IJPSR (2022), Volume 13, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 June 2021; received in revised form, 18 July 2021; accepted, 20 July 2021; published 01 March 2022

FORMULATION AND EVALUATION OF HEPARIN MICRONEEDLE TRANSDERMAL PATCH

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Keywords:

Low molecular weight heparin, Microneedle, Poly (vinyl alcohol), Poly (vinyl pyrrolidone), Transdermal drug delivery;

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ABSTRACT: There is an urgent need to replace the injection currently used for low molecular weight heparin (LMWH) multi-dose therapy with a non-invasive delivery device. In this study, unsaturated polyester resin and peroxide were used to fabricate microneedle mould by using 3M microneedle. Dissolving microneedle arrays transdermal patch was prepared by using 20 % w/v polymers of PVA and PVP (polyvinyl alcohol and polyvinyl pyrrolidone) and active drug 20 mg (IU) low molecular weight heparin (LMWH). The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy suggested the absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to weight variation, drug content, folding endurance, percentage of moisture content and water uptake. All prepared formulations indicated good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. The formulation prepared with PVP: PVA 1:2 showed best ex-vivo skin permeation through rat skin (Wistar rat) as compared to all other formulations. The release profile of the optimized formulation F2 (R^2 = 0.9933 for Higuchi) indicated that a diffusion mechanism governed the permeation of the drug from the patches. Microneedle transdermal patches were successfully prepared for LMWH, and their evaluation suggested it can have potential applications in the therapeutic arena, offering advantages in terms of effective non-invasive delivery with improved patient compliance and bioavailability.

INTRODUCTION: Transdermal Drug Delivery Systems (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches". When patches are applied to the skin, it delivers the drug through the skin at a controlled rate to the systemic circulation [1]. The delivery of drugs in a controlled manner through the skin is the most challenging field. Thus, the technique for the controlled release of drugs through TDDS is more efficient, appealing, and successful [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(3).1170-78

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(3).1170-78

The skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. The stratum corneum layer behaves like a major barrier as it allows only certain molecules like lipophilic and low molecular weight drugs to pass through it. A significant limitation to transdermal

drug delivery is the inability of large biomolecules to passively diffuse through the dermal layers of skin due to their unfavourable hydrophilicity and macro size. To overcome these drawbacks, various transdermal delivery systems have been investigated for improving drug permeation through the skin, like nano-carrier loaded topical creams, microneedles [3]. Microneedles, three-dimensional (3D) microstructures with micro-scale length, can pierce the stratum corneum and generate transient microchannels through which external molecules can passively diffuse into the skin. Microneedles could be designed in a manner that the penetration depth is superficial enough not to touch nerve receptors in the lower reticular dermis. This results in a painless drug administration. It is promising that this micro needle-based transdermal delivery approach will offer a self-management, patient-friendly and efficient administration route for drug delivery [4, 5].

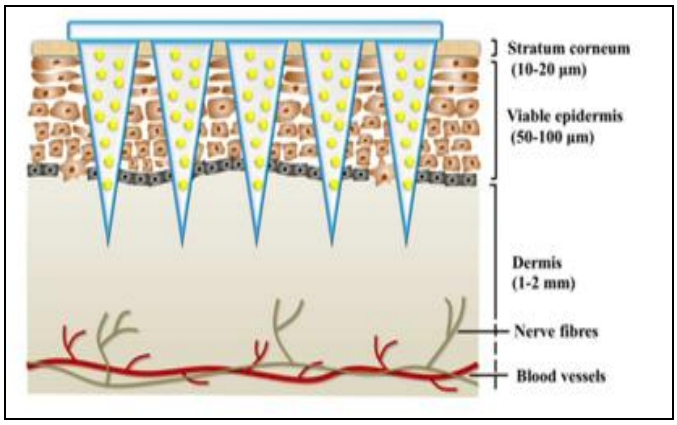

FIG. 1: TRANSDERMAL DRUG DELIVERY USING MICRO NEEDLE ARRAY

Classification of Microneedles [6]: Microneedles can be classified based on applications (medicine, pharmacy, and cosmetology), material (metal, polymer, glass, silicon, ceramic, hydrogel, and sugar), manufacturing technique (etching, injection molding, micromachining, micro-molding, and lithography electroforming replication), or design (hollow or solid). Microneedles should have the appropriate combination of mechanical strength, toughness and hardness to disrupt the SC without fracture and buckling failure. In addition, microneedle size must be small enough to ensure painlessness and minimal invasiveness. Diverse ways of releasing drugs from microneedles [7, 10]. The first is a novel technique called “poke with patch” where solid silicon or metal microneedles are used to create micro-channels and then apply a trans dermal patch to the skin's surface. The transport occurs by drug diffusion. The second is called “coat and poke”, where the needles are first coated with the drug and then inserted into the skin. After that, the drug is released. The third is “Poke and flow” for hollow microneedles delivering a drug like a micro-injection. Finally, “poke and release” is for dissolving microneedles fabricated from polymers or polysaccharides, releasing the drug during the dissolution of microneedles.

Applications of microneedles [11,13] include areas related to health, based on the numerous advantages they offer. Microneedles are used to administer several drugs (anti-cancer drugs, oligonucleotides, vaccines, proteins, DNA, and even nanoparticles) throughout the skin. Moreover, microneedles have many applications in the pharmacy, medicine, and cosmetology fields. Advantages of microneedle drug delivery include administration of large molecules, painless administration of the active pharmaceutical ingredient, avoidance of the first-pass metabolism, faster healing at the injection site than with a hypodermic needle, and no fear of the needle.

Heparin [14, 15] is the anticoagulant of choice when a rapid anticoagulant effect is required because its onset of action is immediate when administered by intravenous injection. Heparin, a sulfated polysaccharide, has been used as a clinical anticoagulant for over 90 years. Newer anticoagulants, introduced for certain specialized applications, have not significantly displaced heparin and newer heparin-based anticoagulants in most medical procedures. LMWHs are anticoagulants acting by inhibition of the final common pathway of the coagulation cascade. The coagulation cascade's goal is to fluid blood into a clot, thus preventing bleeding. The final common pathway is the conversion of fibrinogen into fibrin by the activity of thrombin. LMWH inhibits coagulation by activating antithrombin III. Its use is almost always limited to an in-hospital setting because it must be administered parenterally. When heparin is given in therapeutic doses, its anti-coagulant effect must be monitored and the dosage must be adjusted frequently. Heparin is not absorbed after oral administration and, therefore, must be given by injection. The clinical advantages

of low-molecular-weight heparin include predictability, dose-dependent plasma levels, a long half-life, and less bleeding for a given antithrombotic effect.

MATERIALS AND METHODS: Low molecular weight heparin was a gift sample from Sanofi Ltd., Unsaturated polyester resin and peroxides purchased from Chemzest Enterprises Ltd., Polyvinyl alcohol purchased from Sajan Pvt. Ltd., Polyvinyl pyrrolidone K-30 purchased from Prakash Chemicals Pvt. Ltd.,

Development of Standard Curve of Low Molecular Weight Heparin (LMWH): 50 mg of low molecular weight heparin was dissolved in 50 ml of phosphate buffer pH 7.4. Aliquots were withdrawn from the standard stock solution; appropriate dilutions were made with pH 7.4 phosphate buffer to obtain concentrations in the range 50 to 250 µg/ml. The spectrum was recorded, absorbance was measure at 232 nm and a calibration curve was plotted

Drug Excipients Compatibility Study by Fourier Transform Infra-Red Spectroscopy: The compatibility of drug and excipients is an important prerequisite before formulation. It is, therefore, necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of the product or have any other unwanted effects on the formulation. Drug and excipients compatibility was studied using FTIR spectral analysis. The IR spectrum of LMWH and physical mixtures of LMWH with polymer combinations of polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) (1:1) were recorded using Fourier Transform Infra-Red Spectroscopy (IRT Racer-100). The spectrum was scanned over a frequency range 4000-400 cm^{-1} and the resultant spectra were compared for any spectral changes.

Preparation of Microneedle Mould Cavities: Microneedle moulds [16] were prepared by using mixture of unsaturated polyester resin and peroxide and a 3M microneedle mould. The hardner and resin (1:100) material were taken and mixed well properly. It was then pierced with micron-sized 3 M microneedle tip to get array mould. After preparation of mould arrays, it was dried for 24 h at room temperature for formation of hard solid moulds.

Preparation of Microneedle Transdermal Patch [17]: The polymer solution was prepared as shown in **Table 1.** The required quantity of distilled water was taken, and the temperature of 80 to 900 °C was maintained in a magnetic stirrer. To this PVA was added, and stirring was continued. Once the PVA was dissolved, the required quantity of PVP was added. The solution was kept at room temperature. From the prepared polymer solution, 6 ml was taken and to this 20 mg of low molecular weight, heparin was added and mixed well. The mixture was then added dropwise into the mould cavities and kept overnight at room temperature for drying, as shown in **Fig. 2.** The drug-loaded microneedle patch was peeled from the mould.

TABLE 1: COMPOSITION OF TRANSDERMAL PATCH

Formulation	PVP:PVA ratio
F1	1:1
F2	1:2
F3	1:4
F4	1:6

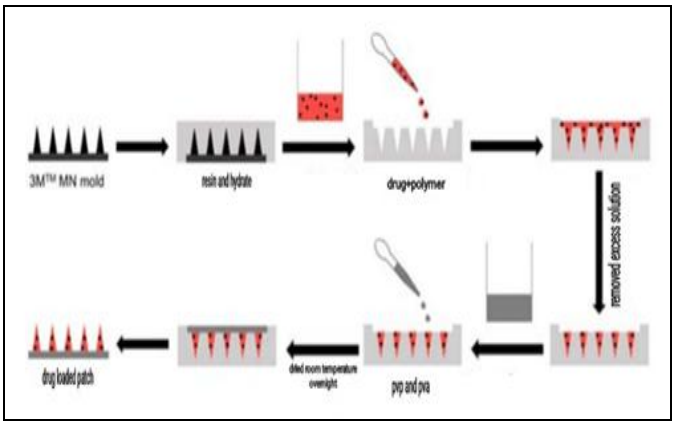

FIG. 2: FABRICATION PROCESS OF MICRO NEEDLE PATCH

Evaluation of the Microneedle Patch:

Physical Examination of Patches: All the formulated patches were evaluated visually for appearance in terms of brittleness, transparency, stickiness, flexibility, and homogeneous appearance.

Weight Uniformity: Weight uniformity was tested by selecting ten patches of area 1.5 cm^{-2} randomly out of each formulation and the average weight was determined. The individual patches were weighed

(Mettler Toledo, 3-MS-S/MS-L, Switzerland) and compared with the average weight.

Folding Endurance: The folding endurance of patches was evaluated by repeatedly folding the 1 × 1 cm film at the same point until it broke. The 1 × 1 cm of the film was taken from the center as well as from the edge of the patch. The test was conducted on three randomly selected patches from each formulation.

Percentage Moisture Content: The percentage moisture content was determined for each formulation. A film of 1 × 1 cm was taken from each patch. These films were weighed individually using a digital weight balance. These polymeric films were then placed in labeled Petri dishes and stored in a desiccator containing silica beads at 25 °C. The films were weighed until a constant weight was achieved. The percentage moisture content was calculated using the following formula.

Percentage moisture content = Initial weight - Final weight × 100 Initial weight

Percentage Moisture Uptake: The percentage moisture uptake was determined for each formulation. Transdermal film of 1 × 1 cm was cut from each patch. Films were weighed individually by using a digital weighing balance. These films were then placed in labeled Petri dishes and stored in a humidity chamber at 25 °C with 84% relative humidity (RH). The transdermal films were continuously weighed until a constant weight was achieved. The percentage moisture uptake was calculated using the following formula:

Percentage moisture uptake = Final weight - Initial weight × 100 Initial weight

Scanning Electron Microscopy: Surface morphology of microneedle patch was examined by Scanning Electron Microscopy (Quanta 200 F) for analysis of array formation and sharpness of the needle.

Drug Content: A specified area of patch 2 × 2 cm was dissolved in phosphate buffer pH 7.4 and shaken continuously for 1 h. Then the whole solution was ultrasonicated for 15 min. After filtration the drug was estimated spectro photometrically at wavelength of 232 using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan) and drug content was determined.

***In-Vitro* Drug Release:** *In-vtro* drug release studies [18] were performed by using a Franz diffusion cell with a receptor compartment capacity of 60 ml. The cellulose acetate membrane was used for the determination of the drug from the prepared transdermal patches. The cellulose acetate membrane having a pore size 0.45 µ was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads, and the temperature was maintained at 32 ± 0.5 °C, because the normal skin temperature of human is 32 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

***In-vitro* Permeation Study:** An *in-vitro* permeation study was carried out by using Franz diffusion cell. Full-thickness abdominal skin of Wistar rat weighing 200 to 250 g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5 °C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. A sample volume of 5 ml was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through Watman filter and were analyzed using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan).

Kinetic study: The release profile of all batches were fitted to various mathematical models such as Zero order, First order, Higuchi, Hixon, and Crowell to ascertain the kinetic of drug release.

RESULTS AND DISCUSSION

Calibration Curve in Heparin: The calibration curve of heparin in phosphate buffer 7.4 was derived from the concentration and corresponding absorbance. Values of linear regression analysis gave the equation for the line of best fit as y = 0.0022 × + 0.0012. Linearity was observed in the concentration range between 50 to 250 µg/ml. The r^2 value is 0.9991 and is represented graphically in **Fig. 3.**

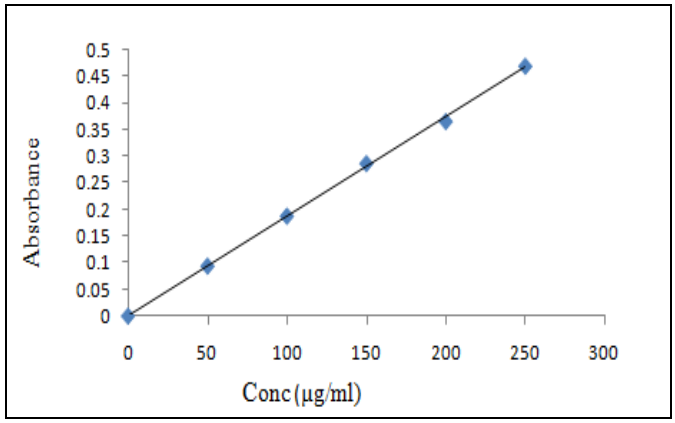

FIG. 3: CALIBRATION CURVE OF HEPARIN USING pH 7

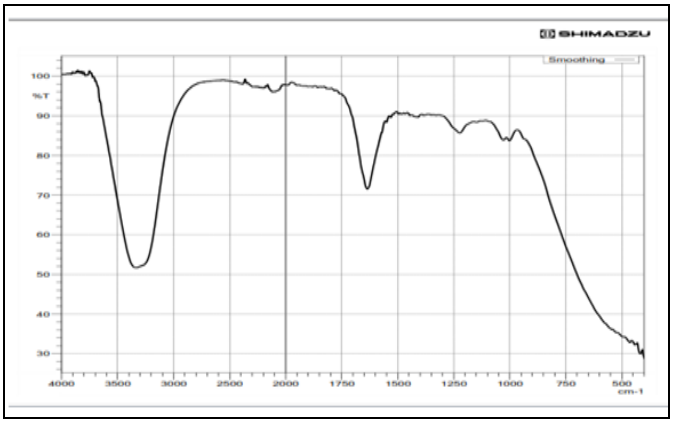

FIG. 4: FTIR SPECTRUM OF HEPARIN

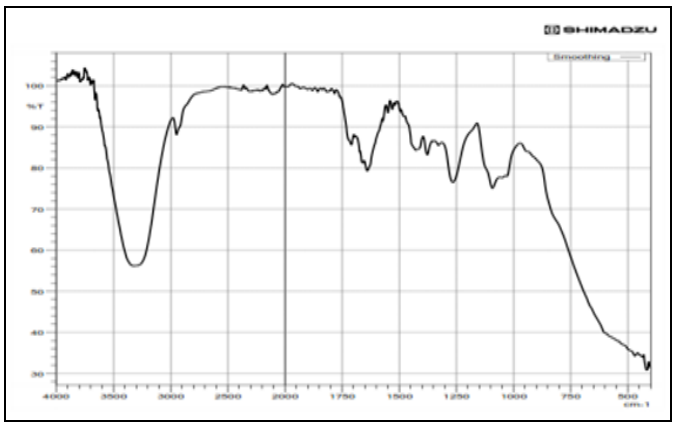

FIG. 5: FTIR SPECTRUM OF PVA AND LMWH

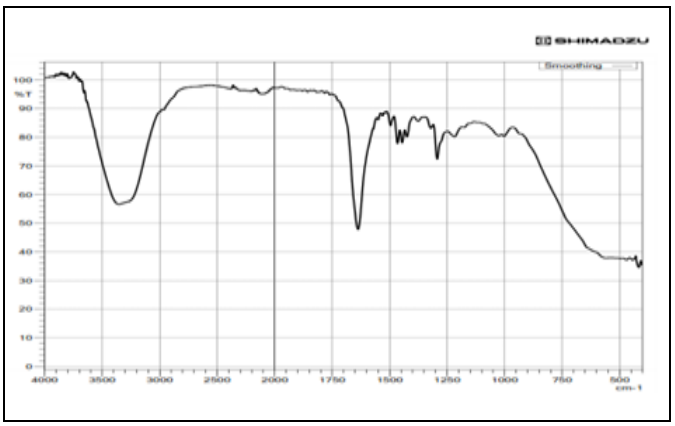

FIG. 6: FTIR SPECTRUM OF PVP AND LMWH

Drug Excipient Compatibility Study:

FTIR Spectroscopy: The spectrum of heparin[19,20] shows characteristic peaks of -OH- stretching band at 3,430 cm^{-1}, strong -COO- stretching band at 1,492 cm^{-1} strong -S=O- stretching band at 1,250 cm^{-1}, C=O stretching at 1,240 cm^{-1}. The spectrum of PVP K30 gives broad -OH stretching of carboxylic acid at 3,400-2,800 cm^{-1}, C=O stretching of carbonyl group at 1,699 $cm^{-1,}$ and C-OH asymmetric stretching band at 1,166 cm^{-1}. The spectrum of PVA displays distinct -CN- stretching at 1,283 cm^{-1}.The result shows the presence of all characteristic peaks compared with standard peaks. No significant change in the spectrum of drug was observed. This it can be concluded that the physical mixture of the drug Low molecular weight heparin does not show any major interactions with formulation excipients. The FTIR spectrums are shown in **Fig. 4, 6.** FTIR spectroscopy: The spectrum of heparin19,20 shows characteristic peaks of -OH- stretching band at 3,430 cm^{-1}, strong -COO- stretching band at 1,492 cm^{-1}, strong –S=O- stretching band at 1,250 cm^{-1}, C=O stretching at 1,240 cm^{-1}. The spectrum of PVP K30 gives broad -OH stretching of carboxylic acid at 3,400–2,800 cm^{-1}, C=O stretching of carbonyl group at 1,699 $cm^{-1,}$ and C-OH asymmetric stretching band at 1,166 cm^{-1}. The spectrum of PVA displays distinct -CN- stretching at 1,283 cm^{-1}. The result shows the presence of all characteristic peaks compared with

standard peaks. No significant change in the spectrum of the drug was observed. Thus, the physical mixture of the drug Low molecular weight heparin does not show any major interactions with formulation excipients. The FTIR spectrums are shown in **Fig. 4, 6.**

Evaluation Parameters of Transdermal Patch: The weight of the prepared transdermal patches for different formulations ranged from 322.5 ±3.56 to 386.1 ± 3.02 mg. The variation of weight uniformity was within acceptable limits **Table 2.** Folding endurance values varied more than 200 for all patches. The result was found satisfactory, indicating that the patches would not break and would maintain their integrity when used **Table 2.**

The moisture content of the formulations was in the range of 2.25-3.56 %. PVP is more hydrophilic than PVA and hence moisture content was more in F1 than in F4. The reason is that F1 has a higher proportion of hydrophilic polymer than other formulations.

The moisture uptake of all formulations was in the acceptable range of 4.03-6.45%. The formulations' lower moisture content helps them remain stable and become a completely dried and brittle film. Low moisture uptake protects the material from microbial contamination and bulkiness. The drug content of the formulations was found in the range of 97.6-99.2% **Table 2.**

TABLE 2: PHYSIOCHEMICAL EVALUATION OF TRANSDERMAL PATCHES

Formulation	Weight Variation (mg)	Folding Endurance	Moisture Content (%)	Moisture Upta (%)	Drug Content (%)
F1	322.5 ±3.56	> 200	3.56	6.45	98.7
F2	339.7 ±4.15	> 200	3.28	6.62	99.2
F3	367.4 ±4.6	> 200	2.75	4.56	97.9
F4	386.1 ±3.02	> 200	2.25	4.03	97.6

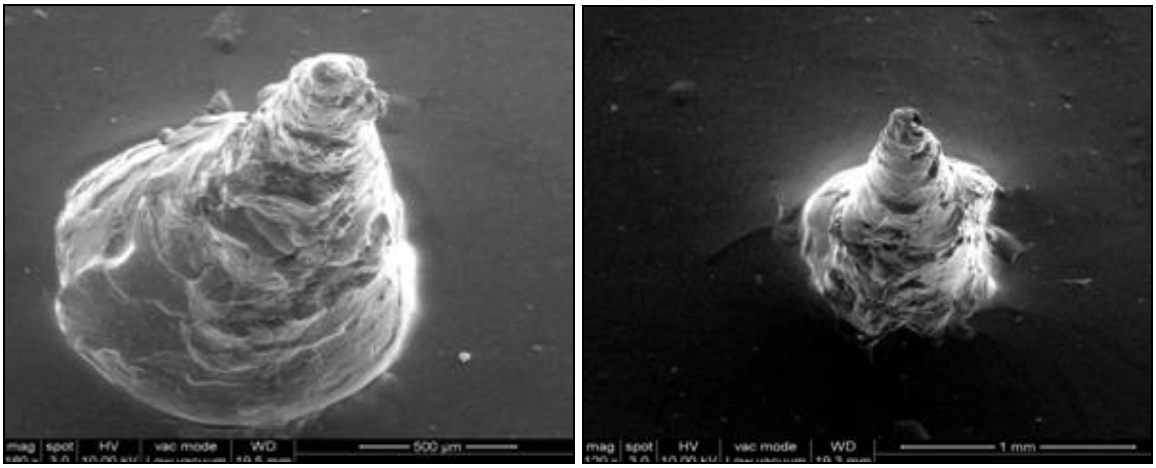

FIG. 7: SEM IMAGE OF MICRONEEDLE FOR ANALYSIS OF SHARPNESS OF NEEDLE

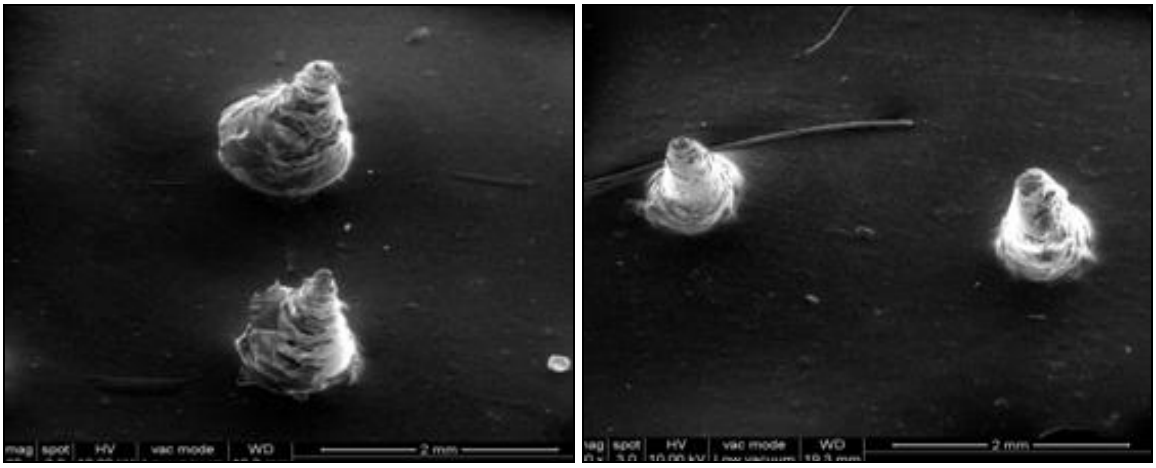

FIG. 8: SEM IMAGE FOR ANALYSIS OF DISTANCE BETWEEN TWO NEEDLES.

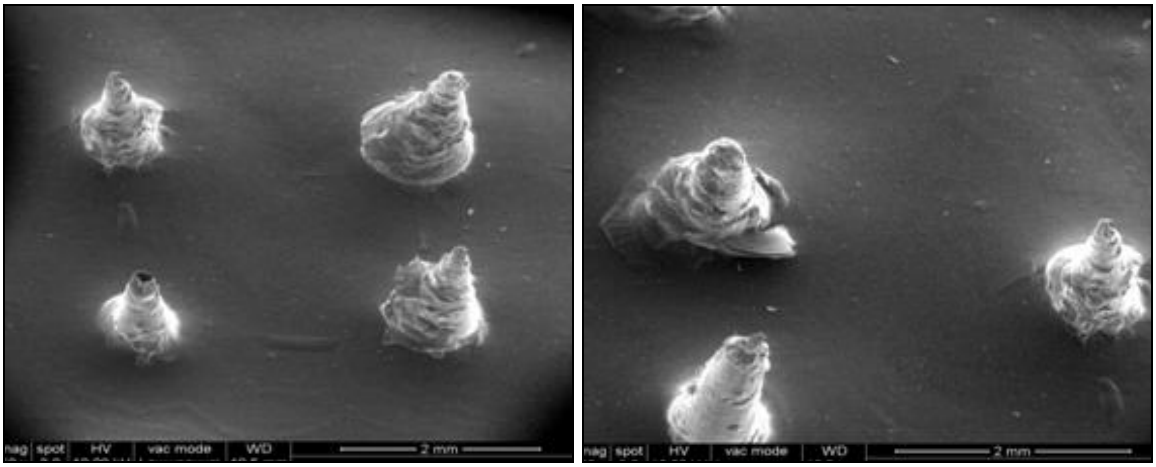

FIG. 9: SEM IMAGE FOR ANALYSIS OF MICRONEEDLE ARRAY AND TIP SHARPNESS.

Scanning Electron Microscopy: The surface morphology of the microneedle patch was examined by scanning electron microscopy and the figures are shown in **Fig. 7, 9.** The scanning electron microscopy (SEM) was used to study microneedles' morphology and dimension and generate SEM images to visualize the freshly fabricated microneedle. The result shows the formation of the array and sharpness of the needle and the dimension of the prepared transdermal microneedle patch. The array of the needle in that, one needle tip is broken due to peeling force from the microneedle mold cavity. The needle has the mechanical strength to breach the stratum corneum and deliver the drug directly into the systemic circulation.

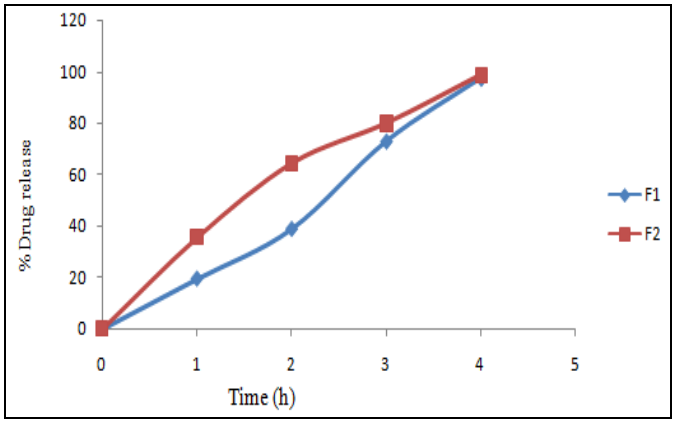

FIG. 10: DRUG RELEASE PROFILE FORMULATION F1 AND F2

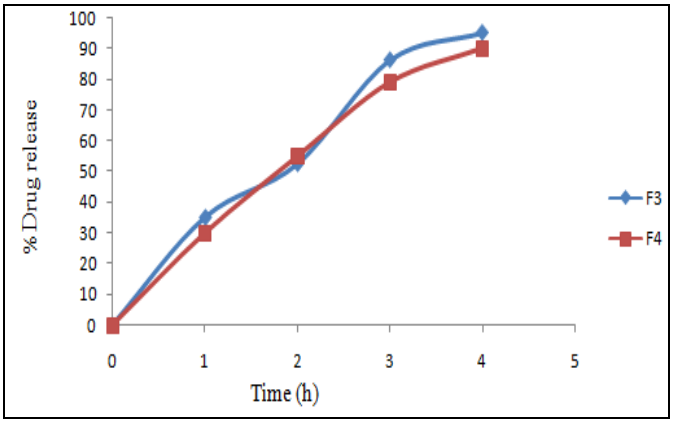

FIG. 11: DRUG RELEASE PROFILE FORMULATION F3 AND F4

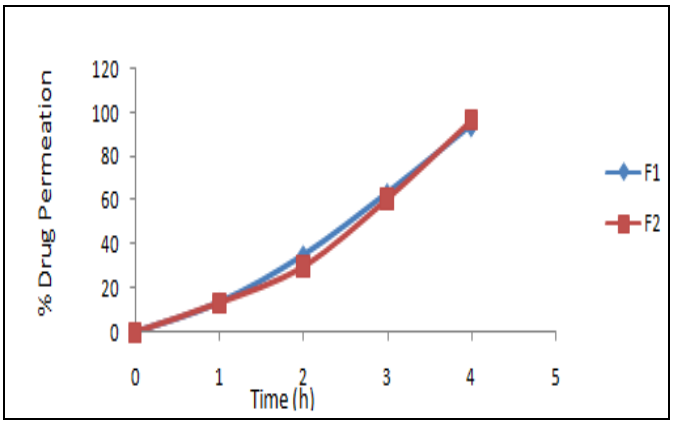

FIG. 12: DRUG PERMEATION GRAPH OF FORMULATION F1 AND F2

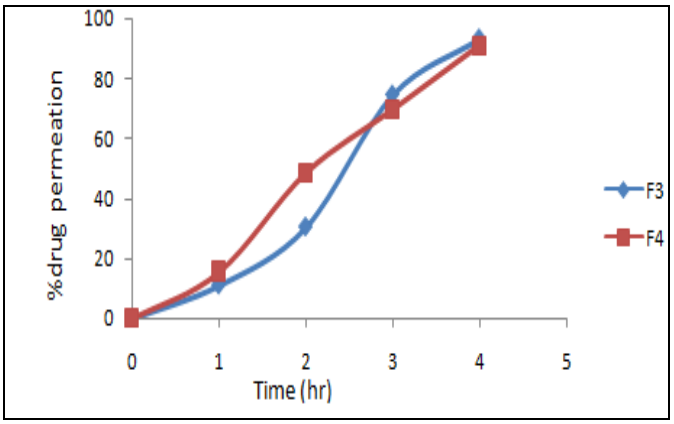

FIG. 13: DRUG PERMEATION GRAPH FOR FORMULATION F3 AND F4

***In-vitro* Release Studies:** All the formulation shows good release (*i.e.* >90%) and shown in **Fig. 10, 11.** For formulation F1 and F2, drug release is found in the range of 97.5% to 98.08%. On the other hand, in formulation F3 and F4, drug release is found in the range of 90.13% to 95.12%. It can be concluded that an increase in PVA content delays the drug release from the transdermal patch.

***Ex-vivo* Permeation Studies:** For formulation F1 and F2, the cumulative percentage of drug diffusion is found in the range of 94.1% to 96.32%. Whereas formulations F3 and F4, drug release is found in the range of 93.17% to 91.02%. From the data obtained from the diffusion study, a higher level of PVA retards the release from trans dermal patches **Fig. 12, 13.**

Kinetics Profile: From the *in-vitro* release data of F1 to F4, formulations fitted well into the Zero-order equation with correlation coefficient values were between 0.9737 and 0.9864. Hixson Crowell and Higuchi's model were applied to test the release mechanism. R2 values are higher for the Higuchi model; hence drug release follows diffusion rate-controlled mechanism **Table 3.**

TABLE 3: KINETICS FOR DRUG RELEASE

Kinetic Profile	F1	F2	F3	F4
Zero order	0.9855	0.9818	0.9864	0.9737
First order	0.9370	0.9254	0.9510	0.9213
Higuchi	0.9891	0.9933	0.9702	0.9916
Hixson Crowell	0.9803	0.9580	0.9529	0.9525

Summary and Conclusion: The current use of anticoagulants is extensive, and it was estimated that this multibillion-dollar heparin market generated sales of high proportion. Unfortunately, the need for repetitive parenteral administration is still a major disadvantage. Poor oral absorption is due to ionic repulsion from negatively charged mucus and epithelial tissue, destruction by gastrointestinal bacteria, and lesser extent by the acidic condition of the stomach. Trans-dermal drug delivery is one potential solution to this problem. Skin is the largest organ of the human body, offers a painless and compliant interface for systemic drug administration. It provides sustained and controlled delivery over long periods with the feasibility of on-demand termination and an attractive alternative to injections. It is evident that because of its large molecular weight, negative charge and hydrophilic nature, passive transdermal delivery may not be feasible. Soluble micro needles which dissolve in the skin have been used in the present study. The LMWH transdermal delivery via microneedles can replace the parenteral dosage forms for the treatment of venous thromboembolism, pulmonary embolism, and cardiovascular events.

ACKNOWLEDGEMENT: The authors are thankful to the management of C. L. Baid Metha College of Pharmacy for providing facilities to carry out the work.

CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest.

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How to cite this article:
Bhuvaneshwaran A and Rathnam G: Formulation and evaluation of heparin microneedle transdermal patch. Int J Pharm Sci & Res 2022; 13(3): 1170-78. doi: 10.13040/IJPSR.0975-8232.13(3).1170-78.