Research Article

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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF ATENOLOL

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ABSTRACT

This study was carried out to develop matrix based transdermal patches containing Atenolol. A 2 factors HPMC (hydroxyl propyl methyl cellulose) K4M and PVP (Polyvinyl Pyrolidone) 3 level (2^3) factorial design was done using Design Expert® which gave 13 experiments. The patches were prepared by Solvent casting method. Propylene glycol (3%) and Tween 80 (6%) were used as plasticizer and permeation enhancer respectively. Physicochemical characteristics and In-Vitro permeation study of formulated transdermal patches were carried out. Contour plot suggested 770mg of PVP and 265mg of HPMC K4M in Optimized formulation.

Keywords: Atenolol, Transdermal Patches, In-Vitro permeation study, permeation enhancer, HPMC, PVP

INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the advantageous routes of drug administration (Ibrahim *et al*., 2014). TDDS is particularly important because it by-passes first-pass metabolism. However, this route of delivery is challenged by the barrier nature of skin. Various medicines are available in TDDS (Sun *et al*., 1997).

TDDS basically consists of adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a preprogrammed rate (Ahmed *et al*., 2011), which is able to penetrate through different layers of skin to reach the systemic circulation (Chander *et al*., 2013). Currently, the transdermal route, along with oral treatment, ranks as the most successful innovative research area in drug delivery (Saroha *et al*, 2011). Baking layer, drug containing layer, rate controlling membrane, adhesive and release liner are the components of TDDS (Jhawat *et al*, 2013; Prejeet *et al*., 2011; Chein *et al*., 1987) though all layers may not be available in all types of TDDS as there are several types of transdermal patches. There are single layer drug in adhesive, multilayer drug in adhesive, vapour patch, reservoir system and matrix system (Aulton, 2002). Similarly natural polymers, synthetic polymers, synthetic elastomers and biopolymers have been used in TDDS (Sharma *et al.,* 2012). The biological properties of drug for preparing transdermal patch should be of short half-life, should not produce allergic response and the drug should be potent with a daily dose of the order of a few mg/day (Muller *et al*., 2003). Substances which temporarily diminish the impermeability of the skin are known as permeation enhancers. As the epidermis is the main barrier for penetration of the drug, several chemical enhancers such as sulphoxide, alcohols, fatty acids, polyols, ureas and physical enhancers such as sonophorosis, electroporation, iontophorosis, magnetophorosis have been used in TDDS (Finnin *et al*., 1999; Funke *et al*., 2002; Taylor *et al*., 2002).

This study has been carried out to incorporate Atenolol in matrix-based TDDS. Atenolol is one of the commonly used anti-hypertensive drugs, which acts as a beta-adrenergic receptor blocking agent. After oral administration, the elimination half life of the drug is 6-7h. The absolute bioavailability is approximately 50% due to first pass metabolism (Ghosh *et al*., 2001; Jain *et al*, 1993). Therefore an alternative route (TDDS) is chosen for the delivery of drug.

MATERIALS AND METHODS

Atenolol, HPMC K4M, Tween 80, Sodium hydroxide, and Potassium dihydrogen phosphate and methanol were used during the study. Propylene glycol (3%) was used as plasticizer and Tween 80 (6%) as permeation enhancer.

Table I. A 2^3 factorial design for formulation of matrix based transdermal patches

Ingredient	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
Atenolol (mg)	20	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K4M (mg)	55.17	37.5	37.5	37.5	37.5	37.5	50	25	37.5	37.5	50	19.83	25
PVP (mg)	70	70	70	70	13.36	6.36	115	115	70	70	25	70	25
Tween 80 (%w/w)	10	10	10	10	10	10	10	10	10	10	10	10	10
PEG (%w/w)	5	5	5	5	5	5	5	5	5	5	5	5	5
Methanol (mL)	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43
Water (mL)	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43	1.43

Preparation of standard curve

Absorbance of five known concentrations of Atenolol (20, 40, 60, 80 and 100µg/mL) in Phosphate buffer pH 7.4 were measured in UV-Visible spectrophotometer at V_{max}=275nm. Then Concentration vs Absorbance curve was plotted and correlation coefficient (r^2) value with equation of the curve was determined.

Fabrication of Transdermal Patches

A 2 factor 3 level (2^3) factorial design was done using Design Expert 9.1 which gave 13 experiments (Table I). Then, matrix-based transdermal patches of Atenolol were prepared by solvent casting method using aluminum foil as a backing layer. The two independent factors were HPMC K4M and PVP. The mixture of solvent casting method consisted of solvent (distilled water and methanol), permeation enhancer (Tween 80; 10% of total weight of drug + polymer) and plasticizer (PEG; 5% of total volume of solvent). Dose of drug was adjusted in such a way that circular patch ($4cm^2$) consisted of 20mg of Atenolol.

Evaluation of transdermal patches

Weight variation

The matrix film was cut into $4cm^2$. Weight of five patches was taken individually and averaged (mean ± standard deviation).

Thickness variation

The matrix film was cut into $4cm^2$. Thickness of five patches was measured individually by digital vernier caliper and then averaged (mean ± standard deviation).

Percentage of moisture absorbed

Accurately weighed patches were placed in a desiccators for 72h. After 72h, the patches were reweighed and the percentage moisture absorption was calculated using the formula:

$$\%\ Moisture\ content = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times 100\%$$

Folding endurance of the patches

Patches ($4cm^2$) were cut and repeatedly folded at the same place till it was broken (n=3). The number of times the folding required to be broken was recorded as folding endurance.

Drug content uniformity

A patch ($4cm^2$) was kept in beaker (100mL) with methanol and stirred continuously using a magnetic stirrer for 3h. The sample (1mL) was diluted with methanol in 50mL volumetric flask. The absorbance was taken spectrophotometrically at 275nm using methanol as a blank. The drug content was calculated by using the equation obtained from the standard calibration curve (Figure 1). The experiment for each formulation was triplicated.

Drug permeation study

The in-vitro permeation study was carried out by using Franz Diffusion Cell and cellophane membrane. The Franz diffusion cell has receptor compartment of volume 50mL and internal diameter of 4.5cm. A Transdermal patch was placed on one side of cellophane membrane. The medium on the receptor side was phosphate buffer pH 7.4. The temperature was maintained at 37±2°C. The receptor fluid was stirred by magnetic bead placed in the diffusion cell. During each sampling interval, samples were withdrawn and replaced by equal volumes of fresh receptor fluid.

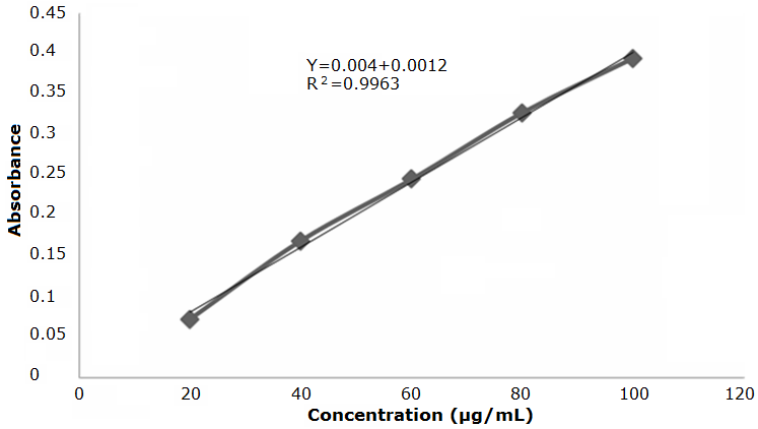

Figure 1. Standard curve of Atenolol

The samples (1mL) was withdrawn at predetermined time interval and diluted with phosphate buffer pH 7.4 in 25mL volumetric flask. The sample was analyzed spectrophotometrically at 275nm.

Drug dissolution study

Dissolution was performed by attaching the patches to the lower surface of a 50mL beaker using a dual side adhesive tape. The beaker was held above another beaker (250mL) by a plastic cap having a hole centrally. The above beaker was held in a cap in such a way that the patch was just touching the medium at another beaker. The receiver beaker was filled with phosphate buffer pH 7.4. The temperature was maintained at 37 ± 2°C and constantly agitated by a magnetic stirrer. Sample were withdrawn at 1, 2 , 4, 6 and 8h and replaced by fresh phosphate buffer pH 7.4. The withdrawn samples were suitably diluted and analysed spectophotometrically at 275nm.

RESULTS AND DISCUSSION

Percentage moisture lost and percentage moisture absorbed were found to be from 5.47 to 16.74 and 5.1 to 9.23, respectively. The minimum and maximum folding endurance were 77 (P5) and 102 (P7), respectively. Drug content of all formulation was found in between 18.67±0.48 (P10) and 20.93±1.32 mg (P8) (Table II and III). The highest and lowest cumulative percentage drug releases in 8h were shown by P7 (87.4 ± 2.20) and P6 (74.3 ± 2.17), respectively (Figure 2). The highest cumulative percentage drug permeation in 12h was shown by P7 (93.70 ± 1.88) while the lowest permeation was shown by P11 (76.50±1) (Figure 3). The contour plot for optimized formulation generated by using Design expert 9.0.3 predicted 770 mg for PVP and 265 mg for HPMC K4M based on 32.8, 49.2, 68 and 80.85% required cumulative percentage drug release in optimized formulation in 2, 4, 6 and 8h respectively (Bangale *et al.*, 2010) (Figure 4). Cumulative percentage drug release for optimized formulation was found to be 30.5, 48.6, 67.8 and 81% for 2, 4, 6 and 8 hr respectively (Figure 5).

Different formulations(p5, and p7) have different folding endurance with same amount plasticizer (Table I) suggest that patch should be made in controlled humidity condition. the different folding endurance could be due to different amount of moisture with patch. Optimized formulation (PVP = 770mg and HPMC K4M = 265mg) developed by Contour plot gave dissimilarity factor towards lower end (1) and similarity factor towards higher end (90) and suggests that cumulative percentage drug release is similar to the reference data (Bangale *et al.*, 2010). The cumulative percentage drug permeated in 12h was found to be the highest for the formulation carrying HPMC K4M and PVP in low ratio (13:10, P7) where as the cumulative percentage of drug permeated in 12h was found to be low in the formulation containing high ratio of HPMC K4M and PVP (2:1, P11).

Table II. Physicochemical properties of matrix-based transdermal patch formulation of Atenolol

Formulation	First Order	Higuchi	Power	n Value	Content Uniformity (Mean±Std. Dev.)	Disimilarity factor (f1)	Similarity factor (f2)
P1	0.99	0.999	0.998	0.662	20.10±1.35	9	62
P2	0.995	0.995	0.998	0.685	20.13±0.31	15	52
P3	0.995	0.995	0.998	0.703	19.77±1.00	15	53
P4	0.998	0.998	0.997	0.698	19.07±1.40	16	54
P5	0-997	0.998	0.989	0.732	19.43±0.72	29	38
P6	0.997	0.995	0.997	0.657	20.23±2.00	34	35
P7	0.989	0.999	0.997	0.656	20.60±1.61	12	56
P8	0.994	0.995	0.997	0.672	20.93±1.32	14	54
P9	0.994	0.982	0.997	0.694	18.67±0.86	14	53
P10	0.993	0.995	0.998	0.687	18.67±0.48	15	61
P11	0.979	0.979	0.99	0.737	20.60±1.61	32	38
P12	0.991	0.999	0.997	0.661	19.67±0.97	20	46
P13	0.989	0.987	0.992	0.655	19.30±1.10	12	66

Table III. Physicochemical properties of matrix-based transdermal patch formulation of Atenolol

Formulation	Thickness (mm)	Weight (gm)	Folding Endurance	Moisture Lost (%)	Moisture Absorbed(%)	Zero Order
P1	0.32	0.309±1.77	98±1.28	9.12	5.36	0.961±
P2	0.346	0.356±1.71	83±1.56	16.1	6.1	0.997±
P3	0.318	0.289±1.6	82±1.29	11.82	6.85	0.969±1.1
P4	0.332	0.028±2.06	85±1.44	16.73	5.1	0.964±2.06
P5	0.346	0.339±1.5	77±1.69	7.83	6.53	0.962±0.7
P6	0.306	0.3±2.17	83±1.45	11.76	6.8	0.959±1.01
P7	0.32	0.301±2.06	102±1.06	5.47	7.03	0.958±1.79
P8	0.336	0.31±1.59	79±1.43	13.3	7.6	0.967±1.08
P9	0.308	0.284±1.69	81±0.83	16.74	8.82	0.968±2.07
P10	0.33	0.352±1.54	82±1.9	10.6	9.23	0.97±1.59
P11	0.382	0.337±	73	7	6.23	0.984
P12	0.324	0.3±	83	12.22	6.82	0.96
P13	0.334	0.34±	82	10.28	6.08	0.97

This could be due to low viscosity and hydrophilic nature of PVP. Similarly, high proportion of HPMC K4M : PVP showed decrease in cumulative percentage drug release (37.5:6.36, P6) and vice versa (2:1, P7) (Table I, II and III) which could be due to viscous nature of HPMC K4M. Moreover, addition of PVP into the formulation tends to enhance its release-rate constants (Gupta *et al*., 2009). This outcome can be attributed to the leaching of the soluble component which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium (Darwhekar *et al*., 2011). Thus, higher the proportion of HPMC K4M against PVP, more control will be in both permeation and release rate of Atenolol. All formulations followed first order that was a concentration dependent release.

Drug release from formulations followed first order l. The n value of Power law for all formulation was seen to lie between 0.5 to 1.0 which suggests that the drug transport mechanism was anomalous (non-Fickian) diffusion (De PK *et al*., 2011) (Table II and III). Anomalous diffusion could be due to diffusion partially through a swollen matrix and water-filled pores in the formulations.

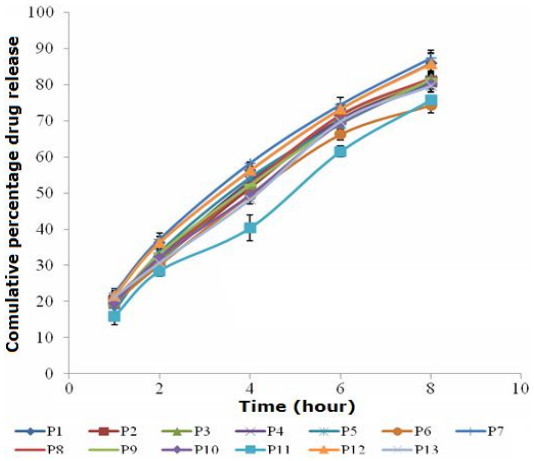

Figure 2. Cumulative percentage drug release vs. time profile of all formulations

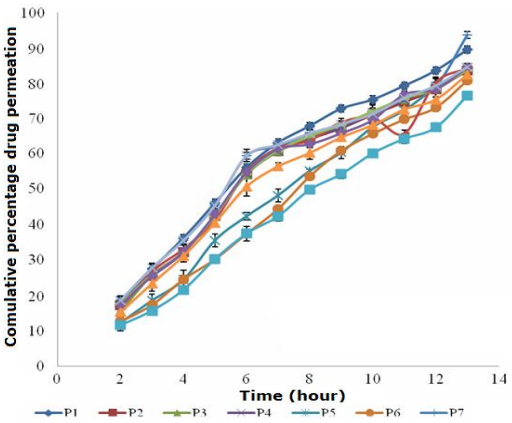

Figure 3. Cumulative percentage drug permeation vs. time profile of all formulations

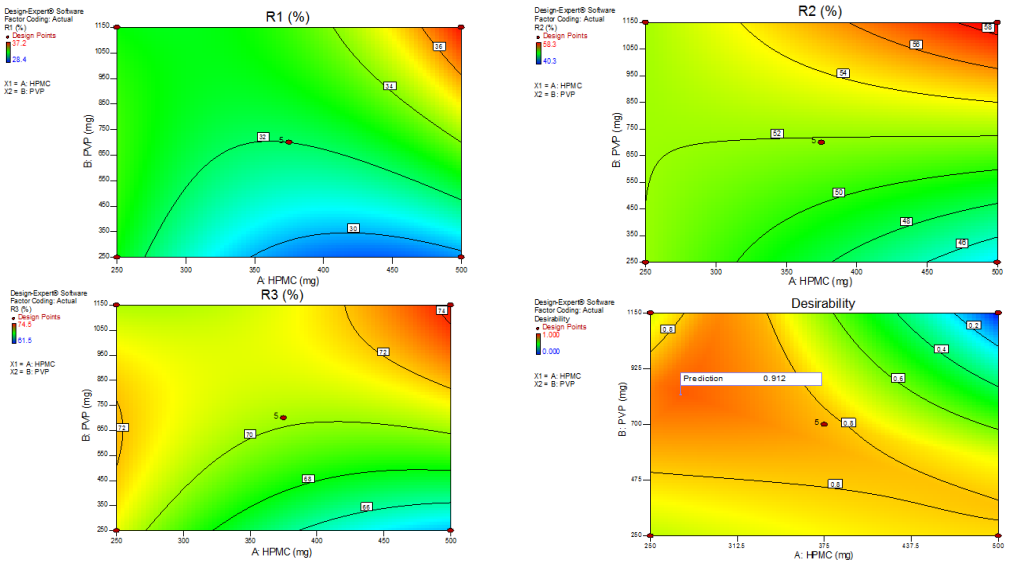

Figure 4. Contour Plot for drug release of PVP vs HPMC K4M at 2nd (R1), 4th (R2), 6th (R3) and 8th (R4) hour and PVP versus HPMC K4M showing the region of desirability for optimum formulation

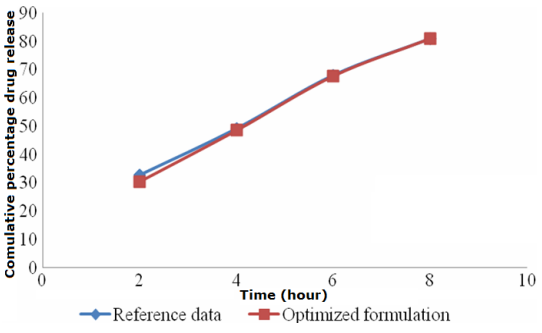

Figure 5. Cumulative percentage drug release of Reference data vs Optimized formulation.

The similar thickness of all patches indicates the physical uniformity of prepared patches. Folding endurance of all formulations indicates good strength and elasticity and can maintain the integrity with general skin folding (Patel *et al*, 2013) (Table II and III). The moisture uptake in the formulations is a function of HPMC K4M and PVP. This may be having high affinity for water and induces higher moisture uptake as the HPMC K4M, PVP ratio in the films increased. The moisture absorption was seen to increase with increasing the concentration of HPMC K4M (Ramesh *et al*., 2015) and PVP as both are hydrophilic in nature. Optimum moisture intake by patches is important as it helps to prevent patches from becoming brittle.

CONCLUSION

This study demonstrated that atenolol can be formulated in matrix-based transdermal patches with in-vitro experiment. In-vivo study should be carried out to further explore the possibility of these patches.

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