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FORMULATION, CHARACTERIZATION AND IN-VITRO EVALUATION OF DULOXETINE HYDROCHLORIDE TRANSDERMAL PATCHES

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ABSTRACT

In the present research work, an attempt was made to formulate, develop and optimize the Duloxetine Hydrochloride Transdermal Patches. Based on the review of literature polymers Sodium Alginate, HPMC-15cps and Methocel K100 was selected and their FTIR studies gave their compabilities between Duloxetine Hydrochloride and Polymers. Out of ten trials, trial T-5 with Sodium Alginate and HPMC-15cps and trial T-10 with Methocel K100 and Sodium Alginate was optimized initially. After comparative drug release and physical characterization of trial T-5 and T-10, trial T-10 was optimized and taken for one month accelerated stability studies at 60C^{o} 80%RH. The drug release after one month stability studies from T-10 transdermal patch was found to be 91% after 480 minutes physical measurement thickness was found to be 18mm, with folding endurance test of 190 times and content uniformity was found to be 99.35 percent. Determination of release rate kinetics was also performed for trial T-10, based on R^2 value the order of kinetics release of drug follows first with Zero Order with 0.997, followed by Koresmeyer Peppas Plot with 0.984, Higuchis Plot with 0.937 and First Order with 0.900.

KEYWORDS: Duloxetine Hydrochloride, Sodium Alginate, HPMC-15cps, Methocel K100, Zero Order-0.997.

INTRODUCTION

Transdermal drug delivery system is a self-reliant distinct dosage form which is fixed to the skin to supply the drug into the blood circulation at fixed and reproducible rate for prolonged period of time. The main aim of the transdermal patches is to exploit the fluidity transversely

the skin and also decrease the retaining and breakdown of the drug. This delivery system is advantageous over oral routes as it escapes first pass breakdown and injections as it increases patient compliance.[1]

Figure no: 1 Transdermal Patch.

ANATOMY AND PHYSIOLOGY OF THE SKIN

Human skin contains three distinct tissues.[2]

A. The stratified, vascular, cellular epidermis,
B. Dermis of connective tissue and
C. Hypodermis

Epidermis: The manifold epidermis differs in thickness extending from 0.8mm on palms and soles down to 0.06mm on the eyelids. It consists of superficial layer as stratum corneum and feasible epidermis.

a) Stratum corneum

It is the chief obstacle for the penetration of the drug. It is the topmost coating of the skin which is also called as horney layer. It is nearly 10mm in thickness when it is in dry state but soak water and swells to numerous times in thickness when it is hydrated. It also contains 10-25 layers of keratinized cells also known as corneocytes which are impermeable. Stratum corneum is a wall like structure where keratinized cells work as protein "bricks" fixed in phospholipid "mortar." The phospholipids are organized in bilayers and it is maintained by the presence of polar free fatty acids and cholesterol.

b) Viable epidermis

It is situated below the stratum corneum; it differs in thickness from 0.06mm on the eyelids to 0.8mm on the palms. It consists of various layers as stratum lucidum, stratum granulosum,

stratum spinosum and the stratum basal. Mitosis of the basale layers continuously reintroduces the epidermis which compensates for the damage of the dead horney cells.

As the cells formed by the basal layer transfer outward they experience keratinization to form the topmost layer of stratum corneum.

Dermis

It consists of background of connective tissue, containing blood vessels, lymph vessels, and nerves. It is 3-5mm thick. The cutaneous supply of blood helps in regulation of the body temperature. It also helps in removing the waste materials. This blood supply makes the dermal concentration very low for permeation, thus resulting concentration difference offers crucial concentration incline for penetration through the skin.

Hypodermis

It is a subcutaneous fat tissue which holds both dermis and epidermis. It acts as fat storage area. It provides nutritional support, mechanical protection and also helps to regulate temperature. It transports major blood vessels and nerves to skin and comprises of sensory pressure organs.

Transdermal delivery system requires the drug to penetrate through these layers and spread into blood circulation while in topical delivery system permeation across stratum corneum and preservation of drug in skin films is desired.

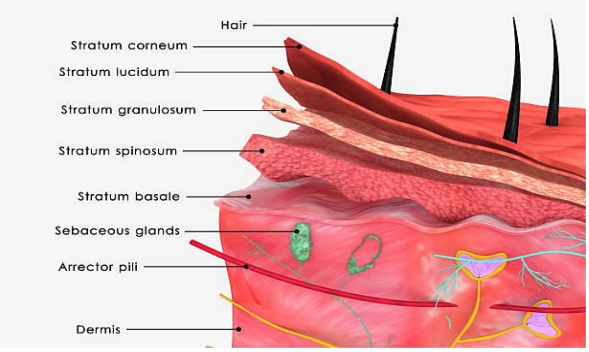

Figure no 2: Structure of Skin.

PATHWAYS OF THE SKIN

When drugs are applied on the apparent layer of the skin, it penetrates into the skin across the various routes. Drugs penetrate either through stratum cornuem (transepidermal) or through appendages (transappendageal).

During penetration through stratum corneum, there are two possible routes can be distinguished,

- Penetration alternating through the corneocytes and the lipid lamellae (transcellular route).
- Penetration along the tortous pathway (intercellular route).

Possible ways for penetration of drug through the skin[3]

Usually it is believed that the principal route of penetration transversely the stratum corneum is the intercellular route. This mostly occurs by the compactly cross-linked cornified covering coating the keratinocytes. However trans cellular carriage for minor hydrophilic molecules such as water cannot entirely be omitted.

The appendage route or shunt route includes either the duct of the ecccrine sweat glands or the follicular duct. The substance of the sweat glands is usually hydrophilic, while the material of the follicular duct is usually lipophilic. This is chiefly because of the sebum expelled into the entrance of the follicular duct.

It is usually believed that because of its larger external area, inert skin penetration mostly occurs through intact stratum corneum.

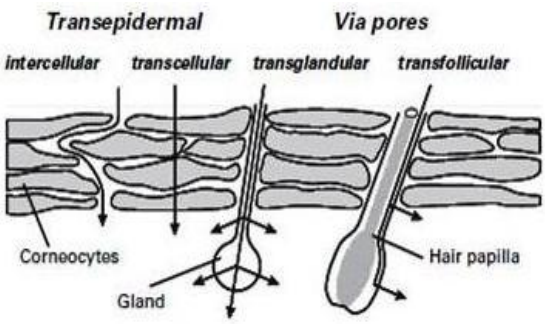

Figure no: 3 Penetration of drug across the skin barrier.

TYPES OF TRANSDERMAL PATCH[4]

Single layer drug –in-adhesive

In this category the adhesive layer comprises of the drug. This adhesive layer sticks the several sheets together, together with whole arrangement to the skin and it is also accountable for liberating the drug. This layer is bounded by impermanent liner and a backing.

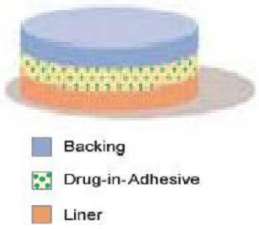

Figure no: 4 Single layer drug in adhesive system.

Multi-layer Drug-in-Adhesive

It is comparable to the single layer adhesive system as both the adhesive layers are responsible for releasing the drug but it add up other layer of drug-in- adhesive which is generally parted by a film. This patch contains impermanent liner and a permanent backing.

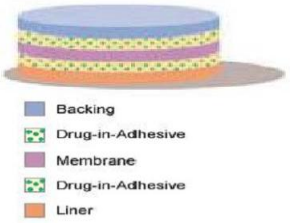

Figure no 5: Multi-layer drug in adhesive.

Reservoir

This transdermal drug transport system has a distinct drug layer. This drug layer is a liquid section which contains drug solution parted by the adhesive coating. This contains backing layer. The release rate in the reservoir system is zero order.

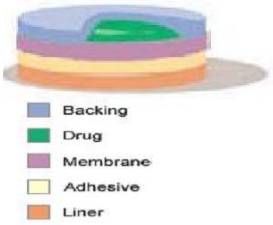

Figure no 6: Reservoir System.

Matrix

This patch consists of drug coat of a semisolid medium which has solution of the drug or suspension of the drug. The adhesive coat environs the drug layer partly covering it.

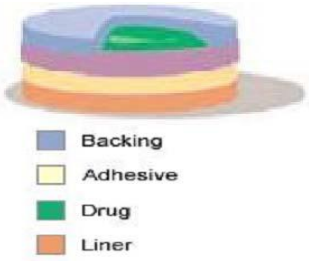

Figure no 7: Matrix System.

Vapor Patch

These patches are newly introduced in market. In these patches the adhesive coating does not adhere the numerous layers but also releases the vapor. They discharge essential oils for about 6 hours and are employed in decongestion.

Controller vapor patches also existing in the market, they enhance the quality of the sleep.

Vapor patches which decrease the number of the cigarettes that one smokes in a single month existing in the market.

TECHNOLOGIES FOR DEVELOPING DRUG DELIVERY SYSTEM[5]

Polymer membrane partition controlled systems

The drug tank is sandwitched amid a drug-impermeable backing laminate and a rate controlling memmbrane (can be microporous or nonporous polymeric membrane) and the drug is permitted to pervade only across the rate controlling membrane. The drug is homogenously dispersed in compact polymer matrix, adjourned in a viscous medium.

E.g.: Alkyl alcohol to make a transparent drug solution.

A thin film of drug compatible hypoallergenic pressure sensitive adhesive polymer is applied on the exterior layer of the polymeric membrane to offer near interaction with the delivery system with the skin surface. e.g. Silicone adhesive.

The permeability coefficient and width of rate controlling membrane can change the drug release rate upon changing the configuration of drug reservoir formulation.

E.g. some FDA permitted systems- Transderm-Nitro used for angina pectoris, Transderm-Scop used for motion sickness.

The intrinsic drug release rate is defined by

$$\frac{dQ}{dt} = \left[\frac{k_{m/r}k_{a/m}D_aD_m}{k_{m/r}D_mh_a + k_{a/m}D_ah_m}\right]C_R$$

Where,

C_R: drug concentration in reservoir compartment

$K_{m/r:}$ Interfacial partition coefficient for dividing of the drug beginning from the reservoir to the membrane.

$K_{a/m:}$ Interfacial partition coefficient apportioning of the drug beginning from memebrane to adhesive.

D_a: Rate controlling membrane diffusion coefficient.

D_m: Adhesive layer diffusion coefficient.

h_a: rate controlling membrane thickness

h_m: thickness of adhesive layer

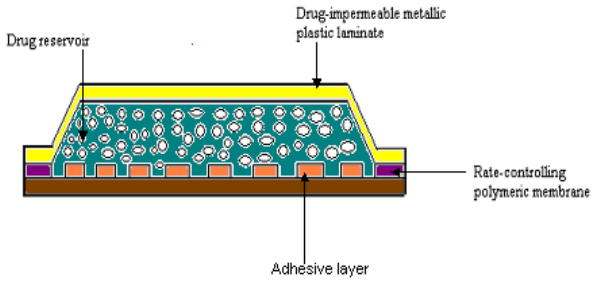

Figure no 8: Polymer membrane partition controlled system.

Polymer matrix diffusion controlled systems

Drug reservoir is designed by diffusing the drug in a hydrophilic or lipophilic polymer matrix. The medicated disks are formed by molding the medicated polymer with definite surface-area and thickness. The drug reservoir with medicated disks is fixed on occlusive baseplate in a section which is made-up of drug-impervious plastic support. The adhesive polymer is applied along the edge of the patch. It forms a band of adhesive rim around the medicated disk.

E.g. Nitro-Dur and NTS system used for treatment of angina pectoris.

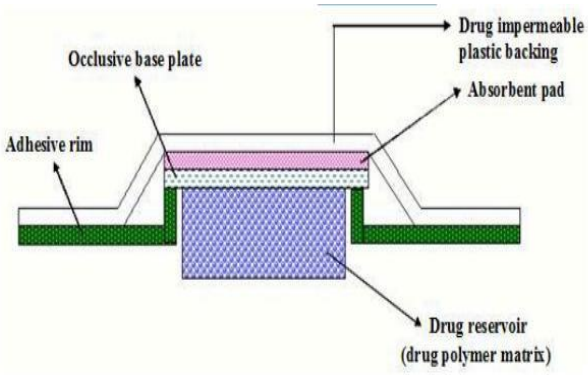

Figure no 9: Polymer matrix diffusion controlled systems.

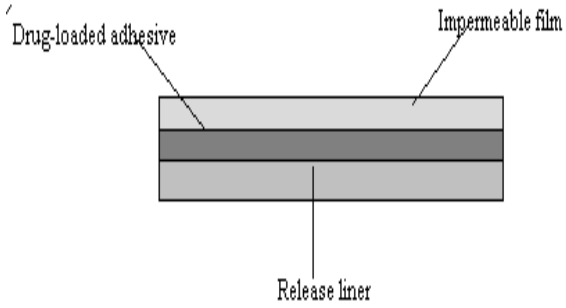

Figure no 10: Cross sectional view of an adhesive polymer drug dispersion-type TDD system showing various major structure components.

The release rate from polymer matrix drug diffusion controlled system.

$$\frac{dQ}{dt} = \left[\frac{L_d C_p D_p}{2t}\right]^{1/2}$$

Where,

L_d: drug loading dose primarily distributed in polymer matrix

C_p: drug solubility in polymer matrix

D_p: drug diffusivity in polymer matrix

Only drug dissolved in polymer matrix can diffuse, $C_p$is practically equal to C_R.

This type of the system can also be made-up by directly diffusing drug in pressure sensitive adhesive polymer e.g. Polyacrylate and then it is coated by using solvent casting or hot melt method onto a flat film of drug impervious backing laminate to obtain a layer of drug reservoir, this results in thin patch.

Drug reservoir gradient controlled delivery system

Polymer matrix drug dispersion type can be modified by increasing the drug load level to form a grade of drug reservoir together with the diffusional pathway through the multi-laminate adhesive coatings. The drug release from drug reservoir gradient is controlled.

In this of system, thickness of diffusional pathway rises with time. This system is designed to proportionally increase drug load level in order to compensate time dependent upsurge in diffusional path. e.g. Deponit system consisting of nitroglycerine used for angina pectoris.

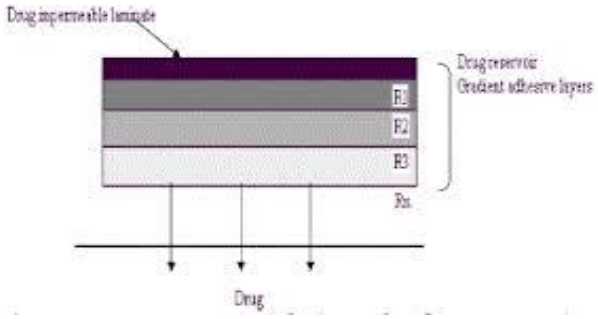

Figure no 11: Drug reservoir gradient controlled delivery system.

Micro-reservoir dissolution controlled delivery system

This system is fusion of both the reservoir and matrix dispersion type delivery system which contains drug reservoir made by principal appending the drug in a solution of drug solubilizer which is miscible with water.

E.g. propylene glycol homogeneously disperse drug suspension by using large shear mechanical force in lipophilic polymer with controlled aqueous solubiilty to form thousands of microscopic drug reservoirs.

E.g. Nitrodisk system used for management angina pectoris.

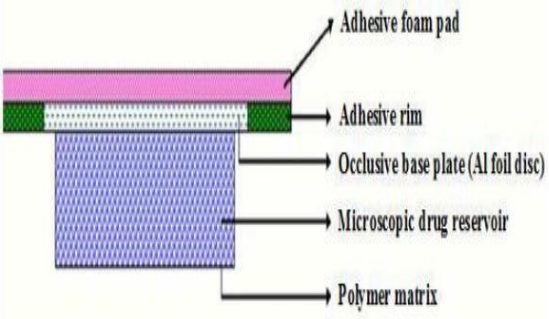

Figure no 12: Micro-reservoir dissolution controlled delivery system.

Advantages[6]

1. They avoid first pass hepatic metabolism
2. They are used for the drugs which have narrow therapeutic window.
3. They are non-invasive which helps in avoiding inconvenience occurred in parenteral therapy.
4. They are applicable as substitute for oral administration of the medicine in case of vomiting and diarrhea.
5. This system avoids gastrointestinal drug absorption complications which occur due to gastrointestinal p^H, activity of enzymes and interaction of the drug with food, drink and other drugs which are administered orally.
6. They provide prolong therapy by applying it at one time as it improves convenience over other dosage forms, requiring frequent dose administration.
7. Drug therapy isendedquickly in this system just by the removal of the transdermal patch from the skin surface.
8. Because of their physical presence, identifying markings they can be easily identified in emergencies like unresponsive and unconscious patients.

Disadvantages[7]

1. They are not applied in acute conditions. They can be applied only in chronic conditions.
2. Patients may face problems like itching, edema, erythema due to use of patches.
3. Therapeutic efficacy of the drug might be affected as many of the hydrophilic drugs cannot pass or very slowly permeates the skin.
4. The function of the dermal layer to act as barrier differs person to person, or with oldness of the person or with different position on same person.
5. It has inefficient system of delivery of drug.
6. Transdermal system is not companionable with ionic drugs.
7. This system may cause dumping of dose.
8. Drug in blood at high level cannot be obtained.
9. Drugs which have attraction for hydrophilic and lipophilic phases can be utilised.
10. There is a probability of irritation at the site where the drug is administered.

Limitations for selection of TDDS[8]

All types of drugs cannot be directed through the transdermal delivery system, the drugs should have desirable physico-chemical properties

- They are not appropriate for drugs that need high plasma levels.
- They are not appropriate for drugs that irritate the skin and contact dermatitis.
- They are not appropriate for drugs that experience metabolism during the passage through the skin.
- They are not appropriate for high molecular weight materials containing drugs.
- Transdermal route cannot be engaged for large variety of drugs, as skin is very efficient barrier penetration of drugs. Only with low dose can be administered.

Applications of Transdermal Patches[9]

- Nitroglycerine patches are occasionally given for angina pectoris in case of sublingual pills.
- Clonidine an anti-hypertensive drug can be obtainable as transdermal patch.
- Estrogen patches are occasionally approved to manage menopausal symptoms and post-menopausal osteoporosis.
- Contraceptive patch (marketed as Ortho Evra or Evra) are applicable in hormone delivery.
- Two opoid medications like Fentanyl (Duragesic) and Buprenorphine (BuTrans) are employed to deliverrelief for severe pain.
- Nicotine patch deliver nicotine in measured doses which aid in termination of tobacco smoking is the topmost marketing transdermal patch in the United States.
- Transdermal form of MAOI selegiline, used as an antidepressant.

Recent Technology

Drug/Prodrug[10]

The prodrug technology is employed to boost the dermal and transdermal distribution of drugs with disapproving partition coefficients. It involves addition of promoiety to upsurge partition coefficient, solubility and transference of main drug in the stratum corneum. Esterases discharge the main drug by hydrolysis when it reaches epidermis thereby enhancing aqueous epidermis solubility.

Ex: The inherent deprived penetrability of polar 6-mercaptopurine was improved by 240 times utilising S6- acyloxymethyl and 9-dialkylaminomethyl promoieties.[10]

Iontophoresis[11]

This technique comprises application of small level electric current to improve pervasion of therapeutic agent which is applied topically either directly across the skin or secondarily through the dosage form.

Electroporation[12]

This method involves use of greater voltage pulses to skin to encourage creation of transient pores. Electrical parameters which affect permeation rate include pulse properties like waveform, rate and number. This technology is engaged to improve the skin permeability by opposing lipophilicity and size (smaller molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7kDA.23. High voltages (100V) and small management intervals (milliseconds) are more frequently employed.

Micro-needle-Based Devices[12]

The first micro-needle system consisted of drug tank and a multiplicity of projections (micro-needles 50 to 100mm long) extends from reservoir which penetrates the epidermis and stratum corneum to distribute the drug. A micro-needle technology named Macroflux was used either in combination with drug tank or by dry varnish the drug on micro-projections(it is used for intra-cutaneous immunization).

Abrasion[12]

This abrasion technique involves disruption or the direct removing the topmost films of the skin which help in penetration of topically applied drugs. Few of these are built on methods given by dermatologists for skin re-surfacing(e.g. microdermabrasion) used in the management of acne, scars, hyperpigmentation and other skin blemishes.

Needle less Injection[12]

This is a pain free method for administering drugs to the skin. The device is used to supply lidocaine hydrochloride, testosterone and other molecules like calcitonin and insulin. Ultrasonic energy employed to enhance the distribution of solutes called as Sonophoresis. The device used to improve skin penetrability is SonoPrep device which uses low frequency ultra-sound (55 kHz) for period of 15 seconds.

It is a battery operated handheld device which consists of control unit, ultrasonic horn along with control panel, a one-use coupling medium catridge, and a return electrode.

Ultrasound (Sonophoresis and Phonophoresis)[12]

This technique involves utilization of ultrasonic energy to improve transdermal distribution of solutes through pre-treatment. This technique uses small frequency ultrasound for a regular interval of 15 secs to improve skin permeability.

Laser Radiation[12]

This technique includes straight and organized contact of a laser radiation to the skin. Exposure of laser effects causes deduction of the stratum corneumdeprived of considerably injuring the underlying epidermis. This method involves elimination of the stratum corneum used to increase the distribution of lipophilic and hydrophilic drugs.

Basic components of the TDDS[13]

The components of the transdermal devices include

- Polymer matrix
- Drug
- Permeation Enhancers
- Other excipients

Polymer Matrix

The polymer matrix maintains the discharge of the drug through the transdermal patch.

Table no: 01 Types of Polymers.

Natural Polymers	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins,.	**Polybutadiene, Hydrin rubber polyoxane, silicone rubber, Neoprene.**	**Polyvinylpyrrolidone Polymethyl methacrylate, Epoxy, Polyurea, etc.**

MATERIALS AND METHODS

Materials for the present research work was obtained from various resources of which API Duloxetine hydrochloride was obtained form sreepathi pharmaceutical limited, HPMC form Thomas bakers private limited, Mumbai, Sodium Alginate from S.D fine chemicals, Mumbai, Methocel K100 from Burgoyne laboratory; Mumbai, India and PEG 400 from RFCL Ltd., India.

Pre-formulation Studies

DETERMINATION OF MELTING POINT[14]

Melting point of the Duloxetine Hydrochloride was determined by using open capillary tube technique in digital melting point apparatus.

Method: In this method, the capillary tube is closed by gently heating from one end. Then the little amount of the drug Duloxetine Hydrochloride was filled into the sealed capillary tube. Then this tube was tied to the tube having the oil phase in such that the sealed part of the capillary containing the drug was dipped into the oil. Gently the oil bath was heated. When powder starts melting, the heating was stopped and the temperature is noted down at which the drug melts starts melting.

Determination of Partition Coefficient[15]

The partition coefficient of the drug Duloxetine hydrochloride was known by using equal volumes of 1-octanol and aqueous solution in a separating funnel.

For water soluble drugs, drug solution was prepared in distilled water and for water insoluble drugs, drug solution was prepared using 1-octanol.

1-octanol (100 ml) is added to the equal volume of the drug solution prepared in separating funnel by using distilled water and the solutions were allowed to separate with shaking at irregular intervals. Then the drug solution was separated and assayed for drug content.

$$Partition\ Coefficient = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}$$

Determination of Drug Excipient Compatibility[16]

During the preparation of patch formulation, drug and polymers interact when they in contact with each other, which may cause instability of the drug.

FT-IR spectroscopy is employed to confirm the compatibility between the polymer and Duloxetine Hydrochloride. The pure drug and drug with all the excipients are scanned separately.

KBr Pellet method is used and the samples were mixed with dry powder KBr crystals. The blend was compacted to make a disc. This disc was kept in spectrophotometer and spectrum was recorded.

Chemical contact among drug and polymers was found by using the FT-IR spectra.

ANALYTICAL METHODS

Preparation of Standard Stock Solution using distilled water

Accurately weighed 5mg of the drug Duloxetine Hydrochloride is taken in a volumetric flask, and it is completely solubilized in distilled water and make-up the volume to 100ml which gives a concentration of 50µg/ml.

Preparation of calibration curve using Distilled water

The standard stock solution (50µg/ml), appropriate amount of the sample solution are taken into different volumetric flasks and the make the volume to 10 ml using distilled water which gives a concentration of 10, 20, 30, 40µg/ml. The absorbance of the sample solution was measured at 289nm using UV-Visible spectrophotometer. The standard graph is designed by taking concentration on x-axis and absorbance on y-axis.

PREPARATION OF TRANSDERMAL PATCHES[17]

Transdermal patches containing the drug Duloxetine Hydrochloride is formulated by Solvent Evaporation Method by using polymers i.e. HPMC (hydroxyl methyl cellulose), Methocel k100, Sodium Alginate in presence of a plasticizer PEG 400 in all the cases.

The drug Duloxetine Hydrochloride (10 mg) was solubilized in water (15 ml). The polymers are also dissolved in the same solvent system. Then the solution is mechanically stirred to evade lump development. Then the solution is kept in sonicator to remove air bubbles.

The solution is transferred into petri-plate which is already rinsed with glycerine. The solvent is permitted to evaporate in a controlled oven at 60 for 2 hours then it was kept for air drying. After 24hrs the dried films are taken out and kept in desiccators.

Diameter = 8.8cm Surface area = 60.79cm^2

FORMULATION OF DULOXATINE TRANSDERMAL PATCHES

Table no: 02 Formulation trials T-01 to T-05.

FORMULATIONS	T_1	T_2	T_3	T_4	T_5
Duloxetine Hydrochloride	10	10	10	10	10
HPMC-15cps	100	150	200	250	250
Methocel k100	*	*	*	*	*
Sodium Alginate	25	50	75	100	200
PEG 400-ml	1	1	0.5	0.5	0.5
Water	15	15	15	15	15

Table no: 03 Formulation trials T-06 to T-10.

FORMULATIONS	T_6	T_7	T_8	T_9	T_{10}
Duloxetine Hydrochloride	10	10	10	10	10
Methocel k100	25	50	75	100	125
Sodium Alginate	25	50	50	50	100
PEG 400-ml	0.5	0.5	1	1	1
Water	15	15	15	15	15

EVALUATION OF TRANSDERMAL PATCHES[18]

Physical Appearance

All the formulated transdermal patches are visually checked for its color, clarity, elasticity and flatness.

Folding Endurance

The transdermal patch of each type of the formulation is cut into small strips of 2×2 cm and they are folded at the exact point until it breaks or cracks. The total of times it is folded at the same point indicates the value of the folding endurance.

Uniformity of weight

The formulated transdermal patches are weighed using digital weighing machine. Three readings for each transdermal patch are taken. Average of the weight is then calculated.

Drug Content Uniformity

The transdermal patches are cut into pieces of 1 ×1 cm for the formulations made and placed in 50ml of distilled water. The contents are stirred for 2h by using magnetic stirrer. The solution is then sifted by using Whattmann filter paper and diluted suitably by using distilled water. The solution is then analyzed for its absorbance at 289nm. From the above absorbance values, the drug content is determined.

In-vitro drug release studies

The transdermal patches prepared are cut into piece of 1 ×1 cm for all the formulations made and are placed in the middle of the egg membrane and it is tied to the inverted test tube. The test tube is touched to the superficial layer of the distilled water (50 ml) taken in a beaker. The beaker is magnetically stirred on magnetic stirrer. The samples of 5ml were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, up to 24h, analyzed for drug content spectro-photometrically at 289 nm against blank. Then it is exchanged with the equal quantity of distilled water at every time of sample withdrawal.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

The melting point of the Duloxetine Hydrochloride was found to be: 163ºC.

DETERMINATION OF PARTITION COEFFICIENT

The partition coefficient of the Duloxetine Hydrochloride was found to be 26.96.

FTIR STUDIES

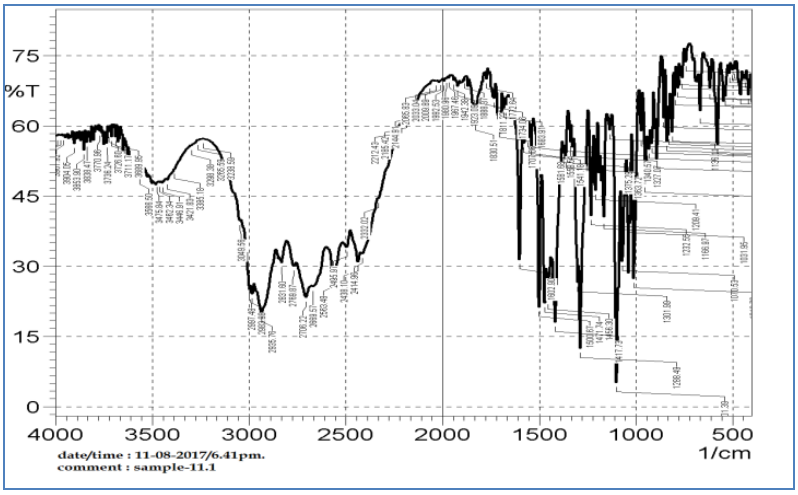

Figure no: 13 Duloxetine Hydrochloride FTIR Spectra.

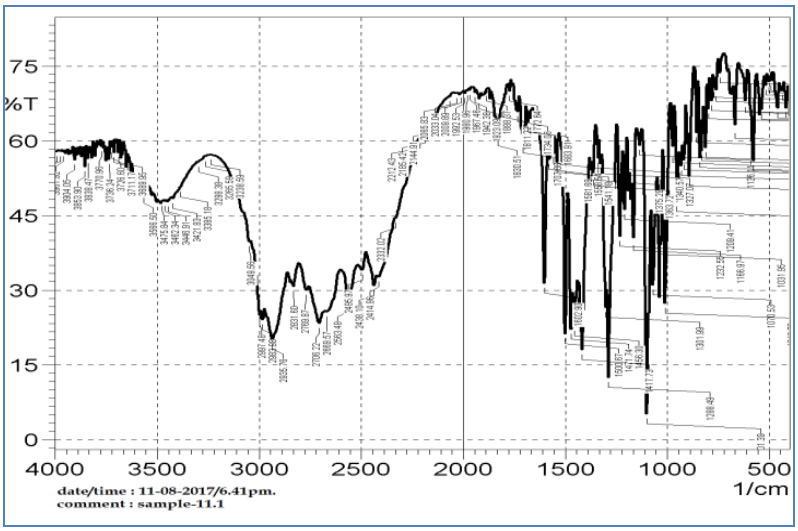

Figure no: 14 Duloxetine Hydrochloride FTIR Spectra.

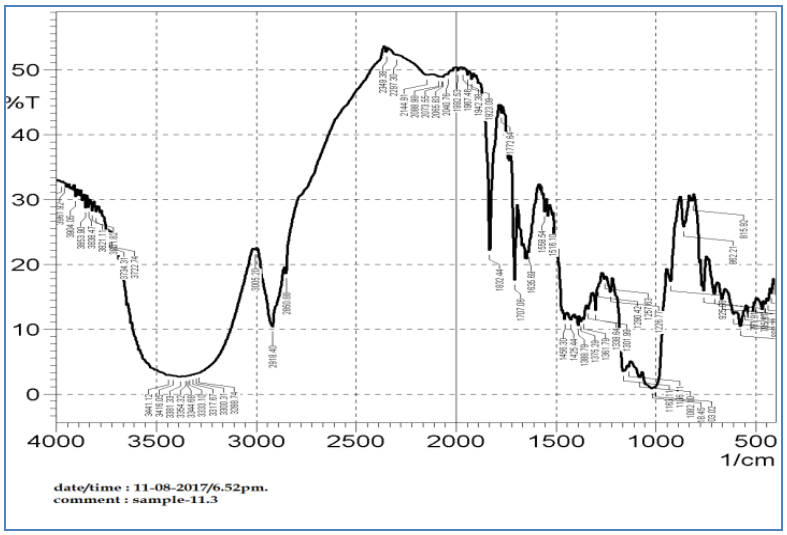

Figure no: 15 Duloxetine Hydrochloride FTIR Spectra.

FTIR studies indicate there is no much interaction between pure drug Duloxetine hydrochloride, sodium alginate and Methocel E-50 as referred in above graphs.

1. N-H starching vibrations close to 3400cm^{-1}.
2. Naphthalene and thiopene groups having peaks orientation between 1600 and 1450cm^{-1}.
3. Above said functional groups have no much interaction between sodium alginate and Methocel E-50.

In-Vitro Evaluation Parameters of In-house Prepared Transdermal Patches:

Table no: 04 Physical and in-vitro evaluation parameters of transdermal patches.

Trials	Wt. mg	NO. OF FOLDINGS	% DRUG (10MG)
T1	17	198	11.54
T2	16	65	11.08
T3	3	89	3.69
T4	11	92	6.23
T5	10	70	7.85
T6	12	181	10.15
T7	6	90	12.69
T8	12	91	12.23
T9	13	91	4.38
T10	13	189	10.23

Table no: 05 Drug release from transdermal patches T-1 to T-4.

TIME	T-1	T-2	T-3	T-4
0	0	0	0	0
30	4.51	6.06	0.25	5.23
60	6.93	22.33	7.84	12.23
120	12.34	27.30	18.24	21.56
180	45.34	40.29	19.39	34.65
240	74.32	48.87	31.35	41.45
300	88.23	64.61	62.62	52.45
360	91.93	93.70	69.62	59.34
420	99.78	93.10	71.44	66.39
480	98.12	96.79	99.18	79.24

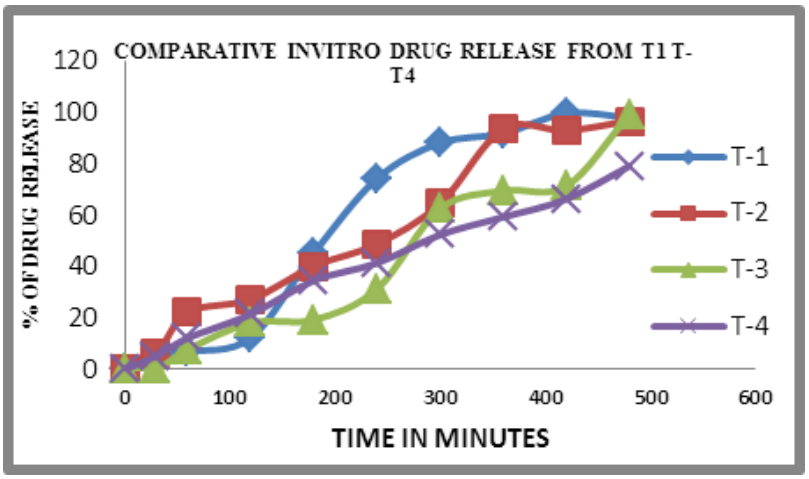

Figure no: 16 Graphical representation of drug release from T-1to T-4.

Table no: 06 Drug release from T5-T10.

SAMPLE TIME	T-5	T-6	T-7	T-8	T-9	T-10
0	0	0	0	0	0	0
30	12.12	10.23	10.23	6.34	12.23	5.23
60	28.23	18.36	20.34	12.45	23.65	15.20
120	34.23	23.56	32.56	15.34	39.45	21.84
180	54.23	56.04	75.35	38.24	49.94	37.23
240	76.93	75.45	88.49	51.34	61.34	39.39
300	88.83	86.45	93.24	69.87	78.82	43.67
360	97.34	92.45	95.78	86.38	82.38	67.56
420	99.30	99.56	99.34	95.12	91.23	66.94
480	78.34	95.45	98.59	96.45	99.40	85.35

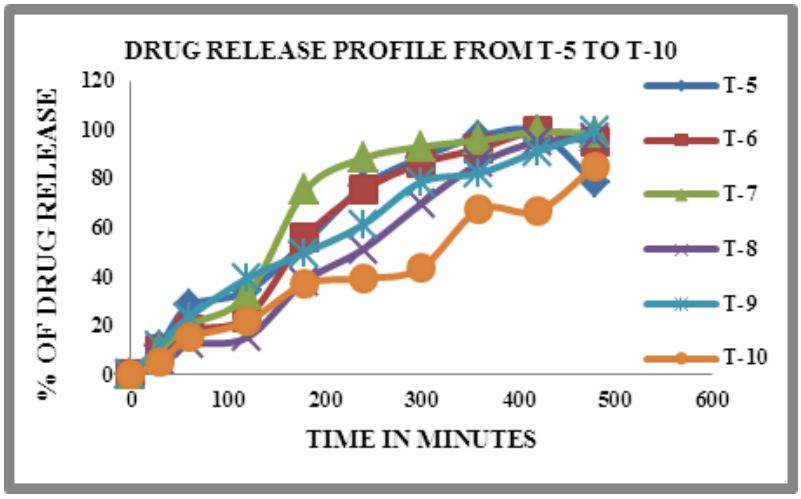

Figure no: 17 Comparative Graphical representation of drug release from T-5 and to T-10.

Table no: 07 Comparative drug release of T-4 and T-10.

TIME IN MINUTES	T4	T10
0	0	0
30	4.30	6.56
60	13.49	15.65
120	24.59	22.78
180	36.26	37.87
240	59.24	49.45
300	66.34	64.78
360	68.92	78.49
420	79.38	89.94
480	94.25	92.45

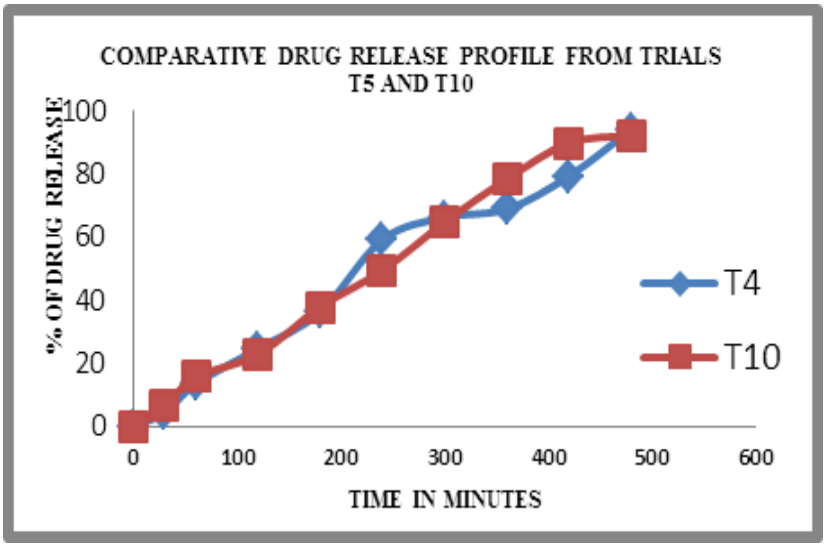

Figure no: 18 Comparative Graphical representation of drug release from T-4 and T-10.

STABILITY STUDIES

Based on the in-vitro evaluation results optimized formulation trial T10 was selected for one month stability studies under accelerated conditions-60^{o}C 80%RH.

The results of T10 transdermal patch was found to be as fallows,

Table no; 08 Physical characterization and assay of T-10 one month stability data.

Physical appearance	Thickness	Uniformity of weight	Drug content uniformity	Folding endurance test
Glossy appearance	0.12mm	16-18mg	99.35%	190

Table no: 09 Drug release form trial T-10 after one month stability studies.

TIME IN MINUTES	T-10
0	**0**
30	**7.34**
60	**16.29**
120	**24.39**
180	**38.29**
240	**45.92**
300	**58.38**
360	**68.48**
420	**83.28**
480	**91.49**

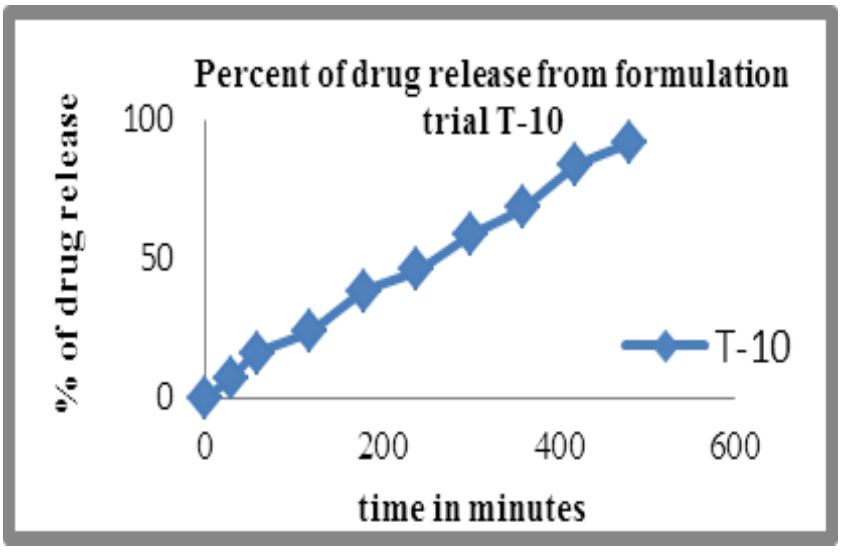

Figure no: 19 Drug release profile of T-10 after one month accelerated stability studies.

DETERMINATION OF RELEASE RATE KINETICS

Table no: 10 Kinetics of drug release from T-10.

Zero order		first order		HUGUCHIS PLOT		KORESMEYER PEPPAS PLOT	
Time-Min	% of Dug Un Dissolved	Time Min	Log 100-Q	Sq. Time	Mean % of Drug Release	Log Time	Log Cumulative % Drug Dissolved
0	100	0	0	0	0	0	0
30	92.66	30	1.97	5.48	7.34	1.48	0.87
60	83.71	60	1.92	7.75	16.29	1.78	1.21
120	75.61	120	1.88	10.95	24.39	2.08	1.39
180	61.71	180	1.79	2.24	38.29	2.26	1.58
240	54.08	240	1.73	15.49	45.92	2.38	1.66
300	41.62	300	1.62	17.32	58.38	2.48	1.77
360	31.52	360	1.50	18.97	68.48	2.56	1.84
420	16.72	420	1.22	20.49	83.28	2.62	1.92
480	8.51	480	0.93	21.91	91.49	2.68	1.96

ZERO ORDER

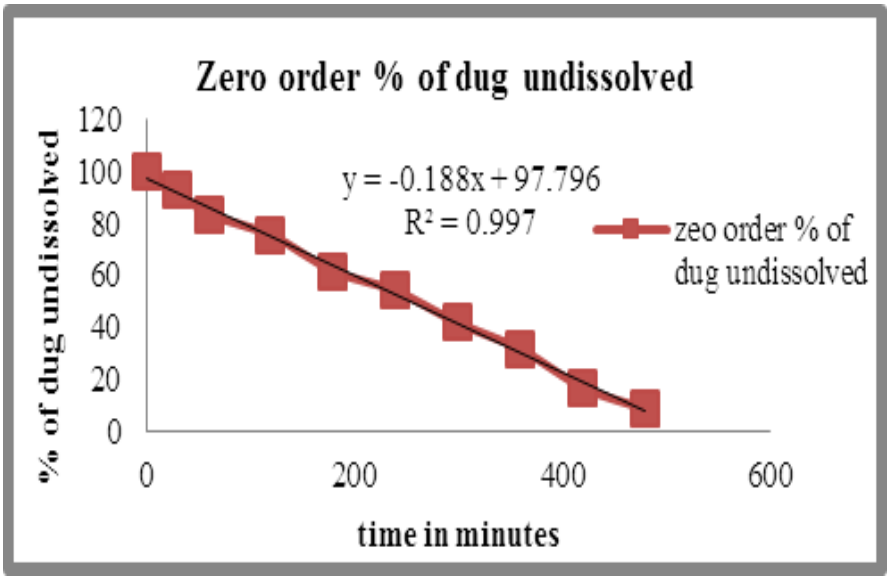

Figure no: 20 Drug release kinetics ZERO ORDER for T-10 after one month accelerated stability studies.

FIRST ORDER

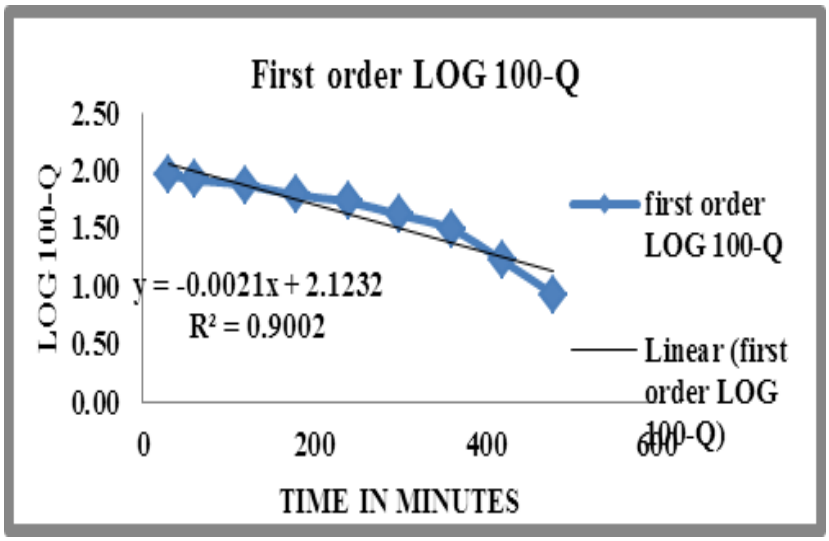

Figure no: 21 Drug release kinetics- FIRST order for T-10 after one month accelerated stability studies.

HIGUCHIS MODEL

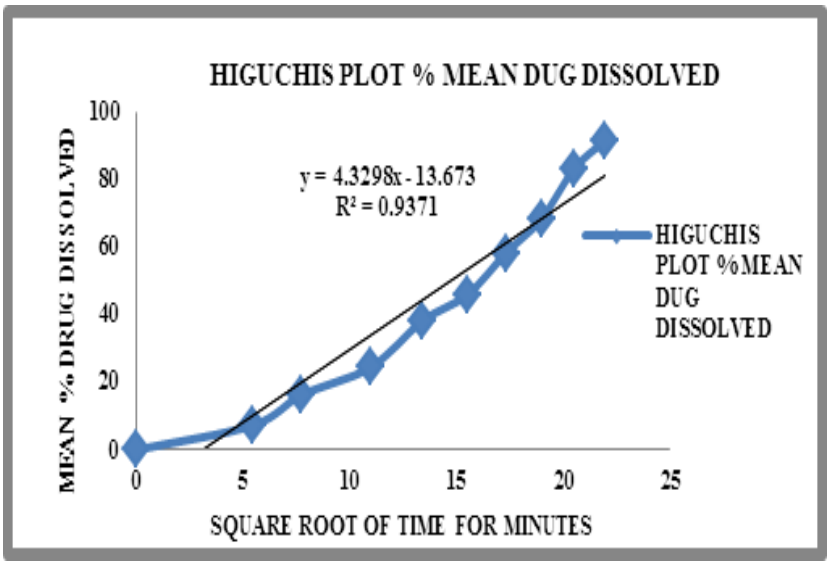

Figure no: 22 Drug release kinetics-HIGUCHIS plot for T-10 after one month accelerated stability studies.

KORESMEYER PEPPAS PLOT

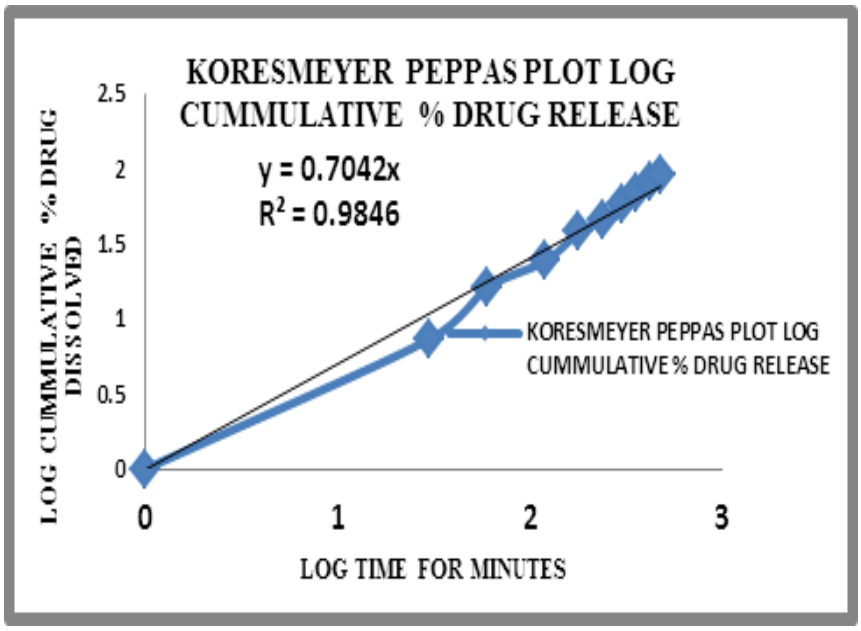

Figure no: 23 Drug release kinetics-Koresmeyer Peppas plot for T-10 after one month accelerated stability studies.

DISCUSSION

In the present research study, all the ingredients and API are selected after through review of literature and a FTIR compatibility studies were also performed in between pure API and other important excipients like sodium alginate and Methocel-k-100.

TRIAL 04 and TRIAL 10 were optimized based on their drug release and physical characterization.

TRIAL 10 was taken for stability studies for one month at accelerated stability condition at $60C^{o}$ and 80% RH.

After one month stability studies trial 10 shown good physical appearances and gave optimum release of drug.

CONCLUSION

After through work done on transdermal patches of duloxetine hydrochloride, conclusions drawn are as:

- Preformulation studies like FTIR were performed and no major incompatabilities were observed between Duloxetine hydrochloride and polymers like sodium alginate and HPMC.

- Total ten preparation trials were performed out of which from trial T-01 to T-05 HPMC-15 and sodium alginate were used and trial T-05 was optimized.
- And from trial T-06 to trial T-10 methocel K-100 was used as release retarding agent along with sodium alginate and trial T-10 was optimized.
- A comparative drug release between trial T-05 and trial T-10 was performed of which trial T-10 was showing good release of six determinants.
- Trial T-10 was selected for one month stability studies under accelerated stability conditions at $60C^{o}$ and 80%RH.
- The physical characterizations and drug release from trial T-10 after one month stability studies was within the limits and specifications.
- Drug release kinetics was also performed for trial T-10 after one month stability studies.

The order of drug release from patches of trial T-10 was determined based in R^2 and the values of different order are as zero order- 0.997, first order 0.900, HIGUCHIS Plot 0.937 and Koresmeyer Peppas plot fallows R^2 of 0.984.

- Based on the R^2 value, it was determined and concluded that the release kinetics from prepared trial T-10 Duloxetine transdermal patches follows ZERO ORDER KINETICS with R^2 value of 0.997.

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