: Preparation of sodium carboxy methyl cellulose gels

Ingredients	Ingredients for 100 mg		
	C1	C2	C3
Diclofenac	1	1	1
Sodium CMC	0.5	1	1.5
Triethanolamine	0.5	0.5	0.5
Purified water	98	97.5	97
Methyl paraben	0.002	0.002	0.002

Table 4: Absorbance of Diclofenac Sodium in different concentrations at wavelength 273 nm

Concentration of Diclofenac Sodium (μg/ml)	**Absorbance at 273 nm**
0	0
2	0.049
4	0.086
6	0.139
8	0.198
10	0.246
12	0.298

Table 5: Estimation of drug content in formulation A2 (1.0% carbopol-934) emulgel

Parameters	**Room Temperature**	**37±0.5 °C**	**4-5 °C**
Visual appearance			
Initial	Transparent	Transparent	Transparent
Final	Transparent	Transparent	Transparent
pH			
Initial	6.9	6.9	6.9
Final	7.1	7.0	6.9
Viscosity (cps)			
Initial	43,000	43,000	43,000
Final	43,000	43,500	43,000
Extrudability			
Initial	+++	+++	+++
Final	+++	+++	+++
Phase separation	Not found	Not found	Not found
Leakage	Not found	Not found	Not found
Nature			
Initial	Smooth	Smooth	Smooth Smooth
Final	Smooth	Smooth	

Note: '+' GOOD, '++' BEST '+++' EXCELLENT

4. Conclusion

This drug Diclofenac was selected for the study due to its good percutaneous absorption and its well

tolerant property. The polymers namely carbopol-934, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose were used for formulation of gels and studied for their drug release from the gel formulations. It is evidence from the IR spectrum that all the polymers used in the gel formulations were compatible with the drug Diclofenac. Out of all prepared formulations, carbopol gel was transparent, non-greasy and smooth on application. However, sodium CMC and HPMC gels were observed opaque, non-greasy and sticking on application. The prepared gel using **1% Carbopol-934** was found maximum drug content (101.72%) than the others. The pH of the formulations ranged from 6.8 to 7.2 and viscosity is from 36,000 to 51,000 cps. Extrudability of carbopol and HPMC gels were excellent than the SodiumCMC gel. Additionally, the spreadability data has shown that the formulation with **1% Carbopol-934** has the highest value (8 cm), where as the others have significant values.

In vitro release studies of the formulations were carried out across the cellophane membrane using a diffusion cell. The release was highest for the formulation **A2** (**1% Carbopol-934**) and further, the drug release was improved on the addition of DMSO as a permeation enhancer. Whereas, the formulation **B2**, **C3** and **D2** also have significant percentage release and drug release was enhanced on addition of DMSO. Hence based on the above results, out of all formulations **A2** (**1% Carbopol-934**) was chosen as the best formulation.

Stability studies were carried out by placing the gels in collapsible tube at 45 °C, room temperature and 37±5 °C for 3 months and also analyzed for various physical and chemical parameters. The result indicates that the prepared gel was stable physically and chemically at all storage conditions. From the skin irritation test it was observed that the formulation **A2** was found to be safer for topical use. Further, In vivo studies were carried out by collecting blood samples from albino rabbits at regular intervals. The plasma drug concentration and pharmacokinetic parameters were determined. From the above data it was observed that the bioavailability of the drug in test was higher than standard. From this investigation, it was concluded that formulation **A2** with **1% Carbopol-934** may be the best formulation having good in vitro release profile, stability and bioavailability. Based on the results from the study further utility of the dosage form may depend on pharmacokinetic data. Forthcoming research work as Diclofenac gel formulation may contribute a challenging area in topical drug delivery system.

Conflict of Interest

The authors declare no conflict of interest in this study.

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