World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 7, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES LOADED WITH PENTAZOCINE HYDROCHLORIDE

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Received on: 05-06-2019; Revised and Accepted on: 11-07-2019

ABSTRACT

The Current research is to develop the Transdermal patches containing drug pentazocine hydrochloride, a narcotic analgesic generally used in cases of moderate to severe pain of various origins, using ethyl cellulose, poly vinyl pyrrolidone as polymer and dibutyl phthalate as a plasticizer. By incorporating different ratios of ethyl cellulose and poly vinyl pyrrolidone different patches were developed. Drug-excipients compatibility studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. Patches were evaluated for thickness, weight uniformity, moisture absorption, drug content uniformity, in-vitro drug release studies and in vitro skin permeation studies. Drug release followed the Higuchi equation in which the amount of drug released is linear to square root of time. The release rate constant varies with different drug load, different polymer and also on concentration of penetration enhancers. Among the various penetration enhancers used Di Methyl Sulfoxide was found to have a significant effect on penetration. The studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

KEYWORDS: *Ethyl Cellulose, Poly Vinyl Pyrrolidone, Pentazocine HCl, Transdermal Patches.*

INTRODUCTION

Pentazocine which is a narcotic analgesic is generally used in cases of moderate to severe pain of various origins like post surgical trauma, cancer, burns, etc. this drug undergoes sudstantial hepatic metabolism and its plasma half-life is 2 hours [1]. As it undergoes extensive hepatic metabolism and due to its low molecular weight and also lipophilicity, it can be selected as a candidate for drug delivery through Transdermal route [2].

Drug delivery through skin attracted many number of researchers as it is having the benefits of delivering the drug via skin which can be used to achieve the therapeutic effect locally and also systemically [3].

The main aim in formulating the Transdermal patches is to obtain a drug delivery which will be in a controlled manner, which can be predictable and release the drug into the blood of the patients in a very reproducible way [4].

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DOI: https://doi.org/10.5281/zenodo.3357179

MATERIALS AND METHODS

Materials:

Pentazocine HCl, ethyl cellulose and poly vinyl pyrrolidone were received as a gift sample from Concept Pharmaceuticals, Aurangabad. The remaining chemicals are of the analytical grade.

Methods:

1. Preparation of transdermal patches: Patches composed of different ratio of ethyl cellulose; poly vinyl pyrrolidone and drug were prepared by mercury substrate method. Dibutyl phthalate was incorporated at a concentration of 10% w/v of dry weight of polymer as plasticizer. Dimethyl sulfoxide (DMSO), Oleic acid and IPM were used as penetration enhancer as depicted in Table 1. The solution of chloroform which contains the drug, polymers and also plasticizer were poured in a petri dish containing mercury sulfate, which was then covered by an inverted funnel to control the rate of evaporation of solvent. Drug films were removed and stored in desiccator in order to prevent the patch from humidity.

Evaluation of Transdermal Patches:

1. Drug content: Drug content percentage of the transdermal patch was determined by dissolving accurately weighed portion of transdermal patch (50 mg) in 25 ml of casting solvent.

The resultant solution was transferred into a volumetric flask and the dilutions were appropriately made by using the distilled water. This final solution is filtered and

analysis was done by using the UV double beam spectrophotometer at 278nm.

2. Thickness: Patch thickness was determined using a screw gauge at five separate points. Five patches were selected randomly and were tested for thickness.

3. Weight Variations: The weight variation of the patches was tested individually by weighing five randomly selected patches and this is carried out for each formulation.

4. Moisture absorption studies: The water absorption capacities of various films were determined at 52% RH [9]. A standardized method for determining water absorption by plastics has been approved by the ASTM and has been designed as ASTM test no. D570-59T. Chamber was set up to produce relative humidity at room temperature (30±2°C). The polymer film or membranes were accurately weighted and placed in the relative humidity chambers. The patches were observed for the increase in weight by weighing after 5, 10, 24, 48 hours, respectively.

Percentage absorption was calculated by using following formula.

$$\frac{\text{Weight of exposed film - weight of unexposed film}}{\text{Weight of unexposed film}} \times 100$$

5. Drug release studies In vitro: The paddle over disk method which was USP5 method was employed for the drug release determination from the transdermal patch[6]. The dissolution medium 500 ml was maintained at a temperature of 37±1°C. The paddle was positioned at a distance of 2.5 cm above the surface of the glass plate and regulated to rotate at a speed of 60 rpm. Aliquots of the samples were taken periodically at predetermined time intervals and analyzed for drug content by spectrophotemetric method using a Shimatzu double-beam UV visible spectrophotometer. After each sampling, an equal volume of blank solution was replaced.

6. In vitro drug permeation studies: In vitro skin permeation studies were carried out using modified Franz diffusion cells [2, 10]. Freshly prepared rat abdominal skin was mounted on the top of the Franz cell with viable epidermis facing receptor compartment. The cell was made up of glass. The receptor compartment had a volume of 20.0 ml. The surface area of the diffusion cell membrane was 3.14 cm^2. The cell was maintained at 37±1° C by an external water jacket. The receptor chamber was filled with distilled water and stirred constantly at 300 rpm. The transdermal film was placed in such a way that the stratum corneum side was in intimate contact with the drug-releasing surface of the patch and viable epidermis facing the receptor compartment [8]. An aliquot of receptor fluid was withdrawn periodically without allowing formation of air bubble and replaced with same volume of distilled water. The concentration of drug in receptor solution was determined after proper dilution and filtration at 278 nm.

6.1.X ray diffraction studies: X ray diffraction pattern of the pure drug and drug in transdermal patches were measured with Philips PSPW 1700 X-ray diffractometer with graphite monochromator, Cu K α radiation (x= 1.5418 A), voltage 30 kV, current 12 MHz, chart speed 2.40/min, divergence slit 2q.

6.2. SEM Studies: The surface morphology of the drug-dispersed patches was examined by scanning electron microscopy (Cambridge stereoscan - 250 MK3). The dried films were mounted on an aluminum stub using double-sticky cellophane tape. Films were gold coated in vacuum evaporator and observed under a scanning electron microscope.

6.3. Infrared spectroscopy studies: The infrared spectrum of drug and its transdermal patch were obtained using Nicolet Magna FTIR 550 Infrared spectrophotometer. Infrared spectra were obtained by preparing solid disc in potassium bromide.

6.4.Stability studies: Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the TDDS in a stability chamber (Newtronic Equipment Company, Mumbai, India) [5]. The samples were withdrawn at 0, 30, 60 and 90 days and the drug content was analyzed by a UV spectrophotometer method.

6.5. Statistical analysis: One way ANOVA followed by post hoc student 't' test was applied to permeation flux data and release rate constant data at $P<0.05$.

RESULTS AND DISCUSSION

The matrix type transdermal patches of pentazocine HCL were prepared using different ratio of EC: PVP. Ethyl cellulose alone and in combination with PVP possessed good film forming properties. Flexible films were obtained by the addition of plasticizer dibutyl phthalate at a concentration of 10% w/w of dry polymer.

Drug content was estimated at different points of film. The results revealed uniform distribution of drug in the film. The thickness of EC-Pz films varies between 0.125 to 0.245 mm. Plain EC films without PVP showed lowest thickness; there was an appreciable increase in thickness with the increase in the concentration of PVP. EC films were also studied for effect of drug load on thickness of film. It was observed that there was no significant change in the thickness of the film with the increase in the drug concentration. Water absorption studies at 52% revealed that as the concentration of PVP in the film increased the water absorption capacity also increased. This could be accounted to the hydrophilic property of PVP. Water absorption capacity of plain EC and EC: PVP films (6:4) were found to be 0.65 (± 0.30) to 2.24 (±0.31).

The Percent drug content, thickness, weight variation and water absorption capacity of different films are reported in Table 2. Addition of different concentration of drug and penetration enhancer did not show any appreciable change in the water absorption capacity of the film.

Effect of polymer composition on release characteristics of Pentazocine:

The paddle over disk method was used to study the release of drug. The release of drug from films followed the diffusion control matrix model. The amount of drug released per unit area is proportional to the square root of time. PVP plays an important role in the release study. As the concentration of PVP in the film increases there is a proportional increase in the amount of drug released. Addition of PVP to EC films increase the release rate from 0.9099 to 1.0891 $mg/cm^2h^{1/2}$ and permeation flux from 36.77 to 39.92 $\mu g/cm^2$/hr for plain EC and EC:PVP film, respectively. The permeation rate constant and release rate constant of Pentazocine increased with an increase in the PVP fraction of the film. This may be due to the dissolution of the water soluble polymer of the film which resulted in the formation of pores and thus led to the decrease

in mean diffusion path length of drug molecules to release into dissolution medium and hence higher release rates. It was also observed that PVP acts as anti nucleating agent which retards the crystallization of drug and thus play a significant role in improving the solubility of the drug in the matrix.

Statistical comparison of permeation rate using one way ANOVA followed by posthoc student t test shows the significant difference at P<0.05.

Effect of drug load:

Skin is made of three different layers of which stratum corneum is the main barrier for permeation. Skin is composed of keratinocytes embedded in lipid domain consisting of hydrophilic and lipophilic layers. In general, the lipophilic compounds penetrate through the intercellular domain of stratum corneum and hydrophilic compound through transcellular route. Changing the drug concentration in the vehicle alters the permeation rate of drug. The increase of drug concentration up to certain level may increase the permeation of and also yields plateau curve because of saturation of the drug thermodynamic activity. The permeation rate of Pentazocine increased with increase of drug loading in the film and resulted in plateau curve because of saturation of surface where the permeation of drug molecule is controlled by stratum corneum.

In vitro dissolution of Pentazocine at different drug load in presence of different penetration enhancer as shown in Fig 1 and 2 depicts an increase in concentration of Pentazocine from 5 to 20% and an increase in the release rate constant, Table 2. Rapid dissolution at higher drug load may be due to the presence of Pentazocine on the surface of film followed by diffusion of drug from the matrix. In vitro drug release at different drug load in presence of different penetration enhancers at 10% concentration like DMSO, OA and IPM shows similar rate constant showing no significant difference at P<0.05 which indicates that the effect of Penetration enhancer occur in the flux values, Table 2.

Statistical comparison using one way ANOVA followed by post hoc student 't' test of permeation flux of Pentazocine from EC: PVP transdermal patches with different drug load showed the significant difference between 5% and 20% drug load at P<0.05.

SEM Study: SEM study of drug and EC: PVP film before and after dissolution was carried out. SEM study reveals that there were formations of pores during dissolution. Ethyl cellulose film showed the uniform distribution of drug throughout the film.

Infrared Spectroscopy: To study the chemical interaction between drug and polymer the FTIR study was carried out for Pentazocine, ethylcellulose: Pentazocine and EC; PVP: Pentazocine, respectively. The spectral observations indicated no chemical interaction between drug and other excipient.

X-ray diffraction Study: The X-ray diffraction pattern of Pentazocine revealed high crystallinity of drug with major diffraction peaks at a 2θ angle approximately 8.7, 13, 16, 20 and 24.7. The comparison of intensity of major peaks shows the sharp decrease in intensity of peaks in presence of polyvinyl pyrrolidone. It can be concluded that during the preparation of Pentazocine - ethyl cellulose film, PVP acts as solid dispersion agent by reducing the crystallinity of Pentazocine, which is confirmed by the in vitro dissolution.

Effect of Penetration Enhancer:

All the penetration enhancer studied showed the concentration dependent effect on Pentazocaine permeation with minimum permeation flux at lowest concentration studied. Of the three penetration enhancers studied DMSO showed maximum increase in the permeation flux from 46.2 to 62.63 μg/cm²/h for 5% to 20% DMSO as shown in Fig 3. DMSO increased the drug permeation by leaching of DMSO soluble component from the stratum corneum.

Oleic acid increased permeation flux of Pz due to its interaction with stratum corneum leading structural changes and thus disturbing stratum corneum lipid structure. Permeation flux achieved with 5%, 10% and 20% OA was 43.41, 53.03 and 57.04 μg/cm²/h.

IPM increased the permeation flux of Pz to 45.88, 55.84 and 60.28 μg /cm²/h for 5%, 10% and 20% concentration of IPM.

Statistical comparison of permeation flux data in presence of different enhancer using one way ANOVA followed by post hoc student 't' test showed significant improvement in permeation flux at P<0.05, Table 3.

Stability studies: All the formulation were selected for stability studies and observed for changes in color, appearance, flexibility and drug content. Temperature and humidity values selected were as per the ICH guidelines and the tests were carried out in a stability chamber. Patches were analysed at an interval of 30 days for a period of 3 months. No physical changes were observed but decrease in drug content was observed at higher temperatures (45±5ºC).

Table No. 1: Formulation of Pentazocine - EC Transdermal patches

Formulation Code	EC:PVP	% Drug Load	% Enhancer		
			DMSO	IPM	OA
PI	10:0	12.5	-	-	-
P2	8:2	12.5	-	-	-
P3	6:4	12.5	-	-	-
P4	6:4	12.5	5	-	-
P5	6:4	12.5	10	-	-
P6	6:4	12.5	15	-	-
P7	6:4	12.5	-	5	-
P8	6:4	12.5	-	10	-
P9	6:4	12.5	-	15	-
P10	6:4	12.5	-	-	5
Pll	6:4	12.5	-	-	10

P12	6:4	12.5	-	-	15
P13	6:4	5.0	10	-	-
P14	6:4	20	10	-	-
P15	6:4	5.0	-	10	-
P16	6:4	20	-	10	-
P17	6:4	5.0	-	-	10
P18	6:4	20-	-	-	10

Table No. 2: Evaluation of Pentazocine - EC Transdermal Patches

Formulation Code	% Drug Content	Film Thickness mm	Weight of Patch mg	% Moisture Absorbed	Release Rate Constant	Permeation flux µg/cm²/hr
P1	97.23 ±0.15	0.125 ±0.13	240 ±0.18	0.65 ± 0.30	0.9099	36.77
P2	95.25 ±0.21	0.148 ± 0.02	241 ±0.24	1.83 ± 0.21	0.9683	37.26
P3	93.64 ±0.40	0.163 ±0.02	238 ±0.61	2.24 ± 0.31	1.0891	39.92
P4	97.25 ± 0.25	0.151 ±0.15	247 ± 0.36	2.60 ± 0.19	1.0962	46.2
P5	98.14 ±0.33	0.202 ±0.16	259 ± 0.2	2.32 ± 0.54	1.5240	58.99
P6	97.34 ±0.28	0.212 ±0.03	281 ±0.31	2.21 ± 0.18	1.4522	62.63
P7	97.26 ±0.42	0.231 ±0.06	245 ±0.15	2.28 ± 0.25	1.0792	45.88
P8	95.23 ± 0.29	0.211 ±0.13	254 ±0.38	2.40 ± 0.31	1.4197	55.84
P9	95,46 ± 0.35	0.230 ±0.10	279 ±0.13	2.22 ± 0.36	1.4512	60.28
P10	94.63 ± 0.27	0.245 ±0.15	248 ± 0.45	2.41 ± 0.21	1.0654	43.41
Pll	95.66 ±0.31	0.245 ±0.13	258 ±0.51	2.21 ± 0.13	1.3505	53.03
P12	98.11±0.34	0.212 ±0.11	279 ± 0.6	2.25 ± 0.51	1.2641	57.04
P13	95.45 ± 0.25	0.211 ±0.13	250 ±0.81	2.20 ± 0.22	0.4361	50.17
P14	98.43 ±0.34	0.227 ±0.15	280 ±0.16	2.52 ± 0.18	2.7869	67.18
P15	96.4 ±0.27	0.215±0.11	247 ±0 .35	2.18 ± 0.23	0.4015	45.92
P16	95.31 ±0.42	0.224 ± 0.09	280 ±0.47	2.24 ± 0.24	2.6636	62.04
P17	97.41 ±0.30	0.221 ±0.13	248 ± 0.45	2.31 ± 0.21	0.3815	42.69
P18	98.54 ±0.23	0.210 ±0.16	278 ± 0.34	2.75 ± 0.26	2.3828	58.55

n= 3

Table No. 3: ANOVA Table

ANOVA for permeation flux data						
Source of variation	SS	Df	MS	F	P-value	F crit
Between Groups	2856.068	11	259.6426	202.4543	7.05E-21	2.21631
Within Groups	30.7794	24	1.282475			
Total	2886.847	35				
ANOVA for release rate constant data						
Source of variation	SS	Df	MS	F	P-value	Fcrit
Between Groups	22.2174	8	2.777175	2537.914	7.37E-26	2.510156
Within Groups	0.019697	18	0.001094			
Total	22.2371	26				

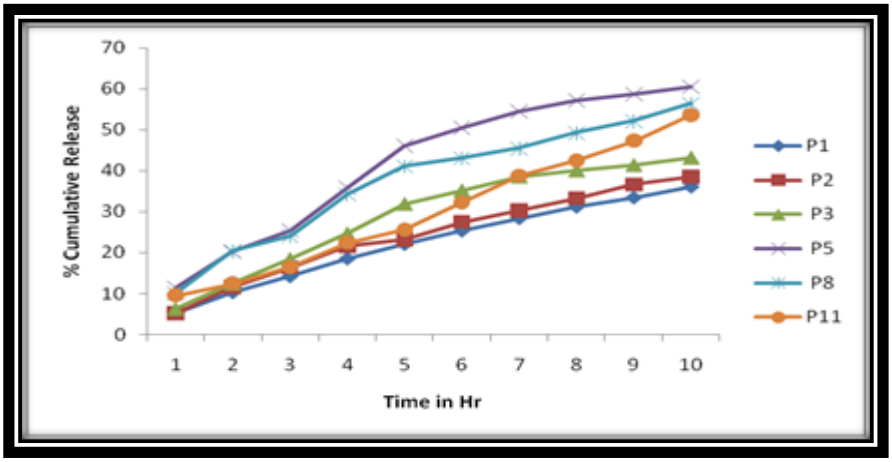

Fig. 1: In vitro cumulative % drug released from EC Pentazocine transdermal patches

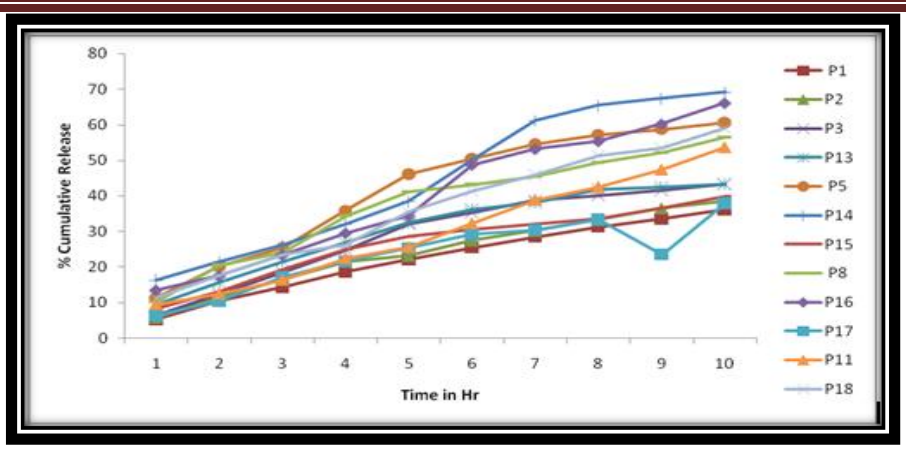

Fig. 2: In vitro cumulative percent Pentazocine released at different drug load

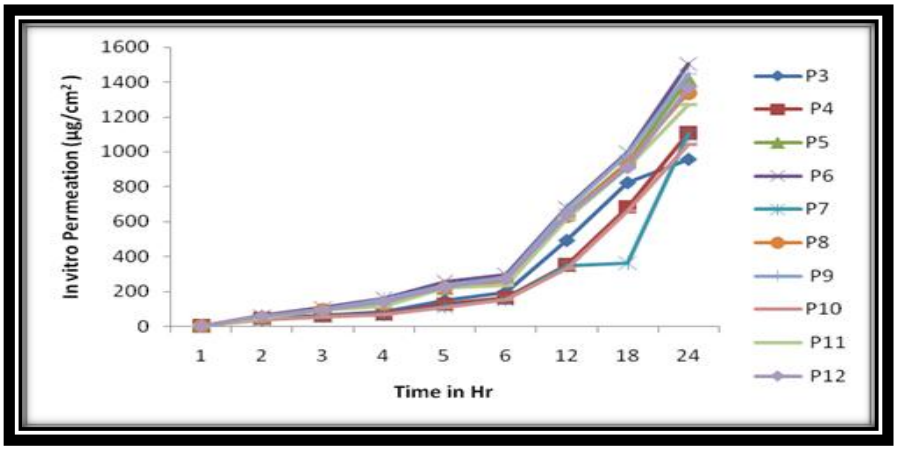

Fig. 3: In vitro Pentazocine permeation (µg/cm²) at different concentration of penetration enhancers

ACKNOWLEDGEMENT

We express our sincere thanks to Concept Pharmaceuticals, Aurangabad for providing Pentazocine Hydrochloride, ethyl cellulose and poly vinyl pyrrolidone.

REFERENCES:

1. Chien YW. Novel Drug Delivery System: Fundamentals, developmental concepts, Biomedical assessments, Marcel Dekker. Inc., New York, **1982**; pp. 301.
2. Ghosal SK, Bhattacharya M, Mandal SC. In vitro release and permeation kinetics of pentazocine from matrix dispersion type transdermal drug delivery systems. *Drug Dev Ind Pharm* **1994**;20:1933-41.
3. Hardman JC, Limbird LE. Goodman and Gilman's The pharmacological basis of therapeutics, 10th ed., McGraw Hill Medical Publishing Division, New delhi, **2001**; pp.456.
4. Jain NK. Advances in controlled and novel drug delivery, 1st ed., CBS Publisher, New Delhi, **2001**; pp.108.
5. Jamakandi VG, Mulla JS, Vinay BL. Formulation, characterization and evaluation of matrix type trandermal patches of a model antihypertensive drug. *Asian J Pharm* **2009**.
6. 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**.
7. Mohamed A, Yasim S, Asgar A. Matrix type transdermal drug delivery systems of Metiprolol tartarate: In vitro characterization. *Acta Pharm* **2003**;53:119-25.
8. Pugh WJ, Hargraft J. Prediction of human skin permeability coefficient. *Int J Pharm* **1994**;103:163-78.
9. Sadashivaiah R, Dinesh B M, Patil U A. Design and in vitro evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers. *Asian J Pharm* **2006**.
10. Shinde AJ, Garala KC, More HN. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. *Asian J Pharm* **2008**.

How to cite this article:

E. Hima Bindu, NL. Mahammed. FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES LOADED WITH PENTAZOCINE HYDROCHLORIDE. J Pharm Res 2019;8(7):458-462. **DOI: https://doi.org/10.5281/zenodo.3357179**

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nils