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Formulation and Evaluation of Transdermal Film of Tolterodine

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ABSTRACT

Historically, developments in transdermal drug delivery have been incremental, focusing on overcoming problems associated with the barrier properties of the skin, reducing skin irritation rates and improving the aesthetics associated with passive patch systems. Transdermally delivery of drugs avoid first pass metabolism, decrease dose to be administered, reduces side effects, eliminate gastrointestinal side effects. Drug with short half life and narrow therapeutic index can be safely administered since better control of release is possible. Transdermal drug delivery-the delivery of drugs across the skin into systemic circulation is distinct from topical drug penetration, which targets local areas¹¹. Transdermal drug delivery takes advantage of the relative accessibility of skin². "TRANSDERMAL" route is most promising and has received a lot of attention because the skin has minimal proteolytic enzyme activity⁷. Route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic system (TTS) in the form of patches¹⁰. The present invention relates to transdermal administration of tolterodine, for achieving more constant serum concentrations during a dosage interval; minimize side effects in comparison to immediate release tablets, while clinical efficacy is maintained.

Keywords: Transdermal, therapeutic index, drug penetration tolterodine

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INTRODUCTION

The heightened focus on specialty pharmaceuticals that add value and patent protection in major pharmaceutical markets by providing better delivery (e.g. oral controlled-release, inhalation, implants, transdermal delivery systems etc.) is increasing pressure to further push the boundaries of the practical applications of basic pharmaceutical research. The negatives of oral route can be overcome by transdermal route and benefits of intravenous drug infusion such as to by-pass hepatic “first-pass” elimination to maintain constant prolonged and therapeutic effective drug level in the body can be closely duplicated without its hazards by using the intact skin as a port of drug administration.¹ Transdermal drug delivery system was first introduced more than 20 years ago. During the past few years, skin has been shown to be a suitable delivery route for drugs formulated in transdermal therapeutic system (TTS)¹. Thus the delivery of drugs transdermally (through the skin) provides several important advantages over traditional oral and intravenous delivery routes². In case of transdermal drug delivery, simple dosing regimen can aid in patient adherence to drug therapy³. Route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic system (TTS) in the form of patches¹⁰. Transdermal drug delivery—the delivery of drugs across the skin into systemic circulation is distinct from topical drug penetration, which targets local areas¹¹. Transdermal drug delivery takes advantage of the relative accessibility of skin². “TRANSDERMAL” route is most promising and has received a lot of attention because the skin has minimal proteolytic enzyme activity⁷.

Attractive areas for transdermal delivery⁵:

- Pain Management
- Fertility Control
- Anxiety Disorders
- Hormone Replacement
- Depression
- Coronary Heart Disease

Advantages of Transdermal Drug Delivery System (TDDS)¹⁴

Avoids hepatic first pass metabolism.

- Maintains constant blood levels for longer period of time.
- Improve bioavailability.
- Decreases the dose to be administered.
- Decreases side or unwanted effects.

Limitations of Transdermal Drug Delivery System (TDDS)¹⁴

- The drug must have desirable physicochemical properties for penetration through skin.
- High dose drug candidates are not suitable for TDDS.

- Skin irritation or contact dermatitis due to drug, excipients and penetration enhancers is another limitation.
- Before development of transdermal product, examination of clinical need must be fulfilled.
- The barrier function of skin changes from one site to another on same person, from person to person and with age.

FACTORS INFLUENCING TRANSDERMAL DRUG DELIVERY¹⁴

A) Biological factors

Skin condition, Skin age, Blood flow, Regional skin sites, Skin metabolism.

B) Physicochemical factors

Skin hydration, Temperature and pH , Diffusion coefficient, Drug concentration

APPROACHES IN TDDS ^{1,19}

Membrane permeation controlled system

In this system, the drug is totally encapsulated in a shallow compartment molded from a drug impermeable plastic laminate and a rate controlling polymeric membrane.

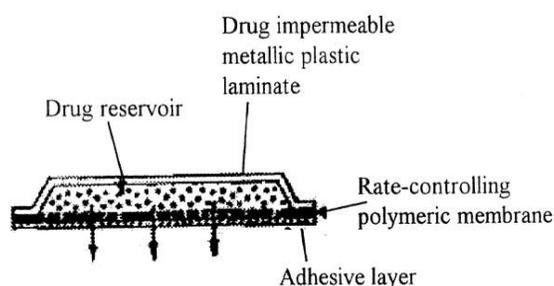


Figure 1: Membrane Moderated Transdermal Drug Delivery System

Adhesive dispersion type system

The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melt method onto a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

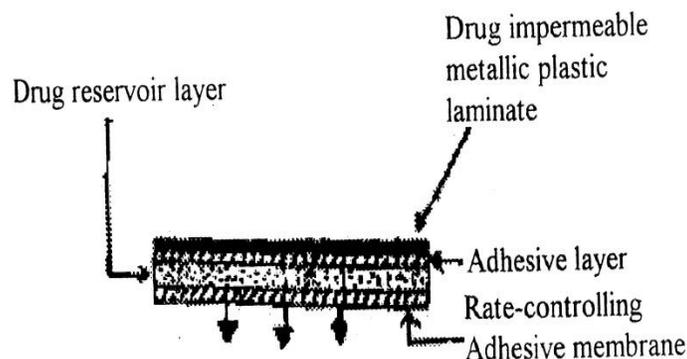


Figure 2: Adhesive –Dispersion Type Transdermal Drug Delivery System

Matrix diffusion controlled system

The drug reservoir is prepared by homogeneously dispersing the drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness.

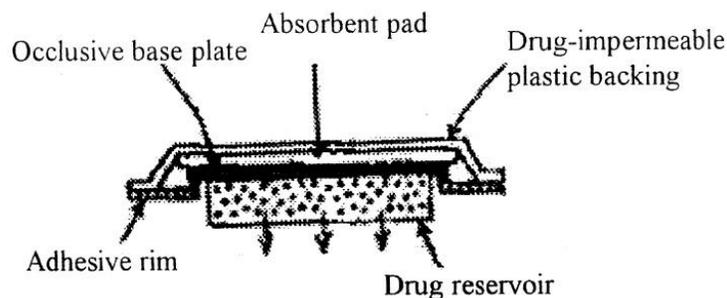


Figure 3: Matrix diffusion controlled Transdermal Drug Delivery System

Micro reservoir system

This is a combination of reservoir and matrix diffusion type drug delivery system. The drug reservoir is formed by first suspending the drug in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer by high energy dispersion technique.

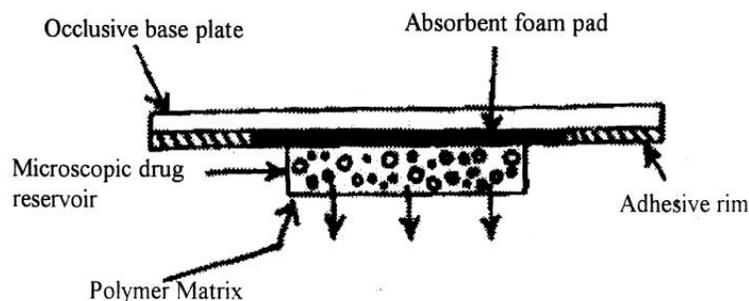


Figure 4: Micro reservoir Dissolution Controlled Transdermal Drug Delivery System

FORMULATION OF FILM¹²

The polymer is dissolved in a suitable solvent or suspended in a suitable non-solvent applied on to the substrate. The properties of dried films are dependent on the solvent used to make solution suspension. The plasticizer like castor oil, dibutyl phthalate can be added to improve the flexibility of the films.

The following substrate can be used for films coating

Mercury substrate:

In mercury substrate technique films are prepared by casting the films on a mercury surface. This method produces films with a controlled constant thickness, which can be controlled by varying the

volume of solution poured. Varying the strength of polymer solution is preferred because varying the volume, changes the drying rate and therefore the clarity and other properties of the films.

Glass substrate:

Glass offers a very inert, highly smooth surface, for film casting. Films are cast by pouring method.

Silicon treated substrate:

Some polymers show adherence problems, even as on highly polished glass surface. Removal of the film without loss of integrity is a problem. In such cases silicon treated substrate is preferred. This surfaces offer a positive spreading coefficient and a low work of adhesion, with respect to the polymer films are cast by simple pouring method.

Teflon coated metal substrate:

Teflon is another agent which facilitates removal of films. Metal substrate have been coated with Teflon to minimized film adherence problems. The films are cast by pouring method as well as by spraying the polymer solution.

Table 1: Examples of recently launched and developmental transdermal products⁵

Compounds	Delivery System	Stage of Development	Company
Alprostadil	Gel-Alprox-TD	Launched in China	Nex Med
Buprenorphine	Patch – Transtec	Launched in Europe	Grunenthal
Dihydrotestosterone	Gel-Andractim	Launched in France and Netherlands	Unimed/Solvay
Estradiol	MDTS	Phase II	Acrux
Estradiol/progestogen	Gel	Phase II in USA	Antares
Ethinylestradiol & norelgestromin	Patch – Ortho Evera	Launched in USA	J & J
Fentanyl	Patch–iontophoresis E-TRANS	Launched in USA	Alza / J & J
Granisetron	MDTS	Preclinical	Acrux
hGH	Microneedle – Macroflux	Phase I	Alza / J & J
Hydromorphone	Patch – thermal	Phase I in USA	Alza / J & J
Insulin	Sonophoresis	Preclinical	Altea
	Patch – Thermal	Phase I in USA	Imarx
Compounds	Delivery System	Stage of Development	Company
Lidocaine	Patch – Lidoderm	Launched in USA	Endo
Methylphenidate	Patch – Methypatch	Launched in USA	Noven
Methyl testosterone	Patch	Phase II in USA	Noven
Oxybutynin	Patch – Oxytrol	Launched in USA	Watson
Parathyroid hormone	Patch – Thermal	Phase I in USA	Altea

MATERIALS AND METHOD

Instruments:

FT-IR Spectrophotometer: Model – 8400S Shimadzu Corporation, Koyto, Japan.

Double Beam UV Spectrophotometer: Model No. UV 2401 PC Shimadzu Corporation, Koyto, Japan.

pH Meter :Model (Systronic 361).

Electronic Balance : Model AW : 220 Shimadzu Asia Pacific Pvt Ltd. Singapore.

Electronic Balance: Model BX 6205 Shimadzu Asia Pacific Pvt Ltd, Singapore.

Dissolution test Apparatus : Veego Scientific Devices, Mumbai -Model No. DA-3.

Thickness Appratus : Cambell Electronics, Mumbai.Model-CWWTDH 500N

Tensile Strength : Instron 4667,U.K.

Materials:

- Tolterodine Tartarate : It was obtained as gift sample from - Aurobindo Pharma Ltd. Hyderabad (A.P.)
- Eudragit RL100 : It was obtained as gift sample from-Degussa India Pvt. Ltd. ,Mumbai.
- Eudragit RS100 : It was obtained as gift sample from- Degussa India Pvt. Ltd. ,Mumbai.
- Polyvinyl Alcohol : Loba chemie Pvt. Ltd, Mumbai
- Chloroform : Loba chemie Pvt. Ltd, Mumbai
- Methanol : Loba Chemie Pvt. Ltd., Mumbai
- DibutylPthalate : Loba Chemie Pvt. Ltd., Mumbai
- Disodium hydrogen phosphate : Loba Chemie Pvt. Ltd., Mumbai.
- Potassium dihydrogen phosphate : Loba Chemie Pvt. Ltd., Mumbai.
- Sodium chloride : Loba Chemie Pvt. Ltd., Mumbai.
- Potassium chloride : Loba Chemie Pvt. Ltd., Mumbai.

PREFORMULATION STUDY

Drug (Tolterodine Tartarate)

Colour: Tolterodine Tartarate is white crystalline powder.

Melting point³⁷ : The melting point of the drug sample was determined by capillary method and found to be 205-210 °C.

Solubility: It is sparingly soluble in water(12 mg/ml at room temperature) which complies with solubility reported in clark⁵⁷.

UV scanning in saline phosphate buffer pH 7.4³⁸ : The scanning of drug was performed in saline phosphate buffer pH 7.4 and λ_{max} was found to be at 280 nm which complies with the λ_{max} reported (280nm)⁵⁷.

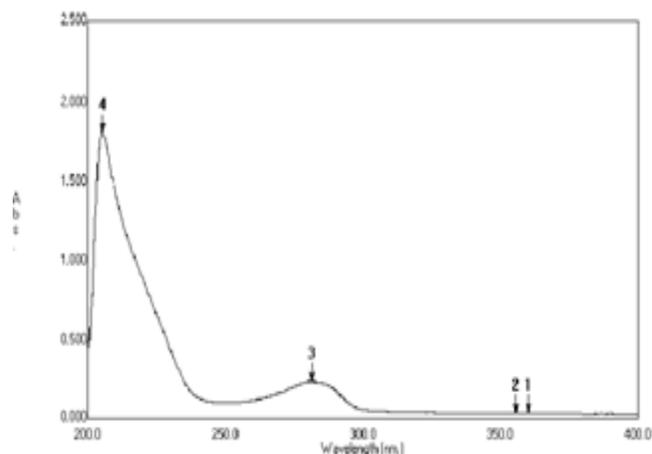


Figure 5: Scanning of Tolterodine Tartarate in 7.4 pH Saline phosphate buffer

Polymer: A) Eudragit RL100 B) Eudragit RS 100

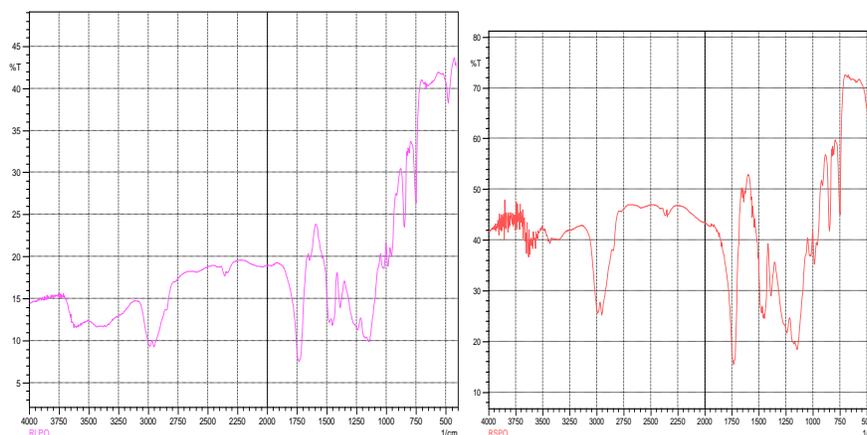


Figure 6: FT-IR Spectra of Eudragit RL 100

Figure 7: FT-IR Spectra of Eudragit RS100

STANDARD CALIBRATION CURVE OF TOLTERODINE TARTARATE

Preparation of pH 7.4 saline phosphate buffer⁴²

2.38gm of Disodium hydrogen phosphate, 0.19gm of potassium dihydrogen phosphate and 8 gm of sodium chloride were taken in 1 liter volumetric flask dissolved in distilled water and volume was adjusted to 1000ml

Scanning of Tolterodine Tartarate in pH 7.4 saline phosphate buffer

Tolterodine Tartarate was scanned in saline phosphate buffer pH 7.4 in U.V range from 200-400nm and it was found to be at 280 nm.

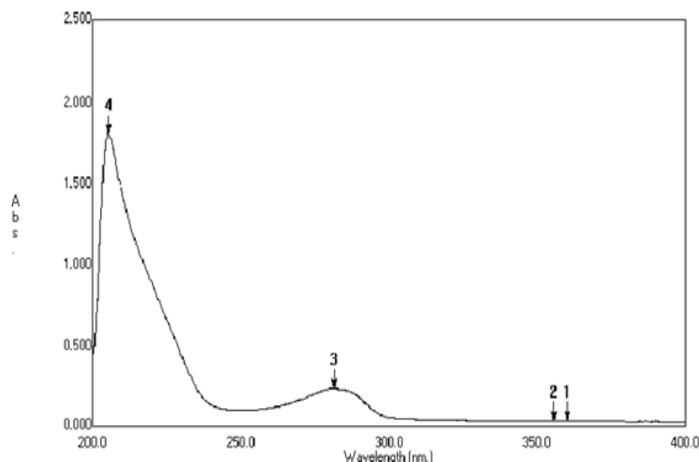


Figure 8: Scanning of Tolterodine Tartarate in 7.4 pH saline phosphate buffer

Standard calibration curve in pH 7.4 saline phosphate buffer

Accurately weighed tolterodine tartarate (50mg) was dissolved in 50 ml volumetric flask and volume was made upto 50 ml with pH 7.4 saline phosphate buffer. From this aliquots samples were diluted to get the concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 μ g/ml. Absorbance were recorded spectrophotometrically against pH7.4 saline phosphate buffer as blank at λ_{\max} 280 nm.

Table 2: Standard calibration curve of Tolterodine Tartarate in 7.4 pH saline phosphate buffer

Concentration (mcg/ml)	Absorbance*
0	0
2	0.019 \pm 0.02
4	0.050 \pm 0.03
6	0.076 \pm 0.02
8	0.103 \pm 0.04
10	0.123 \pm 0.03
12	0.152 \pm 0.02
14	0.175 \pm 0.03
16	0.193 \pm 0.02
18	0.219 \pm 0.04
20	0.248 \pm 0.03

*Represents mean \pm S.D. (n = 3) correlation coefficient (R^2) of 0.9984 and equation of regression line is- $Y = 0.0123X$

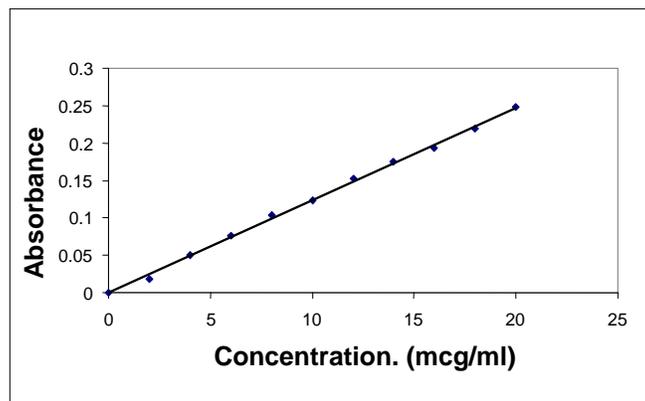


Figure 9: Standard calibration curve of Tolterodine Tartarate in 7.4 pH saline phosphate buffer
Scanning of Tolterodine Tartarate in methanol

Tolterodine Tartarate was scanned in methanol U.V range from 200-400 nm and it was found to be at 280 nm. The spectrum of absorbance is shown in Figure 10.

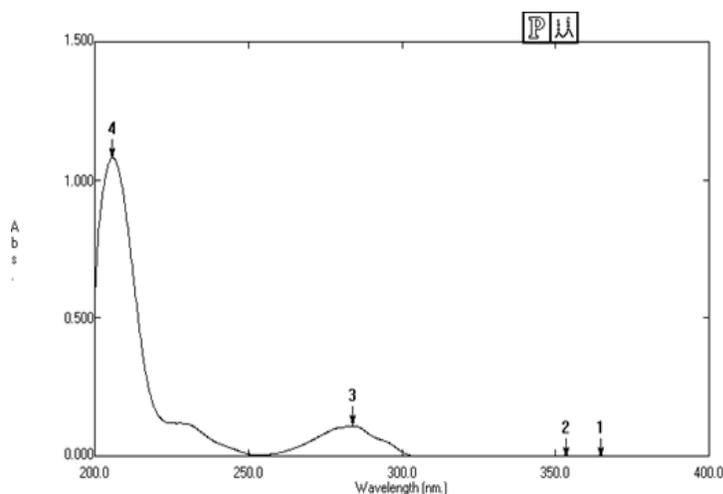


Figure 10: Scanning of Tolterodine Tartarate in methanol

Standard Calibration Curve of Tolterodine Tartarate in methanol

Accurately weighed tolterodine tartarate (50mg) was dissolved in 50 ml volumetric flask and volume was made upto 50 ml with methanol. From this aliquots samples were diluted to get the concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 μ g/ml. Absorbance were recorded spectrophotometrically against methanol as blank at λ_{max} 280 nm. Absorption value are shown in Table 3

Table 3: Standard calibration curve of Tolterodine Tartarate in methanol

Concentration (mcg/ml)	Absorbance*
0	0
2	0.26 \pm 0.02
4	0.44 \pm 0.04
6	0.62 \pm 0.03

8	0.82 ± 0.02
10	0.97 ± 0.02
12	1.14 ± 0.04
14	1.31 ± 0.03
16	1.5 ± 0.02
18	1.67 ± 0.04
20	1.89 ± 0.02

*Represents mean \pm S.D. (n = 3) had correlation coefficient (R^2) of 0.9981 and equation of regression line is- $Y = 0.0908X + 0.0577$.

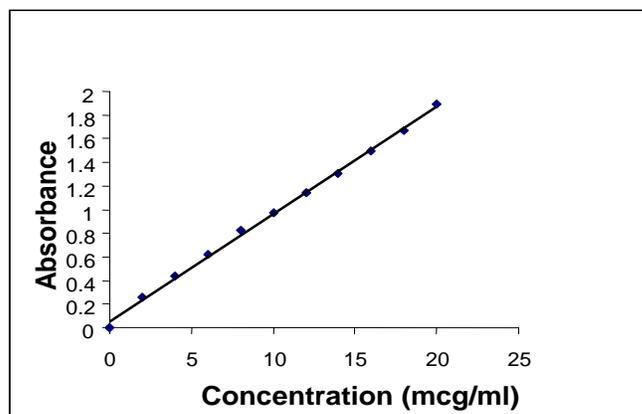


Figure 11: Standard calibration curve of Tolterodine Tartarate in Methanol

PREPARATION OF FILMS OF TOLTERODINE TARTARATE

Films (F1, F2, F3, F4) comprising of different ratio of eudragit RL100 and RS100 were prepared by glass substrate method¹².

Method:

The backing layer of 2% w/v polyvinyl alcohol solution in water was casted with controlled evaporation. The 6% w/v solutions of eudragit RL100 and eudragit RS100 in chloroform as per different ratio given in Table 4 were prepared. To each solution 30% w/w of dibutylphthalate of polymer composition were dispersed slowly with stirring and 12 % w/w of Tolterodine Tartarate of polymer composition were added by dissolving in 5 ml of methanol. The film containing tolterodine tartarate was prepared by casting the solution on previously prepared polyvinyl alcohol film as backing membrane with controlled evaporation. The film with an area of 2.5cm² were cut with help of mould.

Table 4: Films containing different ratio of eudragit RL100 and eudragit RS100

Sr. No.	Films	RL100 / RS100
1	F1	2: 8
2	F2	3: 7
3	F3	4: 6
4	F4	5: 5

EVALUATIONS OF FILM

Thickness:

Uniformity of film thickness is an important parameter which affects almost every other free films property viz. Film clarity, permeability properties, mechanical properties and folding endurance. Change in the film thickness can occur because of change in volume or strength of the polymer solution that is poured²⁸. Thickness of each 3 film was measured individually by thickness tester (Cambell Electronics, Mumbai, Model-CWWTDH 500N.)

Weight Variation:

It determines to ensure that film contains the proper amount of Drug¹³. Weight variation test was done by weighing of each of 3 films individually. The average weight of the film was taken as the weight of the films

Table 5: Weight and thickness of the films

Film	F1	F2	F3	F4
Thickness* (mm)	1.05 ± 0.01	1.063 ± 0.015	1.093 ± 0.015	1.073 ± 0.011
Weight* (gm)	0.1821 ± 0.0004	0.1842 ± 0.0003	0.1838 ± 0.0003	0.1831 ± 0.0002

*Represents mean ± S.D. (n = 3)

Percentage Moisture Content⁴³:

Each of 3 Films Were weighed individually and kept in a dessicator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The Percentage of moisture content was calculated as -

$$\% \text{ moisture content} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Table 6: percentage moisture content study of films

Film	F1	F2	F3	F4
% Moisture Content(% w/w)	2.80 ± 0.10	3.36 ± 0.12	4.09 ± 0.28	5.10 ± 0.12

*Represents mean ± S.D. (n = 3)

Percentage Moisture Absorption Study⁴³:

Moisture has significant effect on the mechanical properties of films. Moisture absorption study determines the affinity of film toward water. Each of 3 films were transferred to a tarred Petri dish and transferred to a glass desiccators maintained at controlled relative humidities of 75% and 85% respectively. The film specimens were accurately weighed, placed in relative humidity chambers increase or decrease in weight and change in physical appearance was then observed. Percent moisture absorption was calculated -

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Table 7: Percentage moisture absorption study of films at different relative humidity.

Films	% Moisture Absorption at Different Relative Humidity*	
	75%	85%
F1	10.01 ± 0.16	11.40 ± 0.28
F2	11.68 ± 0.16	12.52 ± 0.25
F3	12.26 ± 0.14	13.68 ± 0.60
F4	14.64 ± 0.42	15.35 ± 0.45

*Represents mean ± S.D. (n = 3)

Water vapour transmission rate study⁴³:

Water Vapor transmission through films determines the permeability characters of the film. The Water vapour transmission of films was studied at different relative humidity. For Water vapour transmission study, the film of known thickness was fixed over brim of a glass vial containing 1gms of fused calcium chloride as desiccant, using an adhesive. The initial weight of charged vial was taken and kept in desiccators, maintained at 75%(sodium chloride saturated solution) and 85 %(potassium chloride saturated solution) relative humidities. The vial was taken out periodically and weight for period of 48 hours. The WVTR was calculated by following formula. The results in terms of g/hr/cm² were given in Table 8.

The amount of water vapour transmitted was found using the formula:

$$\text{Water vapour transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}}$$

Table 8: Water vapor transmission rate study of films at different at different relative humidity.

FILM	% WVTR X 10 ⁻³ (g/hr/cm ²)			
	75% RH		85% RH	
F1	24 hrs.	48hrs.	24 hrs.	48hrs.
F2	2.62 ± 0.46	5.2 ± 0.056	5.32 ± 0.34	9.47 ± 0.16
F3	4.18 ± 0.11	9.55 ± 0.056	6.39 ± 0.23	12.17 ± 0.16
F4	5.40 ± 0.23	11.02 ± 0.28	8.60 ± 0.34	9.43 ± 0.57
	6.39 ± 0.23	12.21 ± 0.12	9.43 ± 0.57	19.47 ± 0.17

*Represents mean ± S.D. (n = 3)

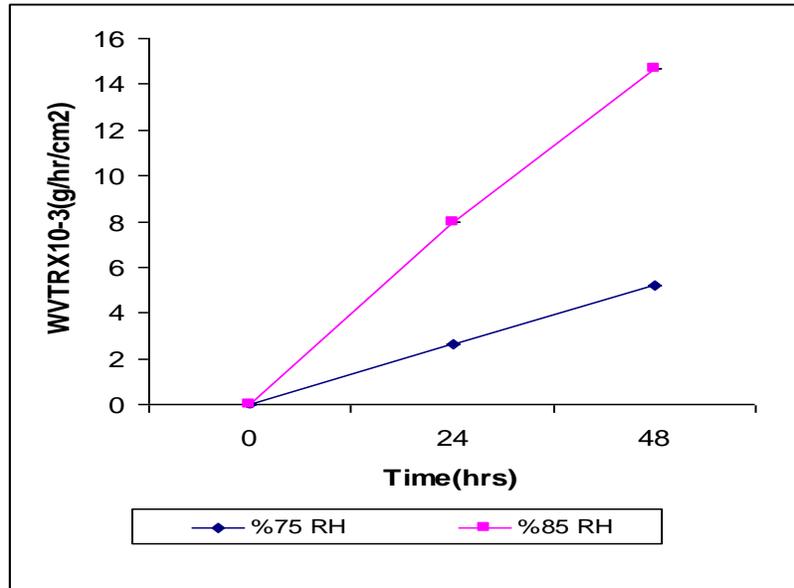


Figure 12: Water vapour transmission rate study F1

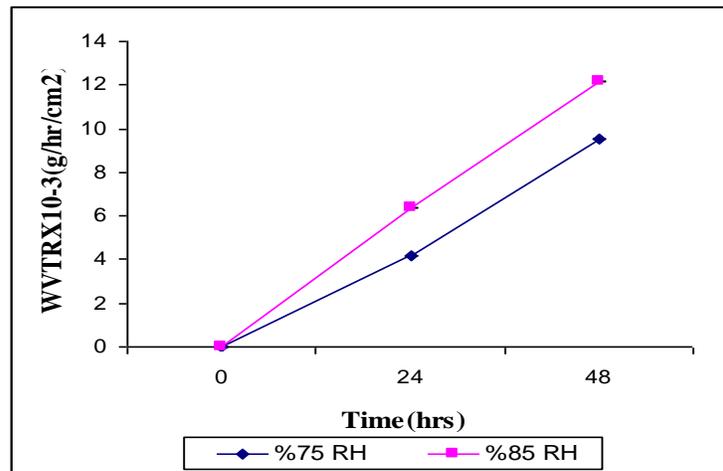


Figure 13: Water vapour transmission rate study F2

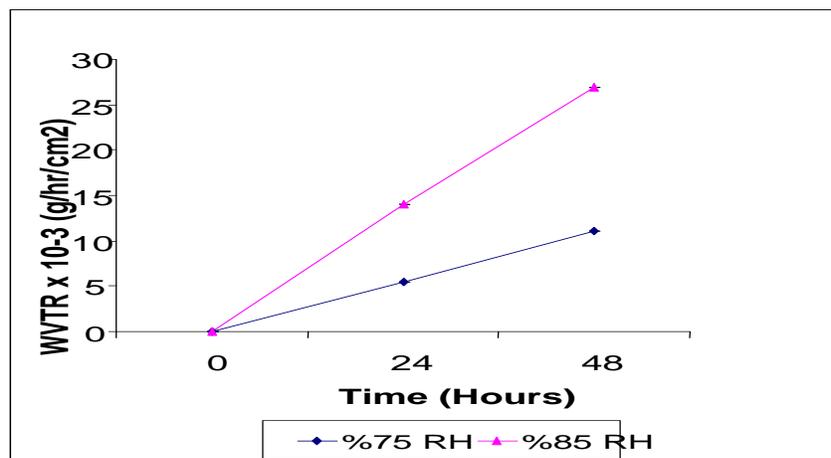


Figure 14: Water vapour transmission rate study F3

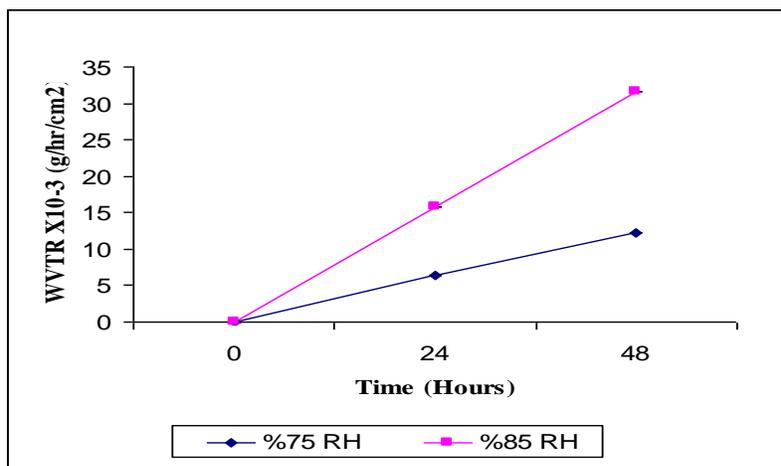


Figure 15: Water vapour transmission rate study F4

Tensile strength and Percent elongation⁴⁴:

This study was performed at Metallurgical And Materials Engg. Department, Mechanical Testing Lab., VNIIT, Nagpur. The following equations are used to calculate the mechanical properties of the films.

Tensile Strength(Kg/mm²) = Force at break (Kg)/ Initial cross-sectional areas of the sample(mm²)

Elongation at Break(%mm²) = Increase in length (mm) / Original Length (mm) X Cross Sectional Area(mm²) 100

Table 9: Tensile strength and Percent elongation of films

Film	Tensile Strength*(MPa)	Percent Elongation*(% /mm ²)
F1	5.971	60.12
F2	5.887	59.40
F3	6.553	65.41
F4	6.412	63.26

*Represents mean ± S.D. (n = 3)

Folding Endurance²⁸:

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.

Table 10: Folding Endurance of films

Film	Folding Endurance*
F1	292.33 ± 6.65
F2	294.33 ± 8.73
F3	295.33 ± 7.37
F4	300.33 ± 5.85

*Represents mean ± S.D. (n = 3)

Drug content and uniformity

Standard Calibration Curve of Tolterodine Tartarate in methanol

Accurately weighed tolterodine tartarate (50mg) was dissolved in 50 ml volumetric flask and volume was made upto 50 ml with methanol. From this aliquots samples were diluted to get the concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 μ g/ml. Absorbance were recorded spectrophotometrically against methanol as blank at λ_{\max} 280 nm. Absorption values are shown in Table 11 and Standard calibration curve in Figure 16.

Table 11: Standard calibration curve of Tolterodine Tartarate in methanol

*Represents mean \pm S.D. (n = 3)

Concentration (mcg/ml)	Absorbance*
0	0
2	0.26 \pm 0.02
4	0.44 \pm 0.04
6	0.62 \pm 0.03
8	0.82 \pm 0.02
10	0.97 \pm 0.02
12	1.14 \pm 0.04
14	1.31 \pm 0.03
16	1.50 \pm 0.02
18	1.67 \pm 0.04
20	1.89 \pm 0.02

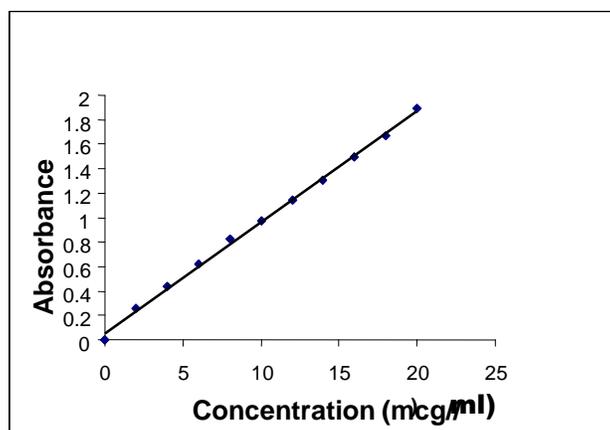


Figure 16: Standard calibration curve of Tolterodine Tartarate in Methanol

Determination of drug content²⁸ :

Film containing drug was kept in glass beaker containing 10ml methanol and covered with aluminum foil to avoid evaporation. After 24 hrs. this solution was filtered through whatman filter paper No. 42 & from the filtrate only 2 ml filtrate was taken and diluted upto 20ml with methanol. The content of the drug was estimated spectrophotometrically by using the results of standard calibration curve plotted at λ_{\max} 280 nm.

Table 12: Drug Content in formulations

Films	F1	F2	F3	F4
Drug Content*	99.56± 0.28	99.055 ± 0.74	99.675± 0.33	99.14± 0.15

*Represents mean ± S.D. (n = 3)

In vitro diffusion study

In vitro release of tolterodine tartarate from films was measured through dialysis membrane (HIMEDIA) using keishary chien cell with diffusion area of 2.5cm².

Table 13: %Cumulative Drug Permeation of films

Time (Hours)	%Cumulative Drug Permeation*			
	F1	F2	F3	F4
0	0	0	0	0
1	1.28 ± 0.021	2.05 ± 0.043	2.52 ± 0.063	2.60 ± 0.049
2	2.92 ± 0.035	2.62 ± 0.079	3.35 ± 0.098	3.39 ± 0.063
4	4.19 ± 0.049	3.82 ± 0.091	7.43 ± 0.68	4.51 ± 0.29
6	5.9 ± 0.007	6.32 ± 0.15	12.84 ± 0.64	8.15 ± 0.62
8	7.865 ± 0.03	9.52 ± 0.22	19.3 ± 1.59	12.84 ± 1.23
10	10.31 ± 0.06	13.085 ± 0.37	23.7 ± 0.86	18.295 ± 1.30
12	13.72 ± 0.08	17.14 ± 0.36	29.81 ± 1.14	25.82 ± 1.58
14	17.36 ± 0.11	23.26 ± 0.34	36.86 ± 1.31	31.44 ± 1.13
16	21.69 ± 0.15	29.36 ± 0.34	44.52 ± 1.08	37.72 ± 0.48
18	26.55 ± 0.16	35.6 ± 0.58	51.91 ± 1.09	45.62 ± 0.65
20	31.68 ± 0.19	42.08 ± 0.56	59.91 ± 1.25	51.83 ± 0.39
22	36.29 ± 0.21	47.26 ± 0.50	67.28 ± 1.07	57.72 ± 0.38
24	40.61 ± 0.28	52.68 ± 0.67	74.28 ± 1.08	64.12 ± 1.40

*Represents mean ± S.D. (n = 3)

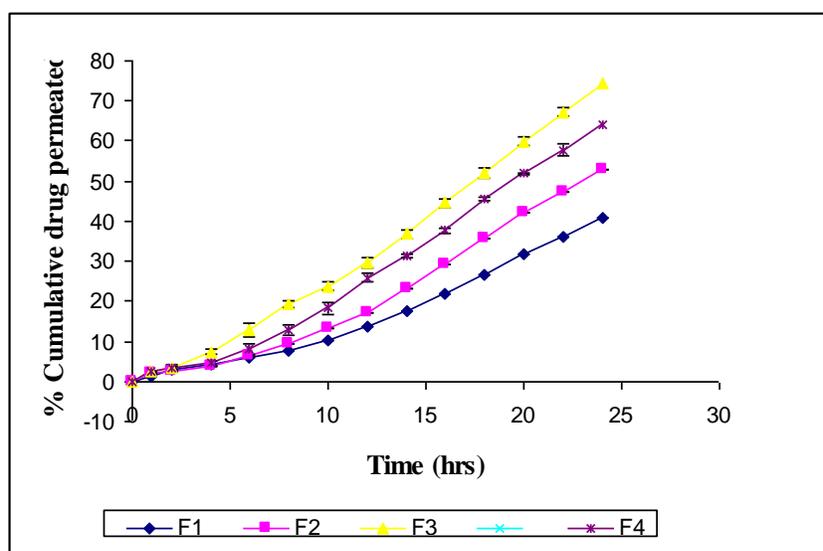


Figure 17 : Cumulative % drug permeation study of films F1,F2,F3,F4.

In vitro Dissolution study³⁶

All samples were analyzed for tolterodine tartarate content spectrophotometrically at wavelength 280nm.

Table 14: %Cumulative Drug Release of films

Time (Hours)	%Cumulative Drug Release*			
	F1	F2	F3	F4
0	0	0	0	0
1	22.42 ± 0.41	24.85 ± 0.21	20.65 ± 0.41	37.03 ± 0.62
2	24.74 ± 0.41	26.47 ± 0.063	27.67 ± 0.41	39.56 ± 0.13
4	25.16 ± 0.62	28.47 ± 0.15	32.85 ± 0.62	46.29 ± 0.41
6	26.61 ± 0.20	32.22 ± 0.20	37.78 ± 0.42	53.44 ± 0.19
8	28.23 ± 0.42	33.8 ± 0.21	43.35 ± 0.61	63.41 ± 0.42
10	29.71 ± 0.43	38.03 ± 0.43	48.83 ± 0.63	70.93 ± 0.21
12	37.26 ± 0.19	41.99 ± 0.65	54.82 ± 0.41	81.58 ± 0.43
14	38.54 ± 0.21	44.59 ± 0.21	60.57 ± 0.63	95.74 ± 0.43
16	41.74 ± 0.40	48.77 ± 0.21	65.94 ± 0.63	-
18	46.91 ± 0.42	53.76 ± 0.43	73.12 ± 0.65	-
20	50.93 ± 0.40	58.17 ± 0.21	81.81 ± 0.30	-
22	54.27 ± 0.21	63.56 ± 0.44	84.63 ± 0.45	-
24	56.45 ± 0.43	69.31 ± 0.23	90.43 ± 0.58	-

*Represents mean ± S.D. (n = 3)

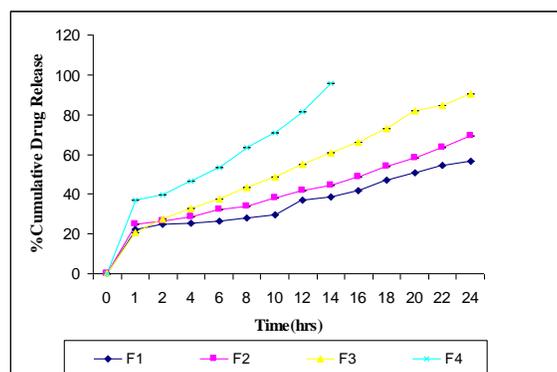


Figure 18: Cumulative % drug release study of films F1,F2,F3,F4

Statistical Analysis:

All the statistical calculation were performed by using **Graph Pad Instat Demo (DATA SET 1.ISD)**.

Table 15: Statistical treatment data of formulation F3

S. N.	Formulation Comparison	P Value	Result
1	F3 Vs F1	P < 0.01	Significant Difference
2	F3 vs. F2	P < 0.01	Significant Difference
3	F3 vs. F4	P < 0.01	Significant Difference

Kinetic Treatment to Dissolution Data⁴⁵

Analysis of drug release from film must be performed with a flexible model that can identify the contribution to overall kinetics, and mechanism of drug release, the dissolution data obtained for optimized formulation was treated with the different release kinetic equations.

1] Zero order release equation

$$Q = K_0 t \text{ ----- (1)}$$

$$\ln(100 - Q) = \ln Q_0 - K_0 t \text{ ----- (2)}$$

3] Higuchi's square root of time equation

$$Q = K_{HT} t^{1/2} \text{ ----- (3)}$$

Where,

Q = Amount of drug release at time (t)

K₀ = Zero order release rate constant

K_H = Higuchi square root of time release rate constant

Table 16: Kinetic treatment of dissolution data of optimized film F3

Sr.No.	Variables	Zero order	First order	Higuchi	Korsemeier Peppas	Hixon-crowell
1	r ²	0.9624	0.9595	0.9770	0.9867	0.9838
2	n	-	-	-	0.5863	-
3	K	7.4012	-0.1412	22.2689	18.2559	-0.0369

Skin irritation study ^{28,46}

In the present study 6 guinea pigs (approved by Institutional Ethical Committee, IPER, Wardha) of either sex weighing between were used. Films were applied once a day for 7 days and sight was covered with cotton bandage and observed for any sensitivity and the reactions if any were graded as

0 - No reaction

0.5- Slight patchy erythema

1 - Slight but confluent or moderate but patchy erythema

2 - Moderate erythema

3 - Severe erythema with or without erythema

Table 17: Skin irritation study of selected film F3

Scores on respective days								
Sr No	Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	Control	0	0	0	0	0	0	0
2	F3	0	0	0	0	0	0	0

CONCLUSION:

At last it can be concluded that F3 was the best formulation. . It also showed much better drug permeation and drug release compared to other formulation. It showed no signs of causing skin irritation when applied for 7 days on guinea pigs. Overall conclusion can be drawn that the overactive bladder is a syndrome that might benefit of a flat serum concentration profile. Thus considering the novel approach, transdermal film containing tolterodine tartarate can be effectively and precisely deliver the medication to relieve overactive bladder and manage it effectively

FUTURE SCOPE :

The future scope of the present work can be concluded as: Optimized formulation can be subjected to clinical trials to confirm its effectiveness. Bioavailability and Bioequivalence study can be carried out. *In vitro* and *in vivo* correlation study to confirm increase in bioavailability. Exploration of technology with aid of other branched cyclodextrins.

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