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AN APPROACH TO THE FORMULATION OF TRANSDERMAL FILM OF OXYBUTYNIN

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ABSTRACT

Overactive bladder (OAB) is a chronic medical condition that often requires long term treatment to maintain control of symptoms which include frequent urination, an urge to urinate immediately and urinary incontinence. Oxybutynin is an anticholinergic agent which acts by inhibiting the binding of acetylcholine to the muscarinic receptors to suppress involuntary bladder contractions in urinary incontinence. Transdermal films of oxybutynin were prepared by solvent casting technique using ethyl cellulose (EC) and carbopol-934P, which are lipophilic and hydrophilic respectively. Propylene glycol (PG) was used as plasticizer. Study was undertaken to report the film forming properties of the polymers used and physicochemical data including in vitro drug release. These films were evaluated for drug content, physical appearance, thickness, tensile strength, folding endurance, percent elongation, water vapour transmission rate (WVTR) and in vitro drug release which was studied using Franz diffusion cell. It was found that EC and carbopol-934P along with PG as plasticizer have good film forming properties. Between the two polymers used results showed that the formulation C4 prepared only with Carbopol-934P with 20% PG was very flexible with highest folding endurance. Further drug release study of C2 and EC11 has shown 87.28% and 88.32% release across the rat abdominal skin. In conclusion combination of EC and Carbopol-934P and PG can potentially be optimized to develop an effective transdermal drug delivery system for oxybutynin to treat OAB.

Keywords: Oxybutynin, ethyl cellulose, carbopol-934P, transdermal film.

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INTRODUCTION

A Transdermal Drug Delivery System (TDDS) can be defined as a self contained discrete dosage form which when applied to the intact skin delivers the drug(s) through the skin at a controlled rate to the systemic circulation. The development of a TDDS using polymeric material has become popular for various reasons. Among the various types of TDDS developed one type utilizes a thin polymeric film as rate controlling membrane which delivers the drug from the drug reservoir for an extended period of time. The permeability of drugs through the polymeric films is dependent upon the characteristics of the polymer [1,2], casting solvent [3] and plasticizer [4] used. Moreover the underlying facts to design TDDS successfully depends on a pondered choice of the drug which must not be an irritant, nor produce allergic disease and when applied in systems of this nature should cross the skin in adequate amounts to produce therapeutic effects. Drugs those produce their effects when small amounts of them are used and have a range of molecular weight between100 to 800 are good candidates [5]. Several important advantages of TDDS include limitation of first pass metabolism, enhancement of therapeutic efficiency, prolonged duration of action of potent drugs with short plasma half life and maintenance of steady plasma level of the drug [6,7]. TDDS for scopolamine, nitroglycerin, clonidine, estradiol etc have already been marketed and have found wide acceptability. Besides such systems are being developed for cardiovascular drugs (isosorbide dinitatre, timolol, propranolol), antihistamines (chlorpheniramine), analgesic (fentanyl) and smoking deterrents (nicotine) [8].

Oxybutynin is an anticholinergic agent used to suppress the involuntary bladder contractions in urinary incontinence. It acts by inhibiting binding of acetyl choline to the muscarinic receptors in the detrusor muscle of the bladder. It is having a half life of 2 to 3 hours, molecular weight of 393.95. The initial dose of this drug in tablet form is 5 mg twice daily and 2.5 mg twice daily in elderly patients [9]. Due to the above mentioned characteristics it is assumed that oxybutynin can be formulated as TDDS.

Thus anticipating that TDDS can be designed to input a drug at a appropriate rate to maintain the suitable plasma drug level for therapeutic efficacy to treat the disease, in our present investigation an attempt has been made to formulate and physicochemically evaluate the TDDS of oxybutynin with two different polymers namely ethyl cellulose and carbopol-934 P.

MATERIALS AND METHODS

Oxybutynin was obtained as a gift sample from Jai Radhe sales, Gujarat; Ethyl cellulose (EC) from BPRL- Bangalore; Carbopol 934P from Otto Kemie, Mumbai; Propylene glycol (PG) from Rankem, New Delhi. All others ingredients used were of analytical grade.

Preparation of transdermal film

Method used for the preparation of film is solvent casting technique [10]. Table 1 and 2 shows composition of transdermal films of oxybutynin with EC, Carbopol 934P alone and in combination respectively. Polymer was dissolved in 50% alcohol. Drug was separately dissolved in 50% alcohol. PG was added to this solution and stirred for 30 minutes on a magnetic stirrer for uniform mixing. Then the solution containing drug and PG was added to the polymer solution and the resulting solution was stirred for 30min. The prepared solution was poured into a petridish and was dried at room temperature for 48 hours. The petridish was covered by inverted funnel, to avoid rapid evaporation of the solvent.

Physicochemical evaluation

The prepared films were evaluated for their physical appearance, uniformity of thickness, weight variation, tensile strength, folding endurance, drug content, water vapour transmission rate (WVTR) and in vitro release studies across the rat abdominal skin.

Weight variation

A 2 cm^2 film was cut uniformly and weighed in digital balance and results are reported in table-3 and 4.

Thickness of the film

Screw gauge was used to determine thickness of the films. It was placed at three different positions by keeping the film in between two glass slides of known thickness and average thickness was calculated and the values are given in table-3 and 4.

Folding endurance [11]

The folding endurance was measured manually. A strip of film having an area of 2cm2 was cut evenly and repeatedly folded at the same place till it broken/cracked. The number of times the film could be folded at the same place without breaking/cracking gives the exact value of folding endurance and the results are reported in table-3 and 4

Tensile strength [12]

Tensile strength was measured using analytical two-pan balance. A patch of 20 mm width and 50 mm length was cut and clamped between two clamps on one side. Weights were added to the pan on the other side until the patch is broken. The weight required for breaking the patch was taken as a measure of tensile strength of the patch and the results are reported in tables-3 and 4.

Percentage elongation

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Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

Percentage elongation = $(L_F - L_O) \times 100 / L_O$. Where L_F = final length, L_O = initial length.

Water vapour transmission studies [11,12]

Previously washed and dried vials of equal diameter were used as transmission cells. 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 dessicator containing saturated solution of potassium chloride (200ml). The humidity inside the dessicator was measured by a hygrometer and it was found to be 80-90% relative humidity. The cells were taken out and weighed after 2, 8, 12, 24, 48 and 72 h. From the increase in weights, the amount of water vapor transmitted and the rate of water vapor transmitted was calculated using the formula, Water Vapor Transmission Rate = W L /S. where W = Gm of water transmitted, L = Thickness of the patch and S = Exposed surface area of the patch.

Drug content [11]

A $2cm^2$ film was cut into small pieces and put in a 100ml buffer (pH 7.4). This was then shaken in a mechanical shaker for 2 hrs to get a homogenous solution and filtered. Then sample solutions from this was prepared by diluting to different concentrations and determined spectroscopically at 344 nm 13. The determinations were carried out in triplicates and the average of three readings were recorded and reported in table 3 and 4.

In vitro release studies across the rat skin [10,14]

The Franz diffusion cell assembly having 100 ml capacity in receptor chamber was used. The rat abdominal 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 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 receptor solution was constantly stirred at 37 ± 1^0C over magnetic stirrer. 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 344 nm and reported in table 3 and 4

RESULTS AND DISCUSSION

Prepared films were thin, flexible, smooth and transparent. Solvent casting technique used to prepare the films was satisfactory. From the physicochemical evaluation data of the films (table 3 and 4) it is evident that there was no physical change like appearance, colour and flexibility when the films were stored at room temperature. The thickness was found to be least for the films prepared with 2% w/v polymers alone and in combination with 20% PG (table 3

and 4). Same observation was attributed for the weights measured of the films. When it comes to tensile strength measurement formulation E2 & C2 and EC2 & EC11 were having the maximum value. It may be due to the fact that at the ratio of 2% polymer with 30% PG may provide the ideal tensile strength required for the film. The calibration plot of oxybutynin was prepared using various standard concentrations. Based on absorbance shown at 344nm percent drug content was calculated and it was found in the range of 95.43% to 98.84% for all the formulations. In case of folding endurance the formulations prepared only with carbopol-934P (C1 to C9, irrespective of the percentage of carbopol-934P used) shown more values than formulations prepared only with EC (E1 to E9). In some cases it showed increase in value up to 2 to 3 fold (E7 = 65, C4 =218, table 3, 4). Same observation is attributed to formulations when EC: Carbopol-934P is used in the ratio of 1:3 (EC10 to EC18). This may be due to the fact that elasticity of carbopol-934P is more than EC. The water vapour transmission pattern was found to be in C1-C9> E1 – E9 and EC10 – EC18 > EC1 – EC9. Further investigation revealed that at 30% and 40% concentration of PG the WVT rate was maximum in case of combination of polymer as well as they are singly used (table 3 & 4). In vitro release study shows that among all the formulations prepared (E1 – E9 & C1 –C9 and EC1 – EC18) polymer concentration at 2% with 30% PG as plasticizer (E2, C2, EC2 & EC11) have maximum release through the rat skin and the best release was shown by EC11 (88.32%, table 4). From this study it is evident that 2% w/v polymer alone or in combination with 30% plasticizer, seems to be the optimum ratio to prepare TDDS of oxybutynin for maximum in vitro release.

CONCULSION

Oxybutynin holds good promise for administration via transdermal route for the treatment of OAB. The various physicochemical parameters that were evaluated help to understand the usefulness and suitability of oxybutynin to be formulated as a transdermal film with different concentrations of polymers. It is evident from the present study that the films prepared with EC: carbopol-934P (1:3) have good tensile strength, percent elongation, folding endurance and most importantly in vitro release. In all the cases as the polymer concentration increases to 3% & 4% the drug release was to be decrease thus there is an opportunity to modify the film composition and additives ratio to get the optimum release over a prolonged period of time. Considering the study results polymer based patches containing oxybutynin can emerge out as an efficient drug delivery system for the treatment of OAB in near future.

Table-1
Formulation composition of transdermal films of Oxybutynin using EC and Carbopol- 934P alone.

S No	Formulation code	EC	Carbopol- 934P	Propylene glycol
1	E1	2%	-	20%
2	E2	2%	-	30%
3	E3	2%	-	40%
4	E4	3%	-	20%
5	E5	3%	-	30%
6	E6	3%	-	40%

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7	E7	4%	-	20%
8	E8	4%	-	30%
9	E9	4%	-	40%
10	C1	-	2%	20%
11	C2	-	2%	30%
12	C3	-	2%	40%
13	C4	-	3%	20%
14	C5	-	3%	30%
15	C6	-	3%	40%
16	C7	-	4%	20%
17	C8	-	4%	30%
18	C9	-	4%	40%

Table-2

Formulation composition of transdermal films of Oxybutynin with combination of EC and Carbopol 934P

S No	Formulation code	EC:Carbopol-934P (3:1)	EC:Carbopol-934P (1:3)	Propylene glycol
1	EC1	2%	-	20%
2	EC2	2%	-	30%
3	EC3	2%	-	40%
4	EC4	3%	-	20%
5	EC5	3%	-	30%
6	EC6	3%	-	40%
7	EC7	4%	-	20%
8	EC8	4%	-	30%
9	EC9	4%	-	40%
10	EC10	-	2%	20%
11	EC11	-	2%	30%
12	EC12	-	2%	40%
13	EC13	-	3%	20%
14	EC14	-	3%	30%
15	EC15	-	3%	40%
16	EC16	-	4%	20%
17	EC17	-	4%	30%
18	EC18	-	4%	40%

Figure 1:Comparative in vitro release study of the formulations E2 and C2

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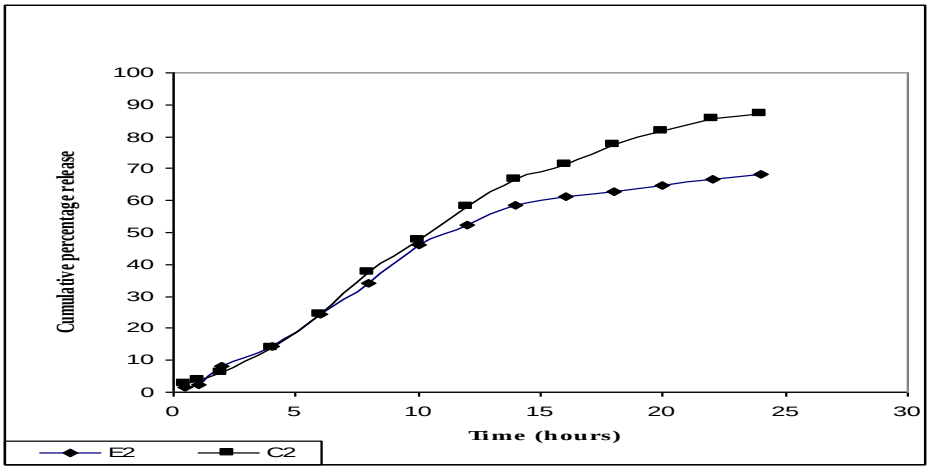

Figure 2:Comparative in vitro release study of the formulations EC2 and EC11

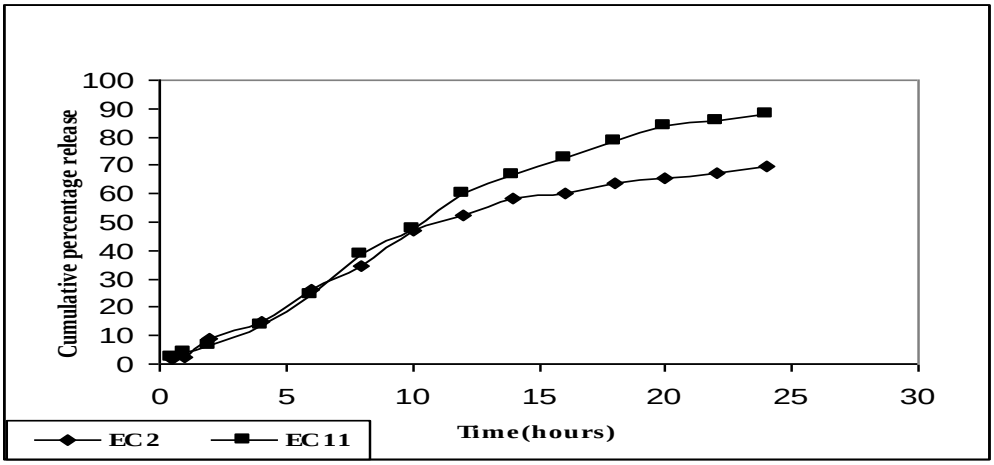

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Table 3:Physicochemical data of transdermal films of Oxybutynin prepared only with EC and Carbopol- 934P

Formulation code	Polymer concentration	Plasticizer concentration	Physical appearance	Thickness (mm) n= 5	Weight (mg) n= 5	Drug content (%) n= 3	Tensile Strength $Gm/10^2cm$ n= 5	Percent elongation n= 5	Folding endurance n= 5	WVTR $g/cm^2/72hrs$	Invitro release studies (%)
Films prepared only with ethyl cellulose											
E1	2%	20%	uniform	0.018 ±0.007	4.752 ±0.49	98.78 ±0.56	43.52 ±0.44	12 ±0.078	92 ±13.8	0.13398	66.28
E2	2%	30%	Uniform	0.021 ±0.006	5.003 ±0.48	98.84 ±0.85	45.02 ±0.26	11 ±0.097	96 ±16.6	0.14201	68.34
E3	2%	40%	Uniform	0.020 ±0.006	4.971 ±0.91	97.38 ±0.48	44.28 ±0.52	11 ±0.065	89 ±17.2	0.14294	67.42
E4	3%	20%	Uniform	0.019 ±0.005	5.075 ±0.62	96.32 ±0.28	39.98 ±0.71	13 ±0.069	79 ±9.3	0.12584	67.68
E5	3%	30%	Uniform	0.022 ±0.007	5.079 ±0.53	97.85 ±0.72	42.26 ±0.67	12 ±0.078	85 ±6.8	0.13109	64.28
E6	3%	40%	Uniform	0.020 ±0.004	5.135 ±0.47	96.89 ±0.32	40.09 ±0.82	11 ±0.065	71 ±14.8	0.12678	63.58
E7	4%	20%	Uniform	0.025 ±0.008	5.291 ±0.21	98.71 ±0.42	39.85 ±0.46	12 ±0.081	65 ±10.2	0.12467	63.21
E8	4%	30%	Uniform	0.029 ±0.009	5.398 ±0.85	97.32 ±0.42	41.71 ±0.38	12 ±0.062	66 ±12.5	0.13013	59.51
E9	4%	40%	Uniform	0.028 ±0.007	5.387 ±0.68	96.58 ±0.78	39.82 ±0.72	13 ±0.076	68 ±9.7	0.13119	58.34
Films prepared only with carbopol 934 P											
C1	2%	20%	Uniform	0.012 ±0.006	4.692 ±0.42	97.19 ±0.56	42.29 ±0.32	17 ±0.020	190 ±14.2	0.14582	86.19
C2	2%	30%	Uniform	0.016 ±0.009	4.713 ±0.35	97.85 ±0.68	48.26 ±0.48	18 ±0.082	200 ±14.8	0.16352	87.28
C3	2%	40%	Uniform	0.016 ±0.004	4.734 ±0.52	96.42 ±0.78	46.09 ±0.39	18 ±0.081	205 ±16.3	0.16911	85.32
C4	3%	20%	Uniform	0.018 ±0.004	4.698 ±0.86	97.53 ±0.83	45.69 ±0.28	20 ±0.067	218 ±20.2	0.13772	86.58
C5	3%	30%	Uniform	0.019 ±0.002	5.019 ±0.79	96.83 ±0.24	47.55 ±0.25	19 ±0.049	186 ±12.5	0.13963	85.42
C6	3%	40%	Uniform	0.022 ±0.003	5.028 ±0.76	98.41 ±0.48	47.68 ±0.42	18 ±0.075	179 ±15.6	0.13857	81.39
C7	4%	20%	Uniform	0.024 ±0.005	5.116 ±0.33	97.13 ±0.64	45.34 ±0.71	18 ±0.064	195 ±12.3	0.13325	80.08
C8	4%	30%	Uniform	0.022 ±0.007	5.186 ±0.48	97.42 ±0.32	46.81 ±0.32	17 ±0.064	190 ±12.5	0.13528	81.29
C9	4%	40%	Uniform	0.023 ±0.005	5.159 ±0.28	97.85 ±0.28	47.02 ±0.62	19 ±0.069	191 ±17.2	0.13532	79.34

Values expressed in nean ± SD. n= number of samples used.

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Table 4.
Physicochemical data of transdermal films of Oxybutynin prepared in combination with EC and Carbopol 934P

Formulation code	Polymer concentration	Plasticizer concentration	Physical appearance	Thickness (mm) n= 5	Weight (mg) n= 5	Drug content (%) n= 5	Tensile Strength $Gm/10^2cm$ n= 5	Percent elongation n= 5	Folding endurance n= 5	WVTR $g/cm^2/72hrs$	Invitro release studies (%)
Ethyl cellulose:Carbopol-934P (3:1)											
EC1	2%	20%	uniform	0.015 ±0.004	4.581 ±0.38	96.23 ±0.54	44.32 ±0.58	13 ±0.069	95 ±0.7.5	0.13521	67.32
EC2	2%	30%	Uniform	0.017 ±0.006	4.982 ±0.42	98.14 ±0.49	46.69 ±0.49	14 ±0.059	108 ±8.2	0.14532	69.45
EC3	2%	40%	Uniform	0.017 ±0.008	4.981 ±0.56	96.32 ±0.47	45.29 ±0.48	14 ±0.045	79 ±3.2	0.14498	67.42
EC4	3%	20%	Uniform	0.015 ±0.003	5.025 ±0.69	96.39 ±0.32	41.28 ±0.57	12 ±0.038	87 ±11.2	0.12845	68.68
EC5	3%	30%	Uniform	0.017 ±0.005	5.082 ±0.73	96.75 ±0.59	41.15 ±0.56	12 ±0.034	98 ±24.8	0.13662	64.38
EC6	3%	40%	Uniform	0.018 ±0.006	5.102 ±0.81	95.43 ±0.68	40.69 ±0.71	13 ±0.071	85 ±18.2	0.12978	66.58
EC7	4%	20%	Uniform	0.020 ±0.007	5.186 ±0.56	96.12 ±0.56	41.13 ±0.62	11 ±0.067	75 ±17.4	0.12667	65.82
EC8	4%	30%	Uniform	0.023 ±0.006	5.239 ±0.57	97.32 ±0.67	39.75 ±0.82	13 ±0.071	77 ±12.1	0.13335	65.92
EC9	4%	40%	Uniform	0.022 ±0.008	5.236 ±0.49	97.18 ±0.78	41.61 ±0.38	12 ±0.072	76 ±18.1	0.13521	66.34
Ethyl cellulose:Carbopol-934P (1:3)											
EC10	2%	20%	Uniform	0.013 ±0.009	4.532 ±0.57	96.34 ±0.83	41.63 ±0.42	17 ±0.052	197 ±10.2	0.14281	86.45
EC11	2%	30%	Uniform	0.017 ±0.006	4.812 ±0.63	98.84 ±0.24	47.64 ±0.62	21 ±0.048	199 ±8.5	0.16032	88.32
EC12	2%	40%	Uniform	0.016 ±0.008	4.853 ±0.82	97.18 ±0.32	45.09 ±0.64	20 ±0.032	197 ±9.8	0.16542	84.38
EC13	3%	20%	Uniform	0.019 ±0.005	4.921 ±0.98	97.56 ±0.32	45.98 ±0.45	18 ±0.016	170 ±8.5	0.13452	85.62
EC14	3%	30%	Uniform	0.020 ±0.002	4.982 ±0.48	96.85 ±0.48	46.36 ±0.47	19 ±0.021	178 ±6.8	0.13619	85.42
EC15	3%	40%	Uniform	0.022 ±0.004	5.012 ±0.81	96.38 ±0.54	46.24 ±0.68	19 ±0.023	176 ±7.2	0.13657	80.39
EC16	4%	20%	Uniform	0.023 ±0.003	5.103 ±0.39	97.72 ±0.49	45.71 ±0.53	20 ±0.042	178 ±6.8	0.13017	81.45
EC17	4%	30%	Uniform	0.023 ±0.005	5.153 ±0.28	97.58 ±0.38	46.05 ±0.62	18 ±0.052	177 ±7.2	0.13225	81.32
EC18	4%	40%	Uniform	0.022 ±0.007	5.149 ±0.42	97.32 ±0.52	45.32 ±0.49	17 ±0.062	177 ±6.2	0.13349	80.45

Values are expressed in mean ± SD. n= number of samples used

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