RESEARCH ARTICLE

# Transdermal Dissolvable Microneedle-mediated Delivery of Controlled Release Ondansetron Hydrogen Chloride Nanoparticles

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## ABSTRACT

**Objective:** Ondansetron HCl (OND) is a potent antiemetic drug used for control of nausea and vomiting associated with cancer chemotherapy. It exhibits only 60–70% of oral bioavailability due to first pass metabolism and has a relative short half-life of 3–5 hours. Poor bioavailability not only leads to the frequent dosing but also shows very poor patient adherence. Hence, in the present study an approach has been made to develop ondansetron HCl nanoparticle loaded microneedle patch to control release of ondansetron HCl for transdermal delivery and to improve patient compliance.

**Methods:** Three formulas of OND (NPs) were prepared using nanoprecipitation technique. The particles sizes and zeta potential were measured using zeta-plus analyzer. The particle morphology was also studied using scanning electron microscopy (SEM). The *in-vitro* release of the drug from the nanoparticles was conducted in phosphate buffer saline pH 7.4. Microneedle (MN) patches of polyvinyl alcohol (PVA) and PVP-K30 was prepared using Polydimethylsiloxane (PDMS) micromolds. The ratio of PVA to PVP-K30 of matrix solution was optimized to attained maximum needle strength. The optimized strip was evaluated for *in-vitro* dissolution, drug release, and *ex-vivo* skin permeation.

**Results:** OND-nanoparticles particle size were in nano size ranged from 95.34 nm to 246.43 nm with positive zeta potential. The drug entrapment efficiency (%EE) was varied with the drug polymer ratio from 48.93–78.45%. The SEM showed uniform shape and regularly distributed particle size. The *in-vitro* drug release study of nanoparticles exhibited sustained release of OND with burst release. The axial fraction force of manganese (MN) increases with the decrease of PVP ratio. Also, the transdermal permeation study show that microneedles permeate more efficiently than simple ordinary patches of the drug through the skin by approximately 4.69 folds.

**Conclusion:** OND nanoparticles were prepared successfully using nanoprecipitation method. The controlled drug release aimed for transdermal drug delivery can reduce dosing frequency, decrease side effects, and improve patient compliance. The microneedle patches loaded with ondansetron HCl nanoparticles were prepared and evaluated.

**Keywords:** Eudragit RS100, Microneedle patches, Nanoprecipitation method, Ondansetron HCl.

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## INTRODUCTION

Nanoparticles offer a number of advantages for dermal drug delivery, including improved drug solubility and stability, adjustable surface properties, increased surface adhesion, drug targeting, controlled drug release and increased drug penetration and permeation through the skin and mucus membrane.[1]

The skin has been an essential route for drug delivery when topical, local, or systemic effects are preferred. However, skin constitutes an excellent barrier and presents difficulties for the transdermal delivery of therapeutic agents, since limited drugs possess the features necessary to penetrate throughout the stratum corneum in adequate amounts to reach a therapeutic concentration in the blood.[2]

Transdermal drug delivery system (TDDS) includes all topically administered drug preparations intended to deliver the active ingredients into the circulation.[3] TDDS can improve drugs' therapeutic efficacy and safety by more precise spatial and temporal employment of the drug within the body, thereby decreasing both the size and number of doses and improving its effectiveness with optimal dose concentrations. Appropriate drug choice and an effective drug delivery system are essential in achieving optimal therapeutic results.[4]

Microneedles-mediated transdermal drug delivery has been extensively considered, the use of MN technology for transdermal delivery of nanoparticles is novel. An optimized MN/ drug-loaded nanoparticles transdermal delivery approach

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may allow modulation of the absorption of the drug of interest. For example, polymeric nanoparticles (NPs) offer a wide range of benefits, including in-skin drug targeting, control of skin permeation, protection of the encapsulated drug from degradation in the biological milieu in addition to reduced dose and side effects.[5]

Ondansetron HCl (OND), a 5HT3 antagonist, is a potent antiemetic drug used to control nausea and vomiting associated with cancer chemotherapy. It exhibits only 60–70% of oral bioavailability due to first-pass metabolism and has a relatively short half-life of 3–5 hours.[6]

This study aims to formulate and evaluate ondansetron HCl nanoparticles for transdermal drug delivery and to improve patient compliance.

## MATERIALS AND METHODS

### Chemicals

Ondansetron HCl (gift from pioneer Co. for pharmaceutical industries), poly-vinyl alcohol (PVA) (Provizer Pharma, India), Eudragit RS 100 (Rhom pharma, Germany), polyvinyl pyrrolidone K30 (PVP-K30) (Provizer Pharma, India), and Ethanol (Thomas Baker chemical, Mumbai, India) were sourced. All other chemicals used were analytical grade.

### Preparation of Ondansetron HCl Nanoparticles

Three formulas of OND nanoparticles were prepared using the nanoprecipitation technique. A certain amount of OND and polymer was dissolved entirely in water-miscible solvent (ethanol). The obtained organic phase was then injected at a speed of 0.3 mL/min using syringe infusion pump into an aqueous phase containing stabilizer (1% PVA) with continuous stirring of 1000 rpm. Precipitation of nanoparticles occurred immediately upon mixing. The precipitated nanoparticles are sonicated for 5 minutes using a probe sonicator. The organic solvent was then evaporated at room temperature.[7] The composition and variable condition of preparation of different formulas of nanoparticles are listed in the Table 1.

**Table 1:** Composition of Ondansetron HCl Nanoparticles

| *Code No.* | *OND (mg)* | *Eudragit RS 100 (mg)* | *PVA %* | *D:P Ratio* | *Aqueous: Organic ratio* |
|---|---|---|---|---|---|
| F1 | 8 | 8 | 1 | 1:1 | 10:1 |
| F2 | 8 | 16 | 1 | 1:2 | 10:1 |
| F3 | 8 | 24 | 1 | 1:3 | 10:1 |

### Characterization of Ondansetron HCl Nanoparticles

*Particle Size Analysis*

Particle size distribution, mean diameters, and polydispersity index of nanoparticles were determined by dynamic light scattering (DLS) techniques using a particle size analyzer (ZetaPlus, Brookhaven, USA) at a scattering angle of 90° at room temperature. For each sample, measurements were achieved in triplicate.[8]

### Zeta Potential

It is a physical property in suspension. It is defined as the difference in charge between the bulk solution (dispersing medium) and the surface of the hydrodynamic shear (slipping plane). It can be used to optimize the nanoparticle formulation for long time stability. It was measured by a zeta-plus analyzer (ZetaPlus, Brookhaven, USA).[9]

### Entrapment Efficiency (%EE)

Weighed samples of drug-loaded nanoparticles (10 mg) were dissolved in 10 mL of methanol under sonication for 2 hours. The samples were filtered through a membrane filter and analyzed spectrophotometrically at $\lambda_{max}$ 310 nm using a UV/Vis spectrophotometer (EMC LAB, Germany). The entrapment efficiency (EE) was determined using the below equation:

$$EE\% = \frac{\text{mass of drug in nanaparticles}}{\text{mass of drug used in preparation}} \times 100^{10}$$

### *In-vitro* Drug Release Studies

Three milliliters of nano-dispersion (8mg drug) were placed in dialysis bags sealed and placed in 500 mL dissolution medium (phosphate buffer pH 7.4 containing 0.25% brij-35). Drug release study employed the USP type II dissolution apparatus (i.e., paddle) at 37°C ± 0.5 and 50 rpm for 12 hours. At each time interval, 5 mL of sample was collected and replaced with fresh buffers. The collected samples were analyzed spectrophotometrically at $\lambda_{max}$ 310 nm.[11]

### Fabrication of Microneedles

In this approach, microneedle patches contained 225 conical microneedles (array size 15×15) measuring 500 µm in height, 200 µm in base diameter, and needle pitch 1500 µm located in a ~4 $cm^2$ area.

### Preparation of Microneedle Matrix Material

Two polymers were used as a matrix material, PVA and PVP-K30, each alone and in different ratios Table 2. To make a polymeric solution, 4 g of each polymer and in combination

**Table 2:** Composition of microneedles formulas

| *Formulas code* | *OND (mg)* | *% Glycerin (w/w) of polymer wt.* | *% Polymeric solution (w/v)* | *PVA: PVP Ratio* | *Volume of polymeric solution* |
|---|---|---|---|---|---|
| M1 | 8 | 10 | 20 | 1:0 | 3 |
| M2 | 8 | 10 | 20 | 1:1 | 3 |
| M3 | 8 | 10 | 20 | 1:2 | 3 |
| M4 | 8 | 10 | 20 | 2:1 | 3 |
| M5 | 8 | 10 | 20 | 0:1 | 3 |

in different ratios were dissolved in 20 mL DW (to form 20% polymeric solution), and glycerin 10% (w/w) of polymer weight mixed spatula thoroughly and heated at 60ºC for 2 hours. Then these polymeric solutions were kept in a sealed glass bottle overnight to get bubble-free clear polymeric solution to be used later to fabricate the microneedles patches.

**Drug Loading into the Mold**

A two-step process was used to introduce polymeric nanoparticles into the microneedle strip, first step loading and dried the OND polymeric nanoparticle (3 mL of polymeric nano-dispersion contain 8 mg OND) in the mold cavities using sonication for 30 minutes and dried under vacuum, then cast the polymeric solution into the mold. This method produced a drug gradient in which the tip of the microneedle had the maximum drug concentration.[12] The mold covered with a polymeric solution was kept overnight in a vacuumed desiccator to facilitate the drying process.[13]

**Characterization of Microneedle Patches**

*Morphology of Microneedle Patches*

A digital microscope (Depstech, China) was used to observe the morphologies and dimensions of the MNs, including the heights, widths, lengths, and interspacing of the polymer MNs, which were analyzed using Image J software and compared with those of the master mold.

**Drug Content**

Three microneedle strips (3 cm × 3 cm) from each formulation batch; these films were placed in 50 mL (25 mL DW + 25 methanol) solutions individually and kept on a magnetic stirrer for 3hr. Then the solution was filtered, diluted suitably and calculate the amount of drug by measuring the absorbance of the drug, using a UV spectrophotometer at $\lambda_{max}$ 310 nm.[14]

**Mechanical Properties of Microneedles**

Mechanical failure of microneedles was considered due to axial loading. Measurement of the maximum force that the microneedle can withstand before failure under an axial load (i.e., force applied parallel to the microneedle axis) by using a displacement force test station (Testometric AX, UK). Stress versus strain curves were generated by measuring force and displacement while the test station pressed an array of microneedles against a rigid metal surface at a 1-mm/min rate. Upon needle failure, the force suddenly dropped; the maximum force applied immediately before dropping was interpreted as the force of needle failure. Needles were examined by digital microscope before and after failure testing.[15]

***Ex-vivo* Skin Permeation Study**

The abdominal skins obtained from rats weighing 250 ± 10 gm were used for *in-vitro* permeation study of nanoparticles.

The rat skin was fixed between the donor and receptor compartment with the stratum corneum facing the upper side of the inverted glass tube in a beaker (modified diffusion cell). The available skin surface area for diffusion was 2.83 $cm^2$. To maintain sink conditions 50 mL (phosphate buffer pH 7.4 containing 0.25% (w/v) brij-35) was added in the receptor chamber. The temperature was maintained at 37 ± 1°C. Receptor media was continuously stirred with a magnetic stirrer at 50 rpm, in a way that the rat skin surface just flushes the diffusion fluid. Apply the simple patch and microneedle patch containing 8 mg of the drug over it using gentle thumb pressure in a donor compartment. At time intervals of 1, 2, 3, 4, 5, 6, 7, 8, and 12 hours aliquots of 2 mL sample were withdrawn from the receptor compartment and replaced as soon as possible with the same volume of receptor fluid. The samples were analyzed for drug content using UV spectrophotometer at $\lambda_{max}$ 310 nm. Each experiment was performed in triplicate. The cumulative amount of drug permeated (Q) at different time intervals and various parameters like steady-state flux ($J_{ss}$), lag time ($T_L$), and Apparent permeation coefficient ($P_{App}$) were calculated.[16]

**Statistical Analysis**

The outcomes of the experimental work are demonstrated as a mean of triplicate models ± SD and were examined concerning the one-way analysis of variance (ANOVA) and t-test to determine if the changes in the applied factors are statistically significant at a level of ($p < 0.05$) and non-significant at level of ($p > 0.05$).

## RESULT AND DISCUSSION

Ondansetron HCl-loaded nanoparticles were prepared by the Nano-precipitation method without the use of toxic, harmful organic solvents.

Eudragit RS 100 was used in preparing controlled release polymeric nanoparticles that show pH-independent drug release properties. Additionally, the ability of eudragit polymers to form nano-dispersion with smaller particle size, positive surface charge (due to the quaternary ammonium groups on the polymer surface), excellent stability, and lack of irritant effect is advantageous.[5]

The effect of the drug: polymer ratio exhibited a broad effect on particle size and distribution ($p < 0.05$). All the formulas confirmed a small mean particle size. The mean particle size varied from 95.34 to 246.43 nm, with a polydispersity index ranging from 0.178 to 0.271 (Table 3). when increasing the drug: polymer ratio increase in particle size was observed.

All formulations with eudragit showed a positive zeta potential due to the present quaternary ammonium group with values ranging from +15.72 to +23.98 mV (Table 2).

**Table 3:** Mean particle size, PDI, Zeta potential and Entrapment efficiency of ondansetron HCl nanoparticles

| *Formulas code* | *Particle size (nm)* | *PDI* | *Zeta potential (mv)* | *Entrapment efficiency* |
|---|---|---|---|---|
| F1 | 95.340 ± 13.24 | 0.271 ± 0.012 | +15.72 ± 0.67 | 48.93 ± 0.63 |
| F2 | 136.69 ± 21.67 | 0.178 ± 0.020 | +23.98 ± 1.44 | 73.76 ± 0.77 |
| F3 | 246.43 ± 24.21 | 0.267 ± 0.021 | +19.19 ± 1.37 | 78.45 ± 2.13 |

The % EE of the drug was range from 48.93 ± 0.63 % to 78.45 ± 2.13% for the prepared formulations. Entrapment efficiency was improved by increasing the ratio of polymer ($p < 0.05$). It has been displayed that an increase in polymer ratio in the organic phase improves drug entrapment due to an increase in viscosity of the organic phase, which enables the diffusional resistance of drug molecules from the organic phase to the aqueous phase, leading to entrapping a greater quantity of drugs in the NPs.[17]

*In-vitro* drug release profile of the prepared NPs using dialysis membrane at the beginning shows a quick release characteristic of ondansetron HCl unrelated to the processing conditions. Rapid release at the beginning may be due to free, unencapsulated, and adsorbed drugs on the surface of the NPs. The release rate was correlated to the ratio of drug and polymer. The *in-vitro* drug release profile of the formulation (F1, F3, and F3) were 94.1, 85.02, and 77.89%, respectively, for 12 hours. Generally, all the prepared nanoparticle formulas exhibited a sustained release, and the burst effect could be detected (Figure 1). It suggests that percent drug release is dependent on the concentration of polymer used.

Based on particles size, zeta potential, encapsulation efficiency, and release profile batch F2 was chosen as a selected formula to fabricate microneedle batches.

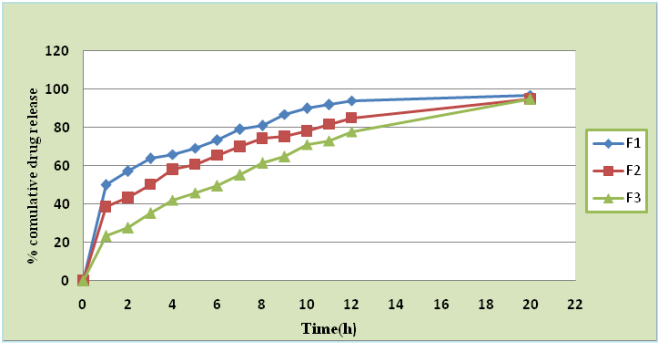


**Figure 1:** Dissolution profile of the prepared OND nanoparticles (F1, F2, and F3) in PBS (pH 7.4)

Dissolving polymer microneedles provide a simple, safe, and negligibly invasive way to deliver the drug by the skin. In this approach, we attempt to concentrate the drug only in the microneedle tip, increase the quantity of drug loaded in microneedles while diminishing wastage, and insert microneedles more fully into the skin.

Two water-soluble, biocompatible polymers (PVA and PVP-K30) were used to prepare the dissolving MN formulations to load with ondansetron HCl nanoparticles.

As described in formulation composition (Table 2), different MN formulations were prepared and the results of the current study display that all MNs prepared showed homogenous polymer mixtures with the resulting MN having sharp needle tips (Figure 2). In addition to this, a simple patch without microneedles (2:1 ratio of PVA: PVP-K30) containing OND nanoparticles was also prepared to allow their comparison with MN containing the OND nanoparticles.

### Mechanical Properties of MNs

The proficiency of an MN array to be successfully introduced in the skin is critical to its use, as the stratum corneum must be pierced for the MN array to give its effect.

Incorporating drug substances, including nanoparticles, into the polymeric solution in producing a dissolving MN can produce a weakening effect on the MNs.[18] Therefore, mechanical examinations must be done as an essential part of construction studies for dissolving MN arrays. Mechanical studies were done for all of the MN prepared in this study. The mechanical strength results of MN show that M1 and M4 (Table 4) give the highest fraction force (29.26 ± 0.235 and 27.61 ± 0.478 N, respectively), and the percent of PVP-K30 increase in the polymeric solution blend the needle fraction force decrease. the same results were shown by P. D. Andi *et al.*[19] and Mofidfar M. *et al.*[20]

The total drug content in the microneedle patch was found 7.8 ± 0.12 to 8.11 ± 0.32 (equivalent to 97.5% to 101.375% of the theoretical amount) for all prepared patches by using UV spectrophotometry indicating that little degradation or loss of drug during processing.

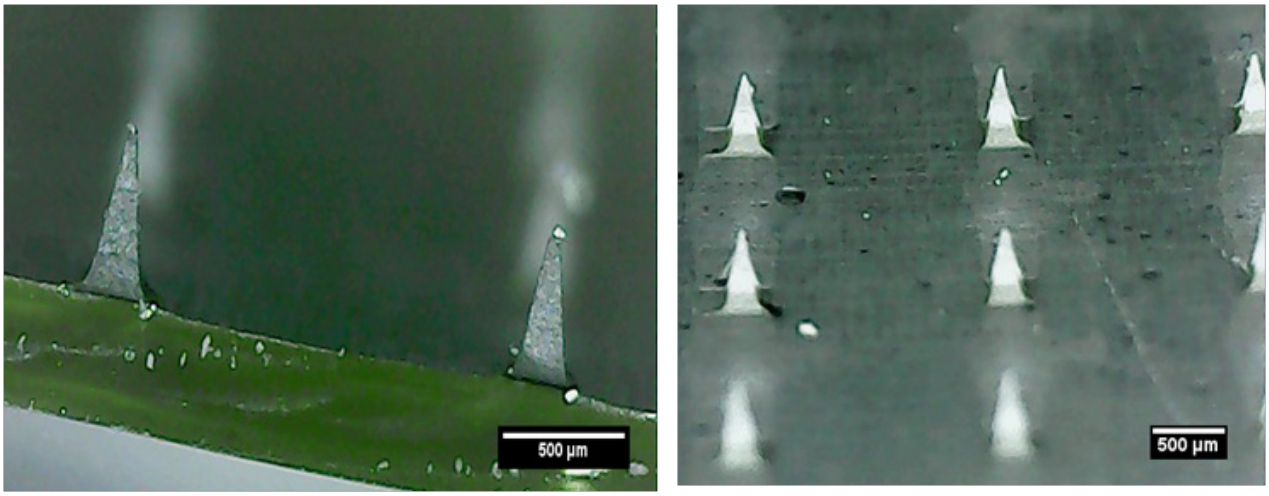


**Figure 2:** Microneedles shape and dimensions using a digital microscope

**Table 4:** Needle fraction force of the prepared microneedle formulas in newton

| *Formula code* | *Needle fraction force (N)* |
|---|---|
| M1 | 29.26 ± 0.235 |
| M2 | 26.10 ± 0.364 |
| M3 | 22.80 ± 0.256 |
| M4 | 27.61 ± 0.478 |
| M5 | 20.65 ± 0.672 |

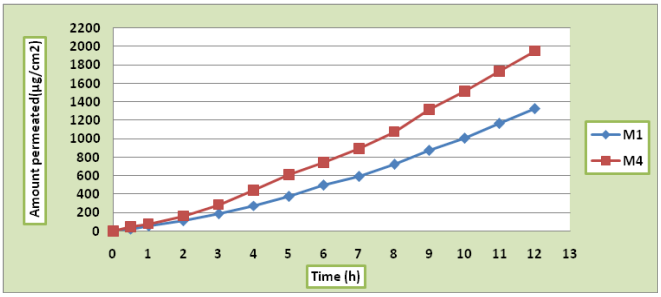


**Figure 3:** Permeation profile of M1 and M4 microneedle patches

To obtain controlled transdermal delivery, patients must apply a patch for a long period, thus causing an uncomfortable sensation and skin irritation in some people. In our organization, the PVA/PVP-K30 associate MNs array assists complete inclusion and is quickly dissolved by the skin interstitial fluid to reduce patch-induced adverse effects.[21]

From Figure 3, it was observed that after 12 hours the drug permeated from the microneedle patch M1 and M4 were 47.03 and 69.06%, respectively, these results may be attributed to that PVP improve the solubility of PVA patch within the skin more efficiently than PVA patch alone, So that, M4 patch was chosen to be the selected formula. While for the simple ordinary patch, OND permeation was only 14.31%. These results indicate that the selected microneedle patch (M4) delivers a drug more efficiently through the stratum corneum than simply.

The *in-vitro* permeation study of the microneedle patch in comparison with the normal simple strip using rat skin shows significant improvement ($p<0.05$) in the penetration of OND (Figure 4).

Transdermal flux (J), the slope of the graph from the figure (3 and 4), gives the steady-state flux of the own formulations. The slope of drug release for the simple strip was found to be 121.86 ± 5.01 and 178.64±4.32 µg/cm$^2$.h for M1, M4 respectively, and 38.08 µg/cm$^2$.h for the simple patch. The steady-state flux ($J_{ss}$) of M4 patch was 178.64±4.32 µg/cm$^2$.h, which was greater than the simple strip 38.08 µg/cm$^2$.h. The permeation was found to be improved by 4.69 fold with a microneedle patch.

The permeation profiles of OND from MN and simple strip are shown in Figure 4. The permeated parameters such as steady-state flux ($J_{ss}$) and Apparent permeability coefficient ($P_{App}$) are given in (Table 5).

The permeation study indicated that MN gave the highest drug penetration ($p<0.05$) compared with the simple strip.

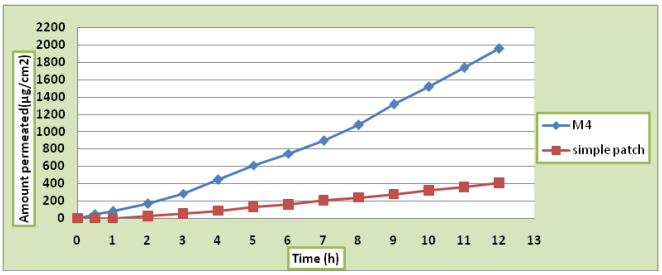


**Figure 4:**Permeation profile of M4 and ordinary simple patch

**Table 5:** Permeation parameters of Ondansetron HCl

| *Formulation* | *Flux* ($J_{ss}$) (µg/ cm$^2$. h)* | *Permeability coefficient* (P) (cm/ h)* |
|---|---|---|
| M1 Patch | 121.86 ± 5.01 | 1.52 * $10^{-2}$ ± 0.0006 |
| M2 Patch | 178.64 ± 4.32 | 2.23 * $10^{-2}$ ± 0.0005 |
| Simple strip | 38.08 ± 3.67 | 0.476* $10^{-2}$ ± 0.00045 |

## CONCLUSION

Ondansetron HCl nanoparticles were prepared successfully using the nanoprecipitation method. Drug: The polymer ratio of the system was important to obtain nanoparticles with the desired size. The %EE was acceptable for all nanoparticles obtained. OND release rates from nanoparticles were dependent on the concentration of the used polymer.

The percentage release for all nanoparticle formulations ranged 77.89–94.1% after 12 hours and 95–97% after 20 hours. The controlled drug release profile of ondansetron HCl aimed for transdermal drug delivery could be obtained by using eudragit RS100 polymer, reducing dosing frequency, decreasing side effects, and improving patient compliance.

In this study, the potential of microneedle loaded with OND nanoparticles for transdermal delivery was introduced. The transdermal permeation study shows that microneedles permeate efficiently than simple patches of the drug through the skin by approximately 4.69 fold.

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