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Development and Evaluation of Biodegradable Microneedle Patches for Sustained Release of Ondansetron: A Novel Approach to Chemotherapy-Induced Nausea Management"

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ABSTRACT

Chemotherapy-induced nausea and vomiting are common side effects of chemotherapy and it affects 70% of the patients. This nausea and vomiting process involves multiple pathways like peripheral signals mediated by serotonin and neurokinin neurotransmitters and cortical pathways involves dopamine and histamine neurotransmitters to activate the chemoreceptor zone. Both the pathways transmit signals for salivation, vasomotor response, respiration and ultimately transmit signals to cranial centres that control vomiting reflex. Nowadays multiple and effective treatment options are available for the treatment of chemotherapy-induced nausea and vomiting. In the present study, the Ondansetron HCL drug was selected for the treatment due to its superiority in decreasing nausea and vomiting at the time of use of anticancer regimen. It's a class of drugs that works by blocking the action of serotonin. In recent work, dissolvable microneedle patches were prepared it's a transdermal drug delivery system that bypasses the challenges encountered by another delivery system. Microneedles are the projections capable of penetrating the epidermis and reaching the upper dermis without contacting nerve fibres or blood vessels so it's a painless drug delivery system. Microneedles has many advanatges like large molecular drugs can be administered, first-pass metabolism is avoided, faster healing than hypodermic needles can be obtained, no fear of needles, controlled drug delivery, sustained drug delivery, targeted drug delivery can be obtained, ease of administration and decreased microbial penetration in the skin. The dissolvable microneedle patches were prepared by the moulding method by taking PVA: PVP as a dissolvable polymer (5: 0.25%) and Hyaluronic acid (50mg) as a polymer and permeation enhancer, all are biodegradable, biocompatible, non-toxic and non-immunogenic polymer with high water affinity. The medium molecular weight of Hyaluronic acid provides sustained release action for 24 hours. After dissolvable microneedle patches were formulated it evaluated for physical structure analysis, mechanical strength, % drug entrapment, % moisture content, % moisture absorption, thickness, adhesiveness properties, weight variation, folding endurance, tensile strength, swelling index, and peel adhesion. All the results confirmed the successful development of dissolvable microneedle transdermal patches for sustained delivery of Ondansetron HCL for

the treatment of chemotherapy-induced nausea and vomiting.

Keywords: *Chemotherapy-induced nausea and vomiting (CINV), Ondansetron HCL, Moulding method, Dissolvable microneedles patches, Medium molecular weight of Hyaluronic acid, Polyvinyl Pyrrolidone (PVP), Polyvinyl Alcohol (PVA).*

1. Introduction

Nausea and emesis are the major side effects during chemotherapy and radiotherapy, which can be prevented by giving Ondansetron HCL in tablet & injection dosage form. Oral is the most convenient and oldest route of drug administration but it has limitations like extensive drug waste due to first-pass metabolism, not being suitable for patients who are vomiting, slow onset of action, less bioavailability not being useful for unconscious patients and enzymatic or acidic degradation. These all problems can be overcome by dissolvable microneedle transdermal patches [(1)].

Injections are administered by hypodermic needle and syringe and require a trained health professional for administration not in dissolvable microneedle transdermal patches. Dissolvable microneedle transdermal patches improved patient comfort. Needle phobia can affect both children and adults. Dissolvable microneedle transdermal patches reduce the risk of sharps and sharp waste because the microneedles disappear after dissolving in the skin. Generally, injections require extra doses in multidose vials but microneedle patches remove this wastage of drug and dry injections require diluent for reconstitution and also require special care, safe storage and transportation of diluent, syringe and needles but dissolvable microneedle transdermal patches don't require it. Dissolvable microneedle transdermal patches have improved stability and the cost of microneedle is also less as compared to injections. It's a novel, effective and efficient drug delivery system for prolonged release. No research has been done so far on this topic.

Nausea and vomiting caused by chemotherapy stand as on significant challenge accompanying chemotherapy, affecting around 70% of patients undergoing treatment. Its distressing nature brings about discomfort, anxiety, dehydration, and electrolyte imbalances, ultimately impacting both physical and mental well-being and diminishing quality of life. Regrettably, some patients option to discontinue chemotherapy altogether due to the severity of these side effects. Despite ongoing research into more effective therapies for CINV, it remains a persistent issue [(1,2)]. Despite the advancements in antiemetic treatments, a significant portion of patients, up to 30%, still grapple with persistent vomiting triggered nausea as well, including postponed nausea and vomiting after Chemotherapy. This highlights the pressing necessity for novel strategies to alleviate this distressing component of cancer therapy.

About twenty years past these events of vomiting and nausea were ranked as the most distressing cancer chemotherapy side effects. Unfortunately, despite progress achieved with the $5HT_3$ receptor antagonists' chemotherapy-induced nausea and vomiting remained a distressing adverse event. As per the data, two studies were carried out and their data showed in clinical practice, nausea still ranks number 1 as the adverse event of chemotherapy of most concern to patients, with vomiting ranking as the 3rd and the 5th most disturbing event [(2,3)].

This may be attributed to the inadequate effectiveness of existing formulations or medications in preventing

delayed emesis, a phenomenon described as vomiting and/or nausea occurring or persisting for more than 24 hours following chemotherapy. Additionally, another factor affecting the outcomes of clinical research is the failure to translate findings into clinical practice. Ondansetron made history in 1991 as the inaugural 5-HT3 antagonist to receive approval from the US Food and Drug Administration (FDA). Initial studies demonstrated its efficacy as an antiemetic among patients undergoing cisplatin-based treatments, and later research revealed its superiority over metoclopramide for patients on both cisplatin and non-cisplatin regimens [4,5,6].

Ondansetron HCL is a medication used to prevent or treat vomiting caused by chemotherapy, radiotherapy or surgery. When taken orally, it is well absorbed by the body and undergoes first-pass metabolism. The oral bioavailability of Ondansetron HCL is about 59%, and a peak plasma concentration of 0.03-0.04 µg/mL is achieved 1.5 to 2 hours after administration. However, administering the drug through the transdermal route can improve its bioavailability because it avoids hepatic first-pass metabolism and delivers the medication directly to the systemic circulation [7].

The oral delivery of Ondansetron HCL is hindered by its low bioavailability caused by first-pass metabolism. Consequently, transdermal delivery using Microneedle technology may present a more effective alternative.

Hence, in present research studied, it intended to formulate the Ondansetron HCL transdermal drug delivery system. It has been noted that transdermal (TD) drug administration offers direct access to the skin's outermost layer, bypassing challenges encountered with other delivery systems. In response to the limitations of traditional methods, microneedle-based drug delivery via the TD route has gained recent popularity. Microneedles are equipped with projections capable of penetrating the epidermis. These microneedles, fabricated from materials like metal, polymer, hydrogel, silicon, ceramic, etc., typically range from 150 to 1500 µm in length [8,9].

The composition and synthesis of Microneedles were developed by using Polyvinyl alcohol (PVA) and Polyvinylpyrrolidone (PVP). Polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) are among the most favoured synthetic polymers for microneedles, renowned for their water solubility, biodegradability, biocompatibility, non-carcinogenicity, and exceptionally low cytotoxicity. These qualities make them highly suitable for a myriad of biomedical applications.

From this studied, the transdermal patch showed sustained drug plasma levels and the most important benefit is that it is a non-invasive technique, which can be easily terminated one of the standout benefits of this method is its non-invasive nature, making it easy to discontinue by simply removing the patch. This simplicity tends to improve patient compliance, compared to other forms of medication, and reduces side effects [10,11]. With this background, it is proposed to develop and formulate the TDDS for antiemetic Drugs (Ondansetron HCL) and the developed patch would be subjected to further studies in animals for pharmacodynamics.

Based on the complete studied of dissolvable microneedle patches, transdermal drug delivery system, chemotherapy-induced nausea and vomiting and its treatment options it was found that the dissolvable microneedles patches are good for transdermal drug delivery of the Ondansetron HCL which increase the

bioavailability and therapeutic efficacy of the drug even also provide sustain release of the drug. Ondansetron HCL is a very useful drug for chemotherapy-induced nausea and vomiting (CINV) and this work is to design, fabricate and evaluate dissolvable microneedle transdermal patches. Dissolvable microneedle transdermal patches have improved stability and can often be stored at ambient temperature, eliminating cold storage, and allowing for easier stockpile and storage. Dissolvable microneedle transdermal patches are smaller in size than accessories of injectables facilitating storage and distribution. The cost of dissolvable microneedle transdermal patches is lower than prefilled syringes (all materials are low cost).

Finally, ondansetron HCL loaded dissolvable microneedle transdermal patches for chemotherapy-induced nausea and vomiting is one of the most efficient drug delivery system dissolvable microneedles patches reach farther into the skin can deliver drug prescribed dosages for prolonged periods by dissolving themselves.

2. Methods and Materials

2.1. Materials

Ondansetron HCL were purchased from Yarrow Chem Products, Ghatkopar West, Mumbai, Maharashtra. Hyaluronic Acid, (PVP) Polyvinylpyrrolidone, (PVA) Polyvinyl alcohol were obtained from Charco Chemicals, Hoshiarpur, Punjab. Microneedle Template also known as M Patch Microneedle template supplied from Micropoint Technologies Pte Ltd, Pioneer Junction, Singapore.

2.2. Methods: The following steps were adopted -

Step 1: Procurement of Microneedle template

Dissolvable microneedle patches were prepared by the moulding method. M Patch Microneedle template was purchased from Micropoint Technologies Pvt Ltd, Pioneer Junction, Singapore. This template is exclusively made for producing dissolvable microneedle patches with excellent quality. This template was made of heat and chemical-resistant silicone, which 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 1.

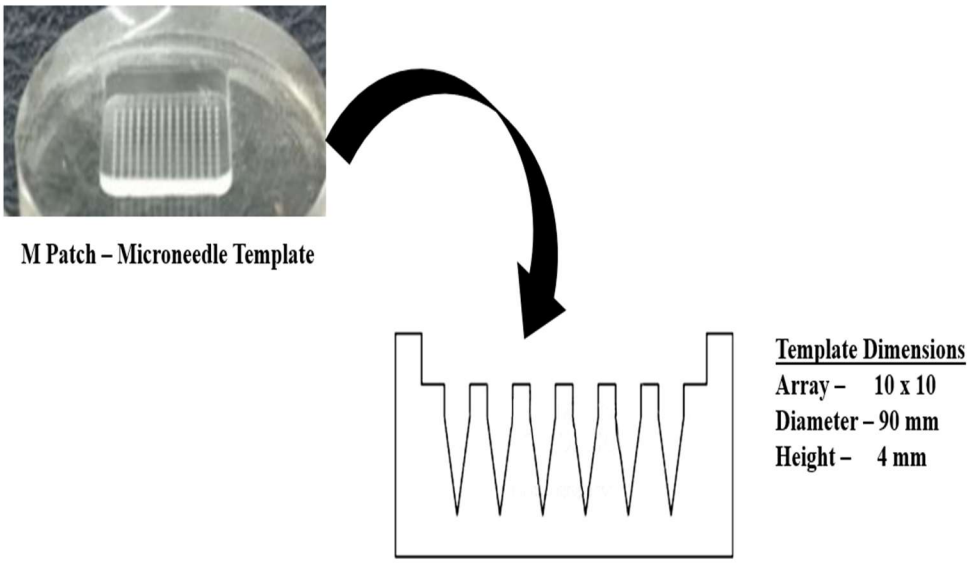


Figure 1: M Patch descriptions

Step 2: Preparation of Dissolvable Microneedles

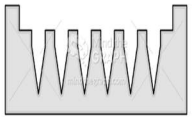
Microneedles were prepared by using a combination of Polyvinyl alcohol (PVA) and Polyvinyl Pyrrolidone (PVP). 5% w/v PVA was dissolved in 2 ml of deionized water at 60ºC. Then 0.25% w/v PVP was mixed in PVA solution and then 16 mg of Ondansetron HCL was added with 50 mg of Hyaluronic acid to this polymeric mixture. Next, 1 ml of the mixture was pipette out and added to 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 2.

To this solution by sti

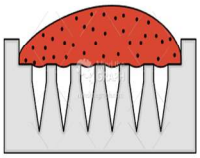
Addition of Ondansetron HCL (16mg) & Hyaluronic acid (50gm) mixed

Hyaluronic acid (60mg) mixed

PVA: PVP (5: 0.25) w/v were dissolved in 2ml Deionized Water

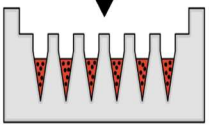


M Patch Microneedle Mould

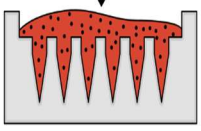


Addition of above solution (1ml) on M Patch microneedle template

Place under Vacuum for 30 minutes



Centrifuge at 2000 RPM for 1.5 hr



Addition of rest of solution on the template for making back plate

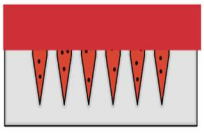


Figure 2: Preparation of Dissolvable microneedles

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 3.

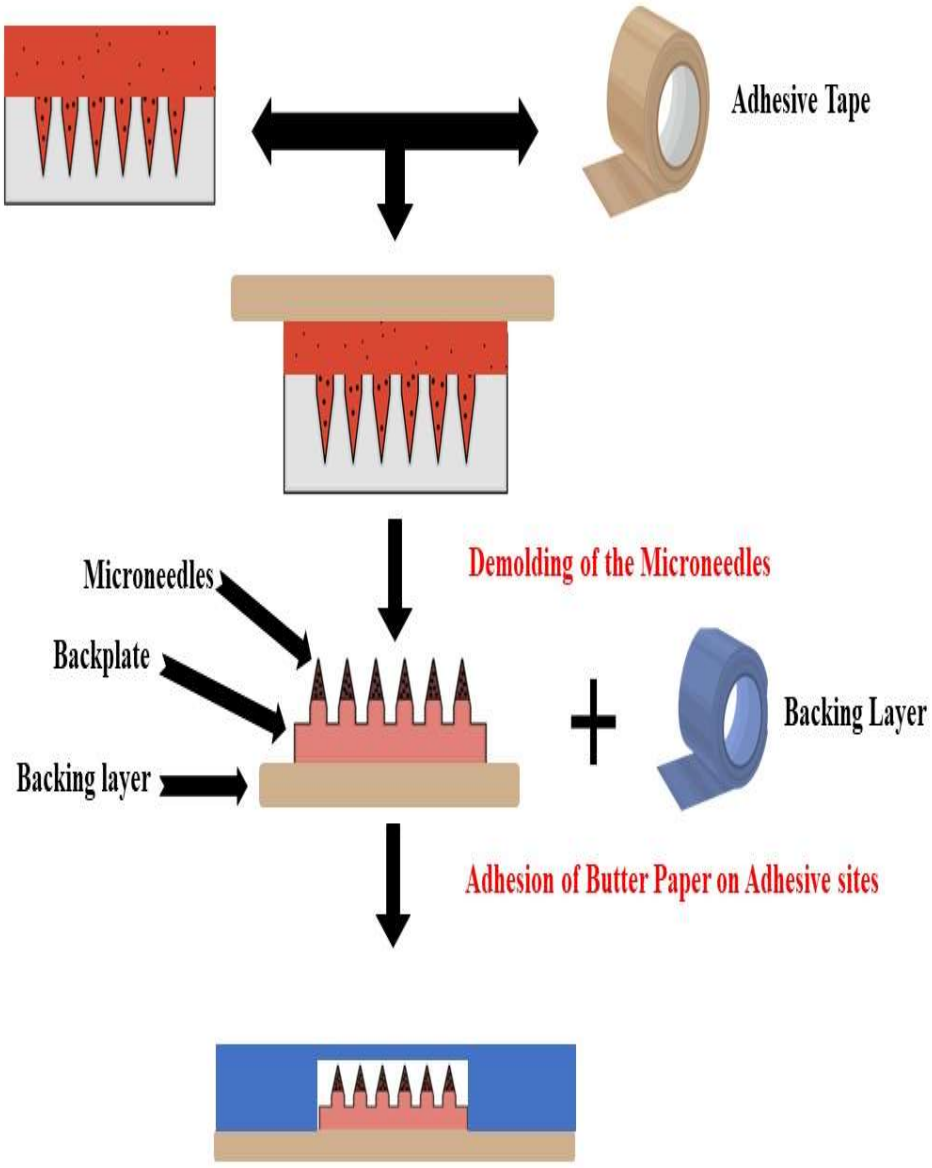
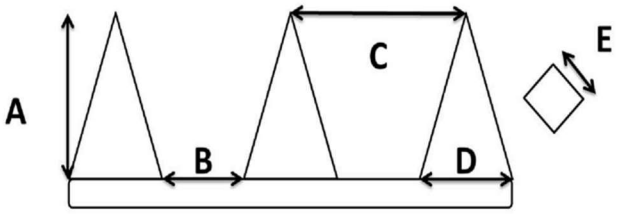


Figure 3: Adhesion of backing membrane (Adhesive tape) on Microneedle patches

2.3. Characterization of microneedles

2.3.1. 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 4 (a), (b) & (c) & Table 1.



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

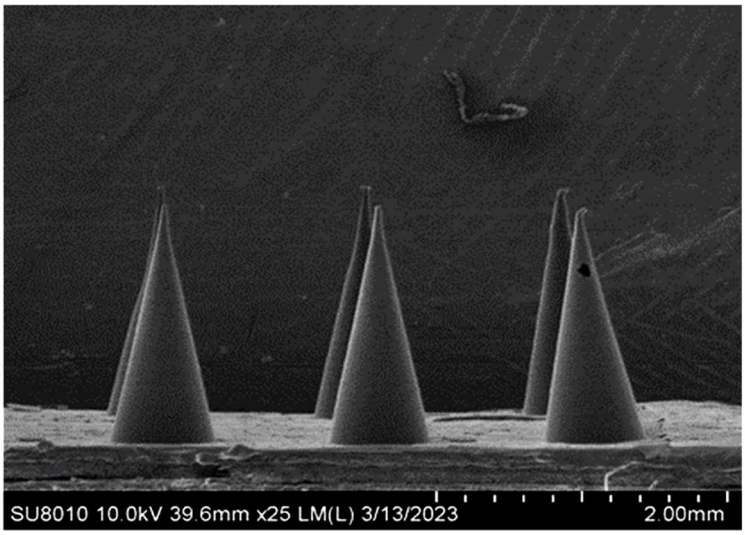


Figure 4 (a): SEM analysis of Optimized Formulation of (MNS6) at x25

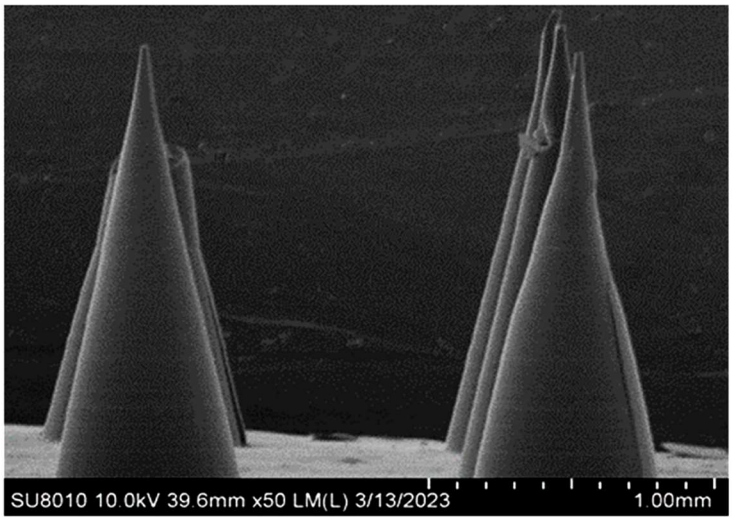


Figure 4. (b): SEM analysis of Optimized Formulation of (MNS6) at x50

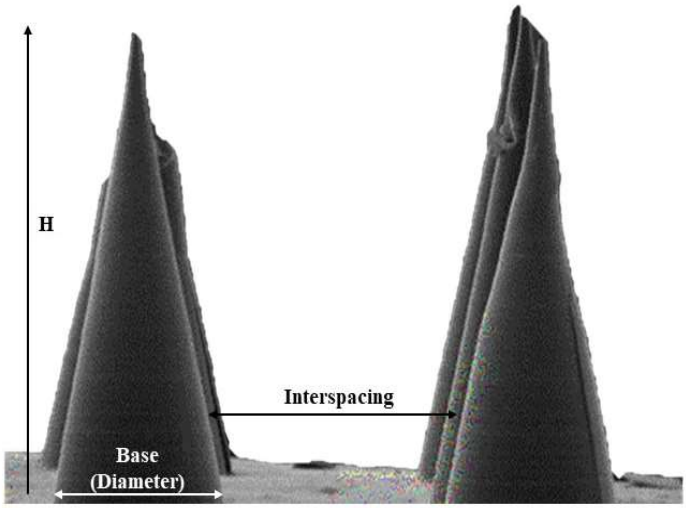


Figure 4 (c): SEM analysis for Optimized formulation (MNS6) showing Height, Diameter, Length & Interspacing

Table 1: Microneedles SEM analysis (X50 LM/L)

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

2.3.2. 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). The deformation or fracture in the microneedle was observed. Upon detecting fracture, the maximum load at the point of fracture is recorded carefully, which represents the fracture strength of the microneedles. This fracture testing provides data on the extent of deformation and fracture characteristics such as crack propagation and fracture surface morphology using microscopy techniques as illustrated in Figure 5 & Tables 2 & 3.

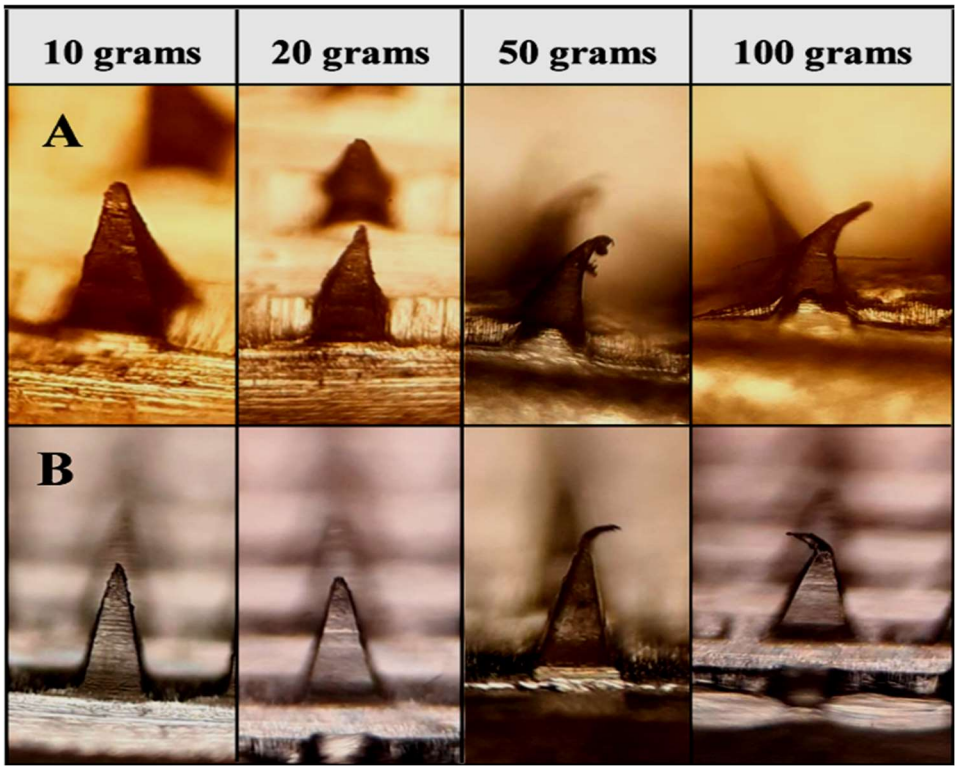


Figure 5: Mechanical strength and tip bending of A) MNS6 B) MNS9

Table 2: 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 gm.

Table 3: 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

2.3.3. Percentage (%) Drug Entrapment

For the determination of percentage (%) drug entrapment efficiency, a 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 ^OC 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 4: 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

2.3.4. 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. The difference in weight between the initial and final weighings was calculated, representing the loss of moisture during the drying process. Using this weight difference and the initial weight of the sample patch, the moisture content was determined as a percentage using the formula below and, the results are given in Table 5.

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

Table 5: 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

2.3.5. 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. The percentage moisture uptake was determined results are illustrated in Table 6 or percentage moisture absorption was determined by using the following formula:

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

Table 6: 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

2.3.6. 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 7.

Table 7: 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

2.3.7. 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 8.

Table 8: Determination of Adhesiveness property

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

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

2.3.8. Weight Variations

The patches were subjected to weight variation by individually weighing patches and the average was calculated; results are shown in Table 9.

Table 9: 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

2.3.9. 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 10.

Table 10: 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

2.3.10. 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 11.

Table 11: Determination of Tensile Strength

Patch code	Tensile strength (kg/cm3) 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

2.3.11. 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:

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

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 12: 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

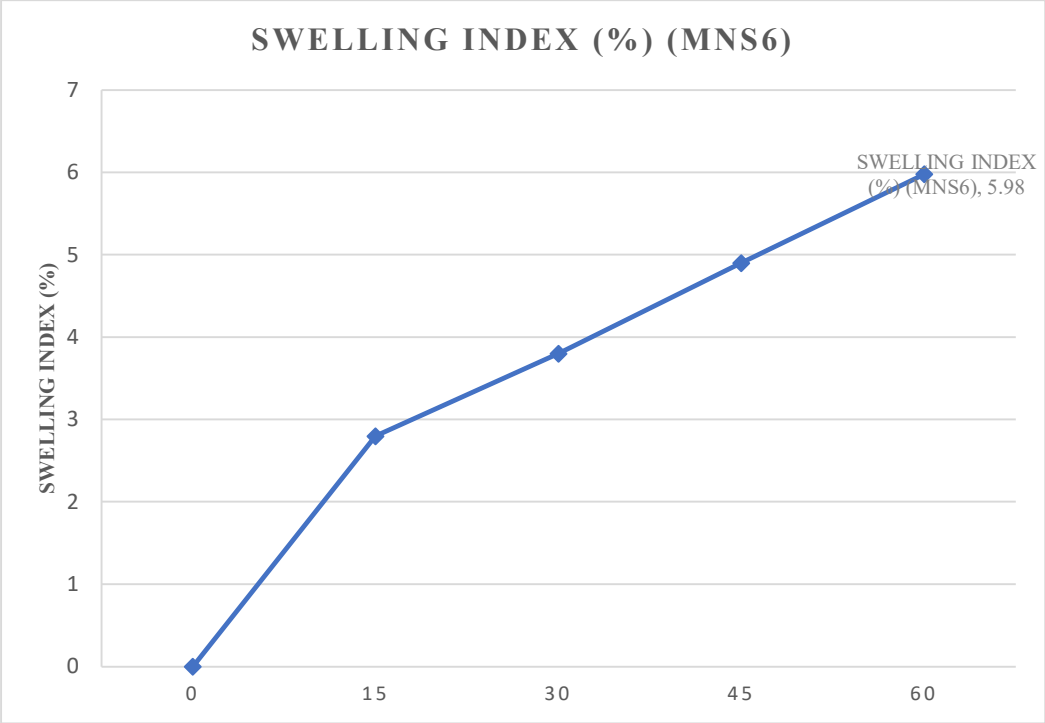


Figure 6: Swelling Index (%) of Optimized formulation MNS6

2.3.12. Peel adhesion

The adhesive nature of the formulated transdermal patch was used to evaluate the peel adhesion by using a texture analyzer by following standard procedures. The peel adhesion test was performed with a 5kg load cell. The optimised 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 the texture analyzer. The release liner was removed before the test. The probe of the 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 13.

Table 13: 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

3. Results and discussions

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 1. 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 2 & 3 and Figure 5. 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 affects the percentage drug efficiency of microneedle 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 4.

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 5.

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 6.

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 7.

Adhesiveness property ensure 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 behaviour 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 8. 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, results shown in Table 9. 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 10.

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 11 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 jeopardise 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 12 and Figure 6.

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 4500gm to 4930gm, results shown in Table 13. Optimized formulation (MNS6) showed 4500gm of peel adhesion and is deemed satisfactory results will not cause pain while intended application of the transdermal patches.

Conclusion

On the basis of the literature survey, formulation studies, characterisation, result and discussion of the complete work of ondansetron HCL loaded dissolvable microneedle transdermal patches we conclude and recommend that it ensures a more accurate, effective and reproducible delivery of drug to the skin as comparison to injections

and tablets.

In chemotherapy-induced nausea and vomiting both injection and tablets are given. Oral is the most convenient and oldest route of drug administration but it has limitations like extensive drug waste due to first-pass metabolism, not being suitable for patients who are vomiting, slow onset of action, less bioavailability not being useful for unconscious patient and enzymatic or acidic degradation. These all problems can be overcome by dissolvable microneedle transdermal patches.

Injections are administered by hypodermic needle and syringe and require a trained health professional for administration. Use of dissolvable microneedle transdermal patches allows for administration by minimally trained personnel, including self-administration, which could reduce the burden on the healthcare system.

Dissolvable microneedle transdermal patches improved patient comfort. Needle phobia can affect both children and adults. Various acceptability studies using pressure sensitive dissolvable microneedle transdermal patches with auditory force feedback indicator found that participants reported no pain or very little pain on self-administration and strongly preferred dissolvable microneedle transdermal patches over IM or SC injections.

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.

More researches are required to assess uncertainty about the cost and capability of large-scale manufacturing of dissolvable microneedle transdermal patches.

In current research work water soluble drug was used to make dissolvable microneedle transdermal patches but more research are required in future if the drug is insoluble. Clinical trials will be needed soon to provide solid evidence and also required to assess the dose accuracy and we hope this research work like all phases of formulation development, in vitro assessment, and in vivo assessment will help to accelerate the translation from clinical trials to clinic. Furthermore, the high cost associated with it and the challenge of registering it as a commercial product is a major difficulty in bringing it to market.

The current research work also is the starting point of developing a holistic approach with maximum effectivity and minimum obnoxious effects in achieving the ultimate betterment of people and society.

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Conflict of Interest

All the authors declare that he has no conflict of interest. This article contains no studies with human subjects performed by any authors.

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