https://doi.org/10.51152/jbarbiomed.v8i1.210

JBAAR
Journal of Basic and Applied Research in Biomedicine
ISSN 2413-7014

Original Article

Design, Formulation and Evaluation of Diclofenac Diethylamine Gel

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Received: 22-2-2022
Revised: 3-3-2022
Published: 26-6-2022

Keywords:
Diclofenac diethylamine, Carbopol 934, Sodium carboxy methyl cellulose, Alovera extract, Release Kinetics.

Abstract: The goal of this study was to produce a topical gel formulation of Diclofenac diethylamine using various gelling agents, such as carbopol 934, Sodium Carboxy methyl cellulose, and alovera extract, to reduce the gastrointestinal side effects associated with oral administration. Topical medication administration can be accomplished by integrating into the gel matrix, preventing first-pass metabolism and allowing for greater local action in anti-inflammatory and analgesic purpose. The gel formulations were tested for homogeneity, grittiness, viscosity, pH, spreadability, drug content, *in vitro* drug release and release kinetics. The effects of polymer composition on the rate of drug release from the gel formulations were examined through dialysis membrane at 37º ± 0.5ºC. The gel formulation consisting of alovera extract (F3) was found to be suitable for topical application based on *in vitro* evaluation. These results suggest the feasibility of the topical gel formulation of Diclofenac diethylamine.

Cite this article as: Das, S., Sarkar, K., Ghosh, B., Saha, C. (2022) Design, Formulation and Evaluation of Diclofenac Diethylamine Gel. Journal of Basic and Applied Research in Biomedicine, 8(1): 4-7. **https://doi.org/10.51152/jbarbiomed.v8i1.210**

1. INTRODUCTION

Topical delivery is the reason for its use on skin or particular local action or percutaneous penetration on mucosal membranes of medications, including protective or emollient characteristics. Gels are typically created from a liquid phase thickened with additional components. (Sheikh *et al*., 2011) The release should be equivalent to that of a simple solution due to the continuous liquid phase allowing molecules to easily permeate through the polymer scaffold.(Shivhare *et al*., 2009) NSAIDs (nonsteroidal anti-inflammatory and analgesic drugs) have strong anti-inflammatory and analgesic effects, but when used orally, they can induce GIT ulcers, liver, and kidney issues. Diclofenac diethylamine is increasingly used topically because of hazards connected to oral formulations.(Maghraby *et al*., 2006)

Topical therapeutic drug delivery has a number of benefits over oral and intravenous drug administration. The poor normal medication penetration rate through the skin is one of biggest drawbacks of percutaneous drug administration. Using enhancers such as surfactants, solvents, azone, essential oils, terpenes, and lipids has been looked upon in order to enhance penetration of drgs. (Parsaee *et al.* 2002) The active ingredient is incorporated into waxes in most lipid formulations. Wax is a fatty material made up of long hydrocarbon chains that may or may not have a functional group attached to them.(Yokomizo, 1996)

Alcohol, ester, ketone, and aldehyde are common functional groups found in waxes. Plants, insects, and marine creatures produce wax esters, which are employed many different ways industrial applications (e.g. cosmetics, lubricants, polishes , surface coating , inks and foods). (Nishihata et al., 1987) Diclofenac diethylamine, benzeneacetic acid derivative, is a strong non-steroidal anti-inflammatory medicine (NSAID) is topically administered as a 1.16 percent gel owing to gastrointestinal issues. (Grace et al., 1999) Many in vitro reports on lipid-based NSAID formulations, (Iannuccelli et al., 2006) such as aqueous gel Diclofenac comes number of ways forms, indomethacin gel ointment containing lipids, niosomal Diclofenac, and pluronic lecithin sorgano-gel of Diclofenac, Which have been issued in last several years.(Gowda *et al.*, 2007)
The latter is useful in reducing elbow discomfort and wrist extensor weakness associated with long-term lateral epieondylitis in the short term. The goal of that particular research was to create diclofenac diethylamine microspheres out of wax could be applied topically to the skin in order to extend the drug's release, eliminate adverse effects from oral administration, and reduce dose frequency.(Nair *et al*., 2010)

The main target of this research work was to prepare Diclofenac Diethylamine topical gel and evaluates it by visual inspection, spreadability, pH determination, viscosity, extrudability, drug content and *in vitro* release study of the formulation.

Advantages of gels of Diclofenac Diethylamine are no irritation in the stomach and intestines, prevent G.I. issues owing to P^H differences, feasible to prevent the consequences of meals on medicine absorption, feasible to avoid active medicament deactivation owing to g.i.t. enzymes, economical, limited impact with little negative impact and when oral medication isn't an option, such as in event of nausea and vomiting, they provide an alternative.(Kikwai *et al*.,2005, Satish *et al*., 2006).

2. MATERIALS & METHODS

2.1 MATERIALS

Diclofenac diethylamine (Yarrow chem. Pvt. Ltd.), Sodium Carboxy Methyl Cellulose and Carbopol 934 (Loba Chemie Pvt. Ltd., Mumbai), Methyl Paraben (Merck Limited, Mumbai), Propylene Glycol, Glycerol (New Bengal Drug House, Kolkata) were used without further purification. All the other chemicals were of analytical grade. Dialysis Membrane was procured from Hi Media Laboratories Pvt. Ltd., Mumbai (Avg. flat width 39.41 mm and avg. diameter 23.8 mm).

2.2 METHODS :

An accurately weighed quantity of polymer was taken and using heat and magnetic stirrer, the polymer was dissolved in distilled water. Then the precise amount of Diclofenac Diethylamine is weighted and homogenized with the polymeric solution using a magnetic stirrer. Then the solution allowed to cool. Glycerine, PEG-400, and a preservative were all added and properly mixed together. Then the finalized formulation was frozen for overnight to stabilize the formulation.(Tanwar *et al*., 2012)

Table 1: Composition of Diclofenac Di-ethylamine Topical gel

Ingredients	F1	F2	F3
Diclofenac Diethylamine	0.5	0.5	0.5
Sodium CMC	0.5		
Carbopol 934		0.5	
Alovera extract			0.5
Glycerol	10	10	10
PEG 400	2	2	2
Methyl Paraben	0.15	0.15	0.15
Distilled Water	qs	qs	qs

3. EVALUATION OF DICLOFENAC DIETHYLAMINE GEL:

3.1 Visual Inspection:

After the gels were set in the container, all generated gel formulations were visually evaluated for homogeneity, colour, syneresis, and the presence of lumps.

3.2 Test of Spreadability:

It was determined by wooden block and glass slide apparatus. To determination the speradability, 0.5 g sample of each formula was squashed between two slides. The upper slide was fitted with a string that was tied with a fixed weight. The weight was suspended from the string after it was passed through a pulley. Under the weight, the upper glass slide took time to slip off. The time was noted. Lesser the time is taken for separation of two slides, better the spreadability. The diameters of spread circles were measured in centimetres and used as comparative spreadability values. The acquired findings were the average of three determinations. (Kaur *et al.* 2010)

Speredability is calculated by using the formula: $S = M.L/T$

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

3.3 pH determination:

The pH of gel was determined using digital pH meter. 2.5 gm gel was stirred in distilled water till a uniform suspension is formed. The volume was made up to 40 ml and pH of the solution was measured. Each formulation's pH was determined by temperature of room. **(**Lakshmi et al., 2011)

3.4 Viscosity:

Brookfield viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to determine the viscosities of the produced gel formulations at 25°C. The spindle (T-D) was turned at a certain speed. When the torque was close to 100 percent, the viscosities of the formulas were more accurate. **(**Ramchandani *et al*., 2013)

3.5 Extrudability:

The material is extruded from the tube as normal in this test. A gel-filled closed collapsible tube was forcefully passed through the crimped end. When the cap is removed, the gel extrudes until the pressure is gone. It was calculated the weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds. The data were reported as extrusion pressure in grams for each formulation.

(Bharadwaj et al., 2012) (Singh et al., 2013)

3.6 Estimation of Drug Content:

A portion of the produced gel was dissolved in 50 mL of phosphate buffer. To ensure full solubility of the medication, the volumetric flask containing gel solution was mechanically shaken for 2 hours. Millipore filters (0.45m) were used to filter this solution. Then, using a UV-Visible spectrophotometer set to maximum 266 nm and phosphate buffer as a blank, the drug absorbance was measured. (Kaur *et al.* 2010)

3.7 *In-Vitro* Release Study:

The study was carried out using dialysis membrane. Fixed quantity of the gel was placed on a circular aluminum foil. The foil was placed on the dialysis membrane and pressed to spread uniformly in order to get a uniform thickness of the gel throughout the foil. The membrane was tied with the open end of a test tube such that the gel remained in the donor side of the membrane placed on a test-tube of defined diameter. The test-tube was then immersed in the vessel containing 100 ml of the release medium, phosphate buffer pH 6.8 maintained at 37°C±0.5°C in a precision water bath. The membrane just touched the release medium at the receptor side. Aliquots (5 ml) volumes of samples were withdrawn at predetermined time interval and were immediately replaced with fresh medium pre-warmed to 37°C±0.5°C. The samples were analyzed in a UV spectrophotometer at specific nm. (Jain *et al.*, 2010 and Das *et al*., 2015)

3.8 Drug Release Kinetic:

The data obtained from the *in vitro* release study were analyzed using linear regression method according to the following equations:

i. Zero order

$$Qt = K0t$$

Where, Q= Amount of drug release in time t
K0 = Zero order rate constant expressed in unit of concentration/time
t = Release time

ii. First Order

$$Log\ Q = Log\ Q0 - \frac{Kt}{2.303}$$

Where, Q0= is the initial concentration of drug, k= is the first order rate constant,
t = release time

iii. Higuchi model

$$Q = Kt1/2$$

Where, k= Release rate constant, t = release time

iv. Hixson-Crowell model

$$W0\frac{1}{3} - Wt\frac{1}{3} = kt$$

Where, *W0* = initial amount of drug in the pharmaceutical dosage form,
Wt = remaining amount of drug in the pharmaceutical dosage form at time *t* and K = rate constant incorporating the surface volume relation

v. Korsmeyer-Peppas model

$$\frac{Mt}{M\infty} = Ktn$$

Where, Mt = amount of drug released at time t
M∞ = amount of drug released after infinite time
Mt/M∞ = fraction solute release
t = release time, K = kinetic constant incorporating structural and geometric characteristics of the polymer system, n = diffusion exponent that characterizes the mechanism of the release of traces. **(** Sakore *et al*., 2013)
The results are shown in the table 2 and figs 1-5.

4. RESULTS AND DISCUSSION:

All of the created gel formulations had a pleasant feel to them and showed no clogging or lumps, indicating that the system's texture was good.

The pH of the gels was in the range of 6-7, which was close to neutral.

Because it impacts the spreadibility, extrudability, and release of the medication, viscosity is an important metric for describing the gels. The viscosities of the formulations ranged from 3600 to 1030 Cps. In terms of patient compliance, easy spreadability is one of the most significant aspects of any topical medication. If it takes the least amount of time to spread across the surface, the gel is regarded good. The F3 formulation exhibits superior spreadability and drug release than the other gels evaluated. The spreadability numbers suggest that the gel can be easily spread with a small degree of shear.**(** Bhanja *et al.*, 2013)

During application and for patient compliance, extrusion of gel from the tube is critical. Extrudability of various formulations ranged from 82 to 92 %. The drug content consistency of all formulations was observed, with the F3 batch having a drug content of 93.12±0.27 %.

Table 2: Physical Properties of Prepared Diclofenac Di-ethyl amine topical gel

Formulation Code	Appearence	pH	Spreadability (cm^2)	Extrudability	Drug Content (%)	Viscosity(cps)
F1	Transparent	6.00±0.05	16.45	82 %	89.37±0.21	3600
F2	White	6.50±0.02	9.53	71 %	91.47±0.18	1247
F3	Light Green	6.60±0.07	18.50	92 %	93.12±0.27	1030

The percent of Diclofenac Di-ethylamine released over a 2-hour period from produced gel formulations with the same initial drug concentration is discussed utilising various polymers. Alovera gel has the highest percentage of Diclofenac Di-ethylamine release. In comparison to the other batches, the F3 batch has a superior release.

Various kinetic models, such as zero order, first order, Higuchi model and Hixon-Crowell model were used to analyse the release data, as shown in figs 1-4. In table 2, the R^2 value was tabulated. The Higuchi model best fit all of the above formulations.

Table 3: Kinetic study of in-vitro release data of Diclofenac Di-ethylamine gel

Formulation Code	Zero Order	First Order	Higuchi Model	Hixon Crowell
Correlation Coefficient (R^2)				
F1	0.983	0.972	0.991	0.976
F2	0.972	0.994	0.998	0.99
F3	0.975	0.975	0.990	0.987

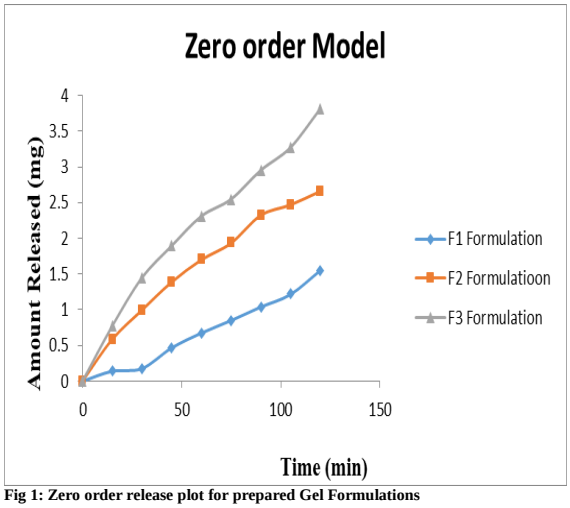

Fig 1: Zero order release plot for prepared Gel Formulations

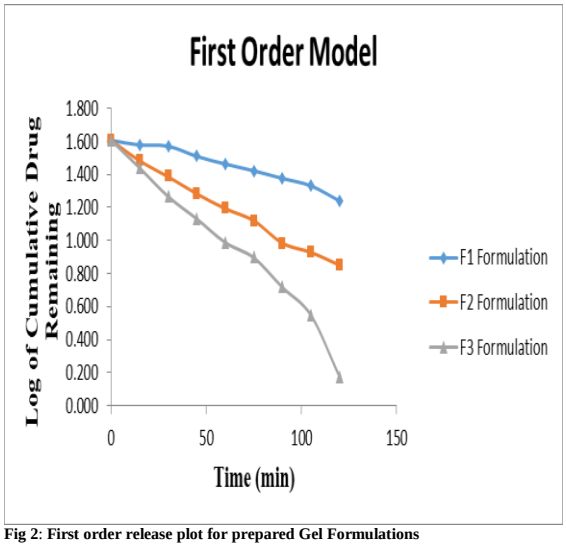

Fig 2: First order release plot for prepared Gel Formulations

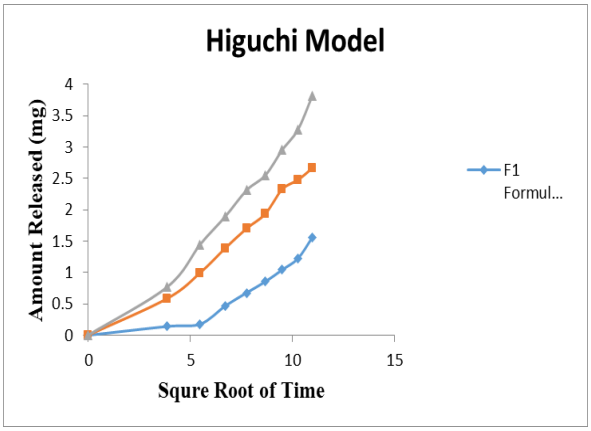

Fig 3: Higuchi release plot for prepared Gel Formulations

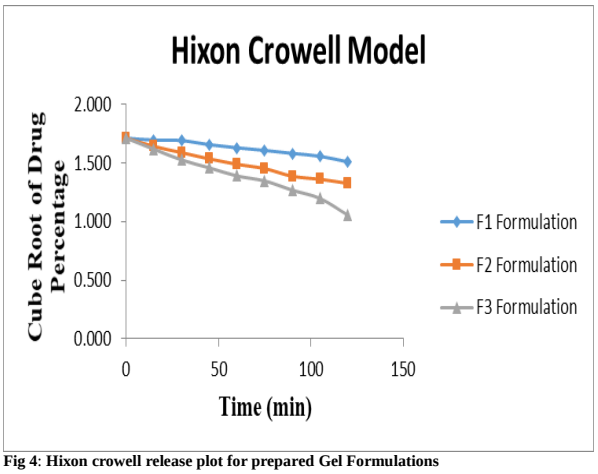

Fig 4: Hixon crowell release plot for prepared Gel Formulations

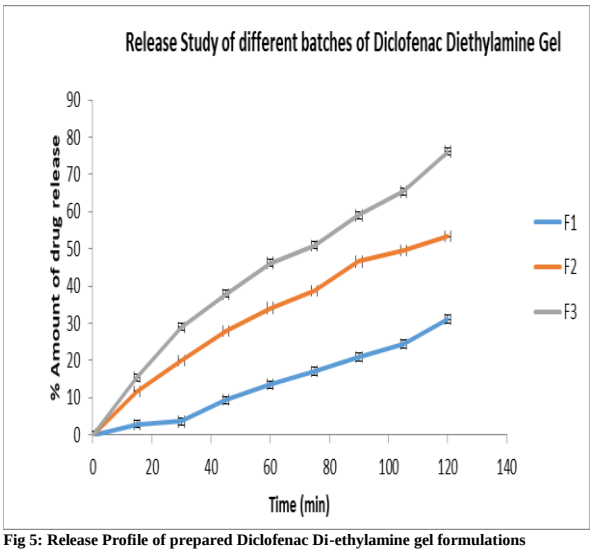

Fig 5: Release Profile of prepared Diclofenac Di-ethylamine gel formulations

CONCLUSION:

According to the results of the investigation, Diclofenac Diethylamine was effectively finished in the topical gel formulation. As a polymer, Carbopol 934, Sodium CMC, and Alovera extract were employed. The F3 batch had the finest release, spreadability, and extrudability, as well as the highest drug content. As a result, the F3 batch is regarded as the most optimized. Though, long term stability study is required for future development of these formulations.

Acknowledgment
The authors thank the Principal and authority of Netaji Subhas Chandra Bose Institute of Pharmacy, Chakdaha-741222, Nadia, West Bengal, INDIA, for providing the necessary facilities.

Declaration of competing interest
The authors declared no conflict of interest.

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