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Comparative evaluation of ibuprofen and ibuprofen sodium nano micelles loaded dissolving microneedles in healthy human volunteers

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Abstract: This study is aimed to fabricate dissolving microneedles of ibuprofen and Ibuprofen sodium to have comparative bioavailability of both based on their pharmacokinetic profiles in healthy humans. Microneedles (MN) are a novel third generation transdermal drug delivery technology that overcomes skin barrier and enables enhanced drug delivery. Ibuprofen has a poor water solubility while Ibuprofen sodium, the salt of ibuprofen offers better solubility in aqueous media and hence quicker absorption into blood stream. The solubility of poor aqueous-soluble ibuprofen was enhanced by Soluplus (SP). The microneedles were fabricated using micromoulding technique. Morphology, drug content, mechanical strength studies, *In-vitro* drug release and *in-vivo* release in healthy humans were carried out. *In-vivo* pharmacokinetic analysis in healthy human volunteers revealed a Cmax of 21.5 µg/ml ±3.28 with the T_{max} of 24h and the MRT of 19.5hrs for ibuprofen, showing a prolonged stay in the body and sustained release into the blood stream. Ibuprofen sodium MNs showed quicker release into the systemic circulation with a Tmax of 2h and quick clearance as compared to ibuprofen MNs. The *in-vivo* findings provided evidence for the use of ibuprofen sodium MNs for acute pain while Ibuprofen MNs for sustained release analgesic effect.

Keywords: Comparative bioavailability; Dissolving microneedles; Ibuprofen; Ibuprofen sodium; Pharmacokinetics

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INTRODUCTION

The Non-steroidal anti-inflammatory drugs (NSAIDs) rank as very frequently prescribed drugs (Sostres *et al*., 2010). Available in different brand names and different formulations, NSAIDs have a common mode of action of inhibition of the enzymes cyclooxygenase 1 (COX1) and cyclooxygenase 2 (COX2). The safety record of these drugs is well established and permits for their use as over-the-counter drugs, however they still carry potential adverse effects (Sostres *et al*., 2010, Bindu *et al*., 2020). The chronic oral administration of NSAIDs have demonstrated a 90% risk of experiencing adverse gastrointestinal (GI) effects, with a 2 - 4% annual occurrence rate of upper gastrointestinal (GI) ulcers (Jones *et al*., 2008, Fosslien, 1998) The transdermal route for delivery of NSAIDs has gained popularity owing to its ability to reduce the adverse effects which come along with oral administration (Barkin, 2015). Transdermal administration of ibuprofen can provide a sustained release of the drug into the systemic circulation for long hours and a maintained therapeutic level leading to better patient compliance (Patel *et al*., 2013). However, achieving the adequate bioavailability of these drugs through the skin remains a challenge (Barry, 2001).The poor aqueous solubility of ibuprofen limits it to be formulated as transdermal patches, which effects rate of release and efficacy of the drug (Ossowicz-Rupniewska *et al*., 2021, Bolla *et al*., 2020). The natural barrier properties of the skin can limit ibuprofen permeation into the systemic circulation affecting the drug's bioavailability and efficacy (Yu *et al*., 2021, Souto *et al*., 2022). Stratum corneum (SC) is the top most layer of the skin which serves as the primary hinderance limiting the drug permeation across the skin (Dixena *et al*., 2024). Microneedles (MNs) have been developed as a novel and promising solution to overcome these challenges (Ita, 2015). These devices can effectively enhance drug permeation and provide a reliable mode of drug delivery, making them a promising tool in the field of transdermal drug delivery (Akhtar *et al*., 2020).

A rapid onset of relief is desirable to treat acute pain conditions. Ibuprofen (Ibu) plasma levels are directly related to pain relief. Ibu has shown complete absorption with nearly 100 % bioavailability, the absorption rate is dependent on the dissolution profile of the specified formulation (Legg *et al*., 2014). Ibuprofen is a carboxylic acid exhibiting minimal solubility in the acidic aqueous environments like that of the stomach (Zappaterra *et al*., 2022). Consequently, substantial pain relief usually requires around 40 to 45 minutes following the consumption of an OTC (over-the-counter) dose of 400 mg of the standard Ibuprofen. However, individuals with acute pain conditions like musculoskeletal pains, headache, menstrual or dental pain would benefit from a quicker onset of pain relief (Janczura *et al*., 2021). Ibuprofen sodium (Ibu Na) has been found to be absorbed more

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rapidly than ibuprofen, yet yielding a comparable extent of absorption in healthy individuals (Legg *et al*., 2014). This results in a faster onset of action, with pain relief typically occurring within 15-30 minutes of taking ibuprofen sodium compared to ibuprofen (45 to 60minutes). Ibuprofen sodium has a higher bioavailability than standard ibuprofen (Dewland *et al*., 2009). The increased bioavailability of ibuprofen sodium is due to its higher solubility, which allows for more rapid and complete absorption (Daniels *et al*., 2009). On the other hand, ibuprofen lysinate, another salt formulation of ibuprofen, also exhibits faster absorption and reaches peak plasma concentrations more rapidly, providing a fast onset of action (Al Lawati and Jamali, 2016). The pharmacokinetic differences between ibuprofen and ibuprofen sodium include faster absorption and shorter time to reach peak plasma concentration for ibuprofen sodium formulations, leading to faster and more profound analgesia compared to standard ibuprofen acid (Taggar *et al*., 2017). Similarly a faster and more profound analgesic effect is achieved when ibuprofen sodium is administered trans dermally, however studies have shown that the topical application of both ibuprofen and ibuprofen sodium can provide similar clinical efficacy though only differing in the time required for the onset of analgesic effect (Bettiol *et al*., 2021).

In our study we aimed at the evaluation of pharmacokinetic parameters of Ibu and Ibu Na achieved in healthy humans when administered through dissolving microneedles prepared with poly vinyl alcohol (PVA). Ibuprofen was selected as a model drug owing to its poor aqueous solubility (BCS-II), suitability for transdermal administration and its potential to benefit from solubility enhancement through nano micelle-based delivery systems. PVA is a biodegradable polymer which has previously been shown to be a promising material for MN fabrication (Chen *et al*., 2018, Oh *et al*., 2022), has been previously used for fabrication of efficient dissolving MNs in terms of strength and performance (Hidayatullah *et al*., 2023). Our study is focused on incorporating the pure and salt form of ibuprofen in microneedles and compare the pharmacokinetic profile of both in humans.

MATERIALS AND METHODS

Materials

Ibuprofen, Ibuprofen sodium and Naproxen was obtained from Macklin Biochemical Co., Ltd. (Shanghai, China), while polydimethylsiloxane (PDMS) molds equipped with 100 microneedles, each measuring 800µm in height, 200µm in base diameter and spaced at 500µm interval, were acquired from Micropoint Technologies (Singapore). Polyvinyl alcohol (1500) from Sigma Aldrich (MO, US). Soluplus® (SP) (BASF; New Jersy; USA). Acetonitrile of purity greater than 99% was obtained from Fisher Scientific (U.K). Methanol with a purity exceeding 99.9%, Dichloromethane (DCM) and Potassium dihydrogen phosphate were sourced from Sigma Aldrich (St. Louis, MO, USA), Ortho-phosphoric acid was acquired from ScharlauChemie in Barcelona, Spain. Sodium Bicarbonate (NaHCO3) with a purity of 99.95% was obtained from Fluka. Sodium Chloride, Di-potassium hydrogen phosphate and Potassium Chloride were purchased from Sigma Aldrich in MO, USA. Distilled water from the Millipore ultrapure water system in Milford, USA.

The Perkin Elmer Series 200 HPLC system (Norwalk, USA) was used, which included an autosampler, UV visible detector, vacuum degasser, pump and Peltier column oven. Perkin-Elmer TotalChrom Workstation Version 6.3.1 connected to the HPLC system via network chromatography interface (NCI 900) was used to acquire and evaluate experimental data. The separation process was conducted utilizing a Welchrom® C8 analytical column (5µm particle size) with dimensions of 4.6x150mm, manufactured by Welch (Zhejiang, China). Additionally, a guard cartridge with corresponding chemistry was affixed to the column.

Methodology

Pre-formulation fourier transform infrared spectroscopic study (FTIR)

The FTIR spectra for the excipients (PVA and SP) and the pure drugs Ibuprofen and Ibuprofen sodium, along with their physical mixture, were collected using potassium bromide (KBr) disc technique on a PerkinElmer Spectrum BX FTIR instrument, manufactured by PerkinElmer in Waltham, MA, USA. The spectral range measured for percent transmittance was from 4000 to 400 cm^{-1}, with a resolution set at 4 cm^{-1} (Mateescu *et al*., 2023).

Preparation of drug solutions and casting solutions

Preparation of drug solution

As ibuprofen is poorly water soluble (<1mg/ml) (Wang *et al*., 2010), Soluplus® (caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) (SP) was used to encourage solubility of the drug through micellization as reported previously (Hidayatullah *et al*., 2023, Gohar *et al*., 2024). Ibuprofen 25% by weight solution was prepared in PBS (pH 7.4) with 8% of SP (Hidayatullah *et al*., 2023). A similar solution of Ibu Na (40% by weight) was prepared in distilled water with 1% SP.

Ibu 25% and Ibu Na 40% (by weight) were gradually added in small portions to respective 5 mL aqueous solutions of SP. Parafilm M was used to cover all the dispersions and were stirred for 24 hours at 200rpm in a shaking water bath set at 36°C (Hidayatullah *et al*., 2023).

Preparation of polymer solution

15% w/v PVA solution was prepared by suspending the accurately weighed amount of PVA in 10 ml of pre-heated deionized water (80 °C) for 4h in shaking water bath (Jeio

Tech, Korea) to obtain a clear gel solution. This gel solution was left overnight to remove any air bubbles.

Preparation of MN casting solution

The casting solution was prepared by mixing the prepared gel solution of PVA and the drug solutions of Ibu and Ibu Na in a 1:1 *w/w* ratio. The blends were mixed using a magnetic stirrer at room temperature for 10minutes and 150 rpm to ensure uniform mixing.

Fabrication of Ibuprofen/Ibuprofen Na MNs

The MN patches were fabricated using the micromoulding technique with vacuum pressure (-90kPa) at 25°C for 10minutes (Park *et al*., 2005). The casting solution was added to the PDMS mold surface and vacuum pressure was applied for effective filling of the mold with the blend. Any extra amount of blend on mold surface was carefully removed. Subsequently, to form a backing layer a small amount of PVA solution without the drug was added on top and vacuum was applied again to facilitate proper filling of the mold cavities. The molds were dried at room temperature for 24 hours. Finally, the microneedle (MN) patches were separated from the mold manually with the help of adhesive tape (Yang *et al*., 2015) and the microneedle patches were stored in a desiccator under controlled conditions of temperature and humidity, specifically maintained at 25 ± 2°C and 60 ± 5% relative humidity (RH) (Paredes *et al*., 2022) until further use .

Characterization of Ibuprofen microneedles

Microscopic evaluation

The fabricated arrays were examined using a light microscope from Olympus, Japan and a scanning electron microscope (SEM) from Jeol, Japan (model JSM-5910) for morphological study and shape of the MNs. Subsequently, the MN patches were coated with gold and further analyzed under the Phenom™ SEM system to investigate the needle morphology and dimensions in greater detail (Zhao *et al*., 2023).

Mechanical evaluation and penetration study

An axial compression test was conducted using a Universal Testing Machine (UTM) to assess the mechanical properties of the fabricated MN patches. The UTM was fitted with a stainless-steel probe measuring 8mm in diameter. The MN patches affixed onto a flat aluminum block were exposed to a force applied perpendicular to the axis of the array. This force was administered at a constant speed of 0.01 mm/s. Upon contact between the motion sensor and the microneedle tips, the applied force was recorded relative to the displacement of the needles. This process was performed in triplicate for accuracy (Ramadon *et al*., 2023, He *et al*., 2021).

Preliminary penetration tests

To assess the penetration capability of microneedle (MN) arrays, Parafilm M (PF) was folded into eight layers, approximating a thickness of 1 mm, which simulated the thickness of human skin (Larrañeta *et al*., 2016) A force of 35N was used to insert he microneedle (MN) patches into the stacked Parafilm M layers for a duration of 30 seconds (Vora *et al*., 2018), using the UTM. The test was performed in triplicate.

After removal of the MN patch, the punctured Parafilm M was examined. Each layer of the film was observed under an optical microscope (Olympus BX51, Olympus Corporation, Tokyo, Japan) and the resulting number of micro punctures per layer was counted. To determine the percent insertion, the formula given as equation 1 was employed.

% Insertion = No. of punctures in parafilm M / Total number of microneedles * 100 Eq. 1

Drug content

To determine the drug content of both Ibu and Ibu Na fabricated MN patches, a single patch of each formulation was dissolved in distilled water in an Eppendorf tube and was subjected to shaking for 24 hours in shaking water bath at a temperature of 80°C to ensure complete dissolution of the polymer PVA (Amodwala *et al*., 2017). The resulting solution was next subjected to centrifugation for 15 min at 10°C and 3000xg followed by discarding the supernatant and reconstitution of the precipitate with mobile phase. Next, the solution underwent sonication, vortex mixing and filtration using a microfilter. Subsequently, it was injected into the HPLC (High-Performance Liquid Chromatography) system for the determination of drug content. Briefly, a sample volume of 50 µl was injected into the Welchrom® C8 column (4.6 x 150mm). The mobile phase consisted of a mixture of acetonitrile with phosphoric acid buffer (pH 2.3) in a ratio of 55:45 v/v. The mobile phase was pumped through the column at a flow rate of 1 ml/min. Naproxen sodium served as the internal standard and UV detection was performed at 220nm. The formula given as equation 2 was used to calculate the percent drug obtained from MN patch.

% Drug content = Peak area of sample / Peak area of standard * 100 Eq. 2

In-vitro drug release

The MN patches loaded with Ibu and Ibu Na were studied for drug release profile, the study was performed in triplicates (n=3). Franz cells with Parafilm M was used for the release study (Larrañeta *et al*., 2016). Parafilm M, stacked in three layers, was employed as a simulated model and mounted on the Franz diffusion cell. Phosphate buffer solution (pH 7.4) to serve as the dissolution medium to fill the acceptor compartment. Stirring was maintained at an rpm of 600 and the temperature was controlled at 37 ± 1°C by water that circulated through a peristaltic pump (McCrudden *et al*., 2014). A microneedle patch loaded with drug was inserted onto the stacked Parafilm M and clamps were secured between the donor and receptor

chambers. At prespecified time periods (0.5, 1, 2, 3, 6, 12, 24 and 48 hours), an aliquot of 0.5mL was collected from the receptor chamber. An equal volume of dissolution medium was used to replace the collected sample. The amount of drug in all the samples at different time periods was assayed using the HPLC method (2009), as discussed.

In-vivo release studies

To assess *in-vivo* pharmacokinetics of the drug and its salt form, a study was designed using healthy male volunteers aged 20 to 25 yrs. The investigation studies were conducted in accordance with principles outlined in Declaration of Helsinki (1975). Informed consent was obtained from all human volunteers participating in the study. Two groups were constituted, group A received microneedles patches of ibuprofen (165µg) whereas group B received microneedles patches of ibuprofen sodium (266.4µg of equivalent amount of ibuprofen). Blood samples were collected from the participants at predetermined time intervals (0, 0.5, 1, 2, 3, 6, 12, 24 and 48 hours) in ethylenediaminetetraacetic acid (EDTA) glass tubes. The collected blood samples were centrifuged at 1600 x g for 10 minutes at 4°C to obtain clear plasma, which was subsequently stored at -20°C for further analysis. To prepare the plasma samples for analysis, 200 µL of plasma was mixed with 10 µL of naproxen sodium (1 µg/mL) as an internal standard. The mixture was vortexed for 5 minutes and then acidified with 120 µL of 1 M HCl. Protein precipitation was carried out by adding 500 µL of methanol, followed by centrifugation at 10°C for 10 minutes at 5500 rpm. The supernatant was collected, and the process was repeated once. The supernatant was then dried using nitrogen gas at 40°C. After drying the sample was reconstituted with required volume of mobile phase and analyzed for ibuprofen and ibuprofen sodium content using HPLC-UV. Pharmacokinetic (PK) parameters were determined using PK Solver software (version 2.0).

Statistical analysis

All samples were collected in triplicate and results were expressed as mean ± standard deviation (SD). Statistical analysis was conducted using GraphPad Prism (version 8.0.2), applying a t-test to compare groups. A p-value of < 0.05 was considered statistically significant.

RESULTS

FTIR

The FTIR spectra (Fig. 1) for the drugs ibuprofen, ibuprofen sodium, the excipients PVA, Soluplus® and the drug-excipient physical mixtures were obtained. The spectral range of 4000 to 400 cm–1 was used to measure the percent transmittance.

Microscopic evaluation

The SEM images of the fabricated MNs are depicted as Fig. 2. The figure shows the top view of the fabricated MNs of Ibuprofen and Ibuprofen sodium, the intact, straight, aligned needles stood uniformly on a flat baseplate.

The lateral images of the fabricated MNs were also obtained using SEM to confirm the morphology and the alignment of the needles on the baseplate. The needle tips were carefully observed for the even distribution of the needles. Fig. 3 shows the lateral view of Ibu and Ibu Na microneedle patches.

Mechanical evaluation and penetration study in Parafilm M

Evaluating the mechanical characteristics of MNs is crucial for their overall performance, especially considering that MN arrays undergo stress during skin insertion, posing a potential risk of system failure. The mechanical response of MN patches was assessed through force-versus-displacement profiles. These profiles were generated by applying axial compression force to the MNs using a Universal Testing Machine (UTM). The resulting plot revealed a continuous and gradual rise in the force per needle value, with no discernible discontinuities as shown in Fig. 4. The figure depicts the Force versus deflection curve derived for both ibuprofen and ibuprofen sodium microneedles.

Following the mechanical strength test, SEM images were captured to examine potential deformations or fractures of the needles under a consistent force of 35N. The SEM image depicted in the Fig. 5 reveals the absence of needle breakage; however, only bent tips were observed.

Percent insertion of fabricated MNs arrays across Parafilm M (PF) sheets refers to the degree or extent to which the microneedles penetrate or pierced the sheets. Fig. 6 illustrates this percentage showing the distribution of microneedle insertion across the surface area of the PF sheets. This measurement is crucial in assessing the effectiveness and uniformity of the microneedle array's penetration, which impacts their functionality in delivering substances or compounds through the skin barrier.

Drug content

Table 1 presents the average drug content and percentage recovery of Ibu and Ibu NA obtained from the MN patch.

In-vitro drug release

The cumulative drug release profile of ibuprofen and Ibuprofen sodium from the MN patch is shown in Fig. 7. The acquired *in-vitro* data indicates that the formulated MNs successfully released Ibuprofen and Ibuprofen sodium in a controlled and predictable manner over a 48-hour period.

The Table 2 displaying the R2 and k values obtained from fitting various kinetic models. The R2 values indicated the degree of correlation between the model predictions and the observed data, providing insights into the model's accuracy in describing the kinetics of the studied process.

On the other hand, the k values represented the rate constants associated with each kinetic model, offering information about the reaction rates and mechanisms under investigation.

The findings demonstrated an initial burst release, succeeded by a sustained release of the drug, confirming a biphasic release pattern. The Zero-order kinetic model demonstrated the best fit for the release data, with R^2 values of 0.98 for ibuprofen and 0.96 for ibuprofen sodium (table 2). The release of ibuprofen and ibuprofen sodium from the microneedles occurred through dissolution, aligning with the predictions of the Hixon Crowell model (R^2= 0.98). However, the obtained n value of 1.8 from fitting the Korsmeyer & Peppas model suggested a super case II transport for drug release from the ibuprofen microneedle patch (Aguzzi *et al*., 2010, Patel *et al*., 2015). The super case II transport corresponds to zero order kinetics (Laracuente *et al*., 2020). The super case II transport, associated with zero-order kinetics (time-independent release), is linked to the relaxation behavior of the polymer occurring when water permeates into the microneedle system, acting as the rate-controlling step (Siepmann and Peppas, 2012). The permeation of water leads to swelling of the matrix, which in turn triggers the degradation and dissolution of the microneedles. However, for ibuprofen sodium, n value of 0.6 indicated anomalous transport, this is supported by the fact that there is enhanced interaction between water and ibuprofen sodium attributed to the high-water solubility of ibuprofen sodium, leading to a preferential interaction with water molecules within the patch. Consequently, lower interaction of water with the polymer matrix. This phenomenon results in a decreased swelling and dissolution of the polymer initially because of the increased interaction of water molecules with Ibuprofen sodium hence a slow initial release as compared to Ibuprofen.

In-vivo release studies

To study the *in-vivo* release profile of the MNs, the study was performed on healthy humans. Non compartmental analysis (NCA) using PK solutions software was used to estimate the pharmacokinetic parameters of the fabricated dissolving MN patches of Ibu and Ibu Na. Three microneedle (MN) arrays were applied to each volunteer on the volar part of the wrist using a spring applicator (n=6). They were secured in place with medical adhesive tape to ensure they remained in position for a duration of 48 hours. The non-compartmental analysis (NCA) pharmacokinetic parameters are shown in Table 3.

Fig. 8 illustrates the plasma concentration versus time plot of ibuprofen MN patch and ibuprofen sodium MN patch. The mean quantity of Ibu in each Microneedle patch was about 52 micrograms whereas the amount of Ibu Na in each patch was 80µg. The pharmacokinetic parameters were determined for both the groups receiving Ibu and Ibu Na. The statistical results suggested significant difference among both the groups as shown in Table 3. The plasma concentrations vs time curve shown as Fig. 8 indicated that the Ibu MNs maintained the drug plasma drug concentration up to 24 hours as compared to Ibu Na MNs which maintained the maximum drug concentration up to 5 hours only.

The other pharmacokinetic parameters of ibuprofen microneedles were also significantly distinct from those of ibuprofen sodium microneedles. Higher values of area under the curve (AUC- 580 µg/ml*h) and area under the moment curve (AUMC- 11334.45 µg/ml*h^2) for Ibu MNs were observed, resulting in an extended mean residence time of about 19 hours and reduced clearance. Although ibuprofen sodium exhibited a comparable peak concentration (Cmax- 21.3 µg/ml) to Ibu MNs (Cmax- 21.51 µg/ml), but its Tmax, AUC and MRT were significantly lower, highlighting the swift behavior of the sodium salt with rapid absorption and elimination characteristics that are typical of salt forms of drugs.

DISCUSSION

FTIR

The FTIR spectrum of pure ibuprofen exhibited intense and well-defined bands at 1700 cm-1 which are characteristic of ibuprofen (corresponding to the carbonyl stretching of the isopropionic acid group) and the bands at 3000 cm-1 associated with hydroxyl stretching. The FTIR spectrum of ibuprofen sodium demonstrated similar spectrum to that of Ibu with an additional broad peak observed at around 3200 cm-1 which is related to the N-H stretching vibration of the sodium salt. The spectra of physical mixtures of ibuprofen-SP-PVA and Ibuprofen sodium-SP-PVA, revealed no chemical interaction between both the drugs and excipients used as shown in Fig. 1.

Microscopic evaluation

As depicted in the SEM images shown in Fig. 3, both the ibuprofen-PVA and ibuprofen sodium-PVA microneedle (MN) patches effectively replicated the shape of the PDMS master mold. This replication resulted in uniformly spaced pyramidal MN projections distributed evenly across the arrays. The total 100 micro projections stand straight with a base width of 200µm and a height of 800µm. Moreover, all the microneedles presented with sharp and well-defined tips.

Mechanical evaluation and penetration study in Parafilm M

The observation shown as Fig. 4 suggests that the needles undergo deformation rather than breakage when subjected to the applied force load. This characteristic is typical of polymeric microneedles (MNs), such as those made from PVA, which exhibit a pyramidal shape, as opposed to conical ones (Lee *et al*., 2008). A 350 N force was applied to microneedle (MN) patches loaded with ibuprofen (Ibu)

and ibuprofen sodium (Ibu Na). The needles exhibited deformation at a 3.5 N force per needle for Ibu and 2.9 N force per needle for Ibu Na. However, they did not break, as evidenced by the SEM image shown in Fig. 5. This suggests that the fabricated MN patch could withstand significant force before reaching the breaking point, confirming its suitability for penetration of human skin (Park *et al*., 2005). The fabricated microneedle (MN) patch demonstrated sufficient strength to penetrate stratum corneum effectively, the insertion force required to cross the skin barrier is approximately 0.098N per needle. With the MN patch withstanding forces of 3.5 N per needle for ibuprofen (Ibu) and 2.9 N per needle for ibuprofen sodium (Ibu Na), it surpasses the required force, indicating its capability to penetrate the skin barrier effectively (Makvandi *et al*., 2021). In case of pyramidal MNs with PVA, previous studies have reported enhanced mechanical strength and optimum performance (Bonfante *et al*., 2020) , the higher concentration of SP(8%) in Ibu MN patch also contributes to the mechanical strength of the formed patch (Anjani *et al*., 2022).

In order to delve deeper into the skin insertion capabilities of the MNs, the patches were positioned atop eight layers of Parafilm M and exposed to an axial force of 35 N for 30 seconds. The MNs demonstrated the ability to penetrate the film, reaching up to 100% depth into the third layer, equivalent to a thickness of 381 µm. This outcome underscores their suitability for effectively crossing the stratum corneum (Larrañeta *et al*., 2014). Practically, all the projections of both ibuprofen (Ibu) and ibuprofen sodium (Ibu Na) microneedles (MNs) penetrated the first three layers of the film, achieving 100% penetration for both cases. Furthermore, 80% and 60% of the MNs penetrated the fourth and fifth layers, respectively, as depicted in Fig. 6. This assessment reaffirms their capability to endure the necessary force for skin insertion without fracturing.

Drug content

The amount of drug loaded into the fabricated patches was found by determining the drug content, the drug content of Ibuprofen MN patches was found to be 99.4% while that of Ibuprofen sodium was 99%. This indicated that the fabricated patches were highly efficient in incorporating the respective drugs, with almost all the total weight of the patches being attributed to the active drug ingredient. High drug content in patches is desirable as it ensures accurate dosing and effectiveness of the medication delivered through the patches.

In-vitro drug release

The *In-vitro* release findings revealed insights into the release kinetics of ibuprofen and ibuprofen sodium from microneedle patches, describing their biphasic release pattern and underlying mechanisms. The observed initial burst release followed by sustained release confirmed the presence of a biphasic release profile. The utilization of kinetic models facilitated a comprehensive understanding of the release behavior. Notably, the Zero-order kinetic model emerged as the most suitable model for describing the release kinetics. This finding underscores the consistent and predictable release of the drug over time which is characteristic of zero-order kinetics. Furthermore, the release mechanism elucidated through the Hixon Crowell model aligns with the dissolution process, indicating that the release of ibuprofen and ibuprofen sodium from the microneedles primarily occurs through dissolution.

Polyvinyl alcohol is well-documented in scientific literature for its capacity to absorb water and relax its molecular structure. This behavior primarily arises from the presence of hydroxyl (-OH) groups along the polymer chain. When PVA comes into contact with water, these hydroxyl groups readily engage in hydrogen bonding with water molecules.

This interaction leads to the absorption of water into the polymer structure, causing it to swell. The formation of hydrogen bonds between PVA and water molecules weakens the intermolecular forces holding the polymer chains together, facilitating molecular relaxation. This intricate interplay between hydrogen bonding and molecular relaxation elucidates the swelling and dissolution behavior observed in PVA. However, the application of the Korsmeyer & Peppas model revealed distinct transport phenomena for ibuprofen and ibuprofen sodium. For ibuprofen, the n value suggested a super case II transport, indicative of zero-order kinetics.

This phenomenon can be attributed to the relaxation behavior of the polymer matrix upon water permeation into the microneedle system, serving as the rate-controlling step. The permeation of water triggers matrix swelling, leading to polymer degradation and microneedle dissolution, facilitating sustained drug release. As water permeates the polymer matrix, it triggers swelling of the PVA, promoting gradual degradation of the polymer. This slow degradation process plays a pivotal role in the sustained release mechanism, allowing for the controlled dissolution of the microneedles loaded with Ibuprofen.

The gradual breakdown of the polymer matrix facilitates the prolonged release of Ibuprofen into the surrounding environment. In contrast, the anomalous transport observed for ibuprofen sodium, as indicated by the n value, highlights a different release mechanism. The high-water solubility of ibuprofen sodium fosters enhanced interaction with water molecules, resulting in preferential water-polymer interactions within the patch. Consequently, reduced water availability impedes polymer swelling and dissolution, delaying the initial drug release compared to ibuprofen.

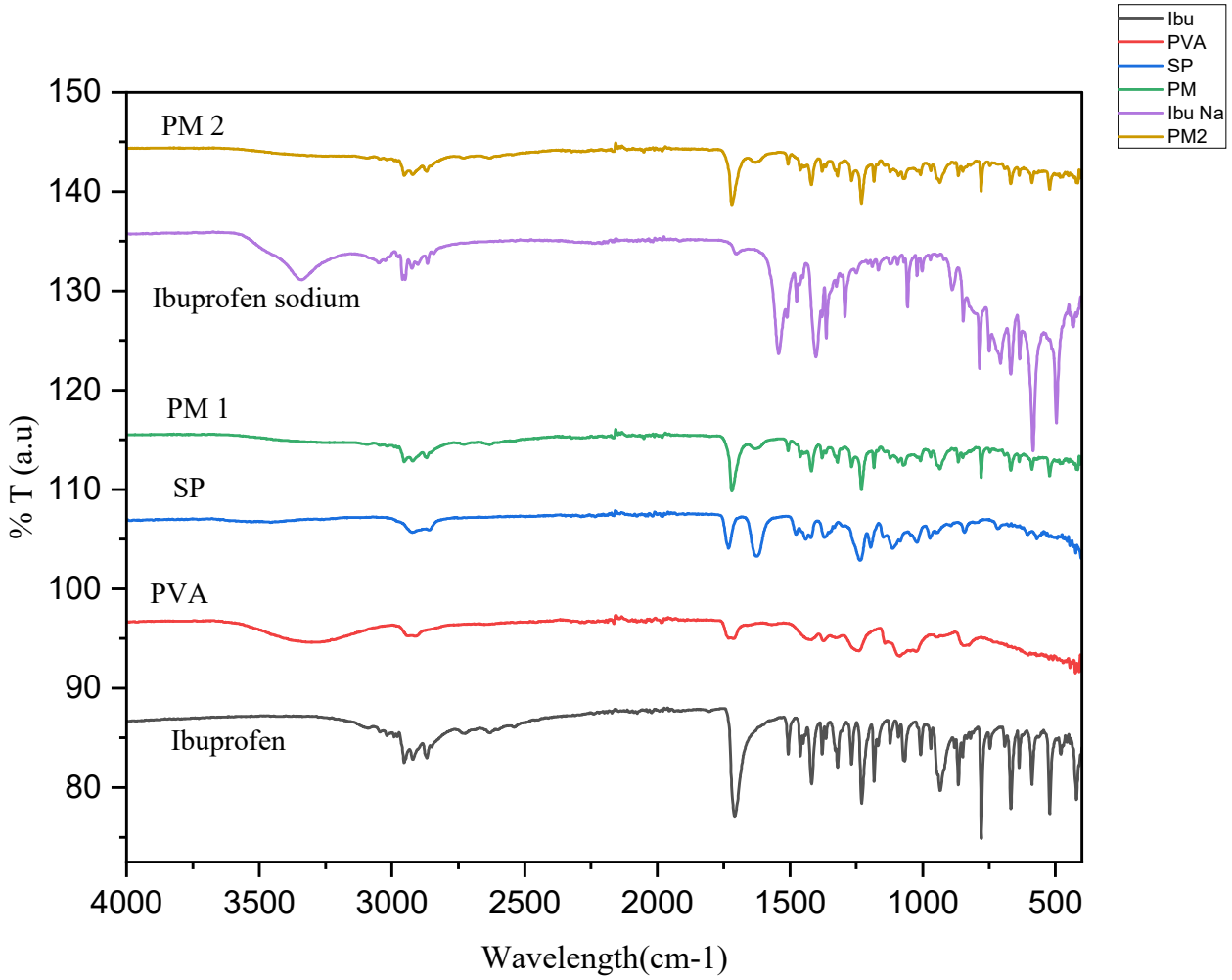
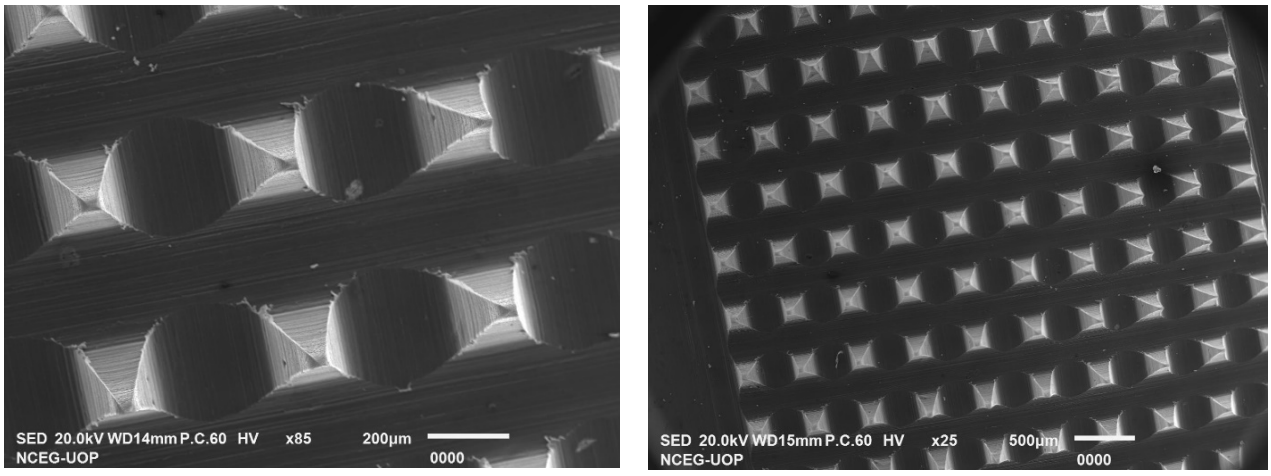
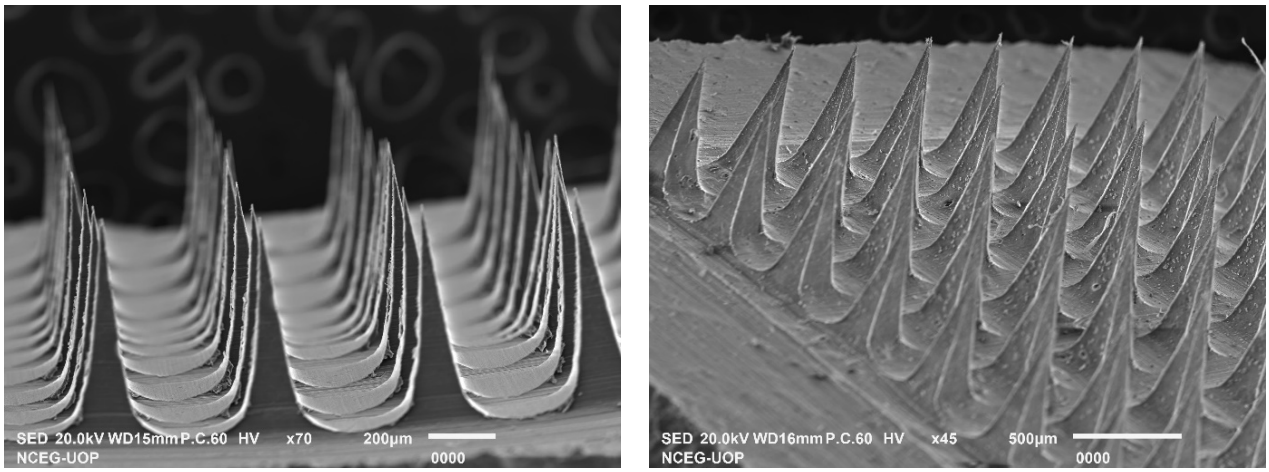


Fig. 1: FTIR spectra of pure drugs, Soluplus, PVA and the physical mixtures



A. **B.**

Fig. 2: (a) Top view of ibuprofen loaded microneedles (b) Top view of ibuprofen sodium loaded microneedles.



A. **B.**

Fig. 3: Lateral view of MN patches. (a) Ibu Na loaded MN patches, (b) Ibu loaded MN patches.

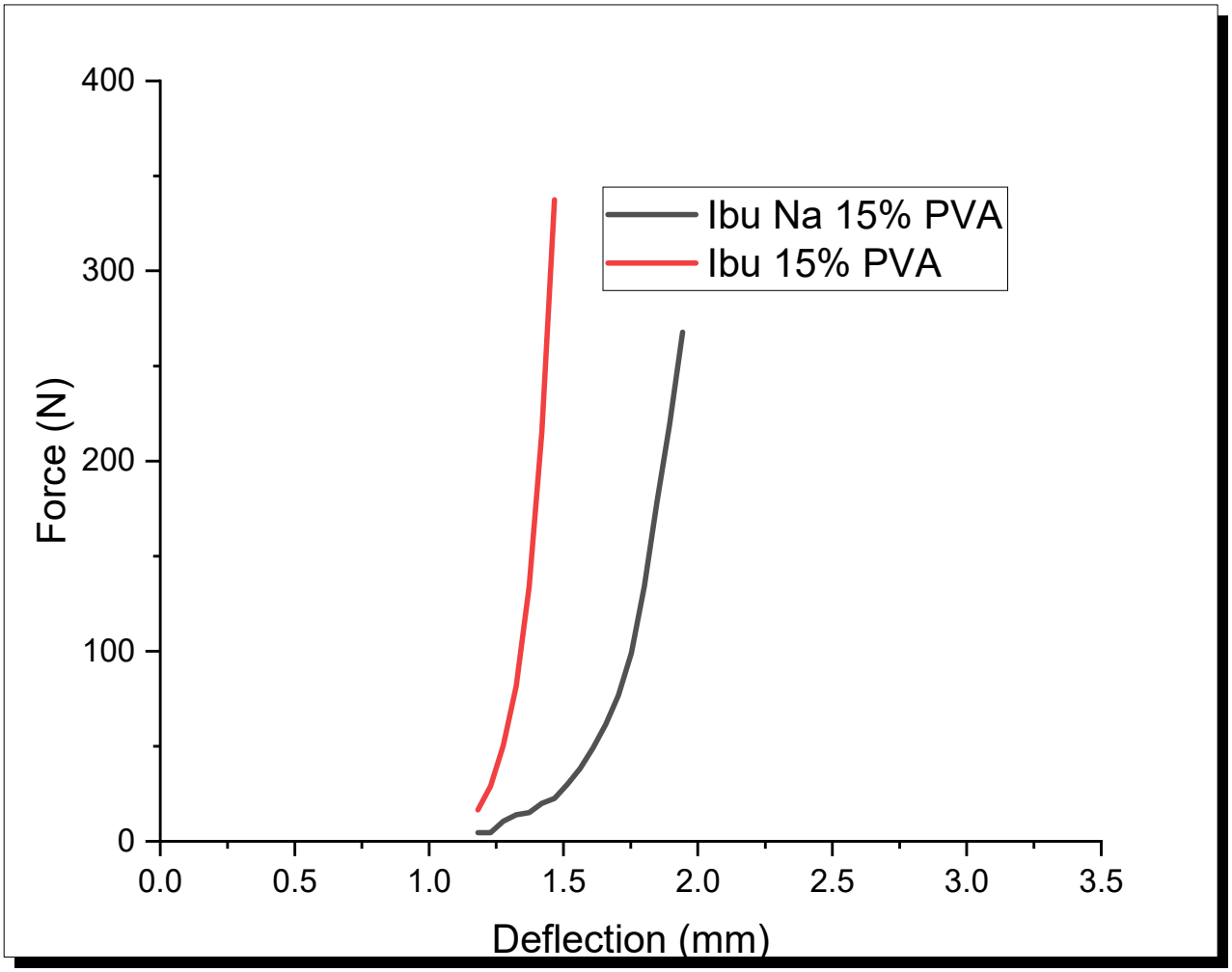


Fig. 4: Force vs Deflection curve obtained for the MN patch.

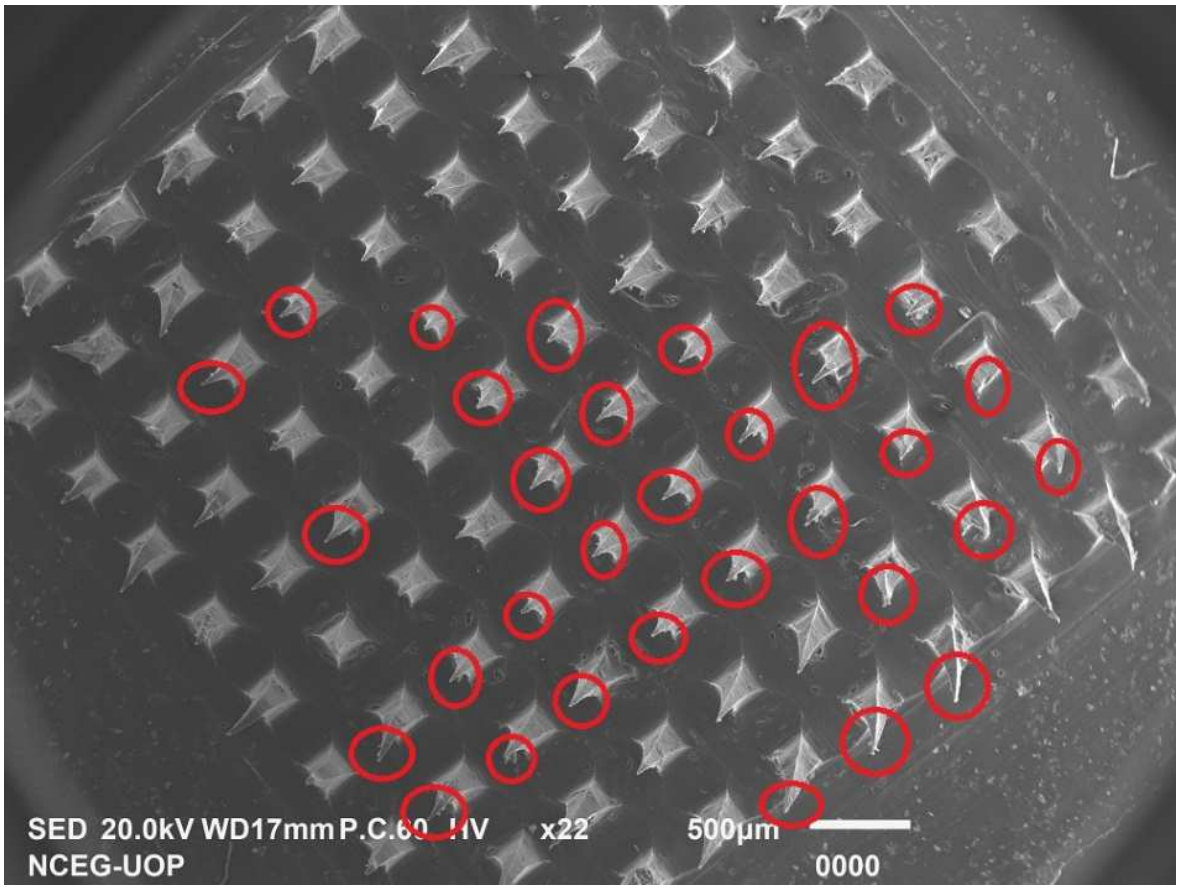


Fig. 5: SEM image of post-strength test MN patch showing deformed needle tips.

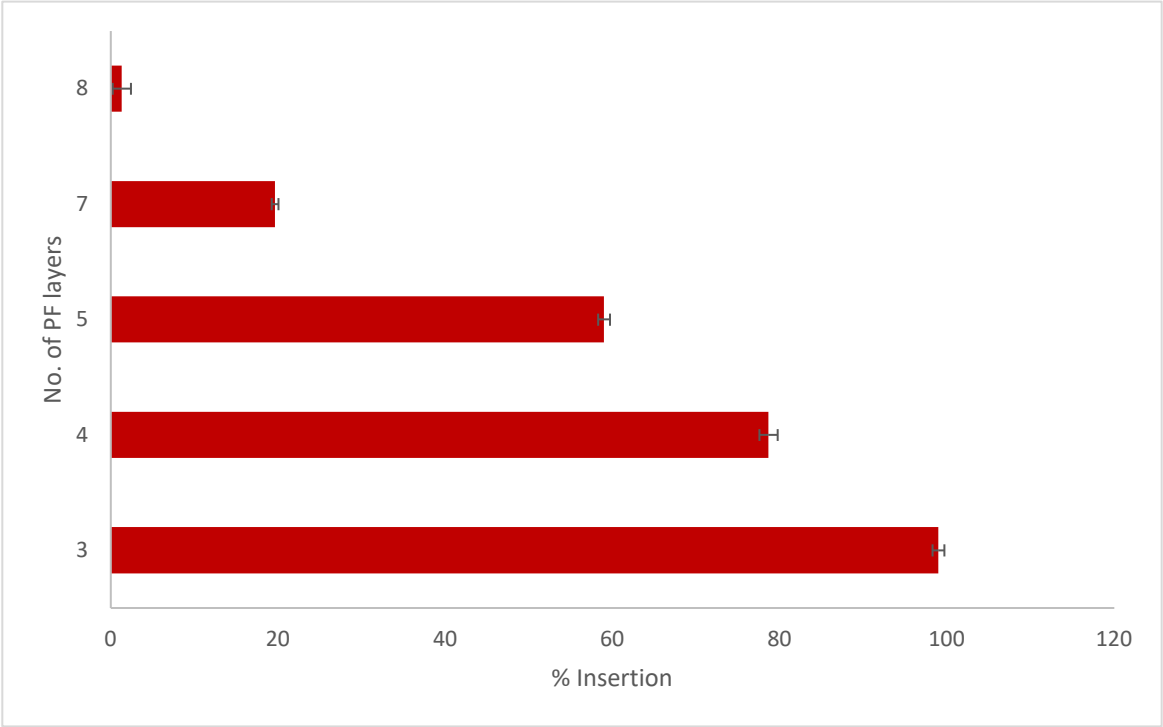


Fig. 6: Microneedles insertion evaluation

Table 1: Percent recovery of Ibu and Ibu Na from MN patch

MN patch (drug loaded)	Amount of drug added to the patch	Mean Drug Content ±SD	% Drug recovery
Ibuprofen	52µg	51.7 ± 0.81	99.4 %
Ibuprofen sodium	80µg	79.2 ± 0.73	99 %

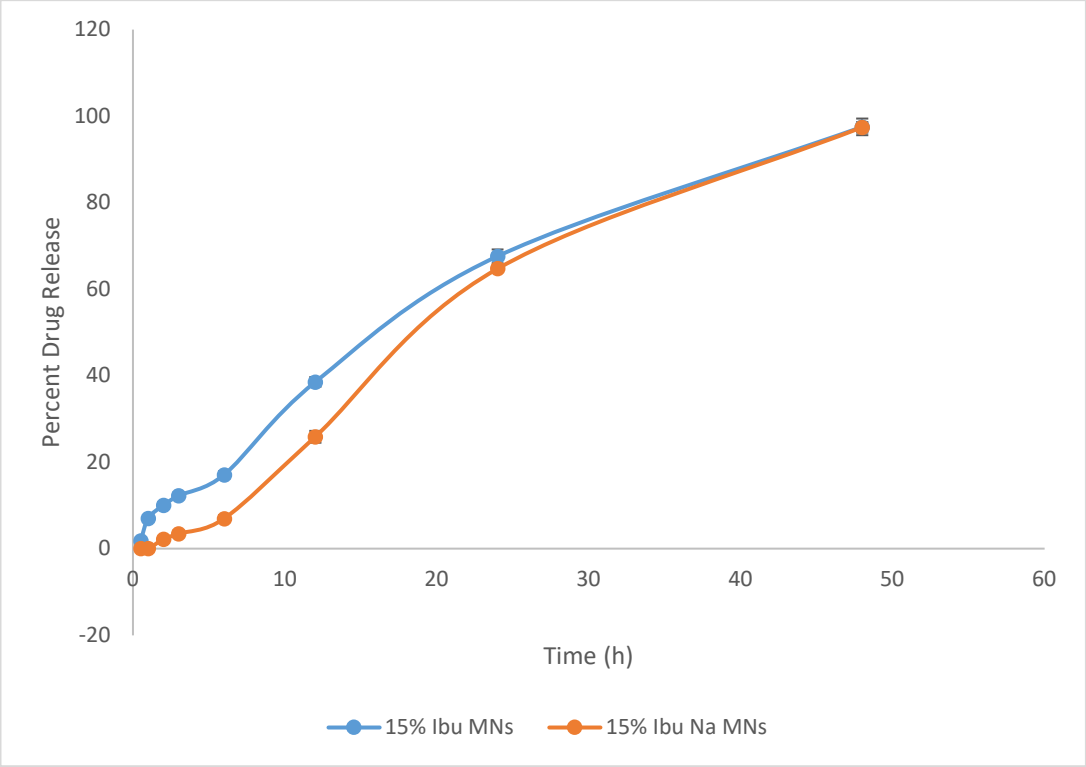


Fig. 7: Cumulative drug release profile of Ibuprofen and Ibuprofen sodium MN patches

Table 2: R^2 and k values obtained by fitting different kinetic models.

Model	15% PVA MNs			Ibu Na PVA MNs		
	R^2	K	N	R^2	K	N
Zero order	0.98	2.205	--	0.96	2.04	
First order	0.57	0.060	--	0.63	0.02	
Higuchi	0.95	16.6	--	0.94	0.531	
Hixon and Crowell	0.97	0.07	--	0.99	0.06	
Korsemeyer -Peppas	0.94	--	1.8	0.94		0.6

Table 3: Pharmacokinetic analysis of MN patches.

Parameter	Units	Ibu MN patch Mean ± SD	Ibu Na MN patch Mean ± SD	Sig. between groups
$t_{1/2}$	Hr	3.0±0.05	13.1±1.73	0.000*
T_{max}	Hr	24±0	2±0	0.000*
C_{max}	µg/ml	21.51±3.28	21.3±1.16	0.920
AUC_{0-t}	µg/ml*h	580.289±46.74	148.8±2.31	0.000*
AUC_{0-inf}	µg/ml*h	580.707±46.75	160.11±3.28	0.000*
$AUMC_{0-inf}$	µg/ml*h^2	11334.45±1203.01	2645.4±228.7	0.000*
MRT_{0-inf}	H	19.46±0.54	16.5±1.18	0.002*
Cl/F	(mg)/(µg/ml)/h	1.43±0.11	5.15±0.107	0.000*

*The mean difference is significant at the level 0.05.

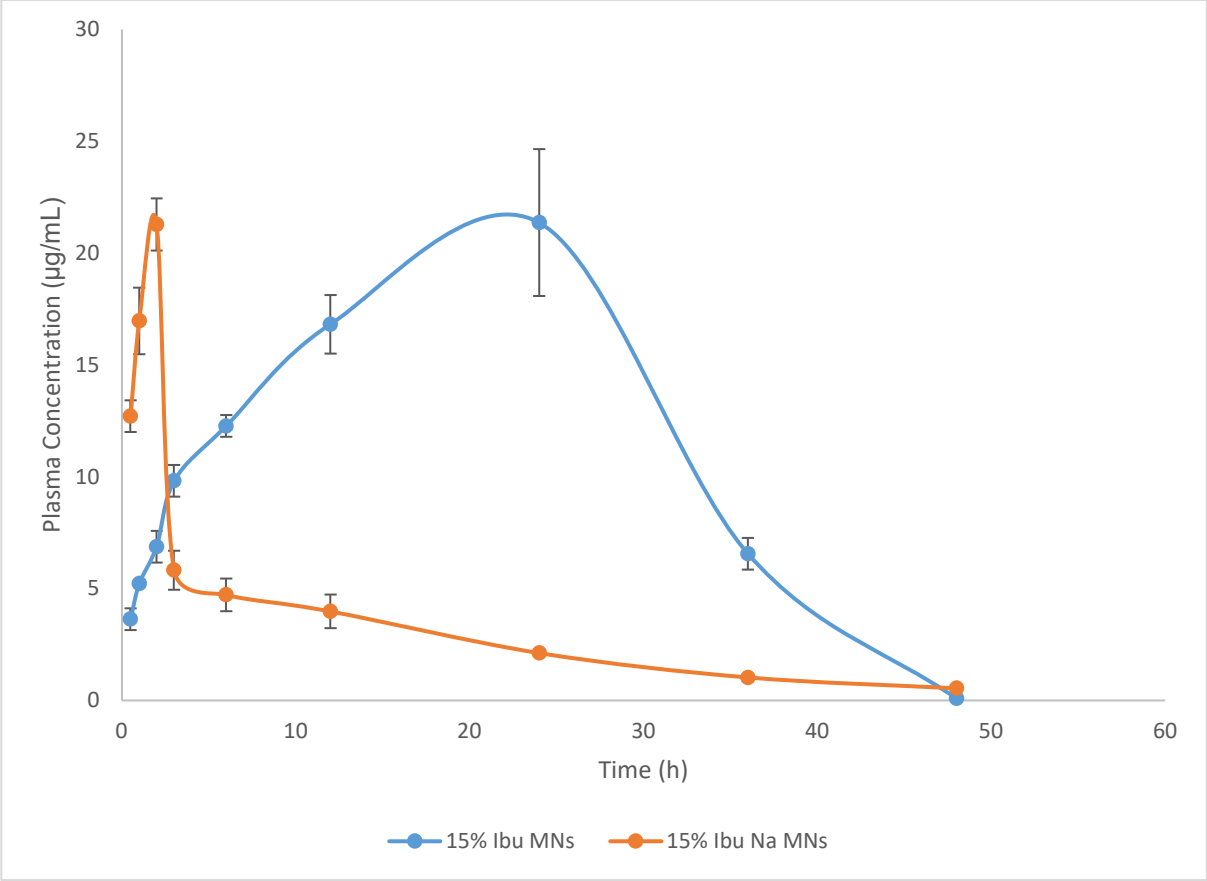


Fig. 8: Plasma concentration versus time plot of ibuprofen MN patch and ibuprofen sodium MN patch.

These findings underscore the importance of considering the physicochemical properties of drugs and their interaction with the polymer matrix in designing effective drug delivery systems. These findings align with previous studies that have demonstrated the biphasic release profile of drugs from microneedle patches, indicating an initial burst release followed by sustained release (Xu *et al*., 2023) (Park *et al*., 2005). Furthermore, our findings corroborate previous investigations that have elucidated the dissolution-driven release mechanism of drugs from microneedles. The observed super case II transport for ibuprofen release, characterized by zero-order kinetics, is consistent with studies that have highlighted the role of polymer relaxation and water permeation in governing drug release from microneedle systems (Donnelly *et al*., 2014). Conversely, the anomalous transport observed for ibuprofen sodium, indicative of reduced initial drug release, adds to the growing body of literature exploring the influence of drug properties on microneedle performance. This provides evidence to the fact that the hydration dynamics of the microneedle material play a crucial role. Slow hydration of the matrix material could delay drug release by limiting water influx and subsequent drug dissolution. Furthermore, the structural integrity of the microneedles may affect drug release kinetics, with denser matrices potentially exhibiting slower release rates.

In-vivo release studies

The prolonged effect of ibuprofen in the systemic circulation stems from the slow and controlled release of ibuprofen from polymeric microneedles. The accelerated release kinetics observed in the context of ibuprofen sodium from MNs is attributed to the inherent properties associated with the salt form of the drug. This quicker release phenomenon is primarily a consequence of the salt's distinctive characteristic, characterized by enhanced absorption kinetics and expedited clearance rates. The molecular attributes intrinsic to ibuprofen sodium contribute to a more rapid and efficient dissolution process, thereby facilitating its prompt release from the microneedles.

In the context of preceding investigations, it has been established that the sodium salt of ibuprofen is bioequivalent to conventional ibuprofen concerning the extent of absorption. However, there is a notable distinction in the rate of absorption, as indicated by a significantly lower Tmax of sodium salt (Dewland *et al*., 2009). Individuals experiencing acute pain seek rapid relief, past researches indicate that the absorption of Ibu may be hindered when taken in its regular acid form during pain episodes (Sörgel *et al*., 2005). However, fast-dissolving Ibu formulations exhibit improved absorption

rates and effectiveness in such situations (Jamali and Kunz-Dober, 1999, Jamali and Aghazadeh-Habashi, 2008) Consequently, the findings of this study provided substantial evidence which supports the utilization of ibuprofen sodium MNs in conditions that require prompt pain relief, particularly in conditions where rapid onset of action is necessary whereas ibuprofen micro needles can be effectively used in conditions where sustained effect is required.

In addition to the pharmacokinetic advantages, the application of MNs is generally well tolerated, with minimal skin irritation due to biocompatibility of PVA. Mild, transient redness may occur but resolves quickly. This localized response contrasts with systemic side effects of oral NSAIDs, such as gastrointestinal and renal toxicity, making MNs a safer alternative for analgesic delivery.

CONCLUSION

The approach of transdermal delivery of pain alleviating drugs through MNs can serve as a great mean for sustained and immediate release of Ibuprofen and Ibuprofen sodium respectively. The MNs fabricated were of uniformly morphology and sufficient strength for efficient drug delivery. The microneedles (MNs) consistently delivered the drug in a predicted form which involved the dissolution of polymer and drug matrix, as affirmed by Hixon Crowell model. Microneedles successfully traversed the top-most stratum corneum of the skin, facilitating the active absorption of Ibuprofen into the plasma at a controlled rate. This mechanism provided a sustained release of the drug, offering prolonged therapeutic effects. In contrast, Ibuprofen sodium from the microneedles exhibited rapid permeation, making it suitable for acute pain conditions where a prompt response is essential. The FTIR study revealed no incompatibility between the drugs and the excipients. The *In-vitro* studies and *in-vivo* Pharmacokinetic assessment substantiate the capability of Ibu MNs for sustained transdermal delivery of ibuprofen. This is evident in the extended Mean Residence Time (MRT) and Area Under the Curve (AUC) values observed. Additionally, the immediate release of Ibu Na from MNs is noteworthy, reflecting the drug's prompt absorption and rapid bioavailability. This dual characteristic underscore the potential of the drug loaded MNs to offer both sustained and rapid administration of ibuprofen through the transdermal route. The use of MNs for the transdermal delivery of the drug in its pure and salt form encourages its use for acute and chronic conditions, can also reduce therapy cost and increase patient compliance. The cost comparison showed that ibuprofen in its pure form has lower manufacturing costs due to widespread availability, the formulation of ibuprofen sodium involves higher production expenses. However, the improved absorption and faster onset of action with ibuprofen sodium delivered via MNs can reduce overall therapy costs by decreasing required doses, shortening treatment duration and enhancing patient compliance.

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Authors' contributions
Conceptualization, [FN, TH]; methodology, [FN, TH]; validation, [FN, MAK]; formal analysis, [TH, SP]; investigation, [TH, SP, ATA]; resources, [FN]; data curation, [TH, SRZ,AR]; writing-original draft preparation, [TH, MAK]; writing-review and editing, [CP, ATA]; visualization, [FN]; supervision, [FN]; project administration, [FN];. All authors have read and agreed to the published version of the manuscript.

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Data availability statement
The datasets supporting the findings are available upon request.

Ethical approval
The study received approval from the Department of Pharmacy University of Peshawar ethical committee under the reference number 505/EC-FLES-UOP/2022.

Conflict of interest
The authors declare that they have no competing interests.

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