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

Deepesh Lall, Neeraj Sharma, Shruti Rathore

Abstract*: Various non-invasive administration has been recently coming as an excellent alternative to conventional administrative mechanism. A transdermal drug delivery system with polymeric microneedles presents the most attractive method among all these because of its low rejection rate, higher bioavailability, super convenience, ease of administration and ease of termination, biodegradable and persistence in the skin care industry. However, the skin physiochemical properties made them to protect the inner environment and this mechanism play as excellent barrier for TDDS, hence polymeric bio dissolvable and biocompatible microneedle can be excellent choice. In this research, we fabricated and characterized the different proportions of polymer blend solution for effective and improved bioavailability and delivery of Ondansetron HCl. We characterized TDDS on progression of mechanically strength determination by folding endurance, flatness study, gelatin sheets beds penetration application, percentage drug content releasement under FT-IR and studied microscopic images the shape and size of microneedle. In addition, desired physical properties and an excellent alternative method had been established with high efficiency inherent to TDDS which expected to find a broad range of application fields.

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

I. INTRODUCTION

This The drug delivery system is term as a series of therapeutic technology which help t control the delivery, and rate or release of drug, which is 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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*Correspondence Author(s)
Deepesh Lall*, Department of Pharmaceutics, Research Scholar, Bhagwant University, Ajmer (Rajasthan), India. Email: Deepesh.lall95@gmail.com, ORCID ID: https://orcid.org/0000-0001-9928-5226
Dr. Neeraj Sharma, Department of Pharmaceutics, Professor/ Principal, Bhagwant University, Ajmer (Rajasthan), India. Email: deepesh.officework@gmail.com
Dr. Shruti Rathore, Department of Pharmaceutics, Professor/ Principal, LCIT School of Pharmacy, Bilaspur (Chhattisgarh), India. Email: Drshrutirathore@gmail.com, ORCID ID: https://orcid.org/0000-0001-6311-6543

Transdermal drug delivery system is becoming most widely routes of drug delivery which is noninvasive delivery into the body passing from 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 drug can delivered without alteration of pH, intestinal tract bacteria and enzymatic activity [2,3]. In addition, transdermal drug delivery makes highly contribution in minimal pain, safest and convenient drug delivery to children or the elderly patients. However, TDDS not fully utilizes the potential because of its skin barriers. Skin is composed of various layers, includes epidermis protective layer, dermis blood vessels are located and produces skin cells and each of these layers interfere the drug delivery via transdermal drug delivery system [4,5,6].

To solve issues arises, various novel TDDS system have been completely studying and have emerged as attractive administration methods in terms of cost effectiveness and therapeutics effectiveness. In addition, TDDS drug delivery enhanced by electrical, mechanical or physical stimuli which are known to enhance the permeation rate of drug or biomolecules through topical application [7,8,9].

The microneedle is representing one of the most popular or intensive method in area of current research in transdermal drug delivery system. Microneedles are short or structurally thin, these micron in sized needle deliver drug or biomolecules through blood capillary area, by following active absorption without causing pain. The microneedles could be of many types, includes solid, hollow, dissolving or metal type microneedles [10,11]. In addition, the fabrication method of microneedles system widely studied with concerning the objective, drug type or target for use. Various methods microneedle could be prepared are, laser-mediated methods, photolithography, 3D structure cutting or ablating method and mold-based fabrication methods of microneedle. Among them, polymeric microneedles or dissolving/hydrogel microneedles widely fabricated by mold-based techniques [12,13].

Ondansetron HCl is a class of drug which is used to prevent nausea and vomiting which 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, this chemical is responsible for vomiting and nausea which trigger during cancer therapy, radiation therapy and other treatment procedures [14].

At present Ondansetron HCl comes as Tablet, rapidly dissolving tablet film, oral solution and IV injection. This usually takes 30 minutes to reach on 1 to 2 hours after chemotherapy and radiation therapy. Drug showing limitation in bioavailability and stability in these dosage form and patient complaints. Tablet packaging should not be punch and through type, gently care taken, IV injection taking difficulty to individual patient. In addition, present study focused on the polymeric microneedles load transdermal patches which can be easily administration and ease to transport and packaging [15,16]. The role of bioavailability difficulty also resolves by microneedle incorporation, this micron needles puncture the upper layer of the skin and makes the path for administration of drug without interfere the pain receptors, patient compliances without feel pain and ease to terminate.

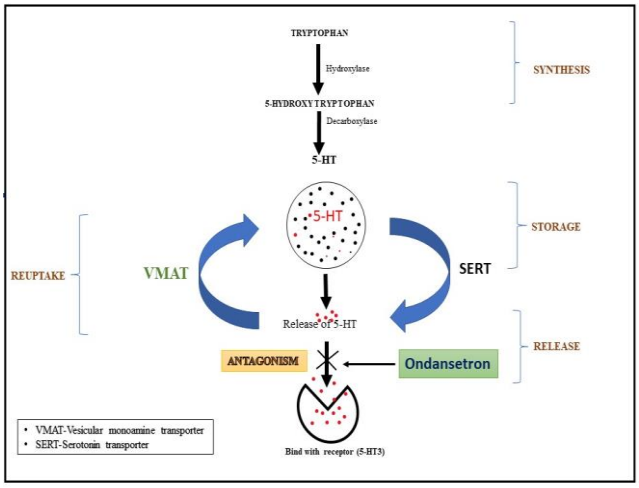

Figure No. 1: Ondansetron HCl mechanism of action present the blocking of 5-HT by inhibiting the binding to 5-HT3 receptors and produced reuptake of serotonin.

Hyaluronic acid which shows good biocompatibility, biodegradability and non-immunogenicity activity. Therefore, hyaluronic acid can be a good carrier as well as good heal properties, cell repairing activity, can be benefit combination with ondansetron HCl [17,18]. In addition, previous studied showed not any toxicity and does not alter the activity of serotonin antagonist (ondansetron HCl) action. In terms of drug delivery hyaluronic acid attracted much intention as a drug delivery carrier of targeted drug delivery as well in cancer therapy [19,20,21].

In this study, an attempt has been focused on the design criteria and fabrication method of polymeric microneedles of PVP/PVA for topical application and summarize hyaluronic acid. In addition, hyaluronic acid help to repair alter microneedle puncture and enhance the cell repair mechanism without altering the drug delivery [22]. However, polymeric microneedle based transdermal drug delivery system was made from polyvinyl pyrrolidone and polyvinyl alcohol. The resultant system exhibited the improved tensile strength of smooth flexible films with higher percentage of elongation and pain less 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 by casting method which provided needle length of 500 micrometer to 600 micrometer and width and a length of 30 x 30 mm^2. The microneedles solution was prepared using two types of polymer solution PVA/PVP (Molecular weight of 74,800, 97-100 mol %, Sigma Aldrich Chemistry Co., Ltd.) used for microneedles patches preparation and for molds preparation hydrated polymer casting solution were used (Yaaro Chemical, Bangalore, India). All other chemical were of analytical grade.

B. Methods of Preparation Transdermal Patches

These are fabricated by process of dry and wet inversion method where polymer (PVP/PVA) dissolved in a solvent to form mixture at 60°C to make homogenise polymer solution. This polymer solution was kept at 40°C for about 24 hours and cast on glass plate. Then this glass plate was evaporated at 50°C for about 30-40 seconds, then immediately this glass plate immersed in coagulation bath for 10 minutes of time duration. At last, make air dry the upper layered film formed on glass plate and removed with the help of gardener knife.

C. Methods of Preparation Polymeric Microneedles

The polymeric patch was prepared by a PVA/PVP blend solution introducing into the mould. The polymer blend of PVA and PVP were used as Low saponification of PVA and high saponification of PVP were used in different ratio 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 analysis the mechanical properties of these different ration blend solution of PVA/PVP. About 10 ml of distilled water were mixed (10 weight in %) to achieved PVA/PVP weight was 1 gram. Then after mixer were continuously stirred in water bath to formed homogenized mixture. The prepared solution was then poured into the mould and kept in oven at 40 degrees to 45 degrees Celsius for 24 hours to prepared a microneedles patch. The active ingredients (Ondansetron HCl) were added to this PVA/PVP based solution which contained 5 weights by percentage of the PVA/PVP solution.

1. Evaluation parameter of transdermal patches

1.1. Thickness of the patches

The thickness can be measure of transdermal patch by travelling the dial gauge, screw gauge or micrometer of microscope at different points of the film and note the reading out.

1.2. Uniformity of weight

Weight variation determine by weighing individually 10 randomly choose patch and calculating the average weight. The weight of individual should not reflect from average weight.

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1.3. Flatness study

Transdermal patch must show a smooth surface and resist sticked against time. This can be demonstrated under flatness study. Flatness study, can be performed by one strip cut from the center of patch and another two from each side cut. The length of each strip measure and note down any variation in length by determination of percentage constriction. For easy calculation, zero percentage constriction consider is equivalent to 100 percent flatness.

Below formula to calculate 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 the steps of folding capacity of the transdermal patches, which frequently goes into extreme conditions of folding. The repeatedly folding process helps to determines the patch endurance value. This process continuous at the same place until patch break, and number of the time patch could be folded at the same place without breading also note down.

1.5. Percentage moisture absorption

The prepared transdermal patch weigh individually and demonstrated the variation in weight after moisture being taken. The patches weighed again after time interval until they show constant weight and this can be calculated by below formula.

% 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 which contained calcium chloride and temperature maintained at room temperature placed for during of 24 hours. The patches get continuously weighing at time intervals until constant weight achieved. The below 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 weighed accurately (about 100mg) then it dissolved in 100ml of solvent and provide continuous stirring for 24 hours in shaker incubator. The obtained solution is sonicated and did subsequent filtration, and the subjected solution is spectrophotometrically analysis by appropriate dilution.

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

The receptor compartment has a volume of 5 to 15 ml and effective surface area were of 5 cm^2. Franz diffusion cell was composed to evaluate transdermal patches. The rate of diffusion buffer was continuously stirred at speed of 600 rpm with the help of magnetic bar. The internal environment temperature was maintained by thermostat. The drug content sample was in time interval of 2 minutes were taken and was analyzed under UV-Vis Spectroscopy and elaborate in 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 gelatin sheet about of 1-5 cm^2 buffer solution at 600 rpm continuously rotating by 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 produced photographs showed uniform structure. In addition, Fourier transform infrared spectroscopy (FT-IR) determined the patch and confirmed the drug in prepared microneedle in desired amount.

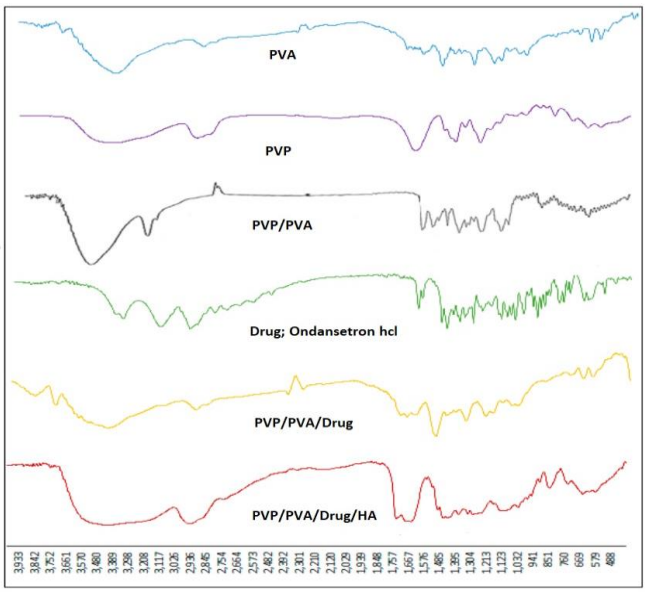

Figure No. 3: PVA, PVP, PVP/PVA, Drug, PVP/PVA/Drug and PVP/PVA/Drug/HA combinational stability and compatible study using FT-IR, graph present the ratio of absorption and standard peak to determine the slopes.

1.10. Differential scanning calorimetry

The measurement of the patch predicted the difference between views of PVA/PVP8 and PVA/PVP7 blend solution. This is because of the change in structure of polymer 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 affected, by formation of crystals in the molecular structure, and crystal structure was increased by increase in the ratio of PVA/PVP ratio with high degree of saponification.

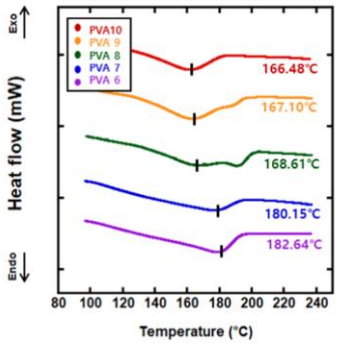


Figure No.4: DSC curved show of PVA/PVP based microneedle patches. The high degree and low degree of saponification affect the degree of degradation by formation of crystal in the structure. The melting temperature (T_m) was 166.48 degree Celsius for PVA10.

1.11. Measurement of mechanical properties of microneedle transdermal patch

The mechanical properties of microneedle loaded transdermal patches were determined by folding endurance, thickness evaluation, flatness study. Therefore, PVA/PVP9 and PVA/PVP10 patch showed high degree of stability and acceptable patch as per the study conducted and data generated.

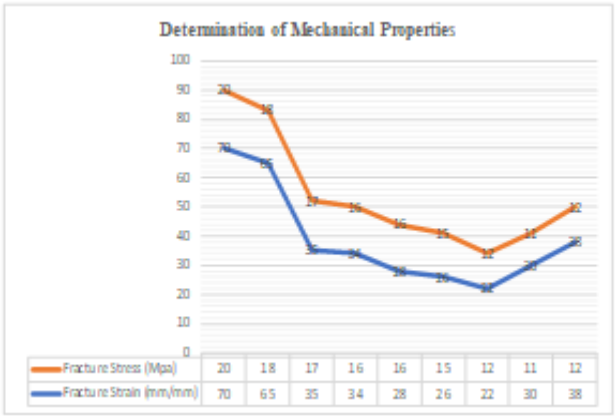


Figure No.5: Graph of the degradability behaviour showing the depending on the PVA/PVP ratio. Where PVA/PVP7, PVA/PVP8 and PVA/PVP9 were completely degraded, and showed 100% weight loss.

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 measurement of the in-vitro permeability of the polymeric microneedle conducted, to check the permeability experiment to see if they could easily penetrate the stratum corneum of the actual skin. The mechanical properties helped it out, the elasticity modulus of the human subjected skin comes about 0.013 MPa, and the gelatin sheet bed formed which produced the 7-weight percentage which confirmed the 0.013 MPa. The penetration experiment conducted on the 7-weight percentage of gelatin sheets bed and observed the resultant microneedle hole in presence of microscopic observations. The last result confirmed the 150 dots were formed with bending the microneedles tops had a high degree of penetration about 100% acceptability as per the observations. Therefore, this study also confirmed the microneedles had dissolve on suitable pH medium if this gelatin sheets bed were immersed in such fluid.

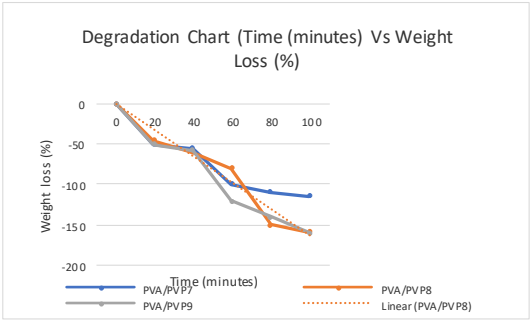
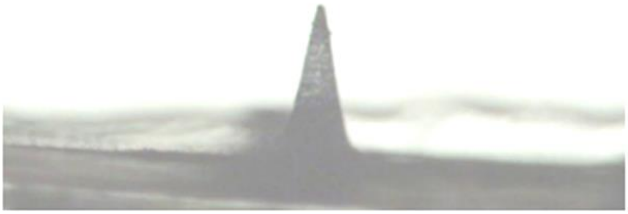


Figure No.6: This graph represents the tensile strength, indicating x-axis PVA/PVP0 to PVA/PVP10 and on Y-axis fracture stress and fracture strain.



(a)

(b)

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

IV. CONCLUSION

The prepared polymeric microneedle (PVA/PVP) high and low saponification methods showed the overall excellent morphological stability and confirmed the delivery of drug at controlled rate and SEM confirmed the well-formed microneedle edges. The microneedle based transdermal patches was formed at best with low and high degree of saponification ratio (PVA/PVP 9:1), and Ondansetron HCl well distributed in the patch.

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In additions, flexibility, determination of folding endurance, percentage of drug content, weight variation and in-vitro percentage drug content release characterized and analyzed the data. All the authors have reviewed and approved the final version of the manuscript.

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DECLARATION

All the authors herewith declared of accountability in this research article.

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Authors Contributions	All authors have equal participation in this article.

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AUTHORS PROFILE

Deepesh Lall has great academic and research record. He is pursuing his Ph. D from Bhagwant University, Ajmer, Rajasthan, India. He is author of more than 15 research and review papers published in reputed journals. He is also author of 7 books and 8 book chapter. He has one Indian Patent design grant and more than 5 patent publications. His area of interest is Formulation, designing and nutraceuticals. He has active professional membership in IPGA & Association of Pharmaceutical Teachers of India.

Dr. Neeraj Sharma has completed his bachelor and masters in pharmacy from Dr H. S. Gaur University Sagar, India. He has completed his Ph.D. from Nirma University, Ahmedabad, India. He got more than 30 publications to his credit. He has more than 6 books and 6 book chapters to his credit. He has got 3 awards in different national and international conferences. Currently, he has working with plant products for the use of cancer treatment.

Dr. (Mrs.) Shruti Rathore is a renowned Professor of Pharmaceutics. She has credited more than 18 years of teaching experienced UG/PG levels. She has bagged Gold Medalist during her academic career. She has duly published more than 20 research paper both National & International Journals. She has more than 6 books and books chapters. She awarded Outstanding Women Award in Health and Medical Sciences-2019 and Achieved Chhattisgarh Young Scientist Award-2012. She has active professional membership in IPGA & Association of Pharmaceutical Teachers of India.

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