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Formulation and Evaluation of transdermal films for the treatment of Overactive Bladder

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ABSTRACT: Overactive bladder is a chronic, and distressing medical condition characterized by urinary urgency and frequency, with or without urge incontinence, that often requires long term treatment to maintain control of symptoms. Tolterodine tartarate is an anticholinergic drug used to treat overactive bladder**.** The suitability of drug with respect to lower dose, solubility, lower molecular weight and short half-life makes this drug as a suitable candidate for administration by transdermal route. A number of polymers such as HPMC, Carbopol-934P, and Ethyl cellulose were employed alone and in combination for the preparation of transdermal films. The films were casted using solvent casting technique. Solutions containing polymer at different concentrations (2%, 3%, 4%, w/w) and a plasticizer (propylene glycol) at various concentrations (20%, 30%, 40%, w/w) were prepared. These solutions were then used to prepare films. Prepared films were then evaluated for various physicochemical properties like physical appearance, weight variation, thickness, drug content, folding endurance and percentage elongation, including in-vitro release study. Among the various polymers examined result show's that the combination of HPMC: carbopol-934P (3:1) with 30% propylene glycol (PG), films formed were very flexible, with high folding endurance and uniform drug content. Further permeation study showed 68.72% and 81.12% release across the rat abdominal skin and cellophane membrane respectively for 12 hours. Thus it may be concluded that transdermal films are a promising drug delivery system for Tolterodine tartarate with more patient compliance in the treatment of overactive bladder.

Key Words: Overactive, Tolterodine, Anticholinergic, Transdermal, Plasticizer.

INTRODUCTION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. Transdermal drug delivery promises many advantages over oral and/or intravenous administration, such as better control of blood levels, a reduced incidence of systemic toxicity, and absence of hepatic first-pass metabolism. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical prerequisites, such as short half- life, small molecular size, low dose etc[1].

Overactive bladder (OAB) is a chronic condition that often requires long term treatment to maintain control of symptoms, which include frequent urination, an urge to urinate immediately and urinary incontinence. Antimuscarinic agents are widely used in treatment of OAB; Tolterodine is one of the active antimuscarinic agents effectively used in OAB. Tolterodine slows the build-up of pressure in the bladder, reduces the sensation to urinate and prevents uncontrolled urination[2]. Tolterodine is a competitive muscarinic receptor antagonist. The purpose of formulating the tolterodine into transdermal film is the suitability of Tolterodine tartarate with respect to dose, solubility, molecular weight (475.6) and half-life (1.9-3.7) prompted the selection of drug for the transdermal drug delivery system.

MATERIALS AND METHODS

Tolterodine was gifted sample from Natco pharma, hyderabad, HPMC from NR chemicals Mumbai, Carbopol-934 from Otto kemi Mumbai, Ethyl cellulose from BPRL Bangalore, Propylene glycol from Rankem New Dehli. All other ingredients were of analytical grade and were used as procured.

Preparation of Transdermal film:

Method used for the preparation of film is by solvent casting technique[3]. Composition of transdermal films

containing Tolterodine tartarate along with polymers such as HPMC, EC, Carbopol-934, alone and in combinations HPMC: carbopol-934, HPMC: EC, EC: Carbopol-934 has been shown in Table 1 and Table 2. Polymer was dissolved in the mixture of alcohol: water (1:1) with help of magnetic stirrer. Drug was separately dissolved in the mixture of alcohol: water, propylene glycol was added to this solution and mixed with for 30mins. The solution containing drug and propylene glycol was added to the polymer solution and stirred for 30mins using magnetic stirrer. The prepared solution was casted in petridish and dried at room temperature by covering petridish with inverted funnel for 48 hours.

Physicochemical evaluation:

The prepared films were evaluated for physical appearance, weight variation, uniformity of thickness, folding endurance, Tensile strength and water vapour transmission rate

***Thickness of the film**:*

The thickness of the film was determined by screw gauge at different position by placing the film in between two glass slides with known thickness and average thickness was calculated.

Folding endurance[4]:

The folding endurance was measured manually for the prepared films. A strip of film ($2cm^2$) was cut evenly and repeatedly folded at the same place till it broken. The number of times the film could be folded at the place without breaking gave the exact value of folding endurance.

Tensile strength[5]:

Tensile strength was measured using modified analytical two-pan balance method. The patch of 20 mm width and 50 mm length were cut and clamped between two clamps on one side; weights were added to the pan on other side until the patch breaks. The weight required for breaking the patch was taken as a measure of tensile strength of the patch.

Water vapour transmission studies [4,5]:

For this study vials of equal diameter were used as transmission cells. These cells were washed and dried in an oven. About one gram of fused calcium chloride was taken in the cell and the polymeric patches were fixed over the brim with the help of an adhesive. Then the cells were weighed accurately and kept in a closed desiccator containing saturated solution of potassium chloride (200ml). The cells were taken out and weighed after 2, 8, 12, 24, 48 and 72 h. From this increase in weights, the amount of water vapour transmitted and rate of water transmitted was calculated using the formula,

WVT Rate= WL /S.

Where, W=Gm of water transmitted, L= Thickness of the patch and S= Exposed surface area of the patch.

In-vitro release studies across the rat skin

Permeation studies of the transdermal patch were carried out using rat abdominal skin. The Franz diffusion cell assembly having 100 ml capacity in receptor chamber was used. The formulated patch with freshly cut rat skin were placed between the upper and lower halves of vertical diffusion cell and clamped with rubber bands. The skin was washed with plenty of water and trimmed in to circular section of about 3 cm diameter. The patch was then placed over the skin with the polymer matrix facing the stratum corneum side and mounted with cap of the diffusion cell and clamped securely on to the receptor compartment with dermis side of the skin facing the receptor solution containing 100 ml pH 7.4 phosphate buffer solution. The area of the film exposed for release was 2 cm^2. The receptor solution was constantly stirred with Teflon magnet and the temperature was maintained at $37^0 \pm 1^0$C. At hourly Intervals, 1ml of the sample was withdrawn and replaced immediately with fresh media. Amount of drug in the withdrawn samples was determined spectrophotometrically at 281.5 nm.

RESULTS

Transdermal films of Tolterodine tartarate were prepared by solvent casting method. Different polymers were used such as HPMC, carbopol-934P and ethyl cellulose (2%, 3%, 4%). They were used alone and also as combinations of polymers. Propylene glycol was used as plasticizer (20%, 30%, 40%). It was found that 30% of propylene glycol helped as ideal concentration. The prepared films were evaluated for physicochemical properties.

Prepared films were thin, flexible, smooth and uniform. The physicochemical evaluation data was summarized in Table 3. The physicochemical evaluation study reveals that all the formulations measured thickness with low standard deviation values ensure the uniformity of the films prepared by solvent casting method. The tensile strength and folding endurance of all the formulation were found to be satisfactory. Water vapour transmission through the films (2%) followed zero-order kinetics. Rate of water vapour transmission was more in HPMC: Carbopol-934 than other films, may be due to more hydrophilic nature of HPMC: Carbopol-934 film formulations.

The results of the in-vitro release study from different transdermal patches across the rat abdominal skin are depicted in Fig. 1. Polymer concentration of 2% w/v in each type of polymer film was found to be best. As the polymer concentration increases to 3%, 4% the drug released was found to be decreased. Propylene glycol in concentration of 20% shows less release pattern compared to 30% and 40%, but there was not much difference between 30% and 40% propylene glycol concentration. The release pattern was found to be in the order of HPMC> carbopol-934P> ethyl cellulose. Among the different combinations of polymers in the ratio of 3:1 the release rate was in the following order HPMC: Carbopol-934P > HPMC: Ethyl cellulose > Ethyl cellulose: Carbopol-934P.

Hence among all the formulation, HPMC: carbopol-934P at 2% polymer concentration with 30% propylene glycol concentration was showing the best release of 68.29%, flux is 1.098 mg/cm^2/h and permeability coefficient is 0.02196 cm/h, over a period of 12h through rat skin.

DISCUSSION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose.

Transdermal drug delivery promises many advantages over oral and/or intravenous administration, such as better control of blood levels, a reduced incidence of systemic toxicity, and absence of hepatic first-pass metabolism. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical prerequisites, such as short half- life, small molecular size, low dose etc.

Overactive bladder (OAB) is a chronic condition that often requires long term treatment to maintain control of symptoms, which include frequent urination, an urge to urinate immediately and urinary incontinence. Antimuscarinic agents are widely used in treatment of OAB; Tolterodine is one of the active antimuscarinic agents effectively used in OAB. Tolterodine slows the build-up of pressure in the bladder, reduces the sensation to urinate and prevents uncontrolled urination.

Selection of drug

Tolterodine is a competitive muscarinic receptor antagonist. Both contraction and salivation are mediated via cholinergic muscarinic receptors, and Tolterodine shows selectivity for the urinary bladder over salivary glands. The main effect of Tolterodine is an increase in residual urine, reflecting an incomplete emptying of the bladder, and decrease in detrusor pressure.

Selection of dosage form

Tolterodine was formulated as transdermal films. The purpose of formulating the tolterodine into transdermal film is

- To formulate more convenient and effective dosage form.
- The suitability of Tolterodine tartarate with respect to dose, solubility, molecular weight and half life prompted the selection of drug for the transdemal drug delivery system.

Analytical Method

Standard graph of Tolterodine tartarate was plotted using distilled water by UV Spectrophotometric method. Concentration of 10µg /ml and 20µg / ml was prepared and the solutions were scanned between 200-400 nm, the drug showed absorption maxima (λmax) at 281.5 nm. Hence all further analysis was carried at 281.5nm. It was observed that Beer's law range was between 5-50µg/ml with R^2 =0.9988 and the straight line intercept was found to be Y=0.0651x.

Permeability study

Pure drug permeation was carried out using an artificial membrane such as treated sheet and a biological membrane such as rat abdominal skin. Permeation studies were carried out using franz diffusion cell and modified franz diffusion cell. The receptor compartment contained 100 ml of 7.4 buffer saline solution and the donor compartment contained drug solution. The solution was continuously stirred at 37^0 C. The cumulative drug release was found to be 68.71% and 55.03 % respectively after 12hours.

Formulation of transdermal films

Transdermal films of Tolterodine tartarate were prepared by solvent casting method. Different polymers were used such as HPMC, carbopol-934P and ethyl cellulose. They were used alone and also as combinations of polymers. The ratio of HPMC: Carbopol-934P (3:1) was found to be best. Propylene glycol was used as plasticizer. It was found that 30% of propylene glycol helped as ideal concentration. The prepared films were evaluated for physicochemical properties. Based on its physical appearance, flexibility, folding endurance, uniform dug content and good release pattern, 2 % w/v of polymer concentration in each type of polymer was found to be best. As the polymer concentration increases to 3% and 4% the drug released was found to be decreased.

20% propylene glycol shows less release pattern compared to 30% and 40%, but there was not much difference between 30% and 40% propylene glycol concentration. The release pattern was found to be in the order of HPMC> carbopol-934P> ethyl cellulose. Among the different combinations of polymers in the ratio of 3:1 the release rate was in the following order HPMC: Carbopol-934P > HPMC: Ethyl cellulose > Ethyl cellulose: Carbopol-934P.

Hence among all the formulation, HPMC: carbopol-934P (HC2) at 2% polymer concentration with 30% propylene glycol concentration was showing the best release of 68.29% over a period of 12 h, through rat skin, flux is 1.098 mg/cm2/hr and permeability coefficient is 0.02196 cm/hr.

Among all the formulation HPMC: Carbopol-934P with 2% of polymer and 30% propylene glycol showed more transmission than the other formulation when water vapour transmission studies were carried out.

Stability studies

Stability studies of all the formulations were carried out at different temperatures (25^0 C, 45^0 C and 60^0 C). Physical appearance of film and drug content was evaluated for four weeks. There was no change in the physical characteristics of the films. And no major change was found in the drug content.

Compatibility study

Interaction between drug as well as formulation was studied using FTIR. The IR spectrum revealed that there were no interaction between drug and excipients.

CONCLUSION

Tolterodine tartarate holds good promise for administration via transdermal route for the treatment of overactive bladder. The possibility to formulate Tolterodine tartarate as a transdermal film and the various parameters that were evaluated helps to understand the usefulness of Tolterodine tartarate as a

transdermal film. From the evaluation studies of films, it may be concluded that transdermal drug delivery system of Tolterodine tartarate can be formulated, which provides better compliance than conventional drug delivery system of tolterodine. Tolterodine tartarate in the form of transdermal films can be used as a drug delivery system for treating overactive bladder for long term therapy.

TABLE 1: COMPOSITION OF TRANSDERMAL FILMS USING SINGLE POLYMERS.

Formulation code	HPMC	Ethyl cellulose	Carbopol-934	Propylene Glycol (PG)
H1	2%	2%	-	20%
H2	2%	2%	-	30%
H3	2%	2%	-	40%
H4	3%	3%	-	30%
H5	4%	4%	-	30%
C1	-	-	2%	20%
C2	-	-	2%	30%
C3	-	-	2%	40%
C4	-	-	3%	30%
C5	-	-	4%	30%
E1	-	2%	-	20%
E2	-	2%	-	30%
E3	-	2%	-	40%
E4	-	3%	-	30%
E5	-	4%	-	30%

TABLE 2: COMPOSITION OF TRANSDERMAL FILMS USING COMBINATION OF POLYMERS.

Formulation code	Propylene Glycol (PG)	HPMC: Carbopol-934 (3:1)	HPMC:Ethyl Cellulose (3:1)	Ethylcellulose: Carbopol (3:1)
HC1	20%	2%	-	-
HC2	30%	2%	-	-
HC3	40%	2%	-	-
HC4	30%	3%	-	-
HC5	30%	4%	2%	-
HE1	20%	-	2%	-
HE2	30%	-	2%	-
HE3	40%	-	3%	-
HE4	30%	-	4%	2%
HE5	30%	-	-	2%
EC1	20%	-	-	2%
EC2	30%	-	-	3%
EC3	40%	-	-	4%
EC4	30%	-	-	-
EC5	30%	-	-	-

TABLE 3: PHYSICOCHEMICAL EVALUATION OF PREPARED TRANSDERMAL FILMS WITH SINGLE POLYMERS

Formulation code	Thickness (mm) n=3	Tensile Strength ($gm/10cm^2$)n=3	Folding Endurance N=3	Cumulative release (mg)
H1	0.078±0.005	38.83±0.47	165 ±11.85	21.56
H2	0.092±0.006	44.70±0.23	168 ±10.23	24.21
H3	0.082±0.004	44.20±0.32	218 ±8.45	24.22
H4	0.092±0.002	39.70±0.28	200 ±12.32	21.70
H5	0.108±0.004	41.00±0.26	186 ±11.24	14.74
C1	0.078±0.006	43.83±0.32	165 ±14.52	20.03
C2	0.086±0.006	45.00±0.26	210 ±12.36	22.27
C3	0.082±0.007	44.20±0.28	218 ±10.52	22.32
C4	0.092±0.005	44.70±0.25	200 ±14.52	20.32
C5	0.108±0.006	45.00±0.25	186 ±12.45	13.52
E1	0.089±0.007	38.00±0.25	88 ±12.34	16.21
E2	0.101±0.005	41.00±0.21	98 ±10.56	19.02
E3	0.098±0.006	38.50±0.23	98 ±12.3	18.96
E4	0.112±0.007	40.20±0.36	95 ±9.62	17.91
E5	0.125±0.008	39.80±0.25	92 ±12.52	14.61

Values expressed in mean ±S.D. n= number of samples

TABLE 4: PHYSICOCHEMICAL EVALUATION OF PREPARED TRANSDERMAL FILMS WITH COMBINATION OF POLYMERS

Formulation code	Thickness (mm) n=3	Tensile Strength ($gm/10cm^2$)n=3	Folding Endurance N=3	Cumulative release (mg)
HC1	0.07±0.006	37.8±0.52	158±8.52	26.56
HC2	0.098±0.005	45.0±0.52	172±10.58	34.35
HC3	0.086±0.007	38.0±0.65	170±10.25	34.28
HC4	0.103±0.005	39.3±0.56	168±9.56	24.56
HC5	0.113±0.007	41.0±0.48	152±13.23	21.91
HE1	0.096±0.007	34.3±0.54	157±7.25	26.04
HE2	0.103±0.008	40.2±0.56	156±10.21	26.08
HE3	0.112±0.006	37.2±0.61	154±8.52	25.01
HE4	0.098±0.006	35.6±0.58	160±10.52	23.64
HE5	0.120±0.008	36.5±0.49	154±8.56	16.82
EC1	0.113±0.008	37.4±0.48	148±7.25	16.85
EC2	0.124±0.006	38.2±0.47	134±10.56	20.32
EC3	0.126±0.005	35.6±0.45	134±12.32	19.56
EC4	0.098±0.008	34.4±0.47	140±12.00	18.89
EC5	0.103±0.008	35.7±0.50	138±10.35	15.96

Values expressed in mean ±S.D. n= number of samples

TABLE 5: RESULTS OF WVT, FLUX AND PERMEABILITY COEFFICIENT

Formulation code	WVT ($g/cm^2/h$)	Flux ($mg/cm^2/h$)	Permeability coefficient(cm^2/h)
H2	0.162572	0.731	0.01462
C2	0.20898	0.708	0.01416
E2	0.141568	0.603	0.0126
HC2	0.342351	1.098	0.02196
HE2	0.162572	0.861	0.0163
EC2	0.150215	0.55	0.011

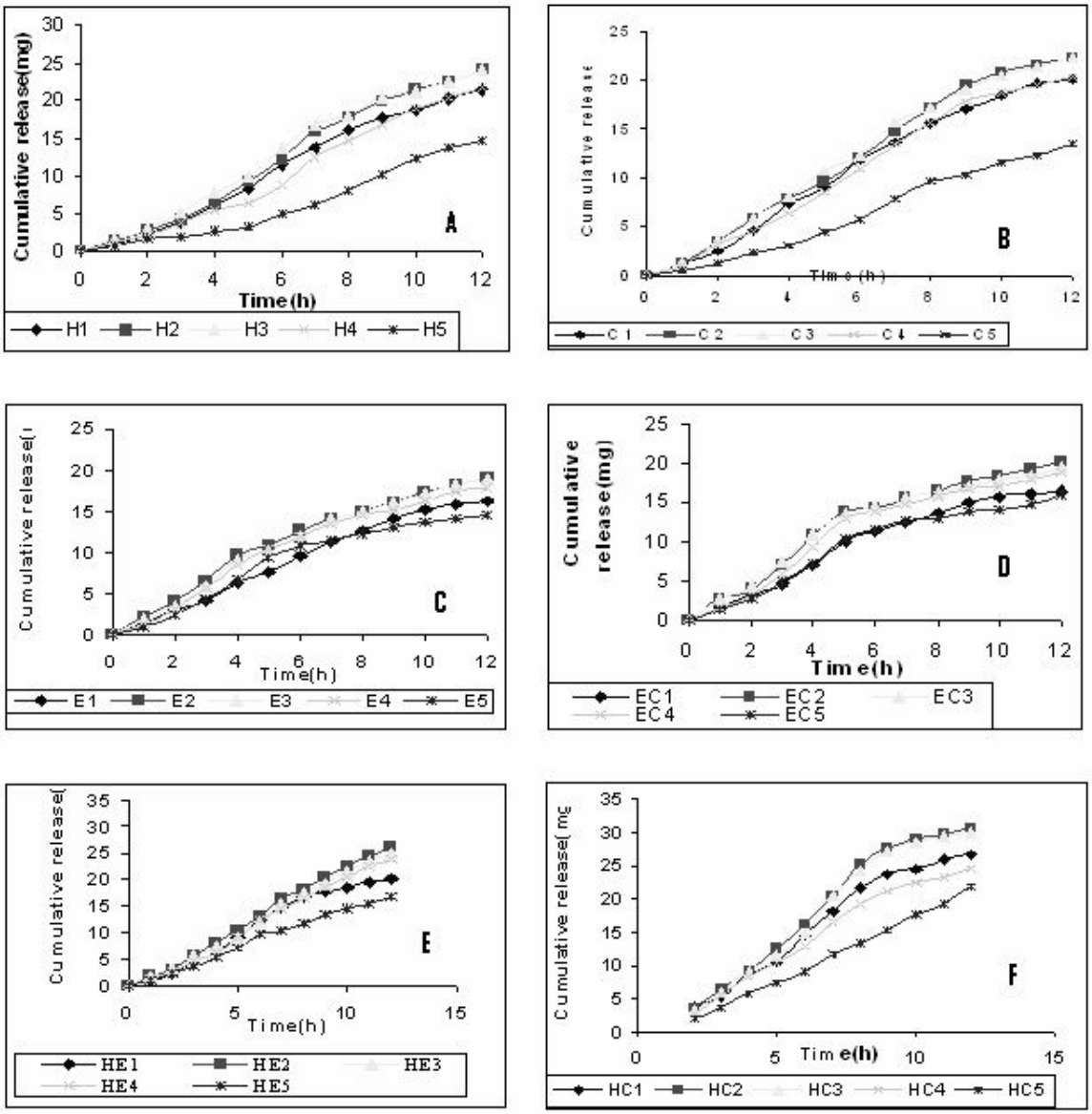

Fig 1: Comparative in vitro release profile of Tolterodine tartarate transdermal patches of A) HPMC B) Carbopol-934 C) Ethyl Cellulose D) Ethyl cellulose: Carbopol-934 E) HPMC: Ethyl cellulose F) HPMC: Carbopol-934

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