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Research Article

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Design, Fabrication and Evaluation of Dissolvable Microneedle Transdermal Patches

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Abstract Polymeric dissolvable microneedles loaded transdermal was successfully prepared by 3^2 full factorial design using the molding method. In this design two factors with different molecular weights Hyaluronic acid and PVP: PVA concentration were independent and their effect was observed on three dependent factors that are Mechanical strength (Tip angle deviation), (%) Percentage drug entrapment and (%) Drug release for 12 hours. Microneedle arrays were characterized for physical structure evaluation under scanning electron microscopy. Microneedles arrays were observed for height, lengths, and interspacing between individual microneedles at different magnifications (25X and 50X). SEM results showed that the microneedles had a height of 150 um, interspacing of 50um, diameter of 50um and length of 150um. The height, length and interspacing between the microneedles array were perfectly matched with the M Patch Microneedle template and following the theoretical geometrics of the M Patch master template. Results revealed that relevant pyramidal needles were inflexible and rigid, the bases were regular, intact and smooth-shaped with sharp needles.

Keywords Mechanical strength, Microneedle, Hyaluronic acid, PVP

Introduction

Anatomically, the skin comprises numerous histological layers, constituting the body's largest organ, accounting for approximately one-sixth of the total body weight. It is typically delineated about three primary tissue layers: [1-8] Administration via the skin is seen to be a desirable substitute for parenteral and oral medication administration. Drug administration by transdermal application has been used for both regional and systemic uses. These systems serve a variety of functions, including topical drug delivery (e.g., local anesthetics), systemic drug delivery (e.g., scopolamine for motion sickness), protective functions (e.g., sunscreens for UV protection), and cosmetic applications (e.g., anti-ageing serums, derma rollers for reducing fine lines and wrinkles). A drug molecule may enter the intact stratum corneum mainly via three mechanisms: transcellular transit, the intercellular lipid domains, or skin appendages (shunt pathways). Usually, a medication diffuses by a mix of different pathways, and the physicochemical characteristics of the molecule dictate how much each pathway contributes to the total flow. Molecular transport is, however, constrained by the skin's barrier qualities.

Novel Drug delivery system (NDDS)

In the recent past, rising knowledge of the toxicity and ineffectiveness of medications and agrochemicals when applied or administered by traditional techniques has drawn more attention to the controlled release idea and technology. As a result, drugs that are taken as tablets, capsules, syrups, injectables, etc., often exhibit substantial

variations in the amount of the drug in the blood and tissues, which leads to unfavorable toxicity and ineffectiveness. Furthermore, for this reason as well as other considerations like recurrent dose and variable absorption, the idea of controlled drug delivery systems, or therapeutics systems, may have originated. A controlled drug delivery system is when one or more medications release continuously from the dosage form in a predefined pattern for a certain amount of time, either systematically or to a designated target organ [9-16].

Recent technical developments have led to the emergence of unique drug delivery methods, which have paved the way for the creation of creative preparations for the administration of antiemetic medications. The following is a summary of the benefits of innovative drug delivery systems (NDDS) over traditional methods:

- Enhancement of solubility,
- Increased bioavailability,
- Protection from toxicity,
- Enhancement of pharmacological activity,
- Enhancement of stability,
- Increase in circulation time,
- Inhibition of resistance,
- Improved tissue macrophages distribution,
- Targeted drug delivery,
- Sustained delivery,
- Reduction in dose,
- Protection from physical and chemical degradation.

Characteristics of Novel Drug Delivery System

1. Increase the bioavailability,
2. Provide controlled delivery of drug,
3. Transport the drug intact to the site of action avoiding the non-diseased tissue,
4. Stable and delivery be maintained under various physiological variables,
5. Easy to administer, safe and reliable,
6. Cost-effective

Advantages of Novel Drug Delivery System (NDDS)

1. **Medical:** Optimum dose, at the right time and at the light location.
2. **Industrial:** Efficient use of expensive ingredients, reduction in production cost.
3. **Social:** Beneficial to patients, better therapy, improved compliance and standard of living.

Material & Methods

Preparation of microneedles-loaded transdermal drug delivery system

Step 1: Procurement of Microneedle template

Dissolvable microneedle patches were prepared by the moulding method. M Patch Microneedle template was purchased from Micropoint Technologies Pte Ltd, Pioneer Junction, and Singapore. This template is exclusively made for producing dissolvable microneedle patches with excellent quality. This template was made of silicone which is heat and chemical-resistant. And also shows repetitive usability and extreme durability. This template had dimensions, 90mm (Diameter) x 4mm (Height) and 10x10 mm microneedle arrays. Dimensions of the microneedles were 200um x (H), 200um (Base) and 500um pitch. After purchasing templates were easily cleaned by using mild soap and letting them air dry completely as illustrated in Figure.

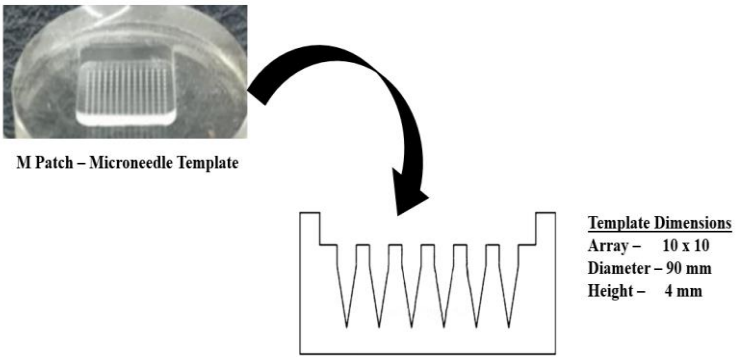


Figure 1: M Patch descriptions

Step 2: Preparation of Dissolvable Microneedles

Microneedles were prepared by using a combination of Polyvinyl alcohol (PVA) and Polyvinyl Pyrrolidone (PVP). 5% w/v PVA was dissolved in 2 ml of deionized water at 60ºC. Then 0.25% w/v PVP was mixed in PVA solution and then 16 mg of Ondansetron HCL was added with 50 mg of Hyaluronic acid to this polymeric mixture. Next, 1ml of the mixture was pipette out and added on the microneedle template. This template was then placed under a vacuum (~50 mbar) for 30 min to remove air from the mixture and to improve the filling of all micro holes. To further improve the filling of the micro holes, the template was placed into a centrifuge with a swinging bucket rotor that allows for a centrifugal force towards the bottom of the micro holes (centrifugation at 2000 rpm for 1.5 h was found to be optimal to ensure that all the microneedles' cavities were filled up). Next, the remaining 1 ml of the mixture was added onto the template to form the backplate of the microneedle array and the microneedle template was placed under vacuum for 30 min. Finally, arrays were dry at 30%-40% relative humidity for 4 to 48 hours and it was stored at room temperature in a desiccator (RH 0%) as illustrated in Figure.

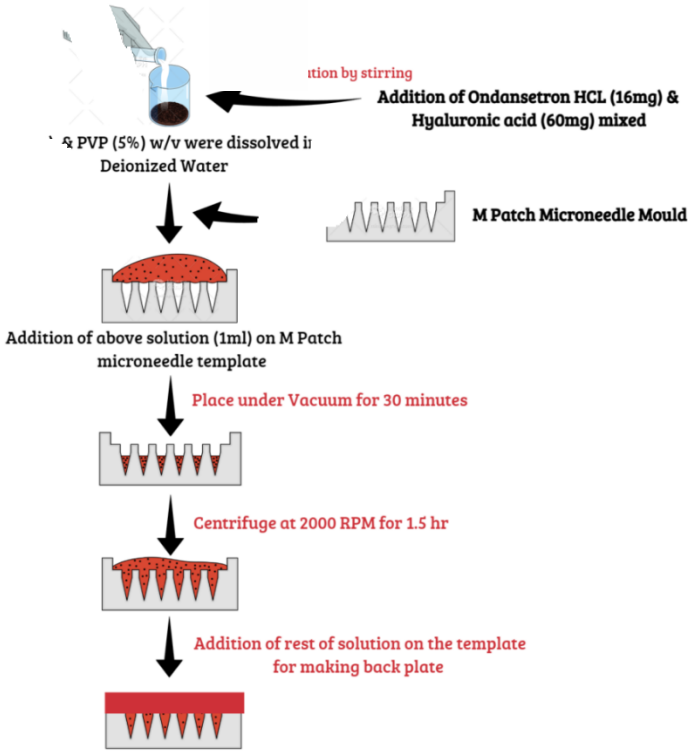


Figure 2: Preparation of Dissolvable microneedles

Step 3: Adhesion of backing membrane (Adhesive tape) on Microneedle patches

Lastly, an adhesive tape was used to vertically de-mould the formed microneedles patches from the template. An adhesion of adhesive sites of the patches with butter paper is illustrated in Figure.

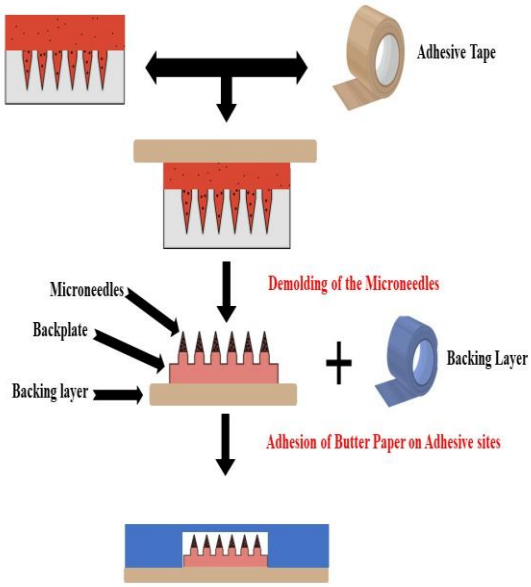


Figure 3: Adhesion of backing membrane (Adhesive tape) on Microneedle patches

Optimization of process variables

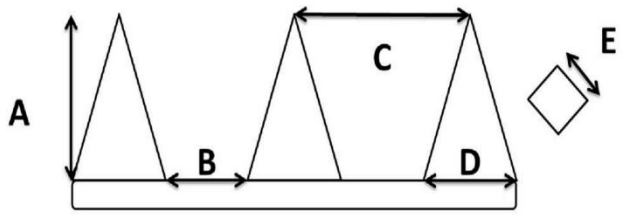
Table 1: Formulation Characteristics of Batches in a 3^2 Full Factorial Design*

Batch Code	Coded Value		Mechanical Strength (N)	(%) Drug Entrapment	(%) Drug release for 12 hr
	HYALURONIC ACID	PVP: PVA			
MNS1	**-1**	**-1**	1.65 N	94.20±0.89	100±0.51
MNS2	**-1**	**0**	1.79 N	95.45±0.48	92.02±0.42
MNS3	**-1**	**+1**	1.80 N	96.25±0.50	89.04±0.50
MNS4	**0**	**-1**	1.63 N	97.45±0.60	70.03±0.61
MNS5	**0**	**0**	1.74 N	97.35±0.64	65.02±0.50
MNS6	**0**	**+1**	**1.81 N**	**98.65±0.68**	**60.06±0.55**
MNS7	**+1**	**-1**	1.40 N	70.25±0.28	40.04±0.35
MNS8	**+1**	**0**	1.46 N	71.45±0.48	35.03±0.41
MNS9	**+1**	**+1**	1.53 N	70.35±0.53	30.06±0.45

*Data expressed (Mean±SD); n=9; Tip angle deviation observed in degree of bending

Physical structure analysis of Microneedles

Scanning electron microscopic method was performed (SEM, JSM-6700F, JEOL Ltd., Japan) with microneedle arrays to observe the surface morphology. Each sample was placed into the aluminium stub with two side adhesive tape and to make it electrically conductive; under reduced pressure of 2.54 Pa, a thin layer of platinum was applied to the aluminium stub. The analysis was operated under 25 mA current with the voltage of 10 kV. The dimension was observed for heights, widths, lengths and interspacing of polymer MNs as shown in Figure & Table.



Aspect ratio= A/D (height/width)
A: Height of MNs in array
B: Interspacing of MNs at base
C: Interspacing of MNs at tip
D: Width of MNs at base
E: Length

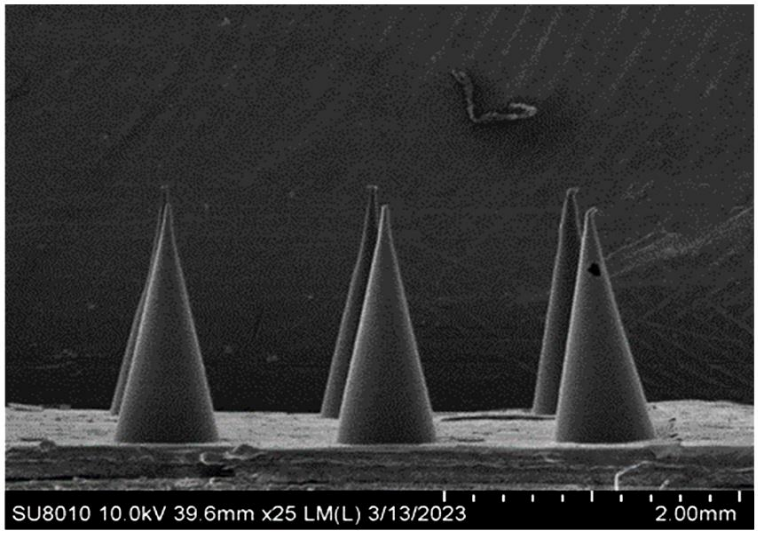


Figure 4: SEM analysis of Optimized Formulation of (MNS6) at x25

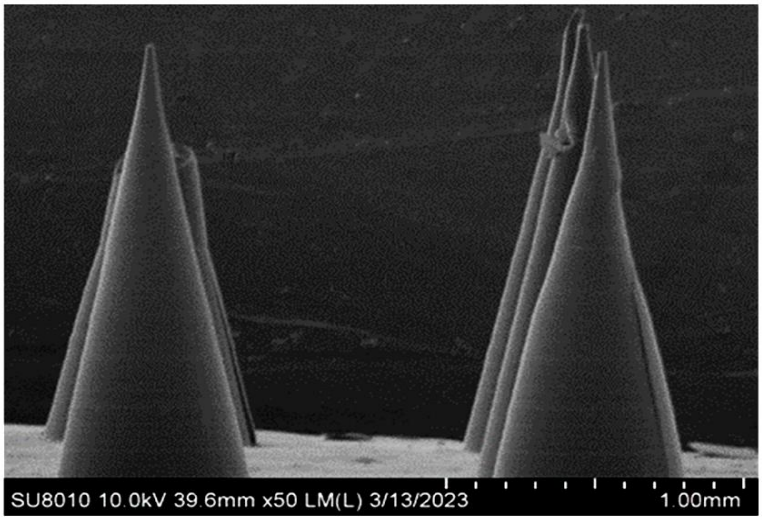


Figure 5: SEM analysis of Optimized Formulation of (MNS6) at x50

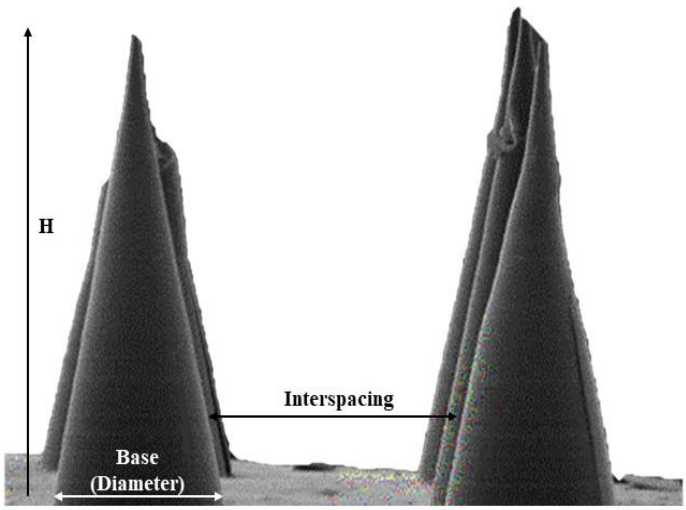


Figure 6: SEM analysis for Optimized formulation (MNS6) showing Height, Diameter, Length & Interspacing

Table 2: Microneedles SEM analysis (X50 LM/L)

Height	150um
Interspacing	50um
Tip Diameter	10um
Base Diameter	50um

Mechanical Strength

In the present study to assess microneedle fracture and for mechanical analysis initially, a set of microneedle specimens were prepared. Subsequently, each microneedle specimen was mounted on the testing apparatus securely to ensure stability during testing. Incremental axial loads were applied to the microneedle under a controlled testing setup, (continuously increasing the force until fracture occurred). Microneedle specimen was continuously monitored for the responses to the applied load (10gm, 20gm, 50gm and 100 gm).

Table 3: Mechanical strength analysis

Microneedle Specimen	**Fracture Strength (N)**
MNS1	1.65 N
MNS2	1.79 N
MNS3	1.80 N
MNS4	1.63 N
MNS5	1.74 N
MNS6	**1.81 N**
MNS7	1.40 N
MNS8	1.46 N
MNS9	1.53 N

Note: Newtons (N) and grams-force (gf) for clarity, as 1 N is approximately equal to 101.97 gf.

Table 4: Optimized Formulation (MNS6) mechanical strength deviation analysis

Patch Code	**Tip Diameter (µm)**	**Tip Angle**	**Height (µm)**	**Deviation from Actual Height (%)**
MNS6	10.00 ± 2.00	120^0 ± 35	145 µm ± 0.97	30^0 ± 0.121

Percentage (%) Drug Entrapment

For the determination of percentage (%) drug entrapment efficiency, 1 cm^2 microneedles array was crushed and dissolved in 10ml Methanol. Then, centrifuged at 6000 RPM for a period of 15 minutes at a temperature of 25 ^{O}C using REMI Centrifuge. The supernatant of the centrifuge tube which contains microneedle dispersion of Ondansetron HCL was separated carefully without the dispersing hard palate of the free drug which was present at the bottom of the centrifuge tube. The hard palate was broken down using acetonitrile – methanol (9:1) for quantitive analysis of Ondansetron HCL. The absorption of the drug was calculated using a UV-Vis Spectrophotometer at a wavelength of 278 nm in supernatant and hard palate dispersion. The percentage entrapment efficiency was calculated with the help of the equation given below.

$$\%EE = \frac{Amount\ of\ entrapped\ drug}{Total\ drug\ added} \times 100$$

Table 5: Percentage (%) Drug Entrapment analysis

Formulation	(%) Drug Entrapment Efficiency
MNS1	94.20±0.89
MNS2	95.45±0.48
MNS3	96.25±0.50
MNS4	97.45±0.60
MNS5	97.35±0.64
MNS6	**98.65±0.68**
MNS7	70.25±0.28
MNS8	71.45±0.48
MNS9	70.35±0.53

Percentage (%) Moisture Content

The moisture content of individual patches was assessed through a meticulous procedure. Initially, each patch was precisely weighed using an analytical balance, and the weight was recorded. Subsequently, these patches underwent a drying process within a desiccator containing fused calcium chloride, maintaining a consistent temperature of 45 ± 0.5˚C. Over 72 hours, the patches were left to desiccate thoroughly. At regular intervals, the patches were removed from the desiccator and reweighed to monitor their drying progress. This weighing process was repeated until a constant weight was attained, signifying the complete removal of moisture.

$$\text{Percentage Moisture Content} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \text{x100}$$

Table 6: Determination of Moisture content

Formulation	Initial Weight (g)	Final Weight (g)	Weight Loss (g)	Moisture Content (%)
MNS1	5	4.52	0.48	10.61
MNS2	5.23	4.81	0.42	8.73
MNS3	4.5	4.32	0.18	7.21
MNS4	4.8	4.31	0.49	11.36
MNS5	5.3	4.85	0.45	9.27
MNS6	5.2	4.85	0.35	4.16
MNS7	5.5	4.93	0.57	11.56
MNS8	5.3	4.90	0.4	8.16
MNS9	5.12	4.76	0.36	7.56

Percentage (%) Moisture Absorption

The Percentage (%) moisture absorption was evaluated for each formulated transdermal patch. Transdermal patches were weighed individually by using a digital weighing balance and noted as (W1) initial weight. After that, these transdermal patches were placed in labelled Petri dishes which contained 200ml of a saturated solution of Potassium Chloride for 84% relative humidity maintained. These placed transdermal patches were continuously weighed for three days, after being weighed immediately and noted reading as (W2) final weight.

$$\text{Percentage Moisture Uptake} = \frac{\text{Final weight} - \text{Inital weight}}{\text{Inital weight}} \text{x100}$$

Table 7: Determination of Moisture Absorption

Patch Code	Initial Weight (W1) (g)	Final Weight (W2) (g)	(%) Moisture absorption
MNS1	5.3	5.8	9.43
MNS2	5.2	5.6	7.69
MNS3	5.1	5.3	3.92
MNS4	4.8	5.2	8.33
MNS5	4.5	4.8	6.66
MNS6	5.2	5.4	3.84
MNS7	5	5.4	8.00
MNS8	5.5	5.9	7.27
MNS9	5.3	5.5	3.77

Thickness

The thickness of all the microneedles patches (MNS1* to MNS9*) was measured three times using a digital micrometre screw gauge, and the average value of thickness deviations was calculated; results are shown in Table.

Table 8: Determination of Thickness

Patch code	Thickness (mm)
MNS1	0.080 ± 0.004
MNS2	0.081 ± 0.009
MNS3	0.085 ± 0.004
MNS4	0.086 ± 0.004
MNS5	0.089 ± 0.004
MNS6	0.090 ± 0.004
MNS7	0.091 ± 0.004
MNS8	0.094 ± 0.004
MNS9	0.095 ± 0.004

Adhesiveness properties

In assessing adhesion, the method chosen depends on the type of stress applied during the specific exercise. These procedures typically involve applying a patch strip onto a rigid standard test plate, typically constructed from stainless steel, ensuring firm contact by applying a predefined pressure. Following a predetermined duration, the strip is then removed from the plate at a specified angle, commonly either 180° or 90°, and at a predetermined speed, often set at 300 mm/min. It is most easy, simple and effortless subjective test to analyse skin-adhesive bonding; results are shown in Table.

Table 9: Determination of Adhesiveness property

Patch code	Adhesiveness property
MNS1	+++
MNS2	+++
MNS3	++
MNS4	+++
MNS5	+++
MNS6	+++
MNS7	+++
MNS8	++
MNS9	++

Note: (+, ++, +++) indicated the good adhesiveness properties.

Weight Variations

The patches were subjected to weight variation by individually weighing patches and the average was calculated; results are shown in Table.

Table 10: Determination of Weight Variation

Patch code	Weight variation average (±10%) (4500mg to 5500mg)
MNS1	4980.4 ± 0.21
MNS2	4990.4 ± 0.21
MNS3	4800.7 ± 0.52
MNS4	4690.4 ± 0.21
MNS5	4695.6 ± 0.56
MNS6	4990.4 ± 0.21
MNS7	4020.1 ± 0.49
MNS8	3501.2 ± 0.51
MNS9	4480.1 ± 1.60

Folding Endurance

The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tended to break. It is determined as the number of times the film is folded at the same place either to break the film or to develop visible cracks; results are given in Table.

Table 11: Determination of Folding Endurance

Patch code	Folding endurance (>150)
MNS1	162 ± 6.93
MNS2	161 ± 6.93
MNS3	160 ± 6.93
MNS4	143 ± 6.93
MNS5	153 ± 6.93
MNS6	163 ± 6.93
MNS7	123 ± 6.93
MNS8	133 ± 6.93
MNS9	140 ± 6.93

Tensile Strength

The percentage tensile strength break was determined through the following procedure. Initially, the length of the material was carefully noted just before reaching the breaking point during the tensile strength test. Subsequently, the percentage elongation was calculated using the following formula:

$$\text{Percentage Elongation} = \frac{\text{Final length of strip} - \text{Intial length of strip}}{\text{Intial length of strip}} \text{x100}$$

This formula allows for the determination of the percentage increase in length of the material at the point of breaking, relative to its original length; results are given in Table.

Table 12: Determination of Tensile Strength

Patch code	Tensile strength (kg/cm^3) Max. 5kg load
MNS1	4.81 ± 0.092
MNS2	4.78 ± 0.109
MNS3	4.67 ± 0.108
MNS4	4.80 ± 0.109
MNS5	4.78 ± 0.109
MNS6	4.80 ± 0.103
MNS7	4.01 ± 0.104
MNS8	3.88 ± 0.109
MNS9	3.86 ± 0.105

Swelling Index (%)

The swelling index was determined for each formulation, and the formulated transdermal patches (10x10) were weighed with provided cover slips individually noted as (W1) initial weight. Then transdermal patches were placed in labelled Petri dishes which contained 10ml of distilled water and these transdermal patches were immersed absolutely in water. The coverslips from the transdermal patches were removed after 60 minutes, wiped off carefully with excessive water using tissue paper weighed immediately and noted as (W2) final weight. The swelling index and percentage (%) weight were increased because of the absorption of water; it was calculated by using the following formula:

$$\text{Swelling index} = \frac{\text{W2} - \text{W1}}{\text{W1}} \text{ x 100}$$

Where W2 is the final weight of the swollen film after time t, W1 is the initial weight of the film at Zero time.

Table 13: Determination of Swelling Index (%)

Patch Code	Swelling Index (%)
MNS1	6.78 ± 1.35
MNS2	6.05 ± 1.44
MNS3	5.97 ± 1.56
MNS4	6.28 ± 1.46
MNS5	6.02 ± 1.33
MNS6	5.98 ± 1.46
MNS7	6.34 ± 1.48
MNS8	6.05 ± 1.45
MNS9	5.95 ± 1.50

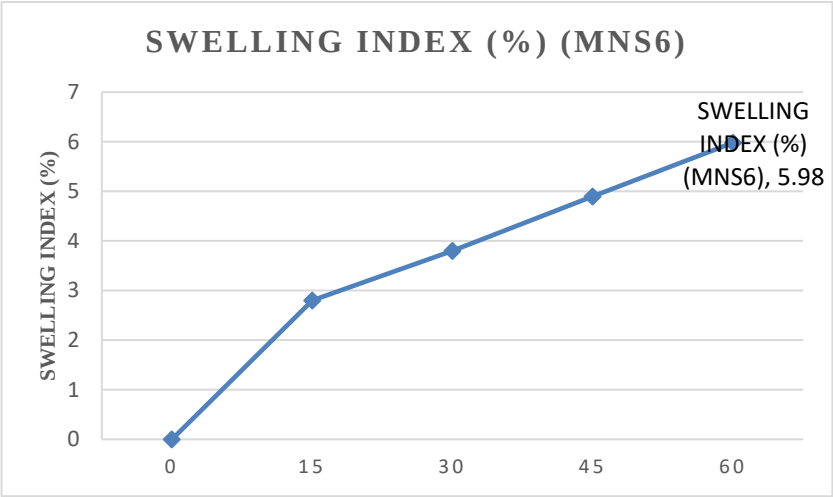


Figure 7: Swelling Index (%) of Optimized formulation MNS6

Peel adhesion

The adhesive nature of the formulated transdermal patch was used to evlaute the peel adhesion by using a texture analyzer by following standard procedures. The peel adhesion test was performed with a 5kg load cell. The optimzed transdermal patch (MNS6) was attached to the metal surface of the instrument and one end of the transdermal patch was attached to the movable probe of texture analyzer. The release liner was removed prior to the test. The probe of instrument was pulled up at 180º at a speed of 30 mm/minute, and the peak load was measured to complete the peel of the patch from the metal surface results are shown in Table.

Table 14: Determination of Peel strength

Patch Code	Peel Adhesion (<5Kg)
MNS1	4800 gm
MNS2	4780 gm
MNS3	4900 gm
MNS4	4920 gm
MNS5	4600 gm
MNS6	4500 gm
MNS7	4930 gm
MNS8	4860 gm
MNS9	4800 gm

In vitro drug dissolution studies

In vitro, drug dissolution studies were performed by using US Pharmacopoeia type II (paddle-type apparatus). An accurately weighed optimized transdermal patch (containing 16mg drug) of the optimized transdermal patch was dropped into 300 ml of phosphate buffer solution (pH 5.5) as dissolution medium, it was maintained at 37 ± 0.5 °C and stirred using the magnetic stirring machine at a speed of 100 rpm. At the different time intervals, 10ml of aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37°C. The collected samples were filtered and analysed at λ_{max} of the drug using a UV-visible spectrophotometer against buffer pH 5.5 as shown in Table. The percentage of drug dissolved at different time intervals was calculated and drug release was calculated using various models. The cumulative percentage release of batches up to 12 hours is shown in Table.

Results and Discussions

Polymeric dissolvable microneedles loaded transdermal was successfully prepared by 3^2 full factorial design using the molding method. In this design two factors with different molecular weights Hyaluronic acid and PVP: PVA concentration were independent and their effect was observed on three dependent factors that are Mechanical strength (Tip angle deviation), (%) Percentage drug entrapment and (%) Drug release for 12 hours.

Microneedle arrays were characterized for physical structure evaluation under scanning electron microscopy. Microneedles arrays were observed for height, lengths, and interspacing between individual microneedles at different magnifications (25X and 50X). SEM results showed that the microneedles had a height of 150um, interspacing of 50um, diameter of 50um and length of 150um as illustrated in Table. The height, length and interspacing between the microneedles array were perfectly matched with the M Patch Microneedle template and following the theoretical geometrics of the M Patch master template. Results revealed that relevant pyramidal needles were inflexible and rigid, the bases were regular, intact and smooth-shaped with sharp needles.

Mechanical properties of the microneedles patches are affected by the molecular weight of the Hyaluronic acid and concentration of PVP, when we increase the molecular weight of the Hyaluronic acid from 10Da to 290Da it causes a decrease in the mechanical strength of the microneedles and the reason behind the formation of tight molecular stacks of small molecular weight Hyaluronic acid during microneedle solidification, resulting in higher mechanical strength. In contrast, the linear structure of high molecular Hyaluronic acid tends to form more turns and bends in molecular packing, resulting in inefficient molecular packing and decreased mechanical strength. In the present study, it is confirmed that 74kDa Hyaluronic acid (medium molecular weight) microneedles had good mechanical strength in comparison with others.

As the PVP concentration increased, the elasticity increased while mechanical strength reduced thus the applied force required to break the microneedles decreased. In the case of, Polyvinyl Alcohol (PVA) polymer enforced hardness and rigidity thus increasing Polyvinyl Alcohol (PVA) concentration results in harder microneedles and higher forces should be applied to break the microneedles but in the present study, the PVA concentration is static so there is no effect of PVA observed. The mechanical strength of the microneedles. Results of the mechanical strength of all the formulations are shown in Table and Figure. The results show formulation MNS6 had the highest mechanical force as it has the lowest concentration of PVP and medium molecular weight Hyaluronic acid.

Percentage entrapment efficiency is also a critical parameter in the development of microneedle patches for TDDS to ensure that the active pharmaceutical ingredient is effectively incorporated into the microneedle and patches which helps in maintaining a constant therapeutic level of the drug in plasma. All the prepared formulations were evaluated for the percentage entrapment efficiency. The molecular weight of Hyaluronic acid effects percentage drug efficiency of microneedles patches. Higher molecular weight Hyaluronic acid showed large viscosity due to which incomplete filling of the M-Patch mould occurs during preparation of the microneedle's patches. So, the formulation MNS7, MNS8 and MNS9 showed the lowest percentage drug entrapment efficiency as comparison to low molecular weight and medium molecular weight of Hyaluronic acid i.e., 70.25±0.28, 71.45±0.48, 70.35±0.53 respectively, a comparison to lower molecular weight Hyaluronic acid and medium molecular weight Hyaluronic acid i.e., MNS1, MNS2, MNS3, MNS4, MNS5 and MNS6 showed 94.20±0.89, 95.45±0.48, 96.25±0.50, 97.45±0.60, 97.35±0.64 and 98.65±0.68 respectively**.** MNS6 showed the highest percentage of drug entrapment efficiency, which fit best among other formulations as shown in Table.

Moisture content evaluation is necessary in terms of stability, adhesion, skin irritation and microbial growth. Moisture content can lead to degradation of active pharmaceutical ingredients (APIs) within the patches. Moisture content evaluation is are important criteria in terms of adhesion also, excess moisture leads to loosened adhesion to the skin, leading to the detachment of patch from the skin. High moisture content in the patch increases the risk of skin irritation due to contamination by bacterial growth, or fungi risks to the patient's health. The percentage moisture content in all the transdermal patches was determined and it was found that the molecular weight of Hyaluronic acid does not affect the moisture content but the concentration of the PVP affects the moisture content. As the concentration of PVP increases moisture concentration also increases. All the formulated transdermal patches showed a percentage moisture content ranging from 4.16 % to 11.56 %, this range comes under satisfactory for the

transdermal drug delivery system. Hence, optimized formulation MNS6 showed a lower percentage moisture content about 4.16%, as lower moisture content percentage imparts long durability, results shown in Table.

Percentage moisture absorption for all the formulated transdermal patches were evaluated. A lower percentage of moisture absorption in transdermal patches confirms in reduced microbial growth minimizes toxicity and irritation to the skin and provides stability of patches, completely dried patch creates brittleness. The obtained result of percentage moisture absorption indicated the transdermal patches can be stable and be safe for long-term during storage, particularly under dry conditions. The percentage of moisture absorption is affected by the PVP concentration as the PVP concentration increases, it higher the percentage of moisture absorption which increases elasticity which cause a decrease in folding endurance, mechanical strength etc. Results indicating the percentage moisture absorption for all the formulations ranges from 3.77 % to 9.43 %. An estimation of 20% to 30% is the upper limit of moisture absorption of total material weight, beyond this percentage, the formulation becomes saturated and less effective at delivering of drug to the skin. The formulation MNS6 showed the percentage moisture absorption of 3.84% which comes under the satisfactory range, results shown in Table.

The thickness evaluation of transdermal patches significantly influences the drug delivery performances, thinner the patches offer faster drug release rate due to shorter diffusion pathways for drug molecules to penetrate though the skin. Excessively thick patches also produce bulky or uncomfortable, leading to poor patient compliance. Thicker transdermal patches could be difficult for conforming to the contours of the skin which leads to poor adhesion and potential detachment. Evaluation of transdermal patch thickness is essential for optimizing drug delivery performance and ensuring patient comfort and adherence. The thickness deviations of prepared transdermal patches yielded satisfactory results, deviations ranging from 0.080 ± 0.004 to 0.094 ± 0.004 mm. Typically, transdermal patches should have an upper limit of thickness deviations around 5% to 10% of the total patch thickness. The obtained data of thickness percentage deviations comes within satisfactory ranges, results shown in Table.

Adhesiveness property ensures effective drug delivery, which impact the wearability of the transdermal patch. Adhesive properties can influence the permeation of drugs through the skin. The stability of the transdermal patch during storage is also impacted by its adhesive properties. Optimizing drug delivery, patient comfort, and compliance while maintaining product quality and stability are crucial considerations. To ensure effective drug delivery and patient compliance, the adhesive property was evaluated based on the type of stress applied during specific exercises. A rigid standard test plate, typically made of stainless steel, applies a defined pressure on the transdermal patches to ensure contact after a predetermined time. The transdermal patch is then removed from the plate at a specified angle (ranging from 180° to 90°) and speed (300 mm/minute). During this detachment process, stress is transferred through the transdermal patch to the backing membrane. This process provides assurance based on the formulation composition, affecting flexibility, elongation, and thickness of the transdermal patches, which can influence behavior during detachment. All the transdermal patches demonstrating satisfactory adhesiveness. The adhesiveness property of the transdermal patches was assessed, with MNS1, MNS2, MNS4, MNS5, MNS6, MNS7 exhibiting a rating of (+++), while MNS3, MNS8, and MNS9 demonstrated a rating of (++), results shown in Table. These observations are deemed to be within acceptable limits for all the prepared transdermal patches.

Weight variation was determined of all the formulated transdermal patches to guarantee uniform drug dosage and efficacy. Weight variation study, provide specific dose of medication over a specified period. Weight variation directly affects the uniformity of the drug content in each patch. Consistent weight ensures that each patch delivery the intended dose, preventing under or over dosing, which could compromise treatment efficacy or safety. Weight of the transdermal patch correlates with the dosing, inaccurate dosing or under dosing of the patches lead to adverse reactions or toxicity. Consistent weight ensures that patients receive the correct dose of medication, minimizing the potential for medication errors and ensuring patient safety. The reliability and efficacy of transdermal patches were assessed through weight variation evaluations in different molecular weights of Hyaluronic acid and differences in PVA: PVP polymer concentrations, yielding the following results, MNS1 4980.4 ± 0.21, MNS2 4990.4 ± 0.21, MNS3 4800.7 ± 0.52, MNS4 4690.4 ± 0.21, MNS5 4695.6 ± 0.56, MNS6 4990.4 ± 0.21 respectively, these results come within the acceptable limits for all formulated transdermal patches, with individual weights had ranging between 4500 mg to 5500 mg to maintain ±10% standard deviation of weight variation. But the formulations MNS7,

MNS8 and MNS9 showed 4020.1 ± 0.49, 3501.2 ± 0.51 and 4480.1 ± 1.60 respectively, these three preparations showed larger weight variation due to incomplete filling of M-Patch mould during preparation with higher molecular weight of Hyaluronic acid. The PVA and PVP has no significant effect on weight variation of the formulation.

The folding endurance measures the ability of the patch to endure repeated folding without cracking, breaking or delaminating. The patches with high folding endurance are less likely to suffer damage during these processes, ensuring product integrity and reliability. Transdermal patches with good folding endurance are more likely to maintain their structural integrity and drug content over time, reducing the risk of degradation or loss of efficacy during storage or use. The value of folding endurance of optimized transdermal patches was 163 ± 6.93 for formulations MNS6 in regards to the concentration of polymer (PVA: PVP) and differential molecular weight of Hyaluronic acid. Folding endurance should be greater than >150, this indicates that the prepared patches demonstrate considerable mechanical resilience and flexibility, crucial for enduring repeated folding without fracturing or compromising their integrity. Such attributes underline the reliability and performance of the patches, suggesting their suitability for practical application scenarios involving mechanical pressure. All the formulations had folding endurance within the range except formulations MNS7, MNS8 and MNS9 had showed folding endurance 123 ± 6.93, 133 ± 6.93 and 140 ± 6.93 respectively, which is less than >150 so all these three formulations are not suitable, results shown in Table.

Tensile strength was determined to check the percentage tensile strength break to providing valuable insights into the material's mechanical properties and performance under tension conditions. Tensile strength is closely related to the adhesive properties of transdermal patches. Proper adhesion to the skin requires the patch to withstand tensile forces without detaching or delamination from the backing materials. Transdermal patch with adequate strength is easier to handle and apply to the skin. It affects the drug delivery performances, patch with low tensile strength produces deformation or breakage during application, leading to uneven drug distribution or compromised drug release kinetics. In the evaluation of tensile strength for transdermal patches, a maximum load of 5 kg was established as the upper limit criterion. This load serves as a benchmark for assessing the patch's ability to withstand mechanical stress during application and wear. With regard to acceptable limits, the upper limit of tensile strength corresponds to the maximum load of 5 kg, ensuring that the patch maintains structural integrity and does not exhibit excessive elongation or deformation under stress. Conversely, the lower limit, indicative of the minimum load required to prevent patch failure, typically ranges between 20% to 40% of the maximum load, corresponding to 1-2 kg in this context. Results of all formulations were shown in Table and reported that the tensile strength of the microneedles patches was affected by the PVP concentration, on PVP concentration increases flexibility increases which increases tensile strength and vice versa. The concentration of Hyaluronic acid in 2% -3% will decrease the tensile strength but all the formulations have the same concentration of Hyaluronic acid and not significantly affect the formulations and all the results are in range. Formulations MNS6 showed the highest tensile strength capability with a medium molecular weight of Hyaluronic acid (50mg) with PVA: PVP (5:0.25) concentration.

Swelling Index is a crucial parameter in the drug delivery system. Excessive swelling may lead to increased skin irritation, and compromised adhesion, and may jeopardize the intended therapeutic effect. Therefore, accurately assessing the swelling index allows the optimized drug delivery. The swelling index affects the rate and extent of drug release from the transdermal patch. Monitoring of the swelling index helps to ensure that patch material maintain compatibility with the skin, minimizing the risk of adverse reaction or allergic responses. It was observed that 6.78 ± 1.35 %, was the maximum swelling index percentage of formulation MNS1, this is due to a higher concentration of PVP present, which is highly hygroscopic and hydrophilic. And, optimized formulation MNS6 showed 5.98 ± 1.46 %. Maintaining the swelling index within this range is essential for effective drug delivery and mitigating potential issues such as patch detachment or compromised drug release kinetics. Results are shown in Table and Figure.

The peeling adhesion is an essential parameter in the transdermal drug delivery system, it is particularly significant as it directly influences patient comfort and adherence. Maintaining a peeling adhesion under standard values, indicating that removing the patch from the skin will not cause pain. Hence, the peel adhesion results obtained range

from 4500 gm to 4930 gm, results shown in Table. Optimized formulation (MNS6) showed 4500 gm of peel adhesion and is deemed satisfactory results will not cause pain while intended application of the transdermal patches.

Conclusion

After selecting appropriate materials dissolvable microneedles patches were produced by moulding methods using PVA: PVP (5: 0.25) and medium molecular weight of Hyaluronic acid (50mg). Scanning electron microscopy revealed that sharp, inflexible, rigid, pyramidal needles with regular intact bases were formed having good mechanical strength, highest entrapment efficiency i.e., 98.65%, with lower moisture content, good folding endurance, with highest tensile strength and satisfactory peeling strength. Adhesiveness, thickness and swelling index all are in the prescribed range. So, it is concluded that satisfactory dissolvable microneedle patches were formed as MNS6 formulation.

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