APPENDIX

APTI ijper

Development and Evaluation of Propranolol Hydrochloride Transdermal Patches by using Hydrophilic and Hydrophobic Polymer

Dey B.K*, Nath L.K, Mohanti B[1], Bhowmik B.B.

Department of Pharmaceutics, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim- 737136

[1]Technical Manager, National Health Care Pvt. Ltd, Birgunj, Nepal

** For Correspondence : E-mail: biplabrumpa@yahoo.com*

Abstract

Propranolol hydrochloride is a non-selective beta-adrenergic blocking agent and clinically used in angina pectoris, cardiac arrhythmia and in hypertension. It inhibits response to adrenergic stimuli by competitively blocking beta-adrenergic receptors in the myocardium, bronchial and vascular smooth muscles. The drug has been reported for potential administration through transdermal route. Present investigation was carried out to study the effect of different proportions of ethyl cellulose and polyvinyl pyrrolidone, a hydrophobic and a hydrophilic polymer respectively, on the permeation profile of the drug across the rat abdomen for the development of a reproducible transdermal therapeutic system of propranolol hydrochloride. Transdermal films were prepared using ten different combinations of the two polymers by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as plasticizer. Several physicochemical parameters like moisture content, moisture loss, thickness, film folding endurance, tensile strength and film elongation were studied. For all the formulations, skin permeation of the drug through rat abdomen was studied using Keshary-Chien diffusion cell. Formulations with highest proportion of polyvinyl pyrrolidone shows faster release over a day's span whereas increasing proportion of ethyl cellulose produces a prolonged regimen of sustained drug delivery through transdermal route for a period of more than a day. The present study has demonstrated the potential of the fabricated matrix films for prolonged release of propranolol hydrochloride.

***Key words**: Propranolol hydrochloride, transdermal therapeutic system (TTS), ethyl cellulose (EC), polyvinyl pyrrolidone (PVP).*

INTRODUCTION

Though the concept of transdermal therapeutic system (TTS) of drug delivery has been well known since 1924, it is only in the year of 1979, with FDA approval of scopolamine transdermal systems, the TTS have received broad impact on the scenario of novel dosage forms[1]. Transdermal therapeutic systems are designed for controlled drug delivery through the skin into systemic circulation maintaining consistent efficacy and reducing dose of the drug and it's related side effects[2-3]. It provides an alternate route of drug delivery avoiding the hepatic first pass effect. It also improves patient compliance, safety and efficacy of the drug[4]. Propranolol hydrochloride is used in the treatment of angina pectoris, cardiac arrhythmia and hypertension. It is the drug of choice for sustained release formulation since it has a low terminal elimination half life of about 3 to 5 hr, which requires frequent dosing necessary to maintain the therapeutic blood level for a long term treatment. The drug shows considerable first pass metabolism in the liver and thereby has poor bioavailability (15-23%) when administered orally[5,6] and the low molecular weight (295.81) of the drug

Indian Journal of Pharmaceutical Education & Research
Received on 28/12/2006; Modified on : 27/8/2007
Accepted on 10/9/2007

gain indicates it's suitability for administration by the ransdermal route. Propranolol hydrochloride ransdermal films were prepared using ten different ombinations of the two polymers namely ethyl ellulose (EC) and polyvinyl pyrrolidone (PVP) by olvent evaporation technique. Polyvinyl alcohol (4% v/v) was used to prepare the backing membrane and libutyl phthalate (30% w/w) as plasticizer. Concentration of drug was maintained at 20% w/w for ll the formulations. Several physicochemical arameters like moisture content; moisture uptake, film hickness, film folding endurance, tensile strength and ilm elongation were evaluated. For all the ormulations, permeation of the drug through the xcised abdominal skin of rat was studied using Keshary-Chien diffusion cell[7-8].

MATERIALS AND METHOD

Ethyl cellulose (20cps), polyvinyl pyrrolidone (K30), polyvinyl alcohol (PVA) and dibutyl phthalate were procured from S.D.Fine Chem. Ltd. Mumbai. Propranolol hydrochloride was received as generous gift sample from Sun Pharmaceuticals Ltd., Baroda, Gujarat. All other chemicals and solvents used were of analytical grade.

Preparation of the transdermal patches:

Matrix type transdermal patches containing propranolol hydrochloride were prepared using different ratios (Table 1) of EC and PVP by solvent evaporation technique in cylindrical glass moulds opened from both nd. The bottom of the mould was wrapped with luminum foil on which the backing membrane was ast by pouring 4% w/v PVA solution in distilled water ollowed by drying at 60°C for 6 h in an oven[9]. The two olymers were weighed in requisite ratio and they were nen dissolved in chloroform. The ratios of the olymers were varied for all the formulations keeping ne total weight fixed at 500 mg. Dibutyl phthalate 0% w/w of polymer composition was added as lasticizer. Propranolol hydrochloride at a oncentration of 20% w/w of polymer was added and tirred with a mechanical stirrer to get a homogeneous ispersion. The dispersion (2ml) was cast on the repared PVA backing membrane in each mould. The ate of evaporation was controlled by inverting a funnel ver the mould and dried at 40°C for 6 h in hot air oven. After drying they were kept in desiccator for further study.

Evaluations of transdermal patches:

Moisture content:

The prepared films were marked, weighed and kept in desiccator containing activated silica at room temperature for 24 h. The individual films were weighed on every alternate day until a constant weight was achieved. The percentage of moisture content was calculated[10] by determining the difference between initial and final weight with respect to final weight. The mean value of three replicates of weight was used for calculation.

Moisture loss:

A weighed film kept in a desiccator at normal room temperature for 24 h, was taken out and exposed to 84% relative humidity (standard solution of potassium chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture loss was calculated[10] by determining the difference between final and initial weight with respect to initial weight. The mean value of three replicates of weight was used for calculation.

Folding endurance:

Folding endurance of the film was determined manually by folding a small strip of the film at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the value of folding endurance, where the cracking point of the films were considered as the end point[11].

Thickness:

The thickness of each film was measured at five different sites using a meter gauge (Mercer, USA) and the mean thickness was calculated[12].

Elongation and tensile strength:

The tensile strength measurement was made using an instrument assembled in the laboratory and following the method used by Sadhana *et al*[12]. The films were fixed individually to the assembly. The required weights to break the films were noted. Percentage of elongation of the films was measured by attaching a pointer mounted on the assembly. Tensile strength was calculated by using the following formula. The results are given in Table 1.

Tensile strength = (break force/a × b) × (1+L/I)

Where, a, b, L and I are the width, thickness, length and elongation of the films.

Skin permeation study:

Skin permeation study of the transdermal therapeutic systems was carried out using Keshary-Chien permeation cell. The skin of an albino rat was removed from the abdominal portion after sacrificing the rat. It was made free from hair and fat by treating with 0.32 M ammonia solution for 35 min. The transdermal therapeutic system of 3.08 cm^2 area was mounted between the donor and receptor compartments of the diffusion cell keeping intimate contact with the stratum corneal side of the skin[13]. The receptor compartment was filled with 25 ml of phosphate buffer of pH 7.4. The cell was placed in a water bath maintained at 37 ± 1°C on a magnetic stirrer and stirring was continued throughout the experiment. At regular intervals over a period of 24 h, samples were withdrawn and simultaneously compensation was made with same volume of buffer. The samples were then analyzed spectrophotometrically at 290 nm against a blank.

Scanning electron microscopy:

The surface morphologies of the films showed better permeation were investigated by using Scanning Electron Microscope, model Jeol JSM-5200, Japan, at 15 kV. Prior to examination, the samples were gold-coated to render them electrically conductive[14].

RESULTS AND DISCUSSION

In this study, various matrix type transdermal patches containing propranolol hydrochloride with variable combinations of EC and PVP were prepared and prolonged release of the drug through the matrix films was demonstrated.

The physicochemical parameters and the release characteristics were studied on the fabricated patches. The moisture content and the moisture loss (Fig 1) of the various formulations exhibit that with the increase in the concentration of hydrophilic polymer (PVP), both the percentage moisture content and the percentage moisture loss was increased. The low moisture content in the formulations helps them to remain stable and prevent from being a completely dried and brittle film. Again, a low moisture uptake protects the material from microbial contamination and limits the bulkiness of the patches. In this respect, formulation TTS6 showed best result amongst all the formulations.

Folding endurance was found to be varied between 61 ± 3.78 to 260 ± 5.20 (Table 1). It was found that films with high proportion of PVP showed drastic reduction in film endurance. Changes in the proportion of EC did not affect much on the mean folding endurance of the films but it is evident from the result that higher the EC proportion more was the film endurance. Formulation TTS6 showed an optimum endurance (240 ± 5.46).

With the increase in the proportion of the PVP in the film, the tensile strength and the thickness of the films was found to be significantly decreased (Table 1), but the variation in percentage elongation was found to be insignificant over the different proportions of EC and PVP used. Formulation TTS6 showed less percentage elongation and high tensile strength in comparison to the formulation TTS5, which indicated that the films containing more proportion of EC are relatively more strong and tough compared to the films containing more proportion of PVP.

The graphical representation of the cumulative percentage of drug permeated as a function of time through the rat skin is presented in Fig 2. From the figure it is evident that high proportion of hydrophilic polymer (PVP) enhances permeation rate. Formulation TTS6 and TTS7 with higher concentration of EC showed prolonged permeation of drug in comparison to other formulated patches. It was observed that from the formulation TTS6 only 39% of the drug was permeated in 24 h whereas the permeation was 85% from the formulation TTS5 within that period.

Fig 3 is the SEM photograph of the film containing both the polymers and the plasticizer without the drug. Fig 4 is the SEM photograph of the drug loaded film before skin permeation study, which exhibits surface uniformity of the film. The pores on the film as visualized in Fig 5 are due to the drug released from the polymer matrix after permeation through skin.

In conclusion, skin permeation of propranolol hydrochloride from its transdermal patches showed that the films containing higher proportion of PVP are suitable for once a day drug delivery and the films containing higher proportion of EC showed suitability for a prolonged regimen of sustained drug delivery through transdermal route for a period of more than 24 h. The results of the study give a rational guideline for formulating a sustained release transdermal therapeutic

Table1: Formulation design and study of various physical parameters of the transdermal therapeutic systems of propranolol hydrochloride.

Sl. No.	Formulation code	Ratio of polymers (EC: PVP)	Mean Thickness (μm) n = 3 (± = s.d.)	Mean Elongation (%) n = 3 (± = s.d.)	Mean Tensile strength (gm/cm^2) n = 3 (± = s.d.)	Mean folding endurance n = 5 (± = s.d.)
.	TTS1	1:2	115 ± 0.9	23.22	251.36	261±5.21
.	TTS2	1:4	116 ± 0.9	24.21	243.67	208±6.74
.	TTS3	1:6	110 ± 0.8	22.28	221.54	183±6.21
.	TTS4	1:8	109 ± 0.4	25.10	215.58	101±5.51
.	TTS5	1:10	104 ± 0.8	23.30	211.45	62±3.78
.	TTS6	10:1	125 ± 0.8	20.40	280.52	240±5.46
.	TTS7	8:1	126 ± 0.4	21.65	280.89	233±6.73
.	TTS8	6:1	119 ± 1.0	20.00	261.48	220±7.84
.	TTS9	4:1	120 ± 1.0	22.10	257.60	211±6.46
0.	TTS10	2:1	117 ± 0.9	21.41	253.52	202±5.37

n = number of repeated observation. ; s.d. = standard deviation.

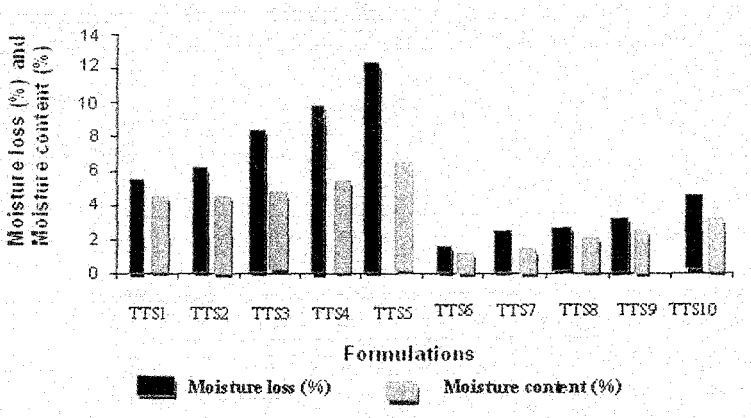
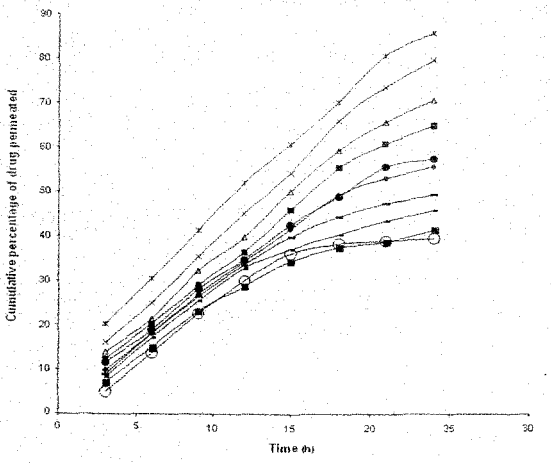


Fig 1: (%) Moisture loss and moisture content profile of the prepared Propranolol hydrochloride transdermal therapeutic systems.



ig 2: Comparison of in-vitro permeation rate profile of matrix diffusion controlled Propranolol hydrochloride TS through rat abdominal skin. Patches with different concentrations of EC and PVP that include (-●-) 1:2, (-▪-) 1:4, (-Δ-) 1:6, (-\-) 1:8, (-×-) 1:10, (-O-) 10:1, (-■-) 8:1, (— -) 6:1, (—— -) 4:1, (-◆-) 2:1.

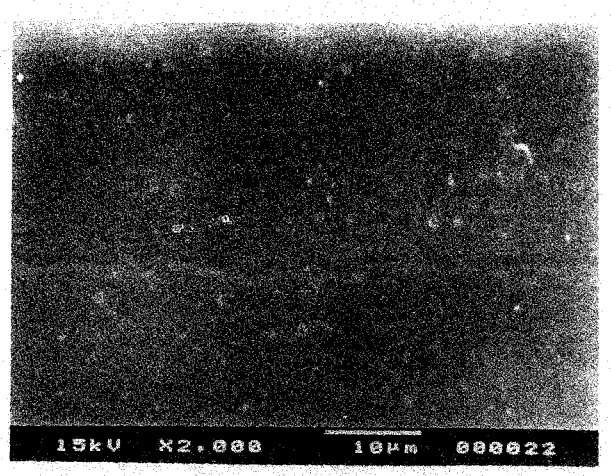


Fig 3: SEM photograph of the blank film containing EC and PVP.

Fig 4: SEM photograph of the drug-loaded film before skin permeation study.

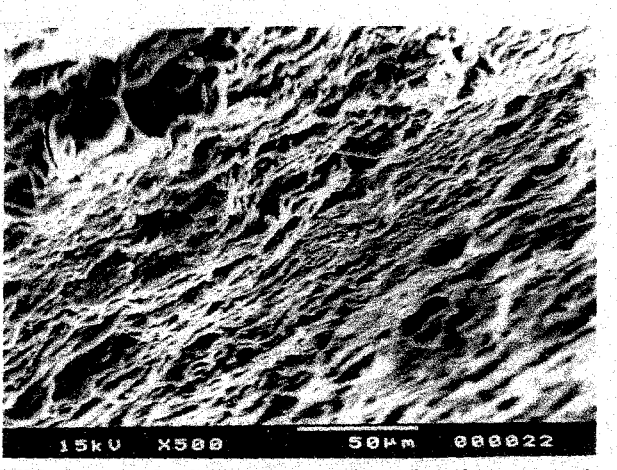


Fig 5: SEM photograph of the exhausted film after skin permeation study

system of Propranolol hydrochloride for effective therapy and prophylaxis of angina pectoris, cardiac arrhythmia and hypertension.

ACKNOWLEDGEMENT

The authors are thankful to Sun Pharmaceuticals Ltd., Baroda, for providing the gift sample of propranolol hydrochloride.

REFERENCES

1. Misra A. Transdermal drug delivery: present and future. The Pharma Review 2004; 92-102.
2. Barry BW. Dermatological Formulations, Percutaneous Absorption. New York: Marcel Dekker; 1987.
3. Robinson JR, Lee VHL. Controlled Drug Delivery, Fundamentals and Applications. 2nd ed. New York: Marcel Dekker; 1987.
4. Paudel Kalpana S, Nalluri Buchi N, Hammell Dana C et al. Transdermal delivery of naltrexone and its active metabolite 6-β-naltrexol in human skin *in vitro* and guinea pigs *in vivo*. J Pharm Sci 2005; 94(9): 1965-1974.
5. Goodman Gilman A. The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill, Medical Publishing Division; 2001.
6. Pharmacopoeia of India, 3rd ed. Vol.II, New Delhi: Controller of Publications, Ministry of Health, Govt. of India; 1996.
7. Kumhar SK, Jain SK, Pancholi SS, Agrawal S, Saraf DK, Agrawal GP. Provesicular transdermal drug delivery system of ethinylestradiol and levonorgestrel for contraception and hormone replacement therapy. Indian J Pharm Sci 2003; 65(6): 620-627.
8. Kulkarni VH, Keshavayya J, Shastry CS, Kulkarni Preeti V. Transdermal delivery of antiasthmatic

drug through modified chitosan membrane. Indian J Pharm Sci 2005; 67(5): 544-547.

9. Sagar P, Kulkarni Raghavendra V, Doddayya H. Development and evaluation of membrane controlled transdermal therapeutic systems. The Pharma Review 2006; 90-92.
10. Raghuraman S, Velrajan G, Ravi R, Jeyabalan B, Benito Johnson D, Sankar V. Design and evaluation of propranolol hydrochloride buccal films. Indian J Pharm Sci 2002; 64(1): 32-36.
11. Manvi FV, Dandagi PM, Gadad AP, Mastiholimath VS, Jagadeesh T. Formulation of a transdermal drug delivery system of ketotifen fumarate. Indian J Pharm Sci 2003; 65(3): 239-243.
12. Gupta Sadhana P, Jain SK. Effective and controlled transdermal delivery of metoprolol tartarate. Indian J Pharm Sci 2005; 67(3): 346-350.
13. Bharkatiya M, Nema RK, Gupta GD, Gaud RS. Designing and evaluation of propranolol hydrochloride transdermal patches. The Pharma Review 2005; 113-116.
14. Das MK, Bhattacharya A, Ghosal SK. Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. Indian J Pharm Sci 2006; 68(1): 41-46.