Original Article

Design, Preparation And In Vitro Evaluation Of Papaverine Transdermal Patches

Archana Pattanaik[1], Souvik Giri[2*], Debashish Mohanty[3], Pritish Kumar Pasayat[4], Suresh Kumar[5], Deepak Kumar[6], Deepak Sharma[7]

[1, 2*, 3, 4]Assistant Professor, Department of Pharmaceutics, Sri Jayadev College of Pharmaceutical Sciences, Bhubaneswar, Odisha, India
[5]Associate Professor, School of Medical and Allied Sciences, G D Goenka University, Gurugram, Haryana, India
[6]Principal, Krishna Institute of Pharmacy, Dhanbad, Jharkhand, India
[7]Associate Professor, Department of Pharmaceutical Technology, School of Medical Sciences, Adamas University, Kolkata, West Bengal, India

***Corresponding Author**: - Souvik Giri

*Assistant Professor, Department of Pharmaceutics, Sri Jayadev College of Pharmaceutical Sciences, Bhubaneswar, Odisha, India, ,
Email Id: souvikrjgiri@gmail.com
DOI: 10.47750/pnr.2023.14.03.177

Abstract

Transdermal patches of Papaverine Hydrochloride were prepared by the solvent casting method using ethyl cellulose, HPMC K15 and Sodium alginate using different ratios. The physicochemical parameters such as flexibility, thickness, smoothness, weight variation, moisture content, hardness and tensile strength were evaluated for the prepared patches. The formulation exhibited flexibility, uniform thickness and weight, smoothness, drug content, and moisture content. The in vitro diffusion studies were carried out using modified Franz diffusion cell using cellophane as the diffusion membrane and the formulation followed the Zero order diffusion and Higuchi's diffusion kinetics. The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in different storage conditions. Compatibility studies indicated that there was no interaction between the drug and polymers. Hence, the aim of the present study was to prepare the sustained release formulation (Transdermal patches) of the drug using different blend of polymers. The formulated patches containing the hydroplilic polymers showed best release rate of drug.

Keywords: Papaverine Hydrochloride, Franz diffusion Cell, HPMC K15, Transdermal Patch

INTRODUCTION:

A recent approach to drug delivery is to deliver the drug into systemic circulation at a predetermined rate via the skin. A transdermal drug delivery formulation or device keeps the drug's blood concentration within the therapeutic window, ensuring that drug levels do not fall below the minimum effective concentration or exceed the minimum toxic dose. Transdermal drug delivery has several advantages over oral and/or intravenous administration, including better blood level control, a lower incidence of systemic toxicity, avoidance of hepatic first-pass metabolism, and improved patient compliance.

A ideal drug for transdermal drug delivery should have several physicochemical properties, such as a short half-life, a small molecular size, a low dose, and so on. However, the stratum corneum's highly organised structure forms an effective barrier to drug permeation, which must be modified if poorly penetrating drugs are to be administered.

Chemical penetration enhancers would greatly expand the number of drug molecules suitable for transdermal delivery. Opium contains the alkaloid papaverine. It belongs to the class of drugs known as vasodilators. It has a direct relaxant effect on smooth muscle, which is due to its ability to inhibit phosphodiesterases. It has been used to treat cerebral, peripheral, and coronary disorders. The oral biological half-life of papaverine HCl is reported to be between 1 and 2 hours. It has a lower solubility in intestine pH.

Papaverine is rapidly absorbed orally and undergoes extensive first pass metabolism in the gut wall and liver; additionally, the bioavailability of papaverine HCl when administered orally is approximately 30%. As a result, the transdermal drug delivery approach was thought to be more suitable for papaverine hydrochloride in order to avoid its extensive first pass metabolism, to improve therapeutic efficacy by improving bioavailability, patient compliance, and to reduce the frequency of dosing and side effects.

The goal of this study was to develop and evaluate a matrix diffusion controlled TDDS in the form of papaverine hydrochloride for in vitro release, ex vivo permeation, and mechanical properties. This is due to the lack of a sustained release formulation and the oral tablet's extensive first pass metabolism.

MATERIALS AND METHODS

Materials:

Papaverine hydrochloride was obtained as a gift sample from Dr. Reddy's Lab. HPMC K15, Ethyl Cellulose, Sodium Alginate, PEG, DMSO, Disodium Hydrogen orthophosphate, Potassium di-hydrogen orthophosphate from AR Chemicals, Hyderabad. All other chemicals and reagents used were of analytical reagent grade.

PREPARATION OF TRANSDERMAL PATCHES:

Transdermal patches containing Papaverine were set up by the solvent casting method. Papaverine was dissolved into the proper amount of solvent. Polymers HPMC K15, Ethylcellulose and sodium alginate were taken in a bubbler cylinder, to this include Papaverine drug which was dissolved in methanol. PEG was taken as a plasticizer and added to the blend and blended well. It was saved for 2 hours to avoid any captured air and was then moved into a formerly cleaned petri dish ($40cm^2$), drying of patches was done in vacuum chamber at room temperature. Dried patches were packed in aluminum foil and put away in a desiccator for further evaluation test.

Table 1: Formulation Design of Papaverine Transdermal Patches

S. No	Formulation code	Ingredients			
		Drug (mg)	HPMC	Ethyl cellulose	Sodium alginate
1	F1	25	500	-	-
2	F2	25	-	500	-
3	F3	25	-	-	500
4	F4	25	250	250	-
5	F5	25	300	200	-
6	F6	25	400	100	-
7	F7	25	250	-	250
6	F8	25	-	250	250

Figure 1: Papaverine Transdermal patch

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance:

All the prepared trans-dermal patches were externally examined for shading, clearness, adaptability and smoothness.

Thickness of the patches:

Thickness of each trans-dermal patch was resolved through using a micrometer screw check set at six particular positions. The normal thickness and standard deviation estimations of six readings were determined for each set of medication.

Weight uniformity test:

A set of three patches from each batch having a diameter of 1 cm^2 were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60°C for 4 h prior to testing.

Drug content:

The patch (1 cm^2) was transferred into a graduated flask containing 100 ml of phosphate buffer pH 7.4. The flask was shaken for 4 h in a mechanical shaker. Then the solution was filtered and after suitable dilutions with phosphate buffer pH 7.4 the absorbance was measured at 272 nm using the placebo patch solution as blank and the drug content was calculated.

Moisture uptake:

Films (1 cm^2) of each formulation were accurately weighed and exposed to ambient atmospheric conditions of temperature (avg. temp 34˚C) and humidity (84%) for 3 days. After 3 days, the films were again weighed and % moisture absorption was calculated. Average % moisture absorption of each film was calculated.

$$\% \text{ moisture absorption} = \frac{(\text{Final Weight} - \text{Initial Weight}) \times 100}{\text{Initial Weight}}$$

Folding endurance:

A strip of 2 cm × 2 cm (4 cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.

In-vitro drug release study:

In vitro drug release profiles were carried out by using modified Franz diffusion cell with the cellophane membrane. The cellophane membrane was soaked in 100 ml of phosphate buffer of pH 7.4 and then cut into pieces of 7 cm^2 area. It was mounted on the diffusion cell and equilibrated with receptor fluid for 15 min and used for the drug release studies. The cell consists of two compartments, the donor and the receptor compartments. The donor compartment was in contact with ambient conditions of the atmosphere. The receptor compartment was in contact with a solution in the receptor compartment (phosphate buffer pH 7.4.) and the contents were stirred by a rod-shaped magnetic bead driven by a magnetic stirrer. One patch of 1 cm^2 was placed in the donor compartment of the diffusion cell. The receptor fluid (5 ml) was withdrawn at predetermined time intervals and replaced immediately with same volume of phosphate buffer pH 7.4. The samples were analyzed for drug content at 272 nm using UV-visible spectrophotometer after suitable dilution with phosphate buffer pH 7.4.

Kinetic study:

To know the mechanism of drug release from these formulations, the data were treated according to first order (log percentage of drug to be released vs time), Higuchi's (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) patterns.

Stability study:

The stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity: 25-30°C (60%RH) and 45-50°C (75%RH) over a period of 3month. The patches were wrapped in aluminum foil and stored in a desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals.

RESULTS AND DISCUSSION

All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky and homogeneous in nature. This may be due to the presence of plasticizer. All the eight patches have showed good folding endurance, and indicated that the patches have good flexibility. (Table 2)

Water absorption studies revealed that as the concentration of HPMC increased the amount of water absorption also increased. Among the patches F7 patch absorbed higher moisture content. This may be due to the hydrophilic nature of the HPMC. The least percentage of moisture absorption was observed for F2 patch as compared to other patches because hydrophobic nature of ethyl cellulose. (Table 2)

Table 2: Physicochemical evaluation of Papaverine transdermal patches

Formulation code	Weight (mg)	Thickness (µm)	Folding endurance	% Moisture Content	Drug content (%)
F1	188	0.24	297	3.14	92.12
F2	200	0.21	274	2.71	93.09
F3	198	0.28	269	3.20	90.26
F4	192	0.18	286	2.97	95.72
F5	186	0.23	277	3.07	96.83
F6	194	0.27	288	3.50	94.24
F7	187	0.24	276	5.26	97.85
F8	194	0.27	288	3.22	94.24

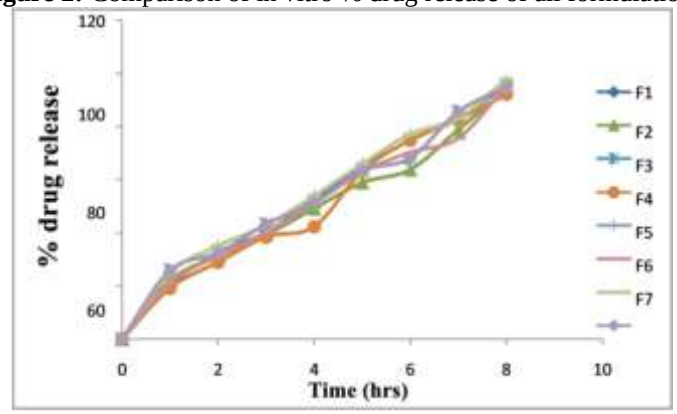
There was no significant difference in the drug content among the patches indicated content uniformity. In vitro drug release study showed that from hydrophilic polymers the drug release was found to be faster compared to the combination of hydrophilic and hydrophobic polymers or only hydrophobic Polymers used in the study. Hence, transdermal patches can be used for extended period of time. The release profile was correlated with the moisture absorption which further reflected by the nature of polymer. (Table 3)

Table 3: In vitro drug release profiles of Papaverine transdermal patch (F1-F8)

Time	% Cumulative drug released

(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	20.40	22.10	25.86	19.25	24.90	21.25	24.90	25.86
2	32.36	31.21	32.50	28.96	35.17	31.28	35.17	32.50
3	40.17	39.32	43.18	38.52	42.85	40.17	42.85	43.18
4	52.40	49.20	51.52	42.35	53.96	51.12	53.96	51.52
5	64.76	58.95	63.42	63.27	65.97	62.91	65.97	63.42
6	74.90	63.86	68.13	74.98	77.16	70.38	77.16	68.13
7	83.34	78.91	85.60	82.75	83.20	75.70	83.20	85.60
8	95.65	93.95	94.90	92.28	95.54	96.86	97.86	94.90

Figure 2: Comparison of in vitro % drug release of all formulations



From the above data, it can be concluded that the release characteristics may be restricted to only in vitro release study, as the in vitro release model mainly favors the hydrophilicity. However, when theses patches applied to the skin results may differ as the lipophilicity may play a major role for the drug transport system.

The release kinetics of the transdermal patches followed Zero order and Higuchi's diffusion kinetics. (Table-4)

Table 4: Drug release kinetics

S.no	Kinetic model	R^2 value
1	Zero order kinetics	0.982
2	First order kinetics	0.604
3	Higuchi model	0.960
4	Korsmayerpeppas	0.565

Stability studies showed that, there is no significant change in physical characteristics and drug content. Based on these results (Table-5) it was concluded that the formulated transdermal patches were found to be physically and chemically stable during the study period (90 days).

Table 5: Stability study for optimized formulation (F7)

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-7	97.86	97.82	96.92	95.98	**Not less than 85 %**
F-7	97.86	97.70	96.60	95.10	**Not less than 85 %**
F-7	97.86	97.25	96.22	94.91	**Not less than 85 %**

Interaction between drug and formulation was studied using FTIR analysis. The FTIR spectrum revealed that there were no interaction between drug and excipients. (Fig 3,4)

Figure 3: FTIR Studies of pure drug

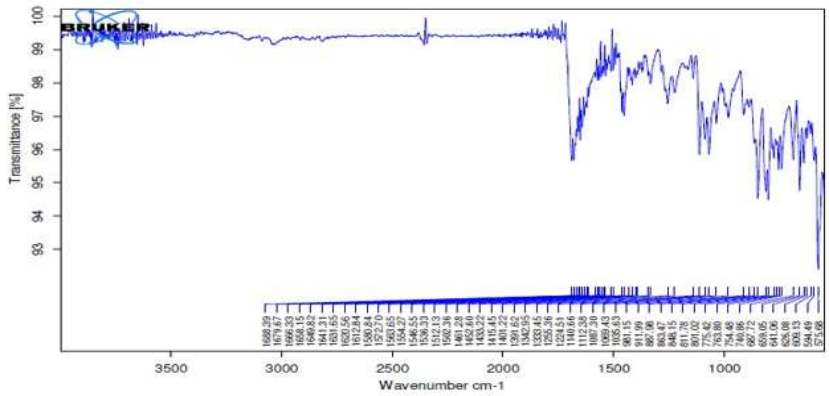
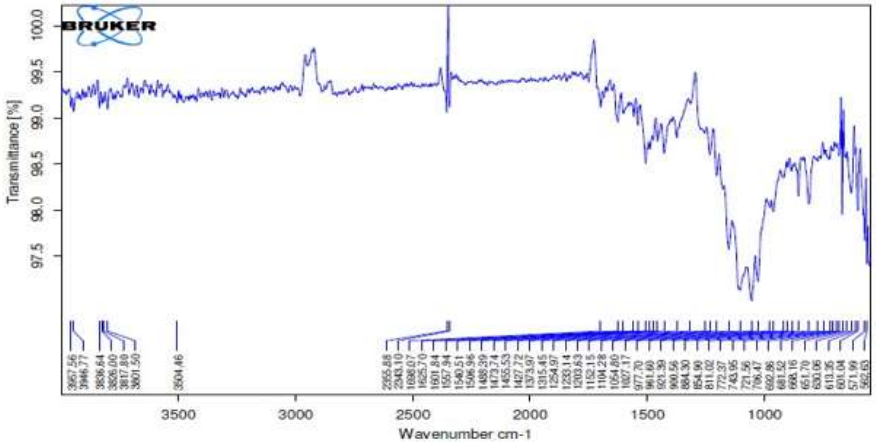


Figure 4: FTIR Studies of physical mixture of drug and excipients



CONCLUSION

Based on the physicochemical parameters and in vitro release studies, formulation F7 was considered as the best formulations. Based on the promising results, the papaverine hydrochloride transdermal patch can be used as a controlled drug delivery system, reducing the frequency of administration. Despite efforts to develop a papaverine hydrochloride transdermal patch, long-term pharmacokinetic and pharmacodynamic studies are required to establish the usefulness of these patches. Furthermore, these findings may aid the industry's transition to commercial production. The transdermal dosage form of papaverine hydrochloride may allow clinicians to provide more therapeutic options to their patients in order to optimise their care.

ACKNOWLEDGEMENT

I especially thanks to Mrs. Madhulita Panda, Associate Professor, College of Pharmaceutical Sciences, Berhampur, Odisha and Dr. Nilima Shukla, Principal, Sri Jayadev College of Pharmaceutical Sciences, Bhubaneswar, Odisha to guide for research work.

REFERENCES

1. Soni M, Kumar S and Gupta GD: Transdermal drug delivery: A novel approach to skin permeation. Journal of Pharmacy Research 2009; 2(8):1184-1190.
2. Naik A, Yogeshvar N, Kalia G and Richard G H: Transdermal Drug Delivery: overcoming the skin's barrier function 2009; 3(9):318-326.
3. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 pp. 298-299.
4. Kunieda H, Nakano A, Akimaru M. The effect of mixing of surfactants on solubilization in a micro emulsion system, J Colloid Interface Sci 1995, 170, 78-84.
5. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz MJ. Ethosomes: novel vesicular carriers for enhanced delivery: characterization and skin penetration properties, J Control Rel 2000, 65, 403-418.
6. Santucci E, Carafa M., Coviello T, Murtas E, RiccieriFM,Alhaique F, Modesti A, Modica. Vesicles from polysorbate 20 and cholesterol: A simple preparation and a characterization, STP Pharm Sci 1996, 6, 29-32
7. Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol, Int J Pharm 2000, 204, 171-182.
8. Mukherjee B, Kanupriya, Mahapatra S, Das S, Patra B.Sorbitan monolaurate 20 as a potential skin permeation enhancer in transdermal patches, J Applied Research2005, 5, 96-107.
9. Costa P, Ferreria DC, Morgado R, Sousa Lobo JM.Design and evaluation of a lorazepam transdermal delivery system, Drug Dev Ind Pharm 1997, 23,939-944.
10. 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, Ind J Pharm Sci 2006, 68, 179-184.
11. Nandy BC, Chourasia SK, Roy S, Mazumdar B, Meena KC, Aujha D, et al. Effect of various polymers on carvedilol transdermal films: In vitro permeation studies. Der Pharm Sinica2011; 2:203-17.
12. Kadam AS, Ratnaparkhi MP, Chaudhary SP. Transdermal drug delivery: An overview. Int J Res Dev Pharm 2014;3:1042-53

13. Latheeshjlal L, Phanitejaswini P, Soujanya Y, Swapna U, Sarika V, Moulika G. Transdermal drug delivery systems: An overview. Int J Pharmtech Res 2011;3:2140-8.
14. Murugan KB, Kumar PP. Transdermal drug delivery system: A novel approach. World J Pharm Sci 2014;3:277-92.
15. Hafeez A, Jain U, Singh J, Maurya A, Lakhan R. Recent advances in transdermal drug delivery system: An overview. J Sci Innov Res 2013;2:733-44.
16. Patel DM, Kavitha K. Formulation and evaluation aspects of transdermal drug delivery system. Int J Pharm Sci Rev Res 2011;6:83-90.
17. Himanshi T, Sachdeva R. Transdermal drug delivery system, a review. Int J Pharm Sci Res 2016;7:2274-90.
18. Kumar JA, Pullakandam N, Prabu S, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res 2010;3:49-54.
19. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
20. Arunachalam A, Karthikeyan, Vinay Kumar D, Prathap M, Sethuraman S, Ashutosh Kumar S and Manidipa S: Transdermal Drug Delivery System: A review. Current Pharma Research 2010; 1(1):70-81.