BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, September 2024. Vol. **21**(3), p. 967-977

Formulation and Characterization of Diclofenac Sodium Nanogel for Controlled Drug Release

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http://dx.doi.org/10.13005/bbra/3277

(Received: 08 July 2024; accepted: 23 September 2024)

Diclofenac sodium (DFS) is used for treating both inflammation and pain-associated arthritis. Oral administration of DFS is limited by its short half-life. Its use may result in serious gastrointestinal issues, including inflammation, internal bleeding, and ulceration. Novel drug delivery systems have been investigated to enhance the bioavailability of DFS. This study focuses on formulating and evaluating a diclofenac sodium nanogel (DNG). A nanogel was produced via a modified emulsification-diffusion process, employing polymers such as eudragit S-100, carbopol-940, and solvents like glycerol and ethylacetate. The properties of formulated DNG, including pH, viscosity, drug content, entrapment efficiency (EE), spreadability, swelling index, and drug release percentage, were evaluated. FTIR spectra confirmed that there is no interaction between the drug and excipients. 7 formulations, F1-F7, have been prepared. The DNG results demonstrated excellent EE, drug release, pH- sensitivity, and stability. 98.9% of drug from glycerin-based nanogels (F2) were released within 8 hours. The kinetic pattern for all formulations was zero-order. This study shows that using nanogel formulation for DNG transdermal delivery can sustain the drug's release for up to 8 hours and have good stability during study period (6 months).

Keywords: Carbopol 940; Diclofenac sodium; Entrapment efficiency; Eudrgit-S-100; Nanogel.

Nanogels are characterized as nano-sized particles consisting of polymer networks cross-linked through physical or chemical means, causing them to swell when exposed to a suitable vehicle. Interconnected bi-functional networks such as poly-ionic and nonionic polymers, such as PEI (Polyethylene imine) and PEG (Polyethylene glycol) were first coined as "nanogel" (NanoGel™) for delivering polynucleotides.[1] Nanogels can be composed of co-polymerized monomers that are either ionic or nonionic.[1-2] Typically, nanogels have a size ranging from 20 to 200 nm.[3] Due to their dimensions, this size range enables them to elude kidney elimination and exhibit a prolonged plasma half-life. Nanogels can absorb large amounts of water or physiological fluids while maintaining their original network structure.

The DFS market is projected to grow from USD 2.5 Billion in 2023 to USD 5.1 Billion by 2030, at a compound annual growth rate (CAGR) of 8% during the forecast period 2023-2030.[4] DFS is the leading NSAID (non-steroidal anti-inflammatory drug) in the market with 27.8% share compared to other NSAIDs.[5]

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Voltaren contains DFS as its active component, an NSAID known for its suitable physicochemical and steric properties. It is pharmacologically beneficial, particularly in acute and sub-chronic inflammation and relieving pain. The compound exhibits a superior efficacy-to-toxicity ratio compared to other NSAIDs. DFS inhibits both the cyclo-oxygenase and lipoxygenase pathways by strongly inhibiting cyclo-oxygenase, reducing arachidonic acid release, and enhancing arachidonic acid uptake.[6] Orally administered DFS can result in significant damage to the gastric epithelial cells through increased acid exposure, hindering their ability to heal and leading to injuries ranging from erosions to ulceration.

The transdermal route for drug delivery provides benefits such as circumventing the first-pass metabolism, increasing performance, stabilizing plasma drug levels, and enhancing patient compliance. Various strategies have been explored to enhance drug penetration to the target site, including the effective transport of active pharmaceutical ingredients to the horny layer of skin for optimal therapeutic efficacy.[7]

Drugs can bypass first-pass metabolism and degradation in the gastrointestinal tract and liver by being administered through the skin. Particularly molecules with limited oral bioavailability and short half-lives are suitable for transdermal delivery, assuming the molecule does not exhibit significant first-pass metabolism through the skin. The zero-order (constant rate of delivery) kinetics of transdermal delivery has been one of the cornerstones in the development of transdermal systems for the treatment, for instance, of pain disorders.[8]

Considering the adverse effects of oral DFS administration, such as ulcers and gastric bleeding; transdermal delivery has been studied as an alternative, exhibiting improved stability and permeability.[9-12] In light of these challenges and in order to improve the absorption rate of DFS, innovative delivery systems of active pharmaceutical ingredients have been investigated. This study investigates the utilization of a nano-delivery system for the preparation of nanogels to extend the discharge of DFS persistently. A modified emulsification diffusion method is employed to produce the nanogel containing the drug. The study aimed to develop and evaluate DNG that achieves extended drug release prolongs the drug's presence on the skin, and consequently enhances its bioavailability.

MATERIALS AND METHOD

MATERIALS

DFS was supplied by coastal laboratories, Nellore, Eudragit S-100 was procured from Evonik Industries in Mumbai. Loba Chemie Pvt. Ltd., Mumbai, provided a free sample of Carbopol 940 and glycerin by Research Lab and Fine Chem. Industries. We procured Tween 80 and Triethanolamine from Yarrow chem., Mumbai Pvt. Ltd. The ingredients and solvents used were analytical grade for this research work.

METHOD

Compatibility studies

FTIR (Fourier Transform Infrared Spectroscopy) analysis was done for the prepared formulations. Compatibility studies were conducted on prepared formulations and the results were discussed in the results section.

Formulation of DFS nanogel

Preparation of nano-dispersion of DFS

A modified emulsification diffusion method was employed to prepare DFS nanodispersion. 0.5 g DFS was weighed and dissolved in a specific volume of organic solvent (10 ml ethyl acetate or 10 ml glycerin) in which polymer Eudragit S-100 was added in different concentrations as mentioned in Table 1. The above organic-drug-polymer blend was incorporated at a rate of 0.5 ml/min using a syringe into the water phase (quantity sufficient: 30-50 ml) containing Tween 80 as a stabilizer, by mixing continuously at 5,000-10,000 rpm using a magnetic stirrer. The resulting mixture was stirred for 6 minutes at 10,000-25,000 rpm and then subjected to sonication for 5-10 minutes. A nano-dispersion was formed gradually by stirring for an hour, enabling the organic solvent to diffuse into the continuous phase.[2]

Preparation of DFS nanogel

The prepared nano-dispersion of DFS was combined with 0.5 g of carbopol-940 using a high-speed stirrer to create carbopol gels. The gel was prepared by adjusting the pH to 7.0 with triethanolamine and storing DFS-enriched gels at room temperature.[13]

Nanogels physical examination[14]

Optical microscopy

The nanogel was observed under a microscope at 40X magnification after dilution onto glass slides. A digital SLR (single-lens reflex) camera was used to capture the photomicrograph of the specimen from the microscope.

Characteristic appearance of gel

A visual inspection was conducted. The Color was determined by visually examining the gelled formulations both under light and against contrasting backgrounds.

Entrapment efficiency (EE)

The nanogels were developed by hydrating the drug for EE. 1gm gel was hydrated with 10 ml distilled water for 30 minutes using a mechanical stirrer, followed by 30 minutes of batch sonication. The gel dispersion was placed in a dialysis bag and dialyzed against 100 ml of 40 % ethanol in water for 4 hours to establish sink conditions. The concentration of the drug inside the dialysis bag was measured as an indicator of the free drug.[15] UV-spectrophotometry at 276 nm was used to determine the concentration of the entrapped drug. The % of EE was calculated using the following formula.

$$\% \ of \ EE = [\frac{At - Af}{At}] \times 100 \quad ...(1)$$

Where A_t =Total amount of the drug, $A_{f=}$ Amount of free drug

Assessment of pH

DFS-nanogel in 1 % solutions was used for pH assessment with a digital pH meter. To maintain stability and skin comfort, a digital pH meter (Labtech, India) is used. The pH of nanogels was determined using a sensor previously calibrated with standard buffer solutions (pH 4 and 7). Each batch was tested three times, and the average pH and standard deviation were calculated for each group. The pH meter was immersed directly into the solution. Electrode analyses were conducted on samples 24 hours after pH adjustment and at 1, 3, and 6-month intervals to check formulation stability.[16]

Viscosity

The viscosity of the batches was measured using a Brookfield viscometer set at 64 and 10 rpm. The assembly was immersed in a temperature-regulated water bath set to 25ÚC. A beaker containing the formulation with known viscosity was fitted with a thermostatic jacket. The spindle was inserted freshly into the nanogel and the reading was taken.

Nanogel, 1 g formulation was filtered through a 0.45 µm membrane filter after the extraction of DFS with 50 ml of phosphate buffer 6.8. 2 ml was diluted to 10 ml. The absorbance of the sample was measured using a spectrophotometer at a wavelength of 276 nm. The DFS concentration was determined using the calibration curve.[17]

Swelling Index (SI)

Nanogel of 1 g quantity was weighed and placed on porous aluminum foil mixed it to a 50 ml beaker having 10 ml 0.1N NaOH. At different time points, samples were drawn from the beaker. Let it dry for a few minutes in a dry location. The initial and final weights are compared by reweighing.

$$\% \text{ of SI} = (Wt- -Wo)/Wo \times 100 \quad ...(2)$$

W_t-Weight of the swollen nanogel; W_o-Weight of the formulated nanogel

Spreadability

The wooden block and glass slide apparatus were used to assess the spreadability of nanogel. nanogel was allowed for 5 minutes between two glass slides when a movable pan with an attached glass slide was placed over a fixed one. The time required to separate the glass sides was measured.

$$S=W.L/D \quad ...(3)$$

Where, S= Spreadability, L= Glass slide length, W=weight fastened to upper slide,
D= Duration required to separate the slides.

Zeta potential and polydispersity index (PDI)

The particle size distribution in the nanogel sample was assessed using the zeta potential analyzer (Zeta sizer Ver 6.20 with serial number: MAL1004428) by measuring its zeta potential in a zeta dip cell. The zeta potential of formulation F2 was determined to be more stable compared to the remaining formulations. The zeta sizer was used to measure the PDI of the optimized

formulation (F2) by positioning it in a disposable sizing cuvette at a temperature of 25°C.

Scanning electron microscopy (SEM)

SEM analysis plays a crucial role in identifying surface morphology and particle size. Scanning electron microscope was used at an acceleration voltage of 15KV, 30KV at work distances (WD) 14 mm,41 mm at different magnifications X500, X800, X600, X400, X1000, X900 and the size and morphology were within the desired shape round and spherical were observed from the images recorded.

Skin tolerance test

Rats weighing 200 – 220 gram were employed for carrying out skin tolerance tests. 24 hours before the experiment, a rat's back was shaved with an electric clipper. 1 g doses of nanogel, containing 70 mg of DFS, were applied to rats' shaved dorsal sides and evenly spread until absorbed (within an area of 0.4 cm^2). Rat skin was observed for any visible signs of oedema, erythema, redness, or rash five days after each daily treatment.

***In-vitro* Drug Studies**

Nanogel of 1g quantity, equivalent to 100 mg of DFS was spread on a cellophane membrane (soaked in medium for 24 hours) and fixed to one end of a tube. The lower end of the tube with the gel was immersed in the 100 ml beaker, filled with 100 ml of pH 7.3 phosphate buffer, allowing it to touch the surface only by 1-2 mm. The assembly was set on a thermostat-controlled hot plate with a magnetic stirrer, maintaining a temperature of 37±2°C while being stirred at 100 rpm for 24 hours; samples of 5 ml were drawn at varying intervals. 5 ml of DFS was diluted to 10 ml with fresh phosphate buffer (pH 7.2) before analyzing at 276 nm in a UV-Vis spectrometer.[18]

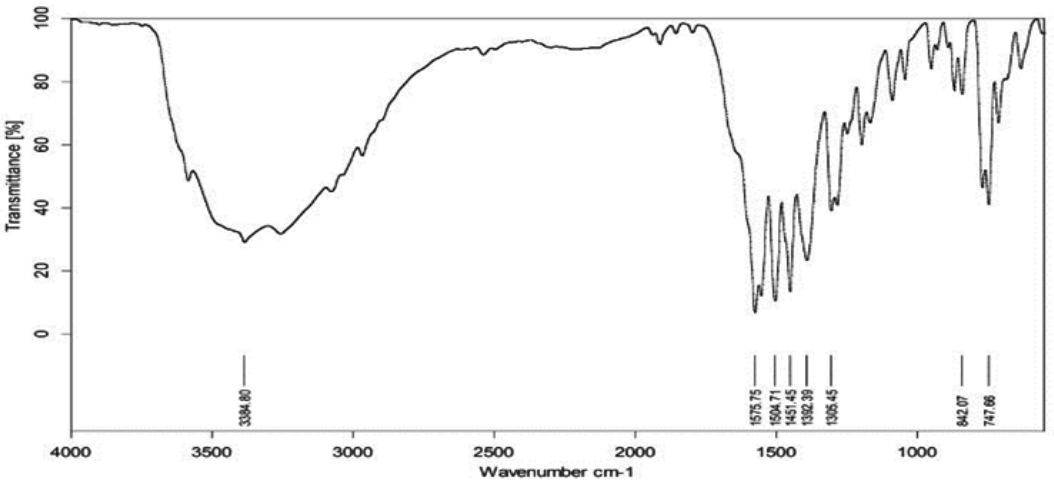


Fig. 1. FTIR of DFS

Table 1. Formulation of DFS nanogels

Formulation	F1	F2	F3	F4	F5	F6	F7
Diclofenac sodium (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Eudragit S-100 (g)	0.5	1	1.5	0.5	1	1.5	
Tween-80 (ml)	1	1	1	1	1	1	
Glycerin (ml)	10	10	10	-	-	-	-
Carbopol-940 (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethylacetate (ml)	-	-	-	10	10	10	-
Triethanolamine (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Release kinetics studies

The kinetic release of DFS nanogel was performed using dissolution characteristics. Each model fitting was evaluated using the R^2 correlation value.[19]

Statistical analysis

All the data generated were expressed as mean ± standard deviation. For group comparisons, one-way ANOVA with duplication was applied. Statistical significance was determined using student t-test, with $p<0.05$ considered to be statistically significant.

RESULTS AND DISCUSSION

From the FTIR, The peaks of pure drug and drug with excipients remained unaltered. Fig 1 and 2 suggest that no significant interaction occurred between the drug and the excipients. All the peaks corresponding to the functional groups present in the structure of DFS. From FTIR spectrum it was concluded that the drug sample was in pure form.

The transformation of the ingredients into nanogel vesicles was observed by optical microscopy

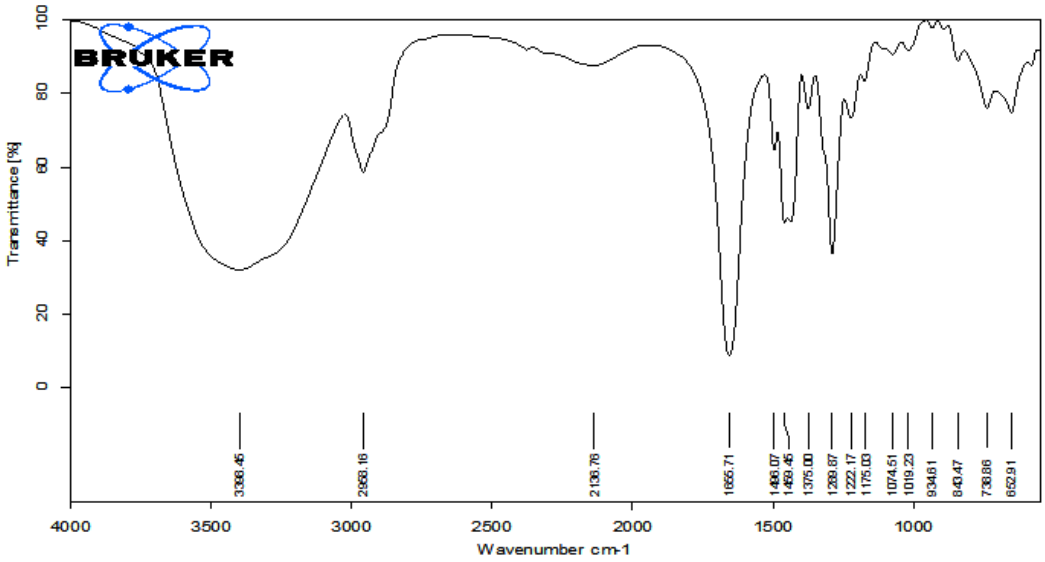


Fig. 2. FTIR of optimized formulation (F2)

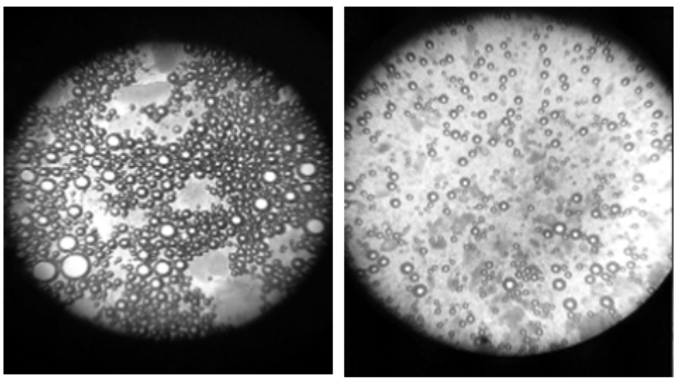


Fig. 3. Microscopic images of nanogel

under 10 X lens of different formulations. Uniform size containing nanoparticles was observed as shown in Fig. 3.

DFS-nanogel % EE was in the range of 74.8-80.75% as shown in Fig. 4. The % of EE was observed to be greater in F2, and F6 formulations. Amounts of polymer employed for nanogel preparation appeared to influence % of EE. As F2 and F6 formulations have more concentration of eudragit-S-100. Eudragit S 100 surrounds the drug particles in the formulation, creating a matrix or shell. Increasing the polymer matrix's concentration thickens it. Increasing the number of encapsulation sites may enhance EE by decreasing drug leakage.

The nanogels' drug content uniformity in all these batches ranged from 79.07-96.2% as shown in Fig. 5.

The DNG exhibited a pH within the range of 7.0 to 7.3, which is skin-compatible and avoid any form of skin reaction. After preparation, the pH was adjusted to the optimum value, then validated both immediately upon use and upon storage for up to 6 months. The formulations maintained

Fig. 4. Representation of entrapment efficiency

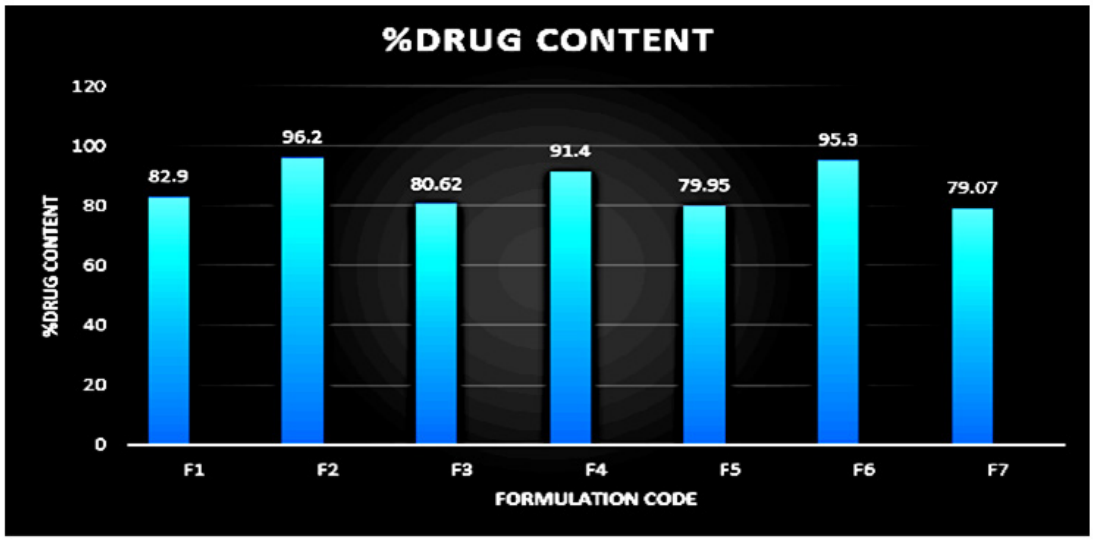
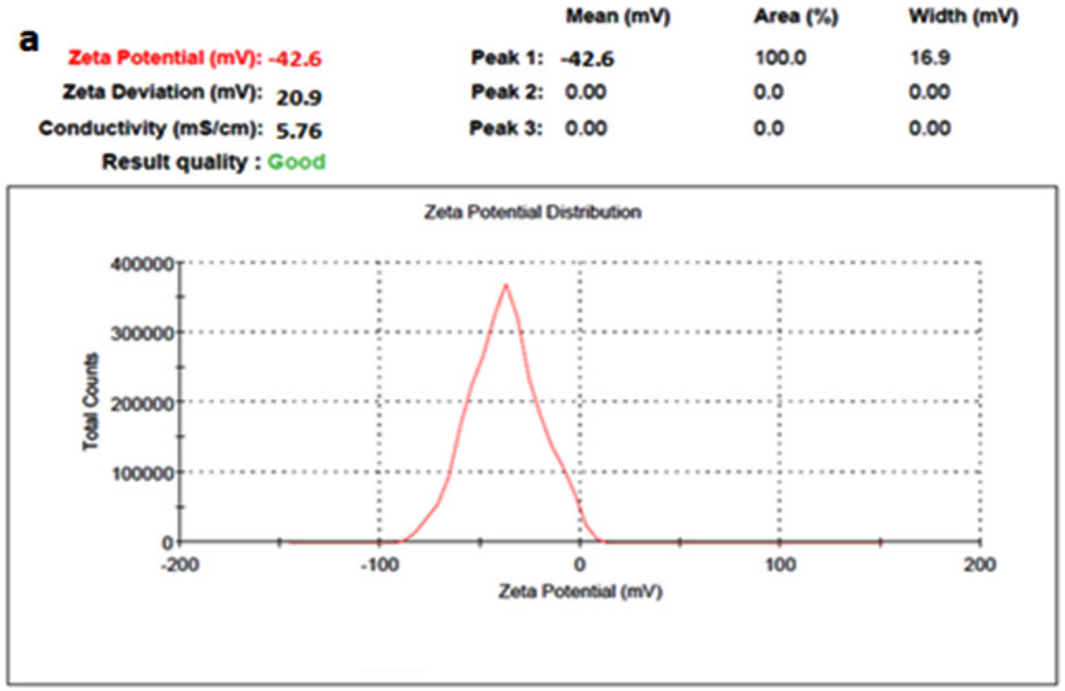


Fig. 5. Representation of % drug content



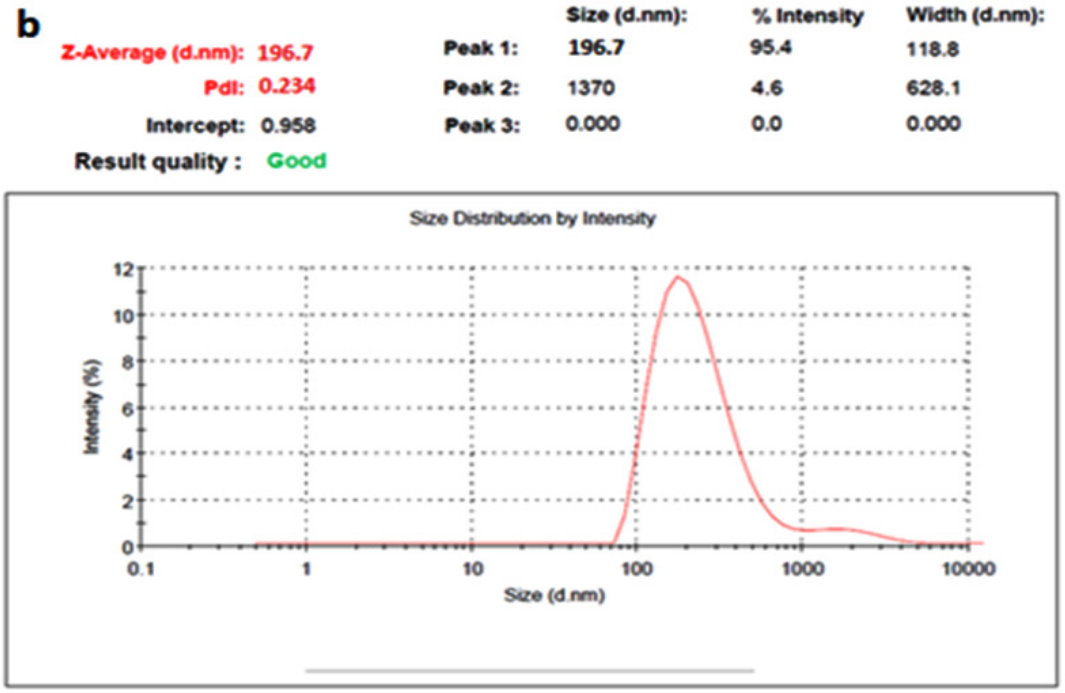


Fig. 6. a-Zeta potential of DNG (F2); b-Polydispersity index of formulation F2

their stability throughout the study. The nanogel formulations had viscosities ranging between 14666 and 16936 cps at 10 rpm. The swelling index of the nanogels was observed to be in the range of 12.4 to 24 %. The spreadability of the nanogels ranged from 16.0±0.19 to 17.2±0.11 g.cm/sec. All the evaluated parameters of the formulated nanogel fell within acceptable limits.

The optimized formulation (F2) has a superior PDI value of 0.234. The value of zeta potential was found to be -42.6 mV for optimized (F2) formulation as shown in Fig. 6. (a & b). It indicates prepared nanogel has sufficient surface charge to prevent aggregation of the vesicles and it is more stable.

The nanogel particles are rather spherical and the particle size distributions are quite narrow as shown in SEM images (Fig 7).

A skin tolerance test was required for assessing the safety of transdermal formulations. No toxicity or skin damage (redness, wrinkling, papules, or dermatitis) were observed with any formulation (placebo or DNG) after five-day application. The GRAS status of all formulation components likely contributed to its skin safety and good tolerance.

The percentage drug release for F1-F7 was given in Table 2. From this, 98.91% of drug release in 8 hours was recorded with F2. Therefore, F2 has been selected as the best nanogel formulation, when compared to other formulations.

At the 15-minutes mark, the F2 and F5 formulations exhibited the highest drug release, with values of 14.14 and 14.25, respectively. All formulations achieved a 50 % drug release rate at both the 3-hour and 4-hour time points.

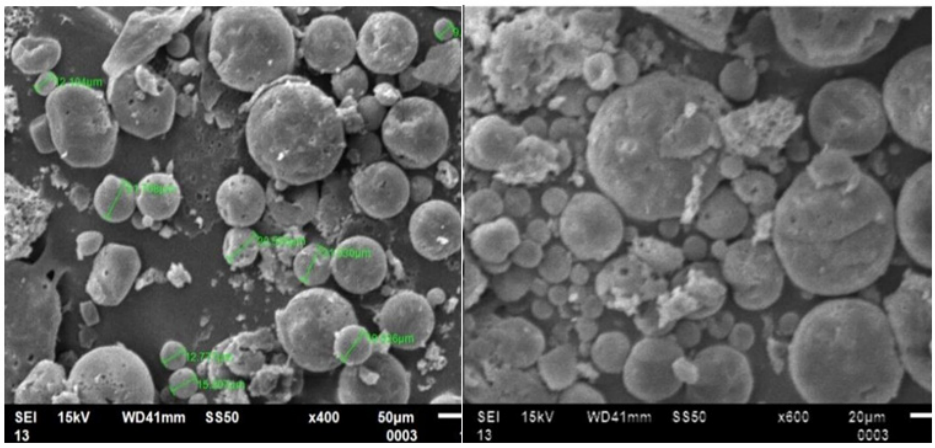


Fig. 7. SEM images of DNG (F2)

Table 2. Cumulative % drug release of nanogel of all formulations

Time (h)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.25	11.15±0.19	14.14±0.12	11.60±0.13	12.92±0.13	14.25±0.12	12.81±0.15	13.44±0.22
0.5	19.48±0.11	24.33±0.18	20.44±0.17	19.98±0.19	23.8±0.05	23.75±0.22	17.51±0.12
1	26.93±0.17	30.88±0.20	36.65±0.14	28.19±0.17	34.37±0.19	34.83±0.15	28.5±0.19
2	38.7±0.08	43.6±0.13	42.33±0.19	33.56±0.12	46.27±0.16	49.09±0.19	32.57±0.06
3	43.68±0.18	53.44±0.19	54.28±0.13	42.8±0.18	52.87±0.22	51.92±0.05	37.05±0.19
4	55.92±0.05	61.81±0.14	58.51±0.13	50.19±0.11	59.14±0.19	59.94±0.18	46.07±0.08
5	64.5±0.14	69.57±0.13	69.48±0.21	59.19±0.21	61.16±0.18	64.59±0.08	57.78±0.14
6	72.02±0.19	76.39±0.15	74.46±0.11	70.66±0.19	72.75±0.22	76.29±0.17	68.33±0.03
7	84.5±0.21	89.15±0.21	82.32±0.18	81.69±0.08	86.73±0.19	81.93±0.21	70.23±0.13
8	90.31±0.08	98.91±0.13	88.13±0.22	94.22±0.06	97.52±0.20	87.32±0.16	74.08±0.16

The drug release of F1 to F7 at 8 hours is found to be 90.31±0.08 %, 98.91±0.13 %, 88.13±0.22 %, 94.22±0.06 %, 97.52±0.20 %, 87.32±0.16 %, 74.08±0.16 % respectively. F7 is a conventional formulation reported 74.08 % of drug release at the end for 8 hours. From the above table, F2 was selected as the optimized formulation with 98.91 % of the highest drug release for 8 hours. A similar % of drug release was reported by Shivalingam *et al*.[20]

Glycerin improves drug release and stability in nanogels by making the matrix more pliable and enhancing drug diffusion. Eudragit forms a barrier that regulates the controlled release rate of the drug from the nanogel. Balanced concentration, 1g of Eudragit-S-100 ensures a high percentage of drug release while maintaining gel structure. Increased concentration of Eudragit-S-100 from 0.5 g to 1.5 g increased the viscosity, thereby recording decreased % of drug release. Carbopol enhanced uniform drug distribution within the gel by forming a matrix. The gel matrix regulates drug release through controlled diffusion. 0.5 g created an optimal gel consistency for efficient drug release.[21]

The above data was fitted into different kinetics parameters such as zero order, first order, Higuchi models, Korsemeyer Peppas models, and graphs were plotted. The zero-order plots of F1-F7 formulations are shown in Fig 8.

In-vitro drug release kinetic profiles of all the formulations are shown in Table 3. R^2 values help to identify the optimal kinetic model for transdermal release data through a nanogel system. Based on R^2 values the prepared nanogels fit to zero-order kinetics model, the nanogel releases the drug at a constant rate over time. From the results given in Table 3, the formulations (F3, F5) follow first-order release, and the remaining formulations (F1, F2, F4, F6, F7) following zero-order release. R^2 values of F1-F7 are 0.972, 0.960, 0.928, 0.976, 0.917, 0.969, and 0.969. Drug release from all the formulations got R^2 values near 1 for Higuchi Kinetics compared to Korse Meyer Peppas.

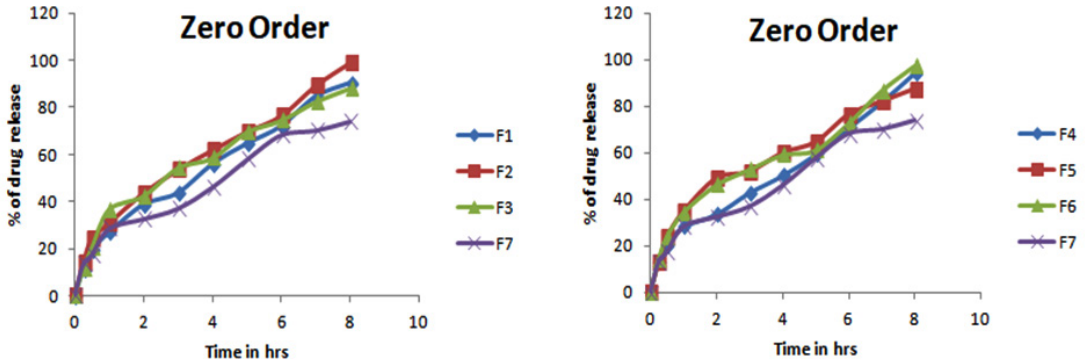


Fig. 8. Zero-order plot of formulations of F1 –F7

Table 3. *In-vitro* drug release kinetics of DFNG

	R^2	R^2	R^2	R^2
Formulations	Zero order	First order	Higuchi plot	Peppa's plot
F1	0.972	0.946	0.984	0.981
F2	0.960	0.958	0.99	0.966
F3	0.928	0.979	0.992	0.970
F4	0.976	0.882	0.982	0.970
F5	0.917	0.974	0.99	0.96
F6	0.969	0.933	0.975	0.958
F7	0.969	0.919	0.977	0.966

This indicates the drug release from the entire formulation follows the diffusion model. Based on the EE, viscosity, and *in-vitro* drug release studies F2 was selected as the optimized formulation.

CONCLUSION

Nanogel has been confirmed as an effective transdermal delivery system for DFS. 100 mg of optimized DFS was evenly encapsulated up to 80% of the drug within nanogels (196 nm in size, PDI 0.234), forming fine spherical particles with a stable charge (-42.6 mV). These nanogels displayed excellent pH stability, viscosity, spreadability, and *in vitro* drug release, leaving a thin film on the skin due to increased hydration and reduced transepidermal water loss. The results of the present study indicated that DNG containing solvents, triethanol amine, polymer, and surfactants prolonged the drug's release for 8 hours and have good stability during study period of 6 months. The nanogels with glycerin solvent sustained the drug release compared to other systems. The nanogel system proved effective for delivering DFS as a drug candidate.

ACKNOWLEDGMENT

We extend our heartfelt gratitude to Dr. L. Rathaiah, Chairman of the Vignan Group of Institutions, for his support and provision of the necessary facilities to conduct this review.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required..

Authors' Contribution

Conceptualization, : S.S.L., P.S and K.S.S.; Writing-original draft preparation, : P.V.K.; writing-review and editing, : S.S.L., P.S and P.V.K.; Visualization : S.S.L. and P.V.K.; All authors have read and agreed to the published version of the manuscript.

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