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Design, Fabrication and Characterization of Antiemetic Transdermal Patches Loaded Dissolvable Microneedles

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Abstract*: Various non-invasive administration methods have recently emerged as an excellent alternative to conventional administrative mechanisms. A transdermal drug delivery system with polymeric microneedles presents the most attractive method among all these because of its low rejection rate, higher bioavailability, convenience, ease of administration, and ease of termination, as well as its biodegradable and persistent nature in the skin care industry. However, the skin's physicochemical properties enable it to protect the inner environment, and this mechanism acts as an excellent barrier for TDDS. Hence, polymeric bio-dissolvable and biocompatible microneedles can be an excellent choice. In this research, we fabricated and characterised different proportions of polymer blend solutions for the effective and improved bioavailability and delivery of Ondansetron HCl. We characterised TDDS by determining mechanical strength progression through folding endurance, flatness study, gelatin sheet bed penetration application, and percentage drug release under FT-IR. We studied microscopic images to examine the shape and size of the microneedle. In addition, desired physical properties and an excellent alternative method have been established, with high efficiency inherent to TDDS, which is expected to find applications in a broad range of fields.

Keywords: Bioavailability, FT-IR, Polymeric microneedles, Ondansetron HCl.

I. INTRODUCTION

This drug delivery system is termed a series of therapeutic technologies that help control the delivery, rate, or release of a drug in its pharmacologically active form. There are various types of routes of administration modalities present, including oral routes, respiratory routes, mucosal administration, parenteral routes and transdermal administration [1,2]. Among them, novel transdermal administration represents the advanced and attractive approach.

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The transdermal drug delivery system is becoming the most widely used route of drug delivery, which is a noninvasive delivery into the body, passing through the skin barriers. Transdermal drug delivery system involves not the passage of drug through gastrointestinal tract (GIT); hence TDDS shows prevention from first-pass, metabolism and in TDDS, the drug can be delivered without alteration of pH, intestinal tract bacteria and enzymatic activity [2,3]. In addition, transdermal drug delivery makes a significant contribution to minimal pain, safest and convenient drug delivery to children or elderly patients. However, TDDS does not fully utilise its potential due to skin barriers. Skin is composed of various laye, ars, including epidermis protective layer, dermis, which contains blood vessels, and produces skin cells, and each of these layers interferes with the drug delivery via the transdermal drug delivery system [4,5,6].

To solve issues that arise, various novel TDDS systems have been thoroughly studied and have emerged as attractive administration methods in terms of cost-effectiveness and therapeutic effectiveness. In addition, TDDS drug delivery is enhanced by electrical, mechanical or physical stimuli, which are known to improve the permeation rate of drug or biomolecules through topical application [7,8,9].

The microneedle represents one of the most popular and intensive methods in the area of current research in transdermal drug delivery systems. Microneedles are short or structurally thin; these micron-sized needles deliver drugs or biomolecules through the blood capillary area by following active absorption without causing pain. The microneedles could be of many types, including solid, hollow, dissolving or metal type microneedles [10,11]. Additionally, the fabrication method of microneedle systems has been extensively studied in relation to the objective, type of drug, or target for use. Various techniques for preparing microneedles include laser-mediated methods, photolithography, 3D structure cutting or ablating methods, and mould-based fabrication methods. Among them, polymeric microneedles or dissolving/hydrogel microneedles are widely fabricated by mould-based techniques [12,13].

Ondansetron HCl is a class of drug which is used to prevent nausea and vomiting caused by various agents such as cancer chemotherapy, radiation therapy and surgery. The serotonin antagonist (Serotonin 5-HT3 receptor blockers). This drug works by blocking the action of serotonin, which is responsible for vomiting and nausea, which are triggered during cancer therapy, radiation therapy and other treatment procedures [14].

Currently, Ondansetron HCl is available as a Tablet, a rapidly dissolving tablet film, an oral solution, and an IV injection. This usually takes 30 minutes to reach, or 1 to 2 hours after chemotherapy and radiation therapy have been administered. The drug exhibits limitations in bioavailability and stability in this dosage form, as well as patient complaints. Tablet packaging should not be of the punch-through type; gentle care should be taken, as IV injections can be difficult for individual patients. In addition, the present study focused on the polymeric microneedles loaded transdermal patches, which can be easily administered and are easy to transport and package [15,16]. The role of bioavailability difficulty is also resolved by microneedle incorporation. These microneedles penetrate the upper layer of the skin, making it easier to administer the drug without activating pain receptors. As a result, patients can comply without feeling pain and terminate the treatment with ease.

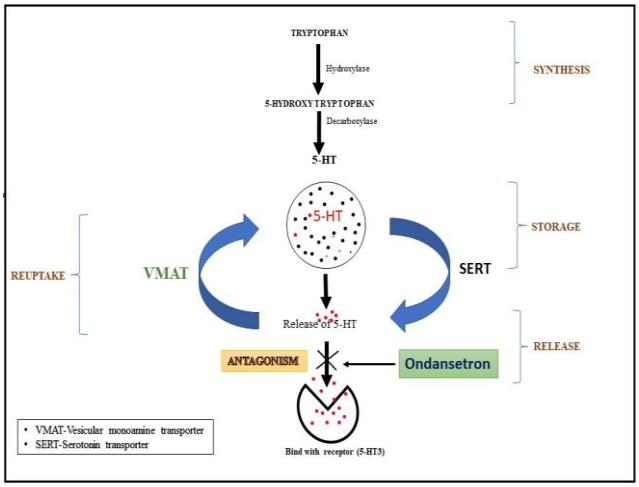

Figure No. 1: Ondansetron HCl mechanism of action presents the blocking of 5-HT by inhibiting the binding to 5-HT3 receptors and producing reuptake of serotonin.

Hyaluronic acid, which exhibits good biocompatibility, biodegradability, and non-immunogenicity. Therefore, hyaluronic acid can be a good carrier as well as having good healing properties, cell repairing activity, which can be a beneficial combination with ondansetron HCl [17,18]. In addition, previous studies have shown no toxicity and do not alter the action of the serotonin antagonist (ondansetron HCl). In terms of drug delivery, hyaluronic acid attracted much attention as a drug delivery carrier for targeted drug delivery as well as in cancer therapy [19,20,21].

In this study, an attempt has been made to focus on the design criteria and fabrication method of polymeric microneedles made of PVP/PVA for topical application, and to summarise the properties of hyaluronic acid. In addition, hyaluronic acid helps to repair and alter microneedle puncture and enhance the cell repair mechanism without changing the drug delivery [22]. However, a polymeric microneedle-based transdermal drug delivery system was made from polyvinyl pyrrolidone and polyvinyl alcohol. The resultant system exhibited improved tensile strength, with a higher percentage of elongation and less painful administration. After evaluation of this system in in vivo models, promising pharmacodynamics and pharmacokinetics performances were obtained and justified [23,24].

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II. METHODS AND MATERIALS

A. Materials

The microneedle template was prepared using the casting method, which provided a needle length of 500 micrometres to 600 micrometres and a width and length of 30 x 30 mm². The microneedle solution was prepared using two types of polymer solutions: PVA/PVP (Molecular weight of 74,800, 97-100 mol% %, Sigma Aldrich Chemistry Co., Ltd.) for microneedle patch preparation and mould preparation, and a hydrated polymer casting solution (Yaaro Chemical, Bangalore, India). All other chemicals were of analytical grade.

B. Methods of Preparation: Transdermal Patches

These are fabricated using the dry and wet inversion method, where a polymer (PVP/PVA) dissolved in a solvent forms a mixture at 60°C to homogenise the polymer solution. The polymer solution was maintained at 40°C for approximately 24 hours and then cast onto a glass plate. Then, the glass plate was heated to 50°C for approximately 30 to 40 seconds. It was then immediately immersed in a coagulation bath for 10 minutes. At last, make the upper layer film air dry and remove it with the help of a gardener's knife.

C. Methods of Preparation: Polymeric Microneedles

The polymeric patch was prepared by a PVA/PVP blend solution introduced into the mould. The polymer blend of PVA and PVP was used, with low saponification of PVA and high saponification of PVP, in different ratios of 10:0, 9:1, 7:3, 5:5, 3:7, 1:9, and 0:10 to prepare the blend solution of polymers. In addition, differential scanning calorimetry (DSC) degradation tests were conducted to analyse the mechanical properties of these different ratio blend solutions of PVA/PVP. About 10 mL of distilled water was mixed (10% by weight) to achieve a PVA/PVP weight of 1 gram. Then, after the mixers were continuously stirred in a water bath to form a homogenised mixture. The prepared solution was then poured into the mould and kept in an oven at 40 to 45 degrees Celsius for 24 hours to prepare a microneedle patch. The active ingredient (Ondansetron HCl) was added to this PVA/PVP-based solution, which contained 5% by weight of the PVA/PVP solution.

1. Evaluation parameter of transdermal patches

1.1. Thickness of the patches

The thickness of a transdermal patch can be measured by travelling a dial gauge, screw gauge, or micrometre of a microscope at different points on the film and noting the reading.

1.2. Uniformity of weight

Weight variation is determined by weighing individually 10 randomly chosen patches and calculating the average weight. The weight of an individual should not reflect the average weight.

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1.3. Flatness study

The transdermal patch must show a smooth surface and resist sticking over time. This can be demonstrated in a flatness study. Flatness study can be performed by cutting one strip from the centre of the patch and two strips from each side. The length of each strip is measured, and any variation in length is noted down by determining the percentage constriction. For easy calculation, a zero percentage constriction is considered equivalent to 100% flatness.

The formula below is used to calculate the flatness of TDDS Patches:

% Constriction = I1-I2 x 100

Where,

I2 Final length of each strip

I1 Initial length of each strip

1.4. Folding endurance

The determination of folding endurance involves assessing the folding capacity of the transdermal patches, which are frequently subjected to extreme folding conditions. The repeatedly folding process helps to determine the patch endurance value. This process continues at the exact location until the patch breaks, and the number of times the patch can be folded at the precise area without breaking is also recorded.

1.5. Percentage moisture absorption

The prepared transdermal patch was weighed individually and demonstrated variation in weight after accounting for moisture. The patches were weighed again after a time interval until they showed a constant weight, and this can be calculated using the formula below.

% Moisture content = Initial weight – Final Weight x 100

1.6. Percentages of moisture content

The formulated patches were individually weighed and placed in a desiccator containing calcium chloride. The temperature was maintained at room temperature, and the patches were left in place for 24 hours. The patches are continuously weighed at time intervals until a constant weight is achieved. The following formula helps to calculate the percentage of moisture content:

% Moisture content= Initial weight – Final weight x 100[4]

1.7. Drug content determination

The weighed patch was accurately weighed (approximately 100 mg), then it was dissolved in 100 mL of solvent and stirred continuously for 24 hours in a shaker incubator. The obtained solution is sonicated and then subjected to subsequent filtration. The resulting solution is spectrophotometrically analysed by appropriate dilution.

1.8. Drug permeation/in-vitro-in-vivo studies:

The receptor compartment has a volume of 5 to 15 ml and an effective surface area of 5 cm². The Franz diffusion cell was used to evaluate transdermal patches. The diffusion buffer was continuously stirred at a speed of 600 rpm using a magnetic bar. A thermostat maintains the internal temperature of the environment. The drug content sample was taken at 2-minute intervals and analysed under UV-Vis spectroscopy, with the results presented in a graph for easy demonstration.

Figure No. 2: Modified static Franz diffusion cell determination of static gelatin sheet beds penetration efficiency. 5-12 mL of compartment fluid and a gelatin sheet of approximately 1-5 cm² are continuously rotated in a buffer solution at 600 rpm using a magnetic stirrer.

III. RESULTS AND DISCUSSION

1.9. Fourier-transform-infrared spectroscopy

The prepared microneedle with low and high saponification PVA/PVP blend showed excellent shape stability. The prepared microneedles formed perfectly; SEM images showed a uniform structure. In addition, Fourier transform infrared spectroscopy (FT-IR) was used to determine the patch and confirm the presence of the drug in the prepared microneedle in the desired amount.

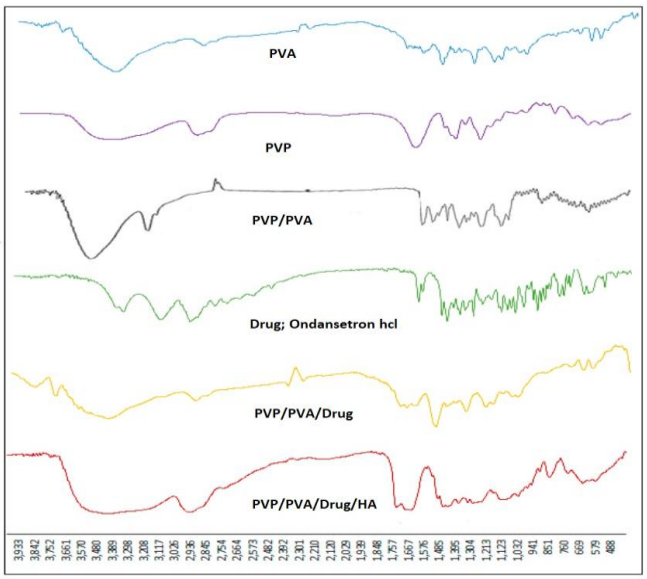

Figure No. 3: PVA, PVP, PVP/PVA, Drug, PVP/PVA/Drug, and PVP/PVA/Drug/HA combinational stability and compatibility study using FT-IR. The graph presents the ratio of absorption and the standard peak to determine the slopes.

1.10. Differential scanning calorimetry

The measurement of the patch predicted the difference between the views of PVA/PVP8 and PVA/PVP7 blend solutions. This is because the change in the polymer's structure, from poly(vinyl acetate) to poly(vinyl alcohol), affected the rate of degradation of the transition in the patches.

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The overall study was affected by the formation of crystals in the molecular structure, and the crystal structure increased with an increase in the PVA/PVP ratio, particularly at a high degree of saponification.

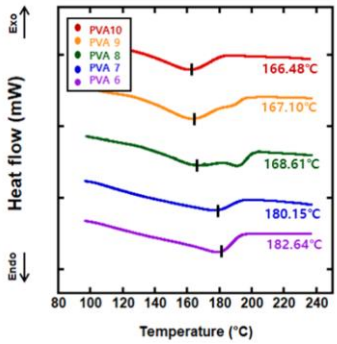


Figure No.4: DSC curve shows PVA/PVP-based microneedle patches. The high and low degrees of saponification affect the degree of degradation by forming crystals in the structure. The melting temperature (T_m) was 166.48°C for PVA10.

1.11. Measurement of mechanical properties of microneedle transdermal patch

The mechanical properties of microneedle-loaded transdermal patches were determined through folding endurance, thickness evaluation, and flatness study. Therefore, the PVA/PVP9 and PVA/PVP10 patches demonstrated a high degree of stability and were deemed acceptable, based on the survey conducted and the data generated.

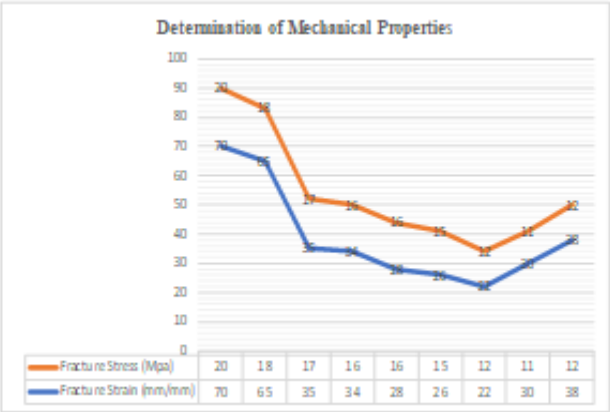


Figure No.5: Graph of the degradability behaviour showing the dependence on the PVA/PVP ratio. Where PVA/PVP7, PVA/PVP8 and PVA/PVP9 were degraded entirely, and showed 100% weight loss.

Table No.1: Characterization of TDDS on various parameters presents, folding endurance, thickness evaluation, % drug content evaluation, moisture uptake.

S.No.	Patch	Thickness (mm)	Folding enduamcce	% Drug contnetn	Moisture uptake
1	PVA/PVP1	145∓6	156∓5	98.45∓0.41	84.56
2	PVA/PVP2	149∓6	150∓6	97.46∓.068	74.52
3	PVA/PVP3	151∓4	167∓5	98.40∓0.68	70.48
4	PVA/PVP4	154∓5	172∓6	99.40∓0.61	91.42
5	PVA/PVP5	152∓6	186∓5	97.40∓0.46	71.56
6	PVA/PVP6	155∓4	175∓2	98.98∓.0.68	86.42
7	PVA/PVP7	154∓5	180∓6	97.42∓0.45	78.41
8	PVA/PVP8	150∓2	182∓5	98.16∓0.47	88.46
9	PVA/PVP9	152∓6	124∓6	99.48∓0.48	97.12

In addition, the in vitro permeability of the polymeric microneedle was measured to verify the permeability experiment and determine if the microneedles could easily penetrate the stratum corneum of actual skin. The mechanical properties helped it out; the elasticity modulus of the human-subjected skin is approximately 0.013 MPa, and a gelatin sheet bed was formed, which produced a 7-weight percentage, confirming the 0.013 MPa value. A penetration experiment was conducted using a 7-weight percentage of gelatin sheets bed, and the resultant microneedle hole was observed through microscopic examination. The last result confirmed that the 150 dots were formed when bending the microneedle tops, which had a high degree of penetration, with an acceptability rate of approximately 100% as observed. Therefore, this study also confirmed that the microneedles dissolved in a suitable pH medium if the gelatin sheet bed were immersed in such fluid.

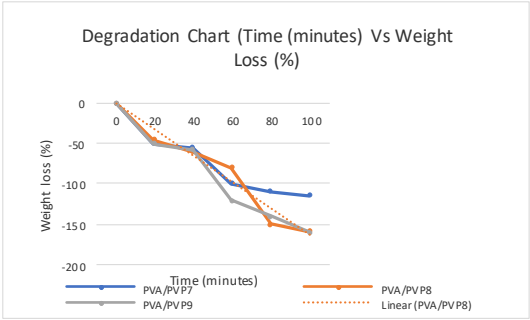
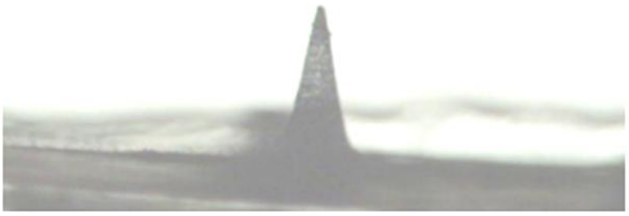


Figure No.6: This graph represents the tensile strength, indicating x-axis PVA/PVP0 to PVA/PVP10 and on the Y-axis fracture stress and fracture strain.



(a)

(b)

Figure No.7: Compression study, Optical microscopic images present the bend of the polymeric microneedle top after the compression test.

IV. CONCLUSION

The prepared polymeric microneedles (PVA/PVP) using high and low saponification methods demonstrated excellent morphological stability overall, confirming the controlled delivery of the drug. SEM confirmed the well-formed microneedle edges.

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The microneedle-based transdermal patches were formed with a low and high degree of saponification ratio (PVA/PVP 9:1), and Ondansetron HCl was well distributed throughout the patch.

Additionally, flexibility, determination of folding endurance, percentage of drug content, weight variation, and in vitro percentage drug content release were characterised and analysed. All the authors have reviewed and approved the final version of the manuscript.

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DECLARATION

All authors hereby declare their accountability in this research article.

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Ethical Approval and Consent to Participate	No, the article does not require ethical approval or consent to participate, as it presents evidence that is not subject to interpretation.
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Authors Contributions	All authors have equal participation in this article.

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