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Formulation Design, Optimization and Characterization of Herbal Bioactive Loaded Transdermal Patch: The State of The Art

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ABSTRACT

Transdermal Drug Delivery is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The present research was aimed to formulate transdermal patch incorporating herbal bioactive *azadirachta indica*. Transdermal patch was formulated by solvent casting method and was evaluated for organoleptic distinctiveness, stratification, weight consistency, flopping fortitude, dampness content, drug content and exterior morphology by scanning electron microscopy (SEM). *in-vitro* release kinetics was performed by utilizing franz diffusion cell with the help of exterior membrane of egg which acted as barricade membrane. The patch was dissolute in Phosphate buffer pH 7.4 with a temperature variance of $37 \pm 1^\circ\text{C}$. A time dependent increase in drug release was obtained throughout the in vitro permeation study of the prepared transdermal patch. The percentage of cumulative drug release was found to be 74.89% in 24 hours. Results of SEM depicted the presence of aggregation in the formulation, which may be attributed to precipitation. Overall, present study assures a novel approach in execution of transdermal delivery technology in the field of herbals.

Keywords: Neem; Drug content; Transdermal drug delivery system; Transdermal Patch; Skin; Herbal bioactive

INTRODUCTION

The Transdermal Drug Delivery System (TDDS) is a novel technique for delivery of therapeutic agent across the blood stream through the exterior surface of the skin.^[1] The prime motive behind formulation of these novel drug delivery systems is to minimize retention and metabolism of drug in the skin and to accelerate the fluctuation through skin parallelly. It also confirms that therapeutic molecules are transported, with preference towards a precise rate into the bloodstream.^[2,3] Unlike conventional dosage forms, certain medications are more convenient to deliver, using this technique, into the systemic circulation. As per the survey reports, an approximate profits of market consists (2009-US\$ 6 billion) for TDDS products, which is mutual between Japan (8%), Europe (33%) and USA (54%) probable to attain an astounding figure of US\$ 11 billion in 2015 and much more in 2020.^[4]

A transdermal patch is a unique delivery system consisting adhesives which on placement at the exterior surface of the skin allows traversing of dose (unit) through the skin into the systemic circulation at a programmed rate to reach at site of action.^[5,6] In recent market trends, patches based on semi permeable membrane system are available as a dosing product. Transdermal drug delivery systems (TDDS), also known as “Transdermal patches” or “Skin patches” (Figure 1) are so designed as deliver a therapeutically effective quantity of drug into the patient’s skin and in the bloodstream.^[7-10]

There are several advantages of the TDDS like avoidance of gastrointestinal drug absorption difficulty, avoidance of the hepatic-first-pass metabolism, and painless needle forms. The drug is only transported to the target site after it permeates into the skin, and enters systemic circulation. The site of administration may or may not be different in condition to produce therapeutic action.^[5]

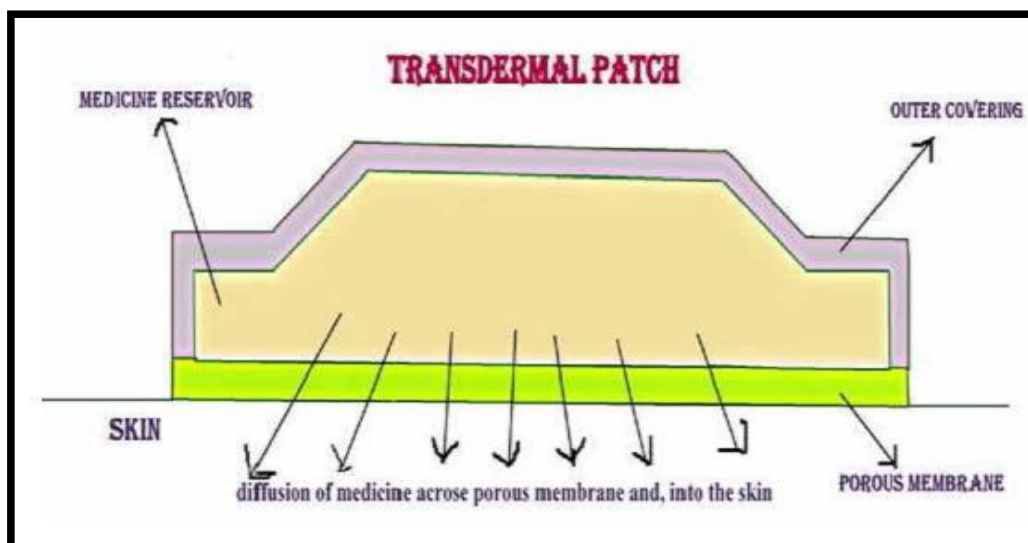


Figure-1. Schematic presentation of parts of transdermal patch

OBJECTIVES

Multi-dose therapy in traditional system of medicine presents several complicated issues. The conventional dosage form complicates the delivery of right amount of medicament at the right target organ if optimal dosing is considered. Another factor influencing the need for the development of NDDS, is their economic concerns. Re-fabrication the components and various alternatives to deliver drugs into the body are much less in demand and more profitable process. To overcome these issues, novel drug delivery systems and controlled release drug delivery system, are best ways to deliver drug, with a programmed rate, into the blood stream.^[11,12]

Controlled drug release can be targeted by transdermal drug delivery systems (TDDS) which supplies medicines through the skin portal over an extended tenure of time.^[13-15] A lot of sensation has been achieved by TDDS during the last decade as it furnished several merits over the traditional delivery systems and oral controlled release delivery systems, including better patient conformity.^[16-17]

MATERIALS AND METHODS

All materials used for the formulation were of analytical grade. The ingredients used in the formulation were purchased from the local market. Any impurities or foreign particles were inspected and discarded. The active pharmaceutical ingredient (Neem Oil) was obtained from Dabur India Pvt. Ltd. HPMC and Ethyl Cellulose were sourced from Merck Specialties. Pvt. Ltd. Methanol and Propylene Glycol were purchased from Oxford Laboratories and PEG-400 and Glycerol from National Drug House, respectively.

Formulation and development of herbal transdermal patch:

Drug-loaded transdermal patches of neem oil were formulated using solvent casting method. Petri-dish having overall area of 50.24cm² was utilized. Polymers were precisely pondered and a clear solution was formed by dissolving 10ml of water: methanol (1:1) solution. Drug was amalgamated with the prepared solution and was subjected to mixing till procurement of a clear solution. In next step, plasticizer and permeation enhancer Polyethylene glycol 400 (30%w/w of total polymer) and propylene glycol (15%w/w of total polymer) was used respectively. Further the obtained solution was allowed to cast on the interiors of petri-dish, which was lubricate with glycerin and dried at room temperature for 24hrs (Figure 2).

The quick evaporation of the solvent was minimized using an inverted funnel which was placed over the Petri dish. On completion of mentioned time, dried out patches was isolated from petri-dish and kept in desiccator for further examinations.^[18]

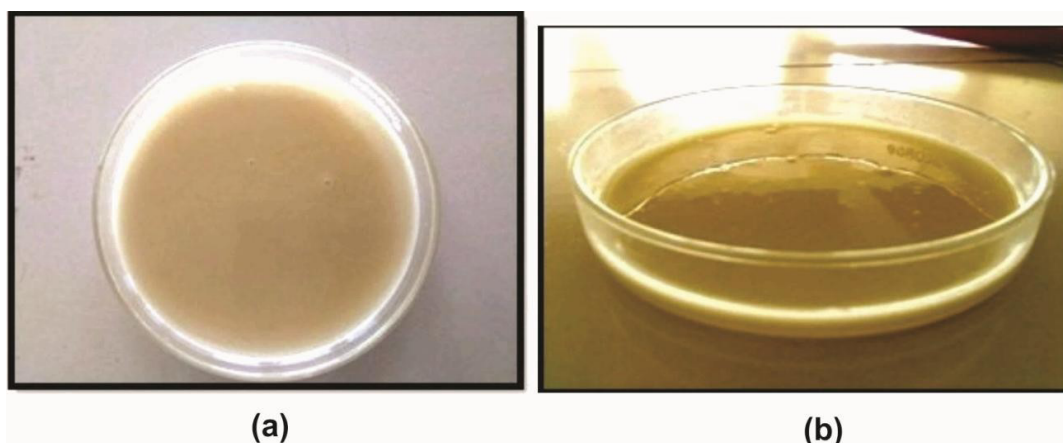


Figure-2. (a) Surface view of prepared solvent castings consisting drug, polymer, plasticizer and vehicle, (b) side view of prepared solvent castings

Characterization of Developed Patches:

Organoleptic Characteristics-The prepared patch was physically examined for its facade, color, clearness, litness, and smoothness.

Thickness- Vernier calipers was utilized to measure the thickness of the patches. Consistency in thickness was deliberated at various locations and mean values were computed.^[19]

Weight Uniformity- Uniformity in weight was determined by taking 3 patches weighed on digital balance and analyzed for distinctions in weight.

Folding Endurance- Developed patch was taken and subjected to repetitive folding at same point until it gets sever. Instances of time when patch folded without breaking was noted down.^[20]

Moisture Content- Developed patch after weighing was placed in a desiccators consisting compounded calcium chloride for 24hrs. Further after taking out from desiccators, patch was re-weighed. Under mentioned formula was used for compute % moisture content:

$$\text{Percentage of moisture content} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100.$$

Drug Content- Drug content was analyzed by dissolving patch in methanol and the residual volume was making up distilled water to 100mL. Further this solution was subjected to filtration and absorbance of the solution was notified at the wavelength of 304 nm, through which the concentration was measured.^[21]

in-vitro permeation study: Shell membrane of egg was taken to determine the in-vitro permeation characteristics of developed patch, since the egg membrane is similar to human stratum corneum as it contains keratin.^[8] In order to maintain a consistent

temperature of the skin i.e. $37 \pm 1^\circ\text{C}$ during the whole time of experimentation, water in the exterior jacket (enclosed on the shell) was continuously warmed. In the receiving section, phosphate buffer solution of pH 7.4 was utilized as a dissolution medium. Patch of desired size of $5 \times 5 \text{ mm}^2$ was taken and implied over the escalated membrane in the diffusion cell. Further, samples were taken out from the receptor compartment at synchronized intermissions. Frequency of sampling time was scheduled at 0, 15, 30 and 60 minutes which was further kept constant at interval of 1hr till 6th hour of discharge. Afterwards the system was allowed to kept in its standard position and further on next day readings were noted down at the completion of 24th hour. 1mL of the receptor solution was collected as sample and parallel the system was replenished with 1mL of phosphate buffer solution for maintenance of similar initial volume of the solution. Finally the absorbance of collected samples were taken with the help of UV-Vis spectrophotometer.^[5]

Scanning Electron Microscopy (SEM) - The exterior surface characteristics of received sample (semi solid; herbal constituents along with presence of polymer) were examined by Scanning electron microscope (Model JSM - 6390LV, Jeol, USA). The sample was placed on plain glass stub and sputter coating of gold was done to make surface of particles electroconductive. Images were recorded using SEM equipped with SEM digital camera.^[22]

Atomic Force Microscopy (AFM) -The shape and surface topography of received samples were determined by using AIST-NT Smart SPM 1000, CA atomic force microscope (AFM). AFM of the sample was carried out at glass substrate in AC mode to characterize the surface roughness which is regarded as one of the most vital surface properties that plays a significant role in membrane permeability and abhorrent behavior.^[23]

RESULTS AND DISCUSSION

Organoleptic Characteristics- The prepared patches were slightly opaque, pale coloured, jellified preparations showing good flexibility and fair smoothness (Figure 3; Table 1).



Figure-3. Surface view of prepared transdermal patch recovered after 24hrs of solvent evaporation

Table-1. Results of Organoleptic property analysis of developed transdermal patches

Serial No.	Physical Appearance	Result
1	Appearance	Jellified Preparation
2	Color	Pale Yellow
3	Clarity	Opaque
4	Flexibility	Good
5	Smoothness	Fair

Results of thickness, weight uniformity, folding endurance, moisture content and drug content:

Developed patches shown optimum thickness in the range of 0.17-0.19 mm. Results of weight uniformity depicted of mean weight of 0.252 gm. ($n=3$) whereas mean folding endurance of prepared patches was 34($n=3$). The average moisture content of prepared patches was calculated to be 2.943%. ($n=3$) and the content of drug was found to be 0.133 mg in w/w ratio in indication to the weight of patch. ($n=3$) (Table 2).

Table-2. Results of thickness, weight uniformity, folding endurance, moisture content and drug content.

Serial no	Thickness	Weight Uniformity	Folding endurance	Moisture content	Drug Content
1	0.17	0.247	31	2.34	0.12
2	0.18	0.253	35	3.12	0.13
3	0.19	0.256	36	3.37	0.15
Mean \pm SD ($n=3$)	0.18 mm \pm 0.001	0.252 gm \pm 0.5	34 \pm 1	2.943% \pm 0.0036	13.33 mg \pm 0.023

***in-vitro* permeation study-** A time reliant enhancement was came into notice all over the study during in-vitro release studies of the developed transdermal patches (shown in Figure 5).

The drug release from patches slowed down after each passing hour, thereafter. The percentage of drug release was 18.21% in 15 minutes which further increased to 22.35% in 30 minutes and reached 31.76% in one hour. The cumulative drug release increased gradually and reached 58.52% in 6 hours. Ultimately at finishing of study, the cumulative drug release achieved a notable peak. i.e. 74.89% in 24hrs, as given in Table 3.

Table-3. Results of *in-vitro* permeation studies of developed transdermal patch

Serial Number	Time of collection	Concentration ($\mu\text{L/mL}$)	% CDR
1	0 minutes	0	0
2	15 minutes	5.98	18.21
3	30 minutes	8.17	22.35
4	1 hours	10.23	28.35
5	2 hours	12.45	34.56
6	3 hours	14.98	41.26
7	4 hours	16.42	46.52
8	5 hours	18.24	51.23
9	6 hours	20.31	58.52
10	24 hours	28.32	74.89

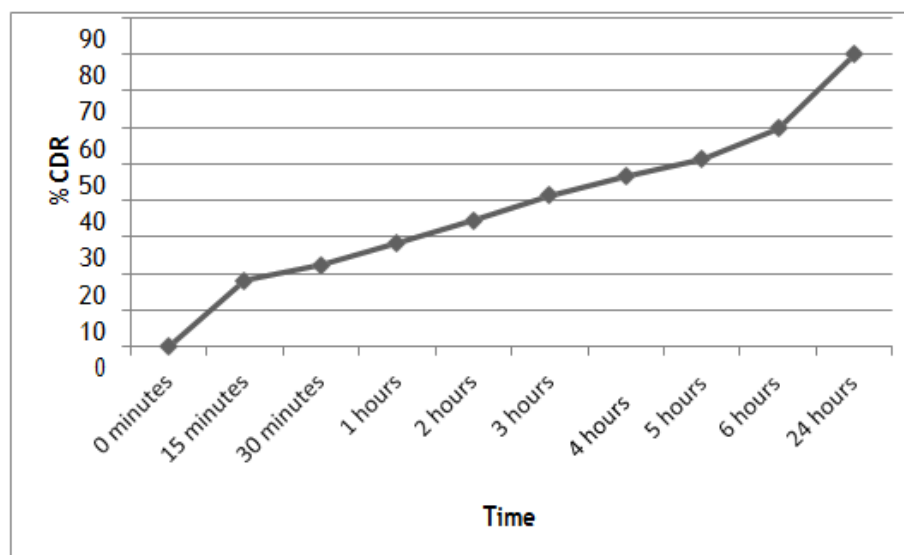


Figure.4. *in-vitro* permeation study of transdermal patch

Scanning Electron Microscopy (SEM) - The morphological features acquired from optimized formulation was photographed using SEM. Images shown presence of irregular shaped crystals with presence of aggregations. Rationales may be attributed to precipitation of the sample.

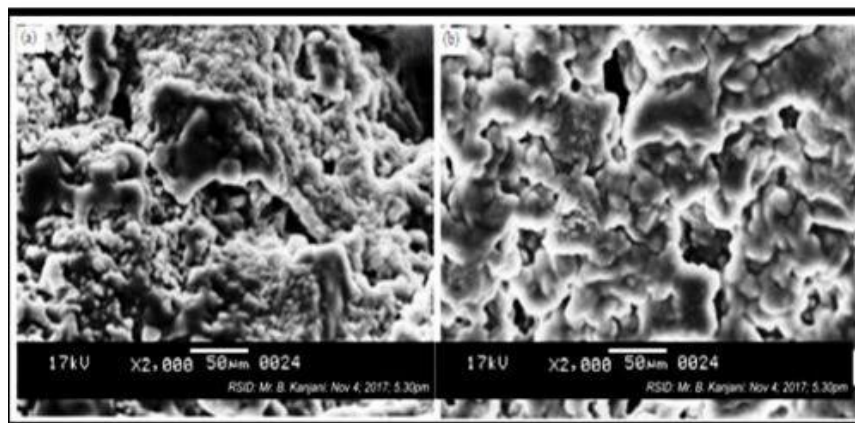


Figure-5: Morphology of *azadirachta indica* loaded transdermal patch, as viewed by scanning electron microscopy

Atomic Force Microscopy (AFM) - The morphology, local surface modulus and shape of sample was visualized under AFM in tapping mode and were found **not appropriate** as per micrometric size range having crystalline surface. Photomicrograph demonstrates the atomic force microscopic images of sample. Using the AFM, sample were envisaged and establish to be relatively constant height, which screening the size of sample.

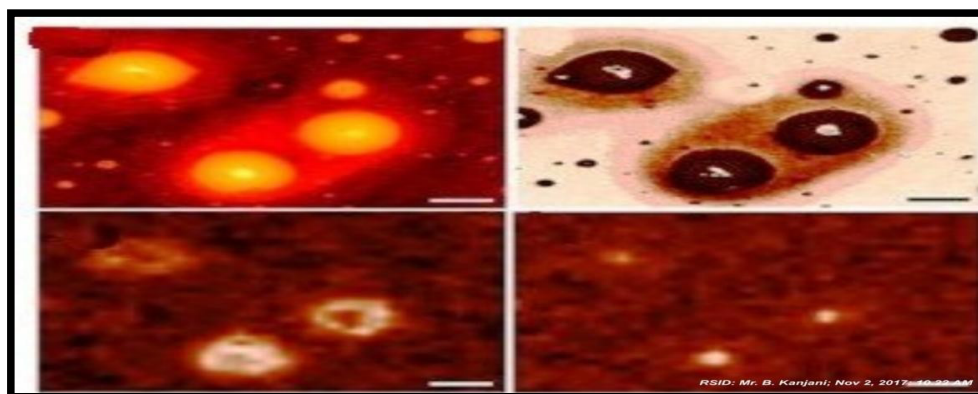


Figure-6. AFM micrograph of developed sample

CONCLUSION

In this novel approach, Herbal extract loaded (NEEM OIL) transdermal patches were productively synthesized using Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose (HPMC) polymers and Propylene glycol plasticizer and with an organic solvent ethanol. The patches were characterized for various parameters, and in vitro studies.

It can be concluded from this project work that, from this novel approach, herbal drugs in the extract/ oil of the product can transformed into Transdermal Patches for the bio active properties pertaining to a stable formulation in accordance with its appropriate formulations.

Although Transdermal systems provide a promising route of delivery for new age drugs, conventional and new dosage forms are equally essential for other drugs to increase their therapeutic efficacy. The patented innovations of TDDS focus on these parameters to make dosage form more patients complied and site specific delivery of the drug. Moreover in vivo performance of the dosage form specifies the ultimate test for the therapeutic efficacy of the drug.

REFERENCES

1. S. R. Rathva, N. N. Patel, V. Shah, U. M. Upadhyay. Herbal Transdermal Patches: A Review. IJDDR. 2012; 2: 397-402.
2. Rani S, Saroha K, Syan N, Mathur P. Transdermal Patches A Successful Tool in Transdermal Drug Delivery System: An Overview. Der Pharmacia Sinica. 2011;2:17–29.
3. Patel P. Herbal Excipients: An Emerging Field as A Penetration Enhancer in Transdermal Drug Delivery System. IJPRD. 2012; 4: 58–68l.
4. Faldu SD. Design and Evaluation of Controlled Release Transdermal Dosage Form Of Cardiovascular Drugs. (*PhD thesis*). Saurashtra University, Rajkot, India, 2010.
5. Finnin BC, Morgan TM. Transdermal Penetration Enhancers: Applications, Limitations, and Potential. J Pharm Sci. 1999; 88: 955–958.
6. Gupta V, Yadav SK, Dwivedi AK, Gupta N. Transdermal Drug Delivery: Post, Present, Future Trends. Int. J. Pharm. Life Sci. 2011; 12: 1096-1106.
7. Ravi S, Sharma PK, Bansal M. A Review: Transdermal Drug Delivery of Nicotine. Int. j. drug dev. res. 2011; 3: 01-08.
8. Patel D, Patel N, Parmar M, Kaur N. Transdermal Drug Delivery System: Review. Int J Toxicol. 2011; 1: 61-80.
9. Sachan R, Bajpai M. Transdermal Drug Delivery System: A Review. IJRDP. 2013; 3: 748-765.
10. Chandiran IS, Sivakumar T, Kumar BP. Preparation and Evaluation of Aceclofenac Loaded Biodegradable Microspheres. IJMBR. 2010;1: 19-23.
11. Kshirsagar NA. Drug Delivery Systems. Indian J Pharmacol. 2000; 32: 54-61.
12. Sadashivaiah R, Dinesh BM, Patil AU, Desai BG, Raghu KS. Design and In-Vitro Evaluation of Haloperidol Transdermal Patches Containing Ethyl Cellulose- Povidone As Film Formers. AJPS 2009; 2: 43-49.
13. Vyas SP, Roop RK. Controlled Drug Delivery Concepts and Advances. Vallabh Prakash Publishers, New Delhi, 2005.
14. Sanap GS, Dama GY, Hande AS, Karpe SP, Nalawade SV, Kakade RS. Preparation Transdermal monolithic systems of solvent casting method of indapamide and the use of vegetable oil as permeation enhancer. IJGP. 2008; 2:129-133.
15. Patel RP, Patel G, Baria A. Formulation and Evaluation of transdermal Patch of Aceclofenac. International Journal of Drug Delivery. 2009; 1: 41-51.
16. Devi KV, Saisivam S, Maria GR, Deepti PU. Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Verapamil Hydrochloride. Drug Dev Ind

- Pharm. 2003; 29: 495-503.
17. Suryadevara PK. Formulation And Evaluation Of Antiemetic Patch Comprising Ondansetron Hydrochloride. 2010. KLE University, Belgaum, India.
 18. Can S, Erdal MS, Gung S, Ozsoy Y. Optimization and characterization of chitosan films for transdermal delivery of ondansetron. *Molecules*. 2013; 18: 5455–5471.
 19. Suryadevara PK. Formulation and evaluation of antiemetic patch comprising ondansetron hydrochloride [M.S. thesis]. 2010. KLE University, Belgaum, India.
 20. Reddy RK, Muttalik S, Reddy S. Once daily sustained release matrix tablets of nicorandil: formulation and in-vitro evaluation. *AAPS Pharm Sci Tech*. 2003; 4: 480–488.
 21. Lewis S, Pandey S, Udupa N. Design and evaluation of matrix type and membrane controlled transdermal delivery systems of nicotine suitable for use in smoking cessation. *Indian J Pharm Sci*. 2006; 68: 179–184.
 22. Jatav VS, Saggu JS, Sharma AK, Sharma A, Jat RK. Design, development and permeation studies of nebivolol hydrochloride from novel matrix type transdermal patches. *Adv Biomed Res*. 2013; 2: 62.
 23. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. *AJPS*. 2017; 6: 487-497