International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Design, Development and Characterization of Transdermal Microneedle For Treatment of Cancer

***Tushar Kanti*[*1], *Shivangni Rathore*[2], *Revathi A Gupta*[3]**

1.Student, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)
2. Assist, Professor, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)
3. Principal, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)
* Corresponding Tushar Kanti
E-mail address:rs5880840@gmail.com

A B S T R A C T

The primary objective of the research is to create microneedles filled with tamoxifen for transdermal delivery of breast cancer treatment.Eudragit Polymeric Microneedles were created to accomplish the goal of maintaining therapeutic action while lowering the dosage and frequency of tamoxifen administration.Different drug and polymer concentrations were utilized to improve the tamoxifen-loaded transdermal microneedle. Transdermal microneedles loaded with tamoxifen were characterised in vitro.The medication has a poor penetration through the skin. To improve transdermal medication delivery, a number of tactics have been employed to get beyond the stratum corneum's superior barrier qualities. Using microneedles to improve percutaneous absorption is one strategy.The negative effects of oral administration of Tamoxifen, including thrombosis, hepatic first-pass metabolism, and endometrial hyperplasia, the current effort aims to create a polymeric microneedle transdermal patch drug delivery method for breast cancer.Transdermal microneedles create micron sized pores in the skin to enhance delivery of the drug across the skin. Micron sized needles are ideal for patient adherence as they do not stimulate nerves that are associated with pain. The use of transdermal patches delivered by microneedles to treat breast cancer has improved medication delivery through this channel and opened the door for more drug penetration in recent years.

Keywords:Microneedle, Trans Dermal Drug Delivery System, quality by design, Tamoxifen, Cancer, Polymeric Microneedle.

1. Introduction

Injection with a painful hypodermic needle is the most frequent alternative when oral medication delivery is not practical because to inadequate drug absorption or enzymatic breakdown in the liver or gastrointestinal system. Drug administration through the skin with a patch is a more patient-friendly method that has the potential for gradual, controlled release. However, because of the strong barrier that the outer stratum corneum layer of the skin imposes, most medications cannot penetrate the skin at therapeutic rates, greatly restricting the use of transdermal distribution.Interest in the field has grown quickly since the first transdermal drug delivery studies were conducted in 1998. The drug delivery industry is developing microneedles for pharmaceutical applications, while the microfabrication community is developing innovative needle fabrication technologies. The idea of microneedles was first put out in the 1970s, but it wasn't empirically proven until the 1990s, when the microelectronics sector.

1.1 Transdermal Drug Delivery System

Transdermal(1) Drug Delivery Systems (TDDS) are classified as discrete, self-contained dosage forms, sometimes referred to as "patches." Deliver the medication to the systemic circulation through the skin at a regulated pace when patches are placed. Dosage forms called TDDS are made to apply a therapeutically appropriate quantity of medication to a patient's skin. Drugs with short biological half-lives can be continuously injected by transdermal delivery, which also prevents pulsed entrance into the systemic circulation, which frequently results in unwanted side effects. Limitations of hepatic first pass metabolism, improvement of therapeutic effectiveness, and preservation of a constant drug plasma level are some significant benefits of transdermal drug administration. The development of TDDS is a multidisciplinary endeavour that includes basic feasibility studies, the selection of the drug molecule, the demonstration of adequate drug flux in an ex vivo and in vivo model, and the creation of a drug delivery system that satisfies all the exacting requirements unique to the patient (comfort and cosmetic) and the drug molecule (physicochemical, stability factors).

1.2 Process for Increasing Transdermal Drug Delivery System

Penetration in skin can be increase by following methods

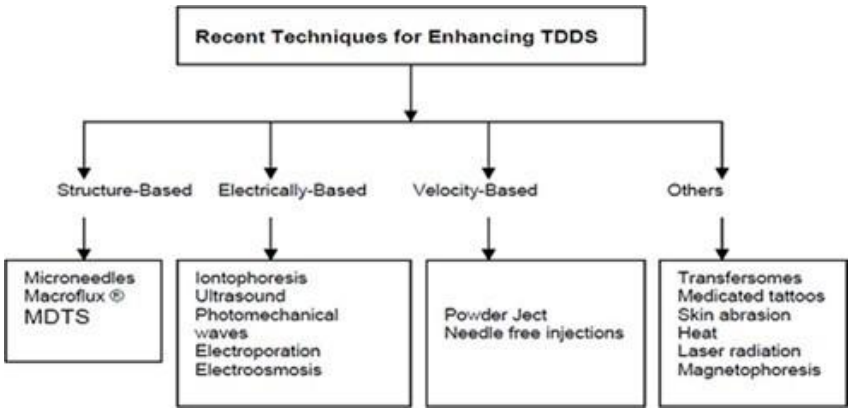

Fig. 1 Technique for Increasing TDDS

1.3 Use of Microneedles as TDDS

The main driving force behind microneedles is their potential to deliver molecules into the skin in a less invasive manner. This objective has led to the employment of a variety of particular techniques for transdermal distribution of microneedles. The majority of research has been on using metal or silicon solid microneedles to create tiny holes in the skin. The "poke with patch" method applies a transdermal patch (or some prototype) to the skin's surface after creating holes using microneedles. If an electric field is provided, transport may happen by iontophoresis or diffusion. Another method is "coat and poke," in which the needles are first injected into the skin after being coated with medication.

1.4 Mechanism of Microneedles incretion in skin

The majority of research on microneedles has focused on manufacturing processes and evaluated their capacity for medication delivery. Despite being crucial to real-world applications, the mechanics of microneedle insertion have gotten very little study. The only microneedles that can penetrate skin are those that have the necessary shape and characteristics. As previously stated, some needle designs benefit from high-velocity insertion, while others merely need manual insertion. Needles may shatter or bend before insertion if the force needed for insertion is too great.
By measuring the force needed for insertion, the force needed for fracture, and their ratio (referred to as the margin of safety) as a function of needle shape and physical characteristics, Davis et al. have specifically addressed these problems. Individual hollow metal microneedles with tip radii ranging from 30 to 80 Am, wall thicknesses of 5 Am to solid tips (corresponding to 58 Am wall thickness), and a constant length of 500 Am were employed in this investigation (Fig. 1).s

2. Material and Methods

2.1 Apparatus and chemicals: Tamoxifen by M/s Cipla Pithampur Indore, Ergot S100 by Dr. Reddy's Laboratories, Hyderabad, , Ethyl Acetate by Bafna Pharmaceutical Ltd., Sacnning electron microscopy by Evo 15, FTIR by Shimadzu

2.2 Methods:

Preparation of Microneedle Mold Cavities Melting beeswax is used to create microneedle moulds, which are then poured into a circular container to solidify. The array mould was then obtained by puncturing it with a micron-sized needle tip. Mould arrays should be prepared and then allowed to dry at room temperature for a day in order to make firm, solid moulds.

Preparation of Drug Loaded Polymeric Microneedle Patch

Polymeric microneedle arrays were fabricated out of eudragit S100 using the micromolding technique.

The detailed procedure was given in the flow chart below,

Tamoxifen + Eudragit in ethyl acetate and kept for stirring

↓

Further glycerine solution is added into it

↓

Centrifugation at 3500 rpm

↓

Product concentrate poured into the micro needle mould

↓

Drying is achieved under reduced pressure using vacuum drier

↓

Solvent Evaporation

↓

The patch is removed from the mould and stored in desiccator

3. Experimental work

3.1 Preformulation Studies

The study of a medical ingredient's physical and chemical properties, both alone and in conjunction with excipients, is known as preformulation. Preformulation studies aim to identify the physicochemical properties and excipients that may affect the manufacturing process, formulation design, and pharmacokinetic-biopharmaceutical aspects of the final product.

3.2 Determination of Solubility

Tamoxifen solubility studies were conducted to determine the impact of pH. Ten milligrammes of the medication were taken in separate test tubes, and then one millilitre of solvent was added. The solvent was added continuously until the sample was fully dissolved. The solvent needed to solubilise the medication powder was used to record solubility.

3.3 Design of Experiment (DOE)

The experimental design was a three-factor, three-level Box-Behnken design. The concentrations of the drug, ethyl acetate, and eudragit S100 were the independent variables under investigation. Drug penetration and microneedle thickness were regarded as dependent variables. There were seventeen experiments in all. The experimental design program (Design Expert® 12) generated a three-factor, three-level Box-Behnken Design. Box-Behnken design (BBD), one of the many response surface methodology (RSM) approaches, is a good way to find out how formulation components and variables (independent factors) affect the response variables (dependent factors). The three-factor, three-level statistical screening method known as BBD was used in our investigation to assess the dependent variables derived from the generated microneedle responses.

4. Result and discussion

4.1 Preformulation Study

4.1.1 Description

Tamoxifen iswhite colour bitter odour less powder.

4.1.2 Result of Solubility

Insoluble in water, Tamoxifen is sparingly soluble in ethanol and soluble in methanol.

4.2 Result of Melting Point

The medicine's melting point was determined to be comparable to the stated value, confirming that the drug samples that were received met the stated specifications. The melting point of a particular pharmacological ingredient will vary depending on any impurities that may be present. The melting point is found 97^0cThe aforementioned test revealed that the sample medication satisfies the Tamoxifen standard test.

4.3UV Spectroscopy

The standard calibration curve of Tamoxifen was studied with pH.7.4 buffers. The λ-max was found at 296 nm. The linearity was found y= 0.004x - 0.0398 and R2 value were shown 0.997 respectively.

Standard Calibration Curve:

Table: 1 Calibration curve of Tamoxifen at pH 7.4

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1.	20	0.042
2.	30	0.081
3.	40	0.115
4.	50	0.161
5.	60	0.202

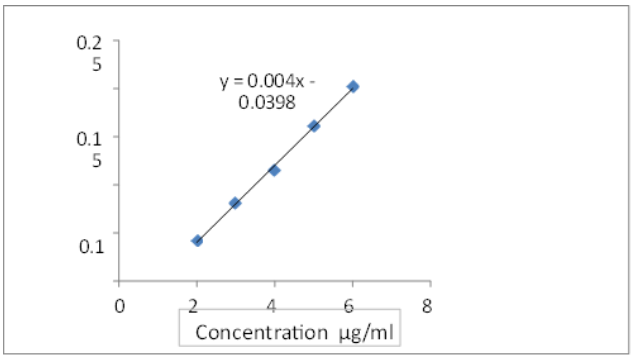

Fig 2. Standard calibration curve of Tamoxifen

4.3 FT-IR Spectroscopy

The potential drug-polymer interaction was investigated using FTIR spectroscopy. The components Eudragit S100 and Tamoxifen were present examined with an infrared spectrophotometer that uses the Fourier transform (FTIR). The majority of the microneedles are derived from the FTIR spectra of Eudragit S100 and Tamoxifen. The peak at 3425 cm−1 showed that the hydroxyl groups were stretching, followed by the alkane's stretching CH at 2916 cm−1, the alcohol's OH bending group at 1369 cm−1, and the secondary alcohol's C-O group at 1093 cm−1.

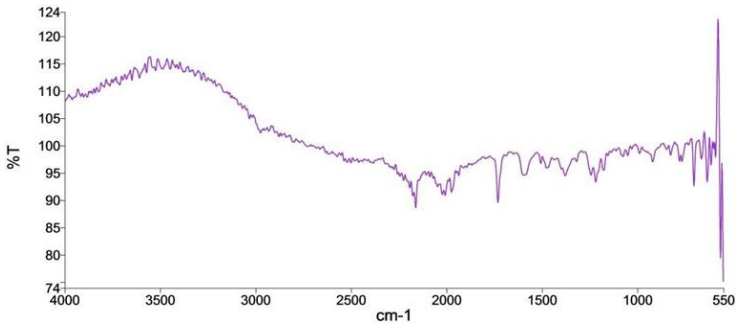

Fig 3. FT-IR of Tamoxifen Citrate

4.4 Drug - Excipients Compatibility Study

FT-IR Spectroscopy

The spectra showed peaks at 3324 cm−1 of NH amine group, 1726 cm−1 of stretching C] O group, 1227 cm−1 of stretching CO (strong alkyl aryl ether) group, and 1110–1148 cm−1 of stretching CN amine group when Eudragit was used to confirm the presence of Tamoxifen. Tamoxifen's FTIR spectrum was displayed. When compared to standard peaks, the result demonstrated the presence of all typical peaks. There was no discernible change in the drug's spectrum. This suggested that the medication and polymer did not interact strongly.

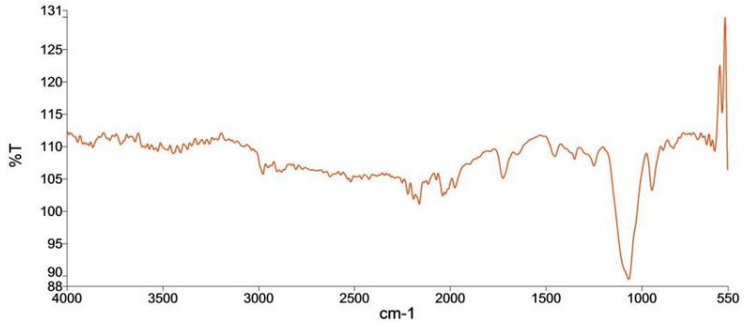

Figure 4 FT-IR Spectra of Polymeric Tamoxifen Microneedle

Table 2: Optimization table for tamoxifen polymeric microneedle

	Factor1	Factor2	Factor3	Response1	Response 2
Formulations	**A:Eudragit Concen-tration**	**B:Drug Concen-tration**	**C:Ethyl Acetate**	**Thickness**	**Drug Perme-ation**
	%	**%**	**%**	**Micrometer**	**%**
1	1.5	0.75	10	360	91
2	4	0.75	10	780	43
3	1.5	1	12.5	380	95
4	2.75	0.75	12.5	650	89
5	2.75	0.75	12.5	650	89
6	2.75	1	15	487	73
7	1.5	0.75	15	360	90
8	2.75	0.75	12.5	689	89
9	2.75	0.5	15	574	68
10	1.5	0.5	12.5	278	77
11	4	0.5	12.5	659	55
12	4	1	12.5	785	35
13	2.75	0.5	10	356	72
14	4	0.75	15	487	73
15	2.75	0.75	12.5	689	89
16	2.75	0.75	12.5	689	89
17	2.75	1	10	705	64

4.5 Characterization of Microneedle

4.5.1 ANOVA

The responses were obtained and adjusted and predicted R2 was determined based on Central composite Design and ANOVA was calculated. The P values, precision, % CV, adjusted and predicted R2 are given in Table.3

Responses	Adjusted R^2	Predicted R^2	ModelP Value	Adequate precision	%CV
Thickness	**0.8970**	**0.3387**	**<0.0001**	**11.74**	**2.40**
Drugpermeation	**0.9512**	**0.6586**	**<0.0001**	**19.60**	**5.22**

4.5.2 Optimization of Formulation Factor:

A Numerical optimization technique based on the desirability was done using the Box Behnken design to determine the optimized formulation. The goal of optimization study was to maximize the Drug permeation and Thickness of the microneedle to achieve a sustained drug release for 12 hr.

Table 4: Optimized formulation based on Behnken model

Factor	EudragitS100 %	Ethylacetate (%)	Drug concentration (%)	Desirability
Optimum formulation	1.503	10.04	0.71	1

4.5.3 Predicted And Observed Values:

The experimental and the predicted values along with the percentage error of the responses were obtained and were tabulated.

Table 5: Experimental and predicted values for drug permeation and thickness.

PointPrediction	Thickness (µm)	Drugpermeation (%)
Predicted	275.1	95.19
Observed	292.4	92.68
%error	6.28	2.63

% error = (observed value-predicted value)/predicted value x 100

The optimum levels of formulation factors for an optimized formulation based on the Central composite design were 1.503% of Eudragit, 10.04% of Ethyl acetate and 0.71% of drug. The optimized formulation predicts 275.1µm of Thickness and 95.19% drug permeation.

4.5.4 Scanning Electron Microscopy Analysis

According to the SEM photomicrograph of the optimised formulation microneedle structure displayed in the corresponding figures, the microneedle had a sharp edge with a height of 500 to 1000 microns.A network of tiny fractures and fissures covers the outside surfaces; these may have developed as a result of ethyl acetate molecules migrating during the drying proceses

4.5.5 Characterization Optimized Formulation:

The characterized value of optimized formulation is given in the table 6

Optimized formulation	Thickness (µm)	Drugcontent (%)	Permeation (%)
MN Opt	296±8.5	95.6	92.4

4.5.6 Thickness of The Microneedle

Thickness of needle projections is taken at 3 different ranges from the optimized formulation and the standard deviation was noted. The thickness measured are 306.4µm, 290.7µm, 295.2µm and mean with standard deviation is 296±8.5µm.

4.5.7 Drug Content

The optimized formulation drug content was found to be 95.6 %. The observed value enables to ensure that the strength of microneedle formulation remains within the desired limits.

4.5.8 Permeation

Table 7: Invitro Drug permeability comparison with free drug

Timeinterval (hours)	Percentagedrugpermeation	
	Conventional dosage form	Microneedles
1	7.63	14.67
2	13.66	21.33
3	18.41	34.44
4	22.79	41.2
5	27.36	57.9
6	36.41	67.68
7	42.9	69.05
8	48.6	75.3
9	52.94	82.48
10	57.1	86.16
11	60.91	89.96
12	64.57	92.68

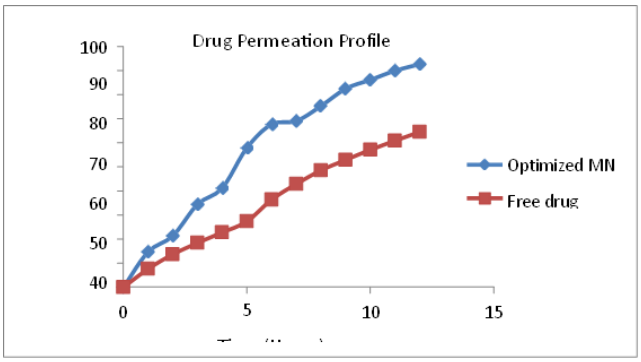

Figure5: Comparison drug permeation profile

Drug permeation of optimized formulation was calculated with the help of Franz diffusion apparatus and noted. The amount of drug permeation was 92.68 %. From the obtained values, the optimized microneedle formulation shows increased drug permeability compared to the conventional dosage form. As it permeates across stratum corneum with the help of microneedles formulation and showed enhanced drug permeability. Further, ethyl acetate also improves the drug solubility and plays a vital role in drug permeability.

4.6 Invitro Permeation Kinetics of Optimized Formulation

In vitro drug permeation studies data and diagram was shown in table and Fig. The result from invitro drug permeation shows that the permeation of drug from patches in optimized formulation is 92.68% in 12 hrs**.**

Table 8: In vitro permeation kinetics profile

KINETICPROFILE	R^2
Zeroorderkinetics release	0.9427
Firstorderrelease	0.988
Higuchi	0.983
Korsmeyerpeppas	0.98
Hixson crowell	0.887

From the in vitro release data, zero order, first order, higuchi type release kinetics of drug permeation were calculated. Korsemeyer-peppas semi empirical models were also employed to find out mechanism of release.A number of release kinetic models, including the zero order, first order, Higuchi, Korsemeyer Peppas, and Hixson Crowell models in the Table, were used to analyse the data from in vitro release investigations in order to clarify the process of drug release from the polymeric microneedle. To examine their impact on drug release, the regression coefficient and slope (rate) were compared across all formulations. The drug release from the microneedles follows the Higuchi model instead of the zero order or first order equations, as shown by the greater correlation coefficient (r2 < 0.983). These findings suggest that the polymeric microneedle's drug release was diffusion regulated. The three primary rate-controlling processes used in controlled release formulations are diffusion, swelling, and erosion. Fickian diffusion provides the greatest description of the drug release from the polymeric system, which occurs mostly through erosion. However, when it comes to formulations that contain swelling polymers, activities other than diffusion—like the relaxing of polymer chains and the imbibition of water, which causes polymers to erode—are crucial in determining the mechanisms behind drug release.

5. Conclusion

In order to boost tamoxifen's therapeutic effectiveness and target the oestrogenic receptors of breast cancer, the current study intends to create and optimise a tamoxifen polymeric microneedle transdermal patch. To improve the solubility of drug particles, ethyl acetate was used as a solvent and Eudragit S100 as a retarding polymer in the preparation of the polymeric microneedle.The Box Behnken design with five centre points optimises the formulation using the Response surface approach. Eudragit S100 and ethyl acetate concentrations were varied to create a polymeric microneedle transdermal patch containing tamoxifen that responded to the microneedle's thickness and drug penetration.Eudragit S100, ethyl acetate, and drug concentrations were optimised with values of 1.503%, 10.04%, and 0.71%, respectively, based on the desirability function (1.00).According to the drug release kinetics results, the drug release fits all of the models, however Higuchi and Peppa's model fits the data the best, with a n value of 0.7308, suggesting that the drug release follows (Non-Fickian) Anomalous transport. Diffusion and erosion are followed by the drug release mechanism. By avoiding the stratum corneum barrier, microneedles improve medication penetration and minimise toxicity by selectively targeting the oestrogen receptor region

Acknowledgements

We are thankful to authorities of Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore for allowing us to carry out the study. We are also thankful to participants for their valuable support to accomplish this study.

References

1. Bhatnagar S, Dave K, Venuganti VVK. Microneedles in the clinic. J Control Release. 2017; 260:164–82.
2. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547–68
3. Bediz B, Korkmaz E, Khilwani R, Donahue C, Erdos G, FaloLD Jr, et al. Dissolvable microneedle arrays for intradermal delivery of biologics: fabrication and application. Pharm Res.2014;31(1):117–35.
4. Indermun S, Luttge R, Choonara YE, Kumar P, du Toit LC,Modi G, et al. Current advances in the fabrication of microneedles for transdermal delivery. J Control Release.2014;185:130–8.
5. Ita K. Transdermal delivery of drugs with microneedles—potential and challenges. Pharmaceutics.2015;7(3):90 – 105.
6. Tuan-Mahmood TM, McCrudden MT, Torrisi BMs, McAlister E,Garland MJ, Singh TR, et al. Microneedles for intradermal and transdermal drug delivery. Eur J Pharm Sci. 2013;50(5):623–37.

7. Bhatnagar S, Chawla SR, Kulkarni OP, Venuganti VVK. Zeinmicroneedles for transcutaneous vaccine delivery: fabrication, characterization, and in vivo evaluation using ovalbumin as the model antigen. ACS Omega. 2017;2(4):1321–32.
8. Donnelly RF, Majithiya R, Singh TR, Morrow DI, Garland MJ,Demir YK, et al. Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique. Pharm Res. 2011;28(1):41–57.
9. Lee JW, Han M-R, Park J-H. Polymer micro needles for transdermal drug delivery. J Drug Target. 2013;21(3):211–23.
10. Park JH, Allen MG, Prausnitz MR. Polymer microneedles for controlled- release drug delivery. Pharm Res. 2006;23(5):1008–19.
11. Zhu Z, Luo H, Lu W, Luan H, Wu Y, Luo J, et al. Rapidly dissolvable microneedle patches for transdermal delivery ofexenatide. Pharm Res. 2014;31(12):3348–60.