RESEARCH ARTICLE

# Development and Characterization of Eudragit Rl100 Nanoparticle Loaded Duloxetine Hydrochloride Gel for Transdermal Drug Delivery

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## ABSTRACT

**Purpose:** The study sought to examine the feasibility of transdermal delivery of duloxetine hydrochloride from a nano-gel and *in-vitro* assessment of the gel to demonstrate improved solubility and drug absorption from *in-vitro* permeation studies using rat skin.

**Materials and Methods:** Six formulas of amorphous duloxetine hydrochloride-loaded nanoparticle (NP) using eudragit RL 100 and Tween 80 as a stabilizer in the different ratios of ethanol by the solvent antisolvent technique. The physicochemical critiques of the amorphous duloxetine hydrochloride-loaded NP have completed the best formulation, NPF6, fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), particle size, and surface morphology analysis. The nano gel on produced using NPF6 in hydroxypropyl methylcellulose (HPMC) and carbopol glycol 934 gelling solutions. Investigated the gel's mechanical and rheological characteristics and *in-vitro* permeation.

**Results:** The chosen solvent-antisolvent precipitation technique might produce NP with desirable physicochemical characteristics. The particle size of the nanoparticle's two factors is regulated by solvent: antisolvent surfactant content and ratio. According to the findings of the FTIR investigation, the medication and excipients were compatible. The scanning electron microscope (SEM) investigation reveals the development of distinct asymmetric NPs. A comparative learning process and statistical analysis discovered that the best thermosensitive nanogel of amorphized duloxetine hydrochloride NPs with higher bioavailability features was carbopol glycol 934 gel.

**Conclusion:** As an outcome, the previously described *in-vitro* assessment of in-place nano gel put an example of the invention's latent for increased solubility, patient compliance, and transdermal distribution of duloxetine hydrochloride.

**Keywords:** Amorphous nanoparticle, Duloxetine hydrochloride, Nano-gel, Solvent antisolvent precipitation, Transdermal bioavailability.

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## INTRODUCTION

Duloxetine hydrochloride the present work focuses on developing and *in-vitro* evaluation of a transdermal thermosensitive *in-situ* nanogel containing the antidepressant medication duloxetine hydrochloride as a model chemical in an amorphous nanoparticle system.[1] The biopharmaceutics drug disposition categorization system states that, duloxetine hydrochloride is classified as a class II medication.[2] After oral controlling organization, it has weak solubility. It has reduced solubility in gastro intestinal (GI) fluids and is a sizeable stretch hepatic processed by p450 isozymes (50 parts in hundred bioavailability). Several investigations found that an oral intake of 60 mg of duloxetine hydrochloride resulted in approximately 6 hours, a maximum plasma concentration of 110 ng/mL. After oral administration, the medication is widely eliminated in the feces and urine type of food consumed impacts the drug's oral absorption. As a result, a transdermal route of administration may be advantageous in overcoming the restrictions of oral bioavailability in weak medicines with severe first-pass metabolism chloride,[3] amorphous NPs, solvent antisolvent precipitation, topical bioavailability, thermosensitive, nano gel.

The transdermal drug delivery system (TDDS) is designed to provide therapeutic emphasis on medicine into circulation

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via the skin. Compared to oral systems, they provide regulated release of medications over a long period, reduce dose frequency, simplify use through self-medication, avoid metabolic pre-systemic, and eliminate absorption discrepancy across gastrointestinal tract (GIT).[4] It also prevents needle anxiety and infection at the injection site, typical side effects of parenteral delivery. Furthermore, the transdermal route offers a vast and diverse surface area for drug absorption.[5] The existing transdermal dosing forms have several restrictions, including ointments, creams, gels, and patches. Semisolid formulations, such as ointments, creams, and gels, are practically difficult to keep in touch with the skin since they are detached by cloths and movement of the patient's body part.[6]

Furthermore, they leave a greasy feeling after application, which results in patient compliance. Also, patches have drawbacks, such as skin discomfort owing to occlusive qualities. Furthermore, owing to its unique rheological qualities, a nano-gel crystallizing system is easy to handle and therapeutically beneficial.[7] As a result, a thermosensitive *in-situ* gel can help to improve the solubility and bioavailability of medications that undergo substantial hepatic processing.[8]

In nanogel improves topical bioavailability by various methods, including increased solubility, increased permeability, and avoidance of efflux transporters. In contrast, NP are a comparable nanotechnology-based method that improves solubility hence, transdermal bioavailability. They are already gaining significant traction in pharmaceutical research, and medicines are already on the market. According to the Noyes–Whitney equation, increasing the interfacial surface area and decreasing particle size to the nano-range can enhance the saturation solubility and rate of dissolution of water-poorly soluble medicines.[9]

A review of the literature[1] found that incorporating class II medicines into an amorphous nanoparticle (NP) system might increase drug absorption. The less ordered or flawed structural matrix of NP has significantly increased medication bioavailability and drug stability.[10]

As a result, the proposed study intends to create a transdermal thermosensitive *in-situ* nanogel containing duloxetine hydrochloride for enhanced bioavailability and longer-term depression therapy.

## MATERIALS AND METHODS

## MATERIALS

Nosch Labs in Hyderabad, India, provided duloxetine hydrochloride (purity > 99%). Dr Reddy's Laboratories in Hyderabad provided Pluronic F 127. Other materials acquired were dialysis membranes from Hi-Media Labs Pvt. Ltd. in Mumbai, carbopol 934 (CP) from QualiChem's fine chem Pvt. Ltd in Vadodara, India, and Eudragit RL100 (E-100) and Tween 80 (T-80) from SD fine chemicals in Mumbai. The remainder of the chemicals and solvents were of analytical grade. Moreover, they were utilized without further processing or purification.

## METHODS

### *Preparation of Amorphous Nanoparticle Carriers of Duloxetine Hydrochloride (DLX-NP)*

The solvent-antisolvent precipitation approach was used to create NP carriers for duloxetine hydrochloride.[11] Methanol solvent was employed as the dispersing drug during the procedure.[11] Before selecting the NP, a preformulation study was conducted. The polymer-surfactant combination was chosen based on the maximum solubility of duloxetine hydrochloride in Tween 80 and Eudragit RL 100 as polymers as the surfactant. Eudragit RL100 and Tween 80 were chosen for preparation as liquid and solid, respectively. Eudragit RL 100 is dissolved in distilled water with methanol and various amounts of tween 80 (1% Tween 80). Both lipids were dissolved in a small amount of methanol. The drug solution was injected dropwise into antisolvent (water containing Tween 80) using a butterfly syringe while constantly stirring on a magnetic stirrer.[12] A magnetic stirrer disseminated 100 mg of medication into this organic phase (1200 rpm). An aqueous phase containing tween 80 (1% w/v) was initiated into the organic phase. The manufacturing system was centrifuged (Remi motors, Mumbai, India) at (7,000 rpm for 10 minutes) to generate a nanostructured dispersion filter.[13] Formulas NP-F1, NP-F2, NP-F3, NP-F4, NP-F5, and NP-F6 tried. The polymer: stabilizer ratio was varied to 1:200, 1:100, 1:66, 1:400, 1:200, and 1:133, respectively. A probe sonicator (Q Sonica, LLC Sonicators, model Q125, USA) was used for 60 seconds at 60W. The drug NP was freeze-dried at -50°C utilizing a vacuum sublimation technique with a freeze dryer (Delvac Pumps Pvt Ltd., Chennai, India). The ratio of solvent to antisolvent was investigated. Methanol, the dispersing solvent, was vacuumed by putting paper on the Buchner flask and swirling until the solvent evaporated under decreased pressure. For further testing, the mixture was dried and kept at room temperature.[14,15]

### *Characterization of NPs*

#### *Surface Charge and Particle Size Distribution*

Malvern Nano ZS (Horiba SZ-100, Malvern instruments Nano ZS, UK) The NPs size distribution and surface charge were determined using each watery sample with demineralized water for testing. Particle size (PS) and zeta potential (ZP) measurements were carried out in triplicate at 24.9°C.[16]

#### *Drug Content (DC)*

Methanol is used to dissolve a known amount of DLX-NPS. Samples were sonicated for 1-hour with vigorous shaking, filtered, and diluted methanol.[17] The drug content samples were analyzed for using a validated UV spectrophotometric technique (Merck, Thermo Scientific Evaluation 201, Shanghai, China.) at 290 nm at room temperature. The analysis of Duloxetine hydrochloride in methanol produced an (R2) value of the regression coefficient of 0.997. At 290 nm, a sensitive and robust spectrophotometric method for quantifying duloxetine hydrochloride in methanol was devised. In each example, a

blank formulation was prepared similarly and utilized as a placeholder to nullify the influence of excipients on reflectance. Every sample was ascertained in three different ways.[17,18]

*Entrapment Efficiency (EE)*

A certain amount of DLX-NPS was disseminated at pH 6.8 in phosphate buffer and centrifuged. The supernatant deposit was removed, methanol-dilution, and then UV measured at 290 nm to estimate the able drug using the formulary below. All experiments were repeated three times. Drug entrapment's effectiveness was estimated using the formula.[19,20]

$$\text{Drug entrapment efficiency}(\%) = \frac{\text{Amount of drug actually present in the supernatant}}{\text{Theoretical drug load expected}} \text{X } 100$$

*In-vitro Release Study*

Samples were dissolved *in-vitro* using the USP XIV apparatus II paddle and dispersed powder technique. At 37 ± 0.5°C, 500 mL of buffer (pH 6.8) swirled at 50 rpm with accurately weighed samples. Several 10 mL aliquots were taken. A cotton-plugged pipette prevented solid particles from pipetting. The dissolution medium was promptly changed. DXH was measured at 290 nm in filtered samples.[21,22]

*Selection of Best Amorphous DLX-NP by Statistical Analysis*

The parameters were evaluated with six being the highest and one being the lowest. Cases with the lowest PS and ZP and the highest DC, EE, and %drug release cumulative received the highest scaling. The best overall score was chosen for further research and the creation of nanogel.[23]

*FTIR (Fourier Transform Infrared) Spectroscopy Study*

The potassium bromide pellet technique conducted FTIR research on the pure drug and the optimal formulation NP, F6 (Shimadzu 8400-S, Tokyo, Japan). Between 4000 and 400 $cm^{-1}$, the material was scanned. To create the spectrum in 12 minutes of scanning.[24]

*Differential Scanning Calorimetry (DSC) Analysis*

The DSC analysis was executed utilizing a PerkinElmer Shimadzu DSC-60, Tokyo, Japan series and a crucible of aluminum. The sample was interrupted for examination at 10°C per minute heating rate from 0 to 400°C. The nitrogen purge at a rate of 50 mL per minute. The analysis included both the pure medicine and the preparation NP, F6.[25]

*Powder X-ray Diffraction (PXRD) Study*

The PXRD diffraction pattern of the pure drug and the innovation NPF6 was investigated using an X Pert-PRO multifunctional X-ray diffractometer (Shimadzu XRD-7000). The source was Ni-filtered Cu Ka radiation. The instrument's settings were 45 kV and 40 mA. There was a scan from 5 to 40 range, with a scan speed of 4°C/min; the diffraction patterns were captured to analyze the reflection angle and peak intensity further.[26]

*Scanning Electron Microscope (SEM) Analysis*

The particle dimensions were measured using an S-3700N SEM (Hitachi Tokyo, Japan). The experiment was carried out at ambient temperature. After deionized water dilution and sonication, formulation NPF6 glass coverslips were treated. Vacuum drying was used to dry the slides. A 20 nm thick gold coating was used to shade the sample in a cathodic evaporator. The images were taken and viewed using a SEM at a voltage of 20 kV. The specimen on the coverslip was examined at several scale ranges.[27]

*Stability Studies Physical Stability*

To investigate the physical stability of duloxetine hydrochloride NPs, they were stored in glass vials at room temperature. At predefined time intervals till 50 days, changes in appearance,

**Table 1:** Assemblage of Amorphous DLX-NP clogged in situ thermosensitive nanogel.

| *Ingredients (% w/v)* | *Gel formulations* | | | |
|---|---|---|---|---|
| | *NP-IG1* | *NP-IG2* | *NP-IG3* | *NP-IG4* |
| DLX-NP | 5 | 5 | 5 | 5 |
| PF-127 | 15 | 15 | 15 | 15 |
| HPMC K 100 M | 0.5 | - | - | - |
| HPC | - | 0.5 | - | - |
| Carbopol 934 | - | - | 0.1 | 0.5 |
| Methylparaben | 0.1 | 0.1 | 0.1 | 0.1 |
| Propylparaben | 0.01 | 0.01 | 0.01 | 0.01 |

**Table 2:** Characterization of DLX-Nanoparticles

| *Formulation* | *particle size (µm)* | *Percentage yield* | *Charge (mV)* | *EE (%)* |
|---|---|---|---|---|
| NP-F1 | 1.64 | 62 | −30.1 ± 4.95 | 61 |
| NP-F2 | 1.56 | 70 | −21.2 ± 3.55 | 71 |
| NP-F3 | 1.44 | 74 | −18.8 ± 0.40 | 74 |
| NP-F4 | 1.12 | 80 | −25.8 ± 2.08 | 79 |
| NP-F5 | 1.03 | 85 | −23.2 ± 2.08 | 82 |
| NP-F6 | 0.82 | 89 | −18.3 ± 1.57 | 84 |

PS: particle size, ZP: zeta potential, EE: entrapment efficiency.
All values are represented as mean ± SD.

particle size, polydispersity index, Ostwald ripening, and settling behavior were observed. SEM was used to measure the size of the particles.

*Duloxetine Hydrochloride Nanogel Preparation*

The thermosensitive gel was made *in-situ* using the cold technique. PF-127, a gelling agent, was progressively added to in a beaker of distilled water with a magnetic stirrer at 500 rpm (Remi motors, Vasai, Mumbai, India). As listed in (Table 1), preservatives and thermosensitive agents were added to the dispersion mentioned above while it was constantly stirred. The entire procedure was carried out at an equalized temperature of 42°C. A transparent gel was created and refrigerated for 12 hours. All four gels, NP-IG1, NP-IG2, NP-IG3, and NP-IG4 in conjunction with formulation with F6 and unity extra gel of pure medication in NP-IG4 base were made using the same process. For 1-hour, the formulation F6 was gently introduced to the various gels while constantly stirring.[28] Triethanolamine was used to adjust the pH of all dispersions to 7.

***Evaluation of Nanogel***

*Drug Content*

In a vortex shaker, weighing each gel about 1-gm was liquefied in methanol (10 mL). A 0.22 µm disposable syringe filter was used to filter an aliquot of the clear solution, which had been appropriately methanol diluted, and the drug concentration at 290 nm was measured spectrophotometrically. Each formulation was subjected to three trials.[29-31]

*Rheological Evaluation of Gel*

The gels' viscosity with the spindle. Using a Brookfield LVT viscometer (UV Scientifics). Viscosity was tested at different shear speeds. Every observation was made in triplicate.[32]

*Ex-vitro Permeation Studies*

In a Franz diffusion cell, rat skin was tested for penetration *in-vitro* (Model BM). This study's albino (Wistar strain) rats were murdered. Using a hand razor, the sacrificial rat's belly hair was precisely shaved. The rat's abdomen skin was surgically removed, and the subcutaneous fat was thoroughly cleansed. Before the experiment, the skin membrane was immersed in phosphate buffer. The rat skin excision was put in the donor compartment on the receptor compartment, stratum corneum side up. The rat skin excision was put in the donor compartment, stratum corneum side up, on the receptor compartment. The formulations, nanoparticle solution, in situ nanogel, and duloxetine hydrochloride plain gel, were evaluated three times each. The receptor compartment was kept at 32.0°C and swirled at 100 rpm using a magnetic stirrer. Aliquots of 1-mL were taken from the sampling port at various time intervals (1, 2, 3, 4, 6, 8, 10, 12, and 24 hours) and replaced with an equivalent quantity of fresh buffer. *Ex-vivo* drug concentrations were measured using UV-spectrophotometry at a maximum wavelength of 290 nm.

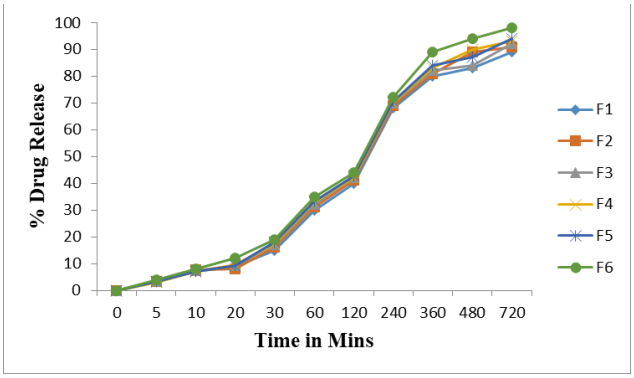


**Figure 1:** Diffusion of Amorphous DLX-NPs *in-vitro.*

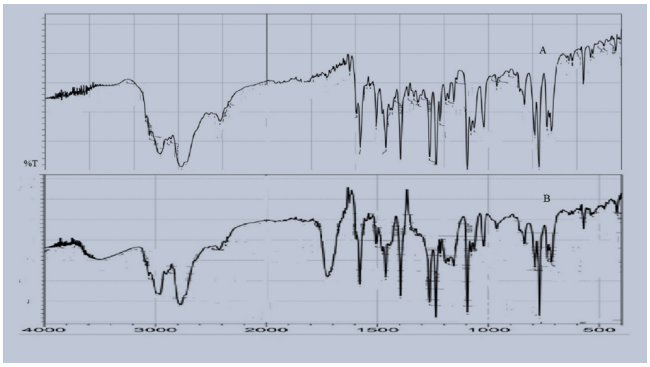


**Figure 2:** FTIR analysis of the pure drug (A) and its formulation (F6) (B).

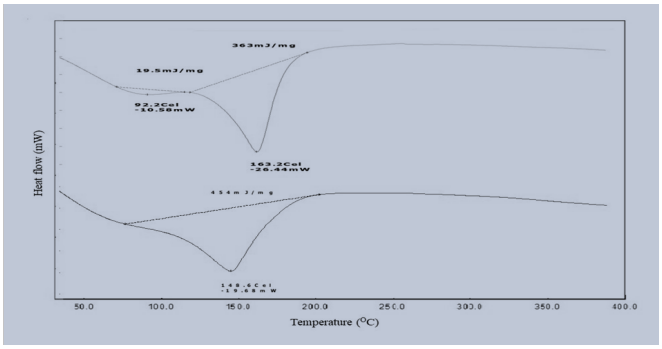


**Figure 3:** DSC pure drug (A) and formulation F6 overlaid graphs (B).

*In-vivo Pharmacokinetic Studies*

All animal investigations were carried out in compliance with the rules provided by the CPCSEA in India. The technique was approved by Guru Nanak Institute of Pharmacy's Institutional Animal Ethics Committee, with the registration number GNIP/CPCSEA/IAEC/2019/07.

As test subjects, wistar rats (weighing 200–260 g) were used. The animals were split into three groups. Group I control, group II oral solution duloxetine hydrochloride, and group III optimized DLX nanogel. A dose of 2 mg was given to each of the tested items.

The selected items were applied to the dorsal side of the rat's abdominal skin. In aliquots, 300 mL of blood

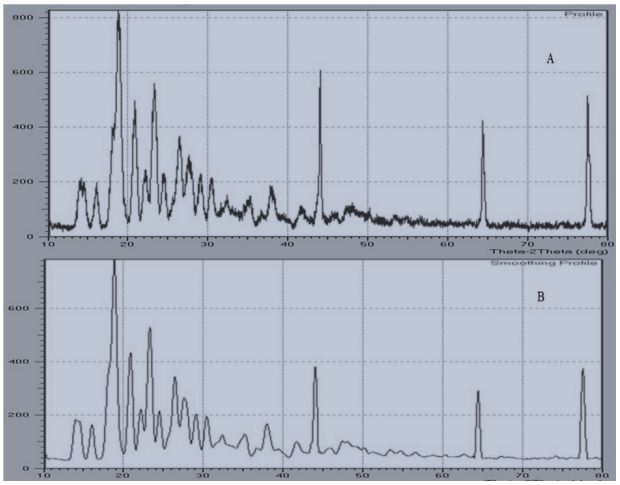


**Figure 4:**PXRD analysis of the pure drug (A) and its formulation (F6) (B)

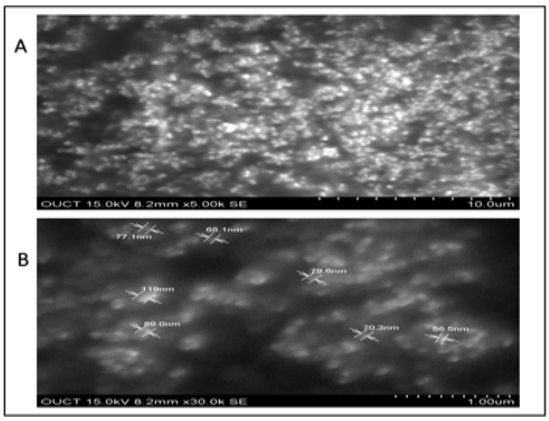


**Figure 5:**SEM images Spherical nanoparticles (A) and formulation NP-F6 (B) scale.

were collected from the rat's retro-orbital sinus and deposited in microcentrifuge tubes containing dipotassium ethylenediaminetetraacetic acid at 0, 1, 1.5, 2, 4, 6, 8, 10, and 11 hours post-dose. The eppendorf microcentrifuge tube was filled with 100 mL blank plasma and 20 mL internal standard.

A 100 mL sample of thawed test plasma was collected, and 200 mL of methanol was added to the tube as a precipitant. The solution was vortexed for five minutes before being centrifuged at 5000 rpm for 15 minutes. The supernatant solution was separated and filtered *via* a 0.45 m pore size filter before being injected directly into a 20 mL HPLC loop injector. The peak area and peak ratios of the various samples were computed. These values were utilized for analysis in the kinetic 2000 software trial.

## RESULTS AND DISCUSSION

### Particle Size Distribution and Surface Charge

The polymer-carriers of duloxetine hydrochloride were discovered to be nanoscale, and dispersion is homogenous. PS and their dispersion of unique DLX-NPs are shown in (Table 2). The polydispersity index and particle size ranged between 75.4 to 150 nm.[32] The particle surface's net charge determines the stability of NPs. The formulas' net surface charge produced by the probe sonication-precipitation method was found to be in the -52.4 to 0.34 mV range.[33]

*Drug Content*

The DC of the different formulations of duloxetine hydrochloride NP was determined to be ideal and more than 89% regarding all algorithms.

*Entrapment Efficiency*

The EE of the substance in the NPs was shown to be more than 84%. As a result, a highly enclosed system was created. As seen in (Table 2), the defective nanostructures of NPs allow for more drug loading.

*In-vitro Diffusion Study*

As shown in (Figure 1), the in-vitro diffusion research revealed a high release of duloxetine hydrochloride from NP. Formulation F6 had the highest release rate (97.63%) in 720 minutes (12 hours).

*FTIR Study*

FTIR spectroscopy of pure duloxetine hydrochloride revealed distinct peaks at 3000 $cm^1$ and 3001 $cm^1$ (C=C-H), 1400 and 1600 $cm^1$ (C=C bend), 1000 and 1300 $cm^1$ (aromatic alkene of C=C), and 1080 and 1360 $cm^1$ (aromatic alkene of C=C) (C-N bend). In formulation F6, similar feature band values and peaks were detected, as shown in (Figure 2).

**Table 3:** Characterization of DLX-NP *in situ*-nanogels

| *Formulation* | *DC (%)* | *Gelation temperature (◦C)* | *Spreadability (gm.cm/min)* | *pH* |
|---|---|---|---|---|
| NP-IG1 | 94.44 ± 2.91 | 31.67 ± 1.53 | 2.50 ± 0.10 | 6.31 ± 0.23 |
| NP-IG2 | 93.50 ± 1.94 | 30.33 ± 0.58 | 2.57 ± 0.15 | 6.58 ± 0.13 |
| NP-IG3 | 95.16 ± 1.18 | 29.67 ± 1.53 | 2.59 ± 0.17 | 6.50 ± 0.15 |
| NP-IG4 | 97.86 ± 1.15 | 28.67 ± 1.53 | 3.00 ± 0.17 | 6.48 ± 0.16 |

**Table 4:** Pharmacokinetic parameters of DXH -nanogel after Transdermal administrations in rats (n=5)

| *Test preparations* | *$AUC_{0\rightarrow\infty}$ (µg.hr/mL)* | *K (hr)* | *$T_{max}$ (h)* | *$C_{max}$ (µg /mL)* | *$t_{1/2}$* |
|---|---|---|---|---|---|
| Pure drug | 101.15 | -0.109 | 2.3 | 13.12 | 6.34 |
| Suspension | 175.13 | -0.06 | 2.15 | 29.85 | 11.51 |
| Nanogel | 428.69 | -0.03 | 1.98 | 81.44 | 12.29 |

*DSC Analysis*

As illustrated in **(Figure 3)**, an endothermic peak at 163.2°C of the pure drug corresponds to its liquescent point and shows its crystalline character. The formulation exhibited a peak shift with a smaller peak area, suggesting substantial drug entrapment during the conversion of crystalline to amorphous form.

*Powder X-ray Diffraction (PXRD) Study*

**Figure 4** depicts the peak intensities of pure drug and DLX-loaded NP preparations. The diffraction patterns of pure drug exhibited peaks of high intensities values of 14.6°, 18.9°, 24.8°, 28.9°, 37.7°, and 44.9°, confirming the crystalline nature of the drug as shown by the DSC thermogram of the pure drug'.

*Surface Morphology*

The particle size is proportional to the particle diameter as determined by the Malvern Zetasizer Nano ZS in the dynamic light scattering system. The SEM analysis of the DLX-NP formulation (F6) depicted in **(Figure 5)**, indicated the production of irregular-shaped nano-sized particles at two distinct sizes.

**Evaluation of Gel**

*Drug Content*

The DLX-NP formulation F6 was equally disseminated in the gel base, resulting in more than 90% drug content in all gel formulations. **Table 3** shows the percentage DC of all formulations ranged from 92.5 to 96.86%.

*Gelation Temperature*

Gelation temperature is the temperature at which the sol-to-gel transition occurs. As indicated in Table 3, all formulations were changed to gel at temperatures ranging from 28.67 to 33.33°C.

*Spreadability*

The capacity of a gel composition to spread uniformLy over the application surface with mild force determines its spreadability. In comparison to the other formulations, the formulation with the highest viscosity had the lowest spreadability. Table 3 shows that formulation G4 had greater spreadability than the other gels.

*Rheological Evaluation of Nanogel*

The rheological parameters of the formulation were examined at both room temperature (25°C) and body temperature (37°C) to observe changes in the gel structure and rheological behavior. As a result, the formulations were evaluated at various shear rates for both sol and gel forms. All formulations were vicious in the sol condition, according to the data. Temperature-dependent gelation was found at greater shear stress levels at higher temperatures.

*In-vivo Animal Studies*

When compared to the oral solution, the plasma concentration profile for *in-situ* nanogel reflected a considerable improvement in drug absorption. The $C_{max}$ and area under the curve (AUC) 0–24 hours of nanogel were roughly three times larger than the plan gel, showing a significant improvement in the topical absorption of duloxetine hydrochloride *in-situ* nanogel when delivered in the form of amorphous *in-situ* nanogel. The improved topical bioavailability can be ascribed to the drug nanogel adhesiveness, higher surface area owing to particle size reduction, increased saturation solubility, resulting in a greater concentration gradient between the skin and blood, and increased dissolution velocity (Table 4).

**DISCUSSION**

The particle size of NPs is critical for topical absorption. Particles with diameters ranging from 100 to 300 nm are optimum for BCS Class-II drugs.[32] The formulations were all discovered to be within the range. A low PDI value indicates a homogeneous formulation. In general, an appropriate PDI value is 0.5, with a higher number indicating a larger distribution. The PDI of all formulations was less than or around 0.5. As a result, the procedure used to prepare NP was discovered to be appropriate for creating a nano homogeneous particle dispersion within the optimal range of topical absorption.[33]

A stable system is indicated by particles with a strongly negative surface charge. According to the published research, the topical membrane bears a negative charge; hence, no matter how tiny, negatively charged nanoparticles may flow through the membrane. As a result, the nanoparticles produced were determined to be stable and suitable for topical application.

The greater DC and EE of all formulations were related to the creation of an unsatisfactory polymeric matrix with a specified percentage of EU, both solid and liquid.[34] According to the solvent antisolvent ratio, formulation had a significant impact on DC and EE The amount of lignin content affected drug entrapment, according to the research.[35] In the manufacturing stage, the progression of evaporating solvent from distinct layers of distinction may have aided in producing more warped structures and may have overseen amplified drug encapsulation.

The drug release from the nanodispersion was discovered to be biphasic. The first gush of release was accounted for by the liquefied drug localization in the micelles at the N. P's outer layer. The solvent and antisolvent technique used throughout the operation causes drug partitioning across distinct surfaces, which might explain the biphasic release.

The analysis of statistics revealed that the requisite nanoparticle properties were largely present in formulation F6. As a result, NPF6 was chosen for future research.

According to FTIR analysis, the functional divisions of DLX were largely conserved in formulation NPF6; however, the strength of several peaks was reduced, perhaps due to the creation of drug and polymer intermolecular hydrogen bonding. As a result, the medication and the excipients were discovered to be in obligations. In formulation F6, the decreased peak area and displacement of the peak suggested drug localization in the matrix.

The formulation's PXRD pattern NPF6 also demonstrated the persistence of the prominent FTIR peaks confirming the FTIR results. When compared to the pure medication at

the same diffraction angle, the formulation's PXRD pattern revealed the emergence of peaks of low intensity. The peak's low intensities in the formulation were due to the strong transformation of the pure drug's crystalline form into the NP a matrix, as confirmed by the DSC analysis. As a result, the FTIR and solid-state characterization studies validated the compatibility and causes for high drug entrapment, respectively.

All formulas had a little low transition temperature. The gelation time was determined to be less than 3 seconds for all formulations. The gelation temperature and duration of G4 were discovered to be the shortest of all formulations. Carbopol's network cross-linking density is determined by the presence of inflated deformable microgel particles that are firmly packed and in close contact.

During administration, viscosity is critical in situ nanogel gelling systems. For simplicity of administration, the formulation should be in a sol condition and should convert into a gel state at body temperature following administration. According to the rheological testing, formulation NPG4 had the best ability for administration with a tdds.

Formulation NPG4 exposed the greatest penetration and diffusion rate of any formulation. it was discovered that there was no significant difference between the nanogels of HPMC (G1 and G2, G3, G4), However, because of its makeup, G4 differs greatly from G1, G2, and G3. related swelling and viscoelastic properties, as shown in Table 4. To increase permeability, the foundation for an *in-situ* Transdermal gel should be of extraordinary quality.

For its syringe administration capacity and extremely good mechanical and rheological qualities, formulation NPG4 was rated superior to the other two formulations. Pure medications were tested for penetration *in-vitro* in the same Carbopol and PF127 gel composition. Pure drug penetration was found to be slow from the gel base. When compared to pure drug gel, the nanocarriers in the NPG4 base might be responsible for greater penetration. As a result, nanoparticle carriers in an appropriate gel foundation can be justified for effective transdermal penetration of duloxetine hydrochloride.

## CONCLUSION

The current research was an effort to accomplish the potential of administering duloxetine hydrochloride through transdermal to increase bioavailability and extend medication activity in treating depression. The duloxetine hydrochloride-loaded NP has shown good physicochemical qualities in terms of PS, ZP, EE, as well as *in-vitro* release. The thermosensitive gel in situ of DLX NP was successfully prepared and showed well *in-situ* gelling capabilities in terms of spreadability and *in-vitro* permeability. The gel formulation comprising carbopol 934 (G4) was discovered to be superlative, with good pharmacokinetics and metrics of permeability. The investigation provides significant evidence that a longer release of thermosensitive via transdermal may be obtained using a DLX-NP-loaded gelling method to increase the drug's solubility.

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