***Chapter 8***
Print ISBN: 978-93-90149-90-2, eBook ISBN: 978-93-90149-91-9

# Microneedle Aided Transdermal Delivery of Antimigraine Drugs

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DOI: 10.9734/bpi/tipr/v1/2388E

## ABSTRACT

Microneedle (MN) assisted transdermal delivery is a novel technology that can overcome the stratum corneum barrier of skin and enable successful permeation enhancement of drugs. Zolmitriptan (ZT) and Rizatriptan (RT) are antimigraine drugs that show poor and variable bioavailability when administered as currently available formulations, owing to hepatic first pass metabolism. Transdermal delivery with MN application as permeation enhancement strategy was tried to efficiently delivering these molecules. For this purpose, *poke and patch* approach was employed. A significant enhancement in transdermal permeation of both the drugs was found with MN application. It was also found that design parameters like the MN length, needle density, etc., play a major role in such enhancement. Overall, MN application, especially via the poke and patch technique seems like a very promising technology that may hold the key to open up transdermal delivery as the major route for drug delivery in the future.

*Keywords: Microneedles; transdermal permeation; triptans.*

## 1. INTRODUCTION

Migraine is the third most common disease in the world affecting about 15% of the global population. The pathophysiology of migraine is still not clearly understood, but is thought to be caused due to dilation of cranial blood vessels. The Global Burden of Disease (GBD) studies ranked migraine as the seventh (in men) and third (in women) leading cause for years lived with disability. Majority of the patients report their pain as severe to very severe that lasts longer than 24 h. The associated symptoms include pulsating and throbbing headache, with sensitivity to light, sound etc. Apart from the pain, the most unpleasant and very common symptoms were described to be nausea and vomiting. The disability experienced during a severe migraine attack was reported to be similar to that observed with conditions like dementia, quadriplegia, active psychosis, etc., by WHO [1–5].

Triptans, 5HT or Serotonin receptor agonists, are the first-line therapy for the management of migraine. Sumatriptan (ST) is the first and most commonly prescribed molecule, as it is the most extensively studied and most familiar among the class. ST is available as oral tablets, nasal spray and subcutaneous injection formulations. It has a short half-life of only 2 h with low bioavailability (BA) (<15%) when administered as oral tablet and nasal spray. Subcutaneous injection offers good BA, but has poor patient compliance. Hence, to improve upon these aspects, several triptans with almost similar acceptability and efficacy (when compared at the respective recommended dose levels), but with marked differences in physicochemical and pharmacokinetic properties were developed over the years. Zolmitriptan (ZT) and Rizatriptan (RT) are among the most commonly prescribed triptans after ST [5–8].

ZT is available in three types of formulations – oral tablet, oral dispersible tablet and nasal spray. All three formulations provide an absolute BA between 40-48% and the maximum daily dose via both the

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routes was reported to be 10 mg/day. Although there is no substantial improvement in the BA or therapeutic efficacy, it was reported that the nasal spray results in rapid absorption and so, faster onset of action. RT is available as oral tablets and oral dispersible tablets at dose strengths of 5 and 10 mg and has an oral BA of only 45%. It was reported to have a faster onset of action when compared to ST, ZT and many other triptans. Both the molecules have a short half-life of 3 h. [5,9,10].

Both these drugs (and most other Triptans) face several challenges like short half-life, low oral BA, patient non-compliance towards oral medication due to nausea and vomiting, etc., making oral route of drug administration less ideal for management of migraine. The phenomenon of 'gastric stasis' during the attacks was found to cause erratic absorption of oral medication, thus bringing high variability in therapeutic efficacy. Although ZT and RT have better success at relieving pain after the first dose, the cases of therapeutic failure are still significantly high (upto 30%) where a second 'rescue' dose is needed to relieve the symptoms or to control the recurrence of the attack within 24 h [11,12].

The inference of several surveys indicated that headache sufferers, including migraineures, are among the most dissatisfied patients with the available medical care. It was estimated that about 50% of the patients stop seeking medical care for their headaches owing to low benefit of therapy. All this emphasize the pit falls of currently available therapeutic options in management of migraine and the need for better therapy [13,14].

Delivery strategies for triptans should aim to improve the drug BA, provide better success rates and therapeutic gain with a single dose administration while improving patient compliance and adherence to therapy. *Transdermal route may check all the above boxes for* of ZT and RT delivery. However, both these molecules are relatively hydrophilic in nature and show limited and clinically insignificant permeation across skin, owing to their physicochemical properties. The use of a suitable permeation enhancement technology may significantly improve the transdermal delivery of ZT and RT.

Microneedle (MN) treatment is the most recent and promising technique to enhance the transdermal delivery of drugs. As the name suggests, MNs are needles with length of a few hundred micrometers and can be a single needle or an array of needles within a unit surface area. These can be described as a hybrid of non-invasive passive transdermal delivery and invasive injectable drug delivery approaches that bring together the best of both worlds – direct systemic administration, bypassing GI related interferences/limitations, ease of self-administration, improving rates of delivery, being minimally invasive and almost painless, good patient compliance, etc. [15-17]. Stratum corneum (SC), the outer most layer of the skin composed of thick, flattened, dead cells is primarily a lipophilic barrier limiting the permeation of relatively hydrophilic molecules. MN application is intended to disrupt only the epidermal layers of skin (especially, SC) and thus improve the delivery of a wide range of drugs. It has been observed to cause skin abrasions that are similar to those encountered in daily life, which makes it very mild when compared to hypodermic injection. Such micro-conduits created in the skin were found to be large enough to permit transport of all the drugs including macromolecules, but small enough to prevent any damage of clinical significance to the skin [17-19].

Literature search reveals that MN treatment improves the transdermal delivery of several molecules with varied physicochemical properties [20-24]. Zosano Pharma, USA, developed a MN based transdermal delivery system for ZT. It is a 3 $cm^2$ array containing 1987 MNs of 340 μm length. 1.9 mg of ZT was coated onto the array and the system can be applied onto the skin using a reusable applicator. The MN array is held in place for the duration of treatment by a 5 $cm^2$ adhesive backing membrane. A recent publication by the innovator reported that the MN system achieved a 77% absolute BA with a $T_{max}$ of 15 min when applied to ventral inner thigh of female prepubescent Yorkshire pigs and 1 h of patch wear time [25].

MNs can be employed via different approaches [20-25]. Among them is 'poke and patch' approach, where solid inert MNs that can be manufactured using a wide range of medically accepted materials are inserted into the skin to disrupt epidermal layers and create microconduits in skin. The MN are removed and any simple transdermal formulation *viz*., a patch or even a gel or a cream can be applied on the same location. Enhanced transdermal delivery can be expected as the barrier is already disrupted by the MN. One main advantage is that it alleviates the limitations of other approaches like the amount of drug that can be loaded in (dissolvable MN) or coated onto (drug coated MN) the MN system. Also, several drugs can be delivered using the same MN device by optimizing simple and well-established formulations like transdermal patches. This can greatly improve the application scope of a well-designed MN device and reduces the time and money that goes into developing a separate MN device for each drug molecule or even different dose strengths of the same molecule.

Consistent with this idea, the present work was designed to study the transdermal permeation enhancement of two antimigraine drugs, ZT and RT, using *poke and patch* approach of MN application. For this purpose, commercially available *AdminPatch® MN arrays* were purchased from *AdminMed LLC*, Sunnyvale, California, USA (US 7658728 B2). These are disk like MN devices made of medical grade stainless steel and excel in tensile strength, hardness and tip sharpness. 4 different MN arrays (0.6, 0.9, 1.2 and 1.5 MN) were procured to compare the effect of length of MN and other design aspects in enhancing the transdermal drug delivery of both the drugs. The MN design and the device are shown in Fig. 1 and various aspects are described in Table 1 [26]. Following the treatment with different MN, skin layer disruption was confirmed by surface visualization while the extent of such disruption was confirmed by histological examination of the skin. *Ex vivo* transdermal permeation studies were carried out using pig ear skin to understand the degree of permeation enhancement achieved using different MN devices. The data was carefully scrutinized to arrive at meaningful conclusions that can form the basis for further studies in this direction.

**Table 1. Design and dimentional aspects of Adminpatch® MN arrays [26]**

| Parameter | 0.6 | 0.9 | 1.2 | 1.5 |
|---|---|---|---|---|
| Length (μm) | 600 | 900 | 1200 | 1500 |
| Number of MNs (1.77 $cm^2$) | 187 | 85 | 41 | 31 |
| Shape | Flat (2D) | | | |
| Thickness of each MN (μm) | 78 (uniform till tip)* | | | |
| Thickness of array base (μm) | 100-200* | | | |
| Material | Medical grade stainless steel (SS 316L) | | | |

**the width and thickness of the MN and the base varies with length*

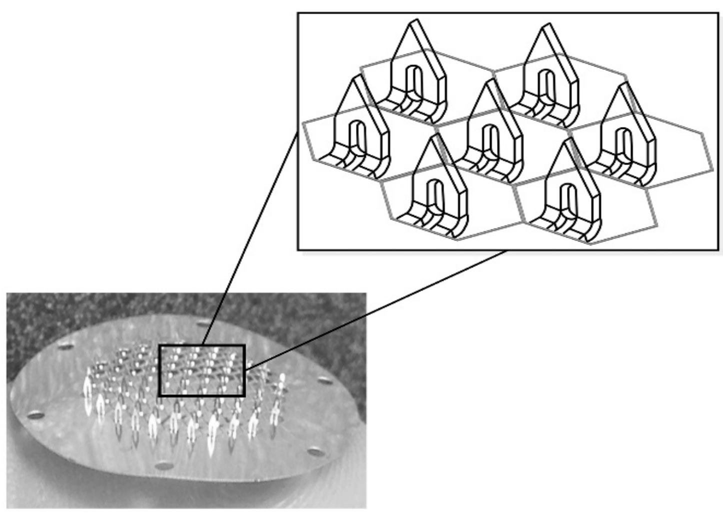

**Fig. 1. Showing the design parameters of Adminpatch® MN array used in the study**

## 2. METHODS

### 2.1 Materials

AdminPatch® MN arrays were purchased from AdminMed, Sunnyvale, U.S.A. Zolmitriptan (ZT) and Rizatriptan Benzoate (RT) were obtained from Mylan Laboratories Limited, Hyderabad, India; Sodium chloride, isopropyl alcohol, propylene glycol and 1% w/v Safranin solution from Loba Chemie, Mumbai, India; Formic acid, acetonitrile, methanol and HPLC water from Merck Specialities Pvt. Ltd, Mumbai, India; Haematoxylin and Eosin stain from Sigma-Aldrich, Bengaluru, India. All the reagents and chemicals used in the study were of HPLC grade. Pig ear skin was obtained from local slaughter house from animals of 6 - 7 months of age. (Note: Although the benzoate salt was used, all the data was calculated and represented for Rizatriptan free base).

## 2.2 Analysis of Samples

Quantitative analysis of both ZT and RT in various samples obtained from different studies were carried out using RP-HPLC method that was validated as per ICH guidelines. A Shimadzu Prominence HPLC system equipped with DGU-20A3R degasser, two solvent delivery LC-20AD pumps, a SIL-20AC HT auto injector and an SPD-M20A photodiode array–UV detector (Shimadzu, Tokyo, Japan) was used for this purpose. LC Solutions software (1.25 version) was used to acquire and integrate data. Throughout the analysis, the aqueous component of mobile phase was filtered through 0.22 µm filter membrane (Millipore®, MA, USA).

Chromatographic conditions included an Agilent Eclipse column (150 × 4.6 mm; 5 µm) maintained at ambient temperature, mobile phase consisting of 0.02% v/v formic acid and HPLC grade methanol at 75:25% v/v. The quantification was carried out at 20 µL injection volume. The run time for each sample was 5 min with the mobile phase set at a flow rate of 1 mL/min. The column was allowed to stabilize under the conditions of analysis, i.e., at the same isocratic mobile phase composition at 1 mL/min flow rate and only upon visually confirming a stable base line, actual analysis was carried out. ZT and RT eluted at 2.8 ± 0.09 and 2.5 ± 0.1 min respectively [27,28].

## 2.3 Solubility Studies

Solubility studies for ZT and RT were carried out prior to ex vivo permeation studies, in order to select an appropriate solvent as the donor vehicle. Solvent combinations of propylene glycol (PG): polyethylene glycol- 400 (PEG) and saline (S) at 70:30, 80:20, and 90:10 w/v ratios were used to test solubility. Excess amount of drug was added to each vehicle to achieve saturation, and the systems were equilibrated in an orbital shaker maintained at 37 ±1°C for 24 h. After 24 h, the samples were centrifuged, for 15 min at 1000 g (3500 rpm, 7 mm rotor head). The supernatant obtained was filtered through nylon syringe filter (0.45 µm), diluted appropriately and analyzed using the abovementioned HPLC method.

## 2.4 Skin Preparation

In the slaughter house, animals of age between 6-7 months were sacrificed using electric current and the whole outer ear was severed immediately from their heads. The same were maintained at cold conditions (2-8°C) using a cooling box during transportation. Initial processing of the skin was carried out as soon as the ears were received in the laboratory. The ears were washed thoroughly to remove any adhering dirt on the skin, blotted dry, and using an electrical hair clipper, the hair on the external side of pinna was removed. Further, skin and any subcutaneous fat tissue of the pinna was carefully detached from the underlying cartilage using a scalpel. This was followed by removing the excess fat underlying the skin to a thickness of 1.2 mm. The dermis side was wiped with isopropyl alcohol to remove the residual adhering fat. Processed skin samples were individually wrapped in plastic bags without air entrapment and stored in a deep freezer at -20°C until further use.

## 2.5 MN Application on Skin

For application of MN, prepared skin samples were taken from the freezer, thawed, and washed with saline. AdminPatch ® arrays of different lengths (0.6, 0.9, 1.2 and 1.5 mm) were applied on the skin surface, by pressing them once using thumb pressure. The MNs were periodically checked during this process for potential damage using a stereomicroscope.

## 2.6 Surface Visualization of Microconduits on MN Treated Skin

After the application of the arrays onto the pig ear skin, the skin was stained with safranin (1% w/v) dye for 1 min to visually confirm the MN's ability to go through the skin and create micropores. The excess dye on the skin was wiped with an IPA dipped cotton swab. Skin samples not treated with MN were also stained and used as control.

## 2.7 Depth of Penetration of MN into the Skin

To evaluate the depth of penetration of MN arrays of different lengths, minimum of 5 skin samples were treated with each MN array (0.6, 0.9, 1.2 and 1.5 MN) and were processed to obtain histological sections of the skin samples. Samples without MN treatment were also prepared. All the skin sections were stained with hematoxylin and eosin (H&E stain) for clear visualization of skin layers and to display the microconduits created by MN penetration. The depth of MN penetration was calculated with the help of ToupView Software (AmScope, Irwin, USA).

## 2.8 *Ex vivo* Transdermal Permeation Studies Using Pig Ear Skin

Vertical Franz diffusion cell apparatus equipped with a circulating water bath system, a water heater and an eight-stage magnetic stirrer (Orchid Scientifics, Nasik, India) was used to perform *ex vivo* transdermal permeation studies. The Franz diffusion cells used for this purpose have a diffusion surface area of 1.77 $cm^2$ and receptor volume of 14 mL.

Prepared pig ear skin samples were held between the donor and receptor cells with the SC of the skin sample facing the donor compartment. Saline was used as the receptor medium which was stirred at 600 rpm throughout the experiment. The cells were examined for entrapped air underside of the skin that could hamper the permeation across it. The skin was allowed to equilibrate at 32°C for about 1 h before starting the study, following which ZT or RT was added in excess to skin as 500 µL of donor solution. Permeation studies, without or with MN treatment for each drug, were carried out for a period of 48 h and samples of 500 µL were collected at every 6 h. The same volume was replaced with fresh saline immediately after collecting each sample. The samples were stored under refrigeration until analysis.

Cumulative amount of ZT or RT permeated per unit surface area of skin (nmoL/$cm^2$) was plotted against time (h) for all the experimental setups (MN treated and untreated) from the data. The slope value of the steady state portion of the plot was considered as the transdermal permeation flux value while the x-intercept of the same was considered as the lag time for steady state for the passive and respective MN treatment studies. Applying Fick's law of diffusion (Eq. (1)), apparent permeability and diffusion coefficient values were computed.

$$\frac{1}{A}\left(\frac{dM}{dt}\right) = J_s = K_p\ \Delta C \quad (1)$$

In Eq. (1), $J_s$, $M$, $A$, $K_p$, $\Delta C$ and $t$ are the steady-state flux (nmoL/cm²/hr), cumulative amount of drug permeating the skin (nmoL/cm²), area of the skin available for permeation (1.77 $cm^2$), apparent permeability coefficient (cm/hr), the difference in concentrations of drug in the donor and receiver compartments and time respectively. The respective saturation solubility concentration of ZT or RT in the donor vehicle were considered as $\Delta C$ values in Eq. (1) since the receiver compartment was maintained at sink conditions throughout the experiment making the drug concentration in the receiver compartment almost zero.

## 2.9 Drug Content in Skin

To understand the difference in disposition of the drug when treated with MNs of different length and density, the amount of drug remaining in the skin sample after the completion of permeation study~~,~~ was determined. To remove the excess drug adhering to the surface of the skin samples at the end of the study, they were washed gently with filtered water and blotted with paper. Thereafter, to facilitate easy extraction of the drug from the tissue, the skin samples were cut into small pieces manually with a scalpel. To the minced tissue, acetonitrile was added at a level of 5mL/g and was equilibrated at 32°C in an orbital shaker set at 100 rpm for 1 h. The extracted solutions were diluted appropriately and analyzed for ZT or RT content using the developed HPLC methods.

### 2.10 Statistical Analysis of the Data

SYSTAT 13 software (Systat Software Inc., San Jose, USA) was used for the statistical analysis of data. One-way ANOVA with Fischer's LSD post hoc test was used to analyze the experimental results. Groups that showed a p value of less than 0.05 were considered to be statistically significantly different. All the experiments were carried out in triplicates and the data was mentioned and plots were constructed using the respective mean and standard deviation values.

## 3. RESULTS AND DISCUSSION [27,28]

### 3.1 Solubility Studies

Although MN treatment is a permeation enhancement technique, the process of drug transport is passive diffusion and a major factor that dictates the rate of drug permeation is concentration gradient across the skin (Eq. (1)). Because of sink conditions *In vivo* and the same being maintained during any *In vitro*/*Ex vivo* experiments, the value for $\Delta C$ is considered as the concentration of drug in donor vehicle (or formulation).

With a finite dose or concentration of drug in the donor compartment, the permeation process may be higher during the initial time points, where most of the administered drug is still in the donor vehicle and may tend to slow down towards the end of the study due to depletion of drug.

Hence an appropriate solvent system with high drug solubility is required. Preliminary studies for ZT and RT with several water miscible, aqueous solvents like different grades of PEG, PG, glycerol, etc., were carried out. It was found that both the drugs showed high solubility in PG and PEG in combination with saline (S). Among the shortlisted solvent systems, significantly higher solubility was observed with PG:S at 70:30% v/v in case of RT ($p<0.05$). In case of ZT, PG:S showed considerably higher solubility when compared to PEG:S, although not statistically significant ($p>0.05$) (Fig. 2). Hence, for both the molecules, PG:S at 70:30% v/v was chosen as the donor vehicle for permeation studies.

### 3.2 Surface Visualization and Depth of Penetration of MN

Following treatment with MN, skin samples were observed for formation of microconduits on the surface with the help of a dye. The samples were also subjected to histological evaluation to understand the extent of MN penetration into the skin layers and the disruption of skin layers. Representative digital images of skin samples before (without) and after treatment with different MN arrays are shown in Fig. 3. Clear distinction was seen in the number of microconduits formed, depending on the MN array that was used (Table 1).

Representative Histological sections images of the skin samples without and with MN treatment are shown in Fig. 4. In contrast to the control sample (without MN treatment) where the SC layer is intact, MN treated samples show clear disruption of SC layer and formation of microconduits of varying depths based on the MN array used. Using the scale provided, the depth of penetration was measured for not less than 5 samples per MN array and the data was shown in Fig. 5. As can be clearly seen from the figure, the depth of penetration significantly increased with increase in MN length ($p<0.05$). The relative standard deviation values (%RSD) of penetration depths were ≤15% for all the treatments, indicating that the force used while applying MN on the skin (manually, under thumb pressure) was consistent across all the experiments.

Furthermore, a linear relationship with $R^2$ of 0.99 was observed for the penetration depths obtained with different MNs used (Fig. 5). This may be a design related factor for Adminpatch® MN arrays that with similar force of application, a proportional increase in penetration can be achieved across different MN lengths.

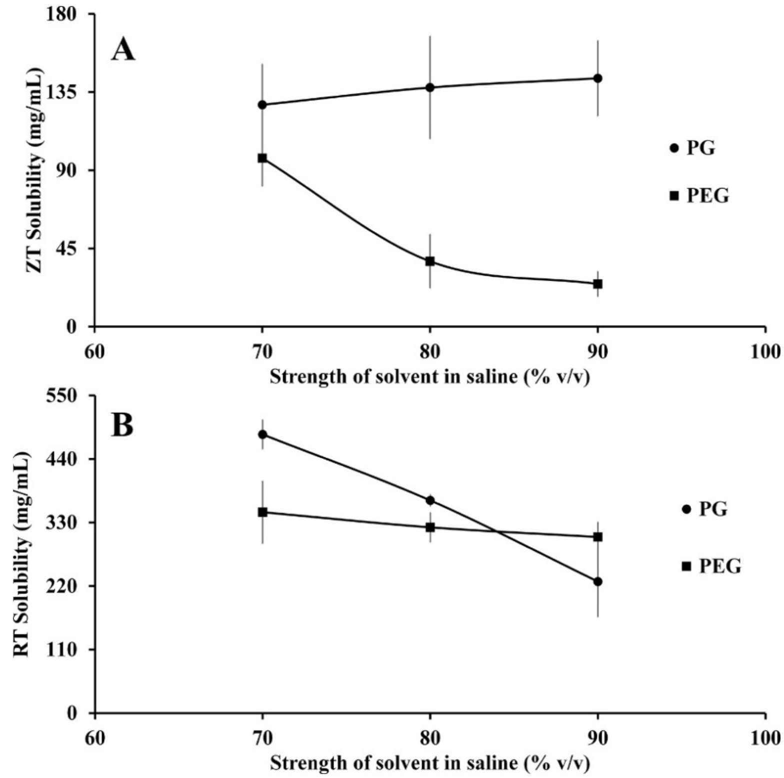


**Fig. 2. Solubility Data of (A) ZT and (B) RT in PG:S and PEG:S Solvent Systems**

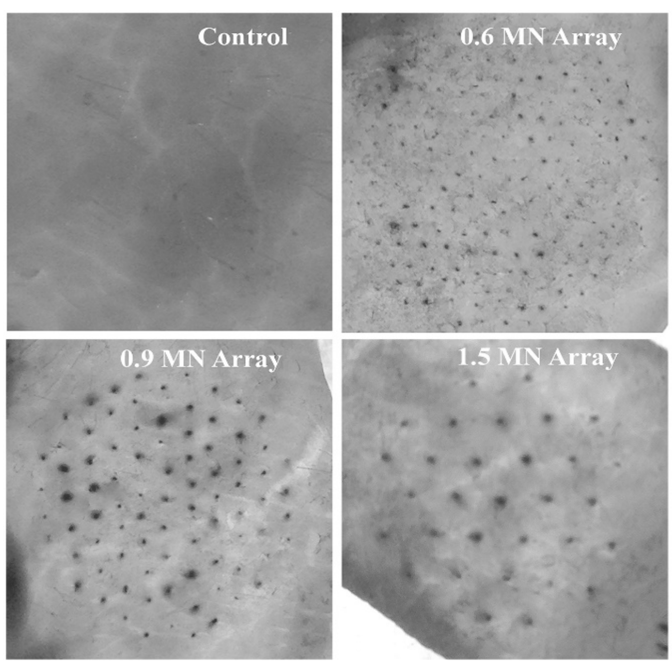


**Fig. 3. Surface images of stained skin without and with MN treatment**

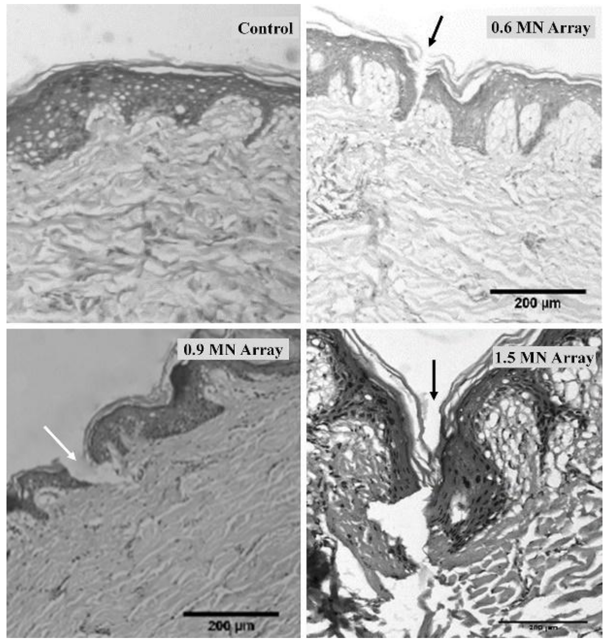


**Fig. 4. Penetration depth calculation of MN in skin**

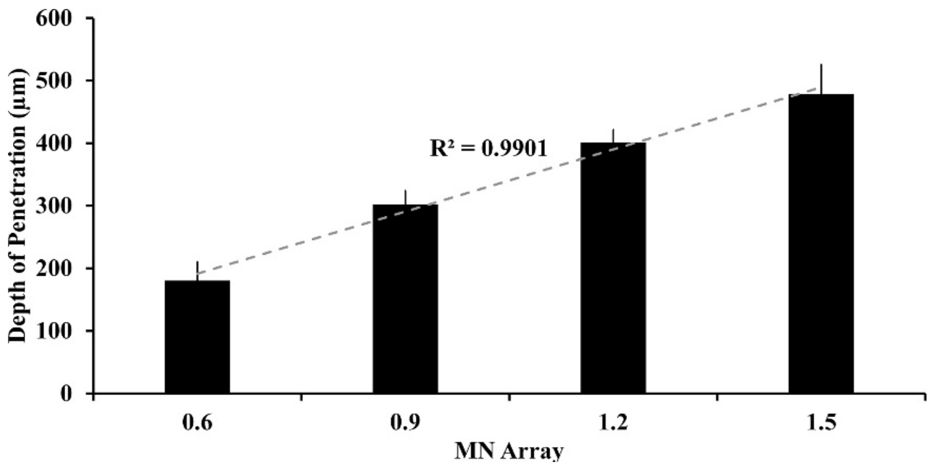


**Fig. 5. Depth of penetration with different MN arrays**

## 3.3 *Ex vivo* Transdermal Permeation Studies

As mentioned earlier in section 3.1, a finite amount of drug in the donor vehicle may show a reduction in the flux values beyond certain time point owing to the depletion of drug in the donor compartment. To avoid this issue, excess amount of drug (ZT or RT) was added so as to maintain a constant concentration of drug in the donor vehicle (equal to saturation solubility) over the entire duration of the study. Maintaining such high concentrations may not be feasible when developing a formulation. However, for the scope of these studies, wherein the comparative effect of different MN lengths and needle densities is being studied, such a methodology was adapted.

Transdermal permeation studies were carried out for both the drugs across pig ear skin under passive (without MN treatment) and with MN treatment (0.6, 0.9, 1.2 and 1.5 MN). Cumulative permeation profiles were constructed from the data to determine various permeation parameters. The cumulative amount of drug (ZT and RT) permeated at the end of 48 h and the transdermal flux obtained were shown in Fig. 6. It was observed that under passive conditions, the cumulative amount of drug permeated (275.919 ± 21.808 and 373.451 ± 77.524 nmoL/cm$^2$), steady state transdermal flux (10.138 ± 0.803 and 12.648 ± 1.212 nmoL/cm$^2$/h), lag time for steady state (20.83 ± 0.63 and 19.69 ± 4.73 h) for ZT and RT respectively are similar ($p>0.05$). Also, both the drugs showed significant enhancement in cumulative amount permeated at 48 h and steady state flux values for all MN treatments when compared with passive studies ($p<0.05$).

In case of ZT, lag times obtained were 17.66 ± 1.37, 14.04 ± 1.71, 14.52 ± 0.97 and 13.20 ± 0.39 h respectively for 0.6, 0.9, 1.2 and 1.5 MN. Similarly, the apparent permeability coefficient values were found to be 6.797 ± 0.074, 6.725 ± 0.180, 8.683 ± 0.594 and 10.361 ± 0.755 (× $10^{-5}$) cm/h for 0.6, 0.9, 1.2 and 1.5 MN treatments respectively. In case of RT, the lag times obtained for 0.6, 0.9, 1.2 and 1.5 MN treatments were 19.69 ± 4.73, 14.84 ± 1.96, 9.98 ± 0.91, 9.87 ± 1.38 and 4.17 ± 0.85 h respectively. The apparent permeability coefficient values were 3.348 ± 0.152, 3.353 ± 0.507, 6.004 ± 0.571 and 11.089 ± 0.756 (× $10^{-5}$) cm/h for MN treatments in the same order.

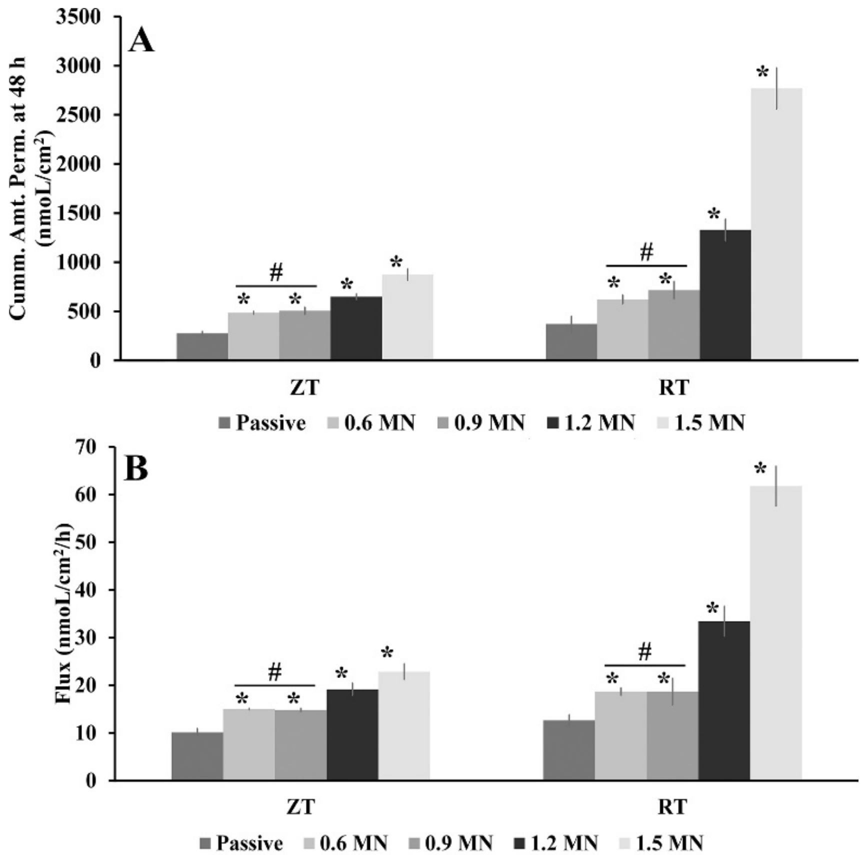


**Fig. 6. (A) Cumulative amount of drug permeated at the end of 48 h; (B) Steady state flux of with passive studies and different MN treatments.**
*[*]Statistically significant difference when compared with passive studies ($p<0.05$). [#]No statistically significant difference between treatments ($p>0.05$)*

The overall trend for permeation enhancement, in terms of amount permeated, flux and permeability coefficient was also similar for both molecules. Significant difference was observed between passive and all MN treatments for both the molecules. The enhancement achieved was not significantly different between 0.6 and 0.9 MN ($p>0.05$), which significantly improved with 1.2 MN and again with 1.5 MN ($p<0.05$) (Fig. 6). For both ZT and RT, the overall order of permeation rates can be represented as – Passive < 0.6 MN ~ 0.9 MN < 1.2 MN < 1.5 MN.

Although the passive transdermal permeation (across pig ear skin) of both ZT and RT was not significantly different, marked difference was observed in the extent of permeation enhancement achieved with MN treatment, especially with 1.2 and 1.5 MN, as can be seen from Fig. 6. Compared to passive studies, RT with 1.5 MN showed approximately 7.5 and 5 fold increase in cumulative amount permeated at the end of 48 h and steady state flux values respectively, while the same in case of ZT showed only 3 and 2.5 fold increase respectively. Among other aspects, this may be attributed to the difference in saturation solubility of the drugs in the selected donor vehicle Fig. 2 (RT is almost 3 times more soluble than ZT). The same may be the reason for the 4 fold reduction in lag time with 1.5 MN when compared with passive studies in case of RT, while only 1.5 fold reduction in the same was achieved with ZT.

The interplay of MN length (depth of penetration) and needle density (number of microneedles present/microconduits created in given area) seems to be affecting the extent of permeation of drugs (both ZT and RT). In the Adminpatch® MN arrays employed, as the length of MN increases, the needle density decreased as given in Table 1. 1.5 MN array has the least number of MNs (6 folds less than that of 0.6 MN) and still resulted in the highest permeation, indicating that the depth and size of microconduits created is a major contributing factor in enhancing permeation. At the same time, although a significantly higher depth of penetration was seen with 0.9 MN when compared with 0.6 MN (Fig. 5), the permeation enhancement was not significantly different among these two treatments for both the drugs. This again may be because the needle density of 0.6 MN was 2 times more than that for 0.9 MN, which may have nullified or compensated the effect of deeper penetration.

## 4. CONCLUSIONS

Although potent molecules are available, the success and patient acceptability of antimigraine therapy is limited by the delivery systems available. Transdermal delivery can to be a good alternative, provided a good permeation enhancement technique can be employed. Likewise, Sumatriptan has been formulated as an iontophoretic patch, ZECUITY® and was also marketed. However, the formulations were withdrawn from the market in 2016 owing to severe application site reactions [29].

MN is a novel technology that was initially introduced in cosmetics. These are minimally invasive and were reported to be well tolerated. Permeation of several drugs, including large molecules like insulin, was reported to be enhanced by this technology [17-24]. In case of coated or drug loaded (dissolvable) MN, drug loading is an issue for most of the drugs. Also, a substantial amount of time and resources should go into research and development of such MN devices for each and every drug molecule. Several aspects from the choice of polymer, design and dimensions of MN, strength of MN to penetrate the skin, stability, etc., should all be addressed to derive any benefit from such a promising technology.

Hence, poke and patch technique was attempted to deliver two anti-migraine drugs, *viz*., Zolmitriptan and Rizatriptan. A significant improvement in the transdermal permeation of both ZT and RT was achieved with MN application. It was observed that MN device parameters like the length, needle density and the design and also the concentration gradient that can be produced by the formulation can have a significant effect on the permeation enhancement of drugs.

As the complexity of the delivery system or formulation increases, large scale applicability in the real world drastically decreases. This is one of the major reasons why most of the formulations that show promising results in laboratory or at research scale are not translated to market. With the advent of low cost and high throughput techniques like micro-injection molding, etc., large scale manufacture of MN devices is now achievable. In the sense of keeping things simple, employing a well-designed MN device that maximizes the skin penetration while being painless and optimizing formulations like transdermal patches for delivery of several drugs following MN application may hold the key to open up transdermal delivery as the major route for drug administration in the future.

## ACKNOWLEDGEMENTS

The authors are thankful to Mylan Pharmaceuticals India Ltd, Hyderabad, for providing a gift samples of ZT and RT; The authors thank Dr. Naveen, Department of Pathology, Dr. Pinnamaneni Siddhartha

Institute of Medical Sciences and Research Foundation, Vijayawada, for providing the required facilities for taking histological sections of skin samples and also to the Siddhartha Academy of General and Technical Education, Vijayawada, for providing necessary facilities to carry out the research work. The authors also extend their sincere thanks to DST, Ministry of Science and Technology, Govt. of India and the British Council, London, UK, for funding this research work under the DST-UKIERI scheme (DST/INT/UK/P-60/2014).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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