Asian Journal of Pharmaceutical and Health Sciences
Journal Homepage : www.ajphs.com

# Formulation Of Transdermal Drug Delivery System Of Metoprolol Tartrate And Its Evaluation.

**Anisree G.S.*, Ramasamy C., John Wesley I., Bincy Mary K.**
Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Pulikkal, Malappuram, Kerala,India.

**ARTICLE HISTORY**

Received 15 - Dec - 2010
Accepted 01 - Jan - 2011
Available online 10 - Feb - 2011

**Keywords:**

Metoprolol tartrate,Transdermal films, Invitro permeation studies.

***Corresponding author:**

E- mail: anisreegs@gmail.com.
Mob: +91 9895669927

**ABSTRACT**

The oral bioavailability of Metoprolol tartrate is poor, different matrix-type transdermal films containing Metoprolol tartrate was formulated with an objective to study the effect of polymers on the release characters. The polymers selected were cellulose acetate butyrate(CAB), polyvinyl pyrrolidone (PVP), ethyl cellulose (EC), and hydroxy propyl methyl cellulose (HPMC).The films were formulated using different blends of the polymers by solvent casting method. The physico chemical evaluation of the polymer matrices was performed for suitability.The interaction among various components of the matrices was studied by performing fourier transform infrared spectroscopy and thin layer chromatography. *In-vitro* permeation studies of ideal films were performed using Franz diffusion cell. The results revealed the amount of drug released in a steady state and in a controlled manner.

## INTRODUCTION

Transdermal drug delivery systems[1] have been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin. Because transdermal drug delivery offers controlled release of drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and improved efficacy over other dosage forms. This route of drug delivery is becoming increasingly popular with the demonstration of the percutaneous absorption of large number of drugs. In addition transdermal films are convenient, painless, and it is generally accepted that they offer improved patient compliance.

Metoprolol tartrate[2] is a beta adrenoreceptor blocking agent used in the treatment of cardiovascular disorders. The drug has a half-life of 3-4 hours and extensive first pass metabolism. This can be minimized by converting the conventional dosage form to one of the novel approaches like transdermal therapeutic system. Transdermally delivered drug provides the patients a unique and convenient dosing schedule while providing nearly constant serum levels of medication over a prolonged period.

In the view of the substantial hepatic first pass effect and the shorter half life, Metoprolol tartrate is chosen as a candidate for exploring its application as transdermal drug delivery system. Drug containing formulations were prepared with different rate controlling polymer[3] matrices. Polymer combinations have been used in the formulation of transdermal matrices. In the view of excellent film forming property, cellulose acetate butyrate, polyvinylpyrrolidone and hydroxyl propyl methyl cellulose has been chosen and studied for its usefulness as polymeric matrix in the development of transdermal films.

## MATERIALS AND METHODS

Metoprolol tartrate (MT) was obtained as a gift sample from Astra Zeneca Pharma IndiaLtd,Mumbai,Cellulose acetate butyrate(CAB) and Ethylcellulose(EC) were obtained from Glaxo Mumbai, Polyvinylpyrrolidone(PVP) was obtained from Loba Chemicals Mumbai, Hydroxypropylmethyl cellulose(HPMC) obtained from High media chemicals, Bangalore, Di n-butyl phthalate obtained from Ranbaxy Mumbai, Isopropyl myristate obtained from SD Fine Chemicals Mumbai. All other chemicals were of analytical grade. The drug samples characterized by means of UV,IR methods along with determination of solubility and pH for their authentication.

### Development of Transdermal Films

In the present study matrix type transdermal films of Metoprolol tartrate were prepared by solvent casting method. Locally fabricated glass mould was used for this purpose. The transdermal films were prepared using the polymers in different ratios. CAB and PVP films were prepared by dissolving CAB in measured volume of chloroform and kept aside for 4 hours to facilitate the polymer to dissolve in the solvent following mixing with required quantity of PVP. To this added specified quantities of dibutyl phthalate and propyl myristate.

The polymeric solution of EC and HPMC were prepared by dissolving separately in methanol- chloroform (1:1) mixture. Both solutions are mixed in different ratios using dibutyl phthalate as plasticizer. The polymeric solution of EC and PVP were prepared by dissolving in chloroform in different ratios.

A weighed amount of drug was dissolved in suitable solvent and dispersed in polymer mixture, poured in to the glass mould placed in a leveled, hard rigid surface.Solvent evaporation was controlled by covering with the placement of funnel in its inverted position. After 24 hours the films were removed and kept in dessicator to remove any adhering solvents. Then the films were cut in circular disc with 3.8cm diameter. These films were wrapped in aluminium foil, packed in self sealing cover and kept in dessicator. The composition of various formulations is given in the Table. 1.

**Table No-1** Composition of various formulation of Metoprolol Tartrate.

| Film Identity | MT in mg | CAB in parts | PVP in parts | EC in parts | HPMC in parts | DBP in %W/W | IPM in %W/W |
|---|---|---|---|---|---|---|---|
| $F_1$ | 15 | 4.5 | 0.5 | — | — | 30 | 20 |
| $F_2$ | 15 | 4.0 | 1.0 | — | — | 30 | 20 |
| $F_3$ | 15 | 3.5 | 1.5 | — | — | 30 | 20 |
| $F_4$ | 15 | 3.0 | 2.0 | — | — | 30 | 20 |
| $F_5$ | 15 | 2.5 | 2.5 | — | — | 30 | 20 |
| $F_6$ | 15 | 2.0 | 3.0 | — | — | 30 | 20 |
| $F_7$ | 15 | 1.5 | 3.5 | — | — | 30 | 20 |
| $F_8$ | 15 | — | — | 4.5 | 0.5 | 30 | 20 |
| $F_9$ | 15 | — | — | 4.0 | 1.0 | 30 | 20 |
| $F_{10}$ | 15 | — | — | 3.5 | 1.5 | 30 | 20 |
| $F_{11}$ | 15 | — | — | 3.0 | 2.0 | 30 | 20 |
| $F_{12}$ | 15 | — | — | 2.5 | 2.5 | 30 | 20 |
| $F_{13}$ | 15 | — | — | 2.0 | 3.0 | 30 | 20 |
| $F_{14}$ | 15 | — | — | 1.5 | 3.5 | 30 | 20 |
| $F_{15}$ | 15 | — | 4.5 | 0.5 | — | 30 | 20 |
| $F_{16}$ | 15 | — | 4.0 | 1.0 | — | 30 | 20 |
| $F_{17}$ | 15 | — | 3.5 | 1.5 | — | 30 | 20 |
| $F_{18}$ | 15 | — | 3.0 | 2.0 | — | 30 | 20 |
| $F_{19}$ | 15 | — | 2.5 | 2.5 | — | 30 | 20 |
| $F_{20}$ | 15 | — | 2.0 | 3.0 | — | 30 | 20 |
| $F_{21}$ | 15 | — | 1.5 | 3.5 | — | 30 | 20 |

## Drug content determination[4]

Randomly selected film from each batch was put into a 100ml standard flask containing the buffer solution (pH- 7.4) and shaken continuously for 24 hours. Then the solution was filtered and drug content was determined with the help of UV spectrophotometer at wave length 225nm.

## In vitro drug Permeation Studies[5]

*In vitro* permeation studies were performed using Franz diffusion cell. The dialysis membrane was mounted between the donor compartment and receptor compartment of the diffusion cell. The dialysis sac was previously soaked for 2 h in PBS. The formulated films were placed over the membrane.

The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37 ± $2^0$C.Samples were withdrawn (2 mL) at predetermined time intervals and replaced with an equal volume of phosphate buffer. The samples were suitably diluted and analyzed for drug content using UV spectrophotometer at a wave length of 225nm.The permeation study was carried out for 24 h.

### Physical Appearance[6,7]

The physical appearances of the films were found out by examining the films opposite to a clear source of light for their transparency, smoothness and flexibility of the prepared films.

### Folding Endurance[6,7]

Folding endurance is determined to identify flexibility of the films.Folding endurance was determined by folding the films repeatedly in the same part of the film until it brokes.

### Film thickness [6,7]

Film thickness is another physicochemical parameter. Five films from each formulation were selected randomly to study the thickness using thickness gauge and average was determined.

### Tensile Strength [6,7]

Tensile strength as determined by using a modified pulley system. Weight was gradually increased so as to increase the pulley force till the film broke. The percentage elongation before the film broke was noted with the help of a magnifying glass on a graph paper and the tensile strength was calculated as kg/$mm^2$.

### Weight Variation test [6,7]

To determine the weight variation of the prepared films, study was carried out by taking the weight of randomly selected five films from each batch with the help of high accuracy electronic balance. The average weight of a film and its standard deviation was calculated.

### Percentage of moisture content[6,7]

Randomly selected films were weighed individually and kept in the platform of the dessicator containing anhydrous calcium chloride at room temperature for 24 hours.Films were weighed separately and repeatedly until a constant weight obtained. The percentage of moisture content was calculated by simplifying the difference between initial and final weight with respect to the final weight.

### Percentage moisture uptake[6,7]

Randomly selected films from each batch were weighed accurately and placed in a desiccator where a humidity condition of 75%RH was maintained by using saturated solution of potassium chloride. After 3days, the films were taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

### Stability Studies[4,5,8,9,10]

The prepared films were placed in USP type 1 amber coloured vials.Perfectly closed and sealed vials were placed in a stability chamber at $37^0$C and an atmosphere of RH=82% for three months. Each time 3 films were withdrawn and evaluated for physical appearance and drug content.

## RESULTS AND DISCUSSIONS

The persent study was aimed to formulate transdermal drug delivery system of Metoprolol tartrate with different combinations of polymers. Thin layer chromatography and infrared spectroscopic results confirms the intactness of the drug with the polymers. In the primary evaluation parameters such as physical appearance, folding endurance, moisture content, moisture uptake meets the ideal properties of the films. As the formulation procedure required fewer processing steps, no major drug loss was observed during the development.

The compatibility studies showed the drug is intact to the polymers. The IR spectra obtained do not have any fluctuations as compared with the combination. Physical appearance studies showed the films are transparent, flexible and translucent. The ideal films have adequate folding endurance, thickness and tensile strength. The results of percentage moisture content and moisture uptake, shows when the concentration of PVP increases, an increase in moisture content and moisture uptake observed. The formulations containing EC and HPMC showed a gain in weight as compared with CAB-PVP and EC-PVP combinations. Drug content of all films was found to be adequate with minor variations. The CAB- PVP film met the exact drug content. The formulations containing EC-HPMC in varying concentration showed an increase in thickness compared to CAB-PVP and EC-PVP combinations. The tensile Strength of CAB- PVP films were found to be more as compared to EC - HPMC and EC - PVP films. The *invitro* release of the selected films containing CAB-PVP in the ratio 3:7 showed better release characteristics. The cumulative release of Metoprolol tartrate released from three polymeric films in 24 hours was found to be 42.9% to 49.2%.The results are tabulated and corresponding figure is represented in Figure No-1. The films $F_{7,}$ $F_{14,}$ $F_{19}$ were taken for accelerated stability studies[5]. This was performed by keeping it under $37^0$C and the drug content and *in vitro* release parameters were determined for an interval of 30 days up to 90 days.

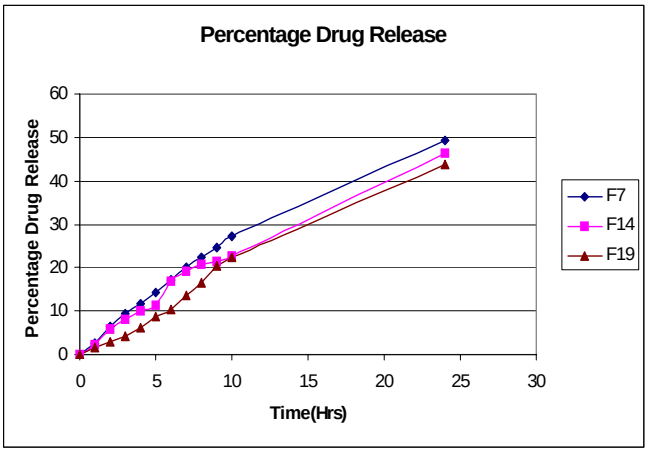


**Fig. 1:** Figure showing Percentage Drug Release of selected Films.

Accelerated stability studies for the selected films indicated that formulated films were having adequate shelf life. From all the above evaluation parameters, the film containing CAB- PVP in the ratio of 3:7 showed better physicochemical properties, good release profile, and has adequate shelf life. The values are presented in Table No-2. Thus the film denoted by the formulation identity number F7(film containing CAB- PVP in the ratio of 3:7) can be used to get a steady state drug concentration in a controlled manner and this will be beneficial for the patient[5].

**Table No-2** Percentage drug content for films $F_7$, $F_{14}$ and $F_{19}$ during accelerated stability studies.

| Time in days | Drug content ($37^0$ c) | | |
|---|---|---|---|
| | $F_7$ | $F_{14}$ | $F_{19}$ |
| 0 | 100 | 100 | 100 |
| 30 | 99.70 | 99.61 | 99.91 |
| 60 | 99.51 | 99.42 | 99.89 |
| 90 | 99.22 | 99.03 | 99.78 |

## CONCLUSION

The purpose of the work was an attempt to develop a transdermal drug delivery system of Metoprolol tartrate using three different polymer combinations i.e. CAB-PVP, EC- HPMC and EC- PVP in different ratios. Total of 21 films were prepared. Out of which the CAB-PVP films were found to have better characteristics than the other two films.

The compatibility studies confirmed the absence of chemical interaction between the drug and other excipients employed in the formulation. They have been evaluated for physicochemical parameters like physical appearance, average weight, thickness, percent moisture content, percent moisture uptake and drug content. Release rates were found out by *in vitro* diffusion studies using Franz diffusion cell.

From the *in vitro* release results observed, it was noticed that films prepared using CAB-PVP proved to exhibit better release characteristics. The results for the physicochemical parameters of CAB- PVP films were also better than the other two films containing EC- HPMC and EC- PVP. Accelerated stability studies indicated that the formulated films were having adequate shelf life. The study concluded that the ideal film can employed for the patient to get a steady state drug concentration, which would improve the patient compliance also.

## ACKNOWLEDGMENT

We thank the Director, Principal, Vice-Principal - Jamia Salafiya Pharmacy College,Pulikkal and Karpagam university Coimbatore for the timely support to carry out this work in a successful manner.

## REFERENCES

1. Banker G S., Rhodes T. Modern Pharmaceutics, Newyork: Dekker; 1991.p.287.

2. Indian pharmacopoeia, Goverment of India, Ministry of health and family welfare, NewDelhi; Controller of publications; 1996.p.486-87.

3. Kandavilli S, Nair V, Panchangula R. Polymers in TDDS. Pharmaceutical technology 2002; p63-80.

4. Fang JY, Sung KC, Hong H, Lang LC. Transdermal iontophoretic delivery of diclofenac sodium from various polymer formulations, invitro and invivo studies. Int.J.Pharm. 1999; 178: 83-92.

5. Gupta SP, Jain SK. Effective and controlled transdermal delivery of Metoprolol tartrate. Indian Journal of pharmaceutical sciences 2005; 67(3): p346-50.

6. Chein YW, Novel drug delivery system. 2nd ed. Newyork: Dekker; p. 306-36,428-29.

7. Vyas SP, khar RK. Controlled drug delivery system. New Delhi: Vallabh Prakashan; 2002. p.412-13

8. Paranjothy, K.L.K., Development of Transdermal patches of Verapamil Hydrochloride using Sodium Carboxy Methyl Guar as monolithic polymeric matrix and their *in-vitro* release studies. Indian J. Pharm. Sci., Mar-Apr 1997; 59 (2) 49-54

9. Manvi, F.V., Formulation of a Transdermal Drug Delivery System of Ketotifen Fumarate. Indian J. Pharm. Sci. May-Jun 2003; 65(3): 239-243.

10. Saraf Swarnlata., Transdermal Formulation and Evaluation of Timolol Maletate. Internet Journal of Pharmacy, 2006, www.priory.com/pharmacol/timolol.htm.