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FORMULATION AND EVALUATION OF ONDANSETRON HCL TRANSDERMAL PATCH

[1]*Divya Bharathi, [1]Ch. Srinivas Reddy, [2]G. Babu and [1]Y. Shirisha

[1]Pharmaceutics and [2]Pharmaceutical Chemistry.

[1]Brilliant Group of Instituitions, Hyderabad.

[2]Anurag Group of Institutions, Kodad, Nalgonda.

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***Corresponding Author**
Divya Bharathi
Pharmaceutics, Brilliant Group of Instituitions, Hyderabad.

ABSTRACT

The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion/penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix. Matrix type systems were developed in the present study. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Ondansetron-HCl with different concentration of various polymers alone and combinations using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F8 formulation has been selected as the best formulation among all the other formulations. The *in-vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the *in-vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows peppas order release by diffusion technique from the polymer.

KEYWORDS: Transdermal drug delivery, hydrophobic polymers, Ondansetron HCl.

1. INTRODUCTION

1.1 Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

1.2 Structure of skin

An average adult skin has a surface area of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97+/-0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss and cushion internal structures.[7,8]

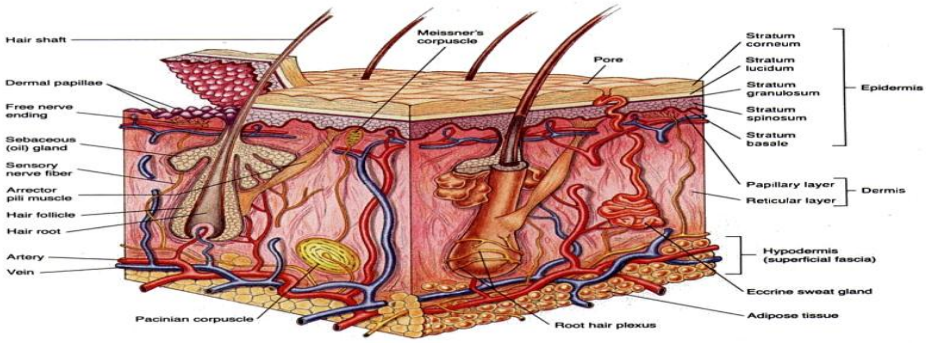


Figure 1: Structure of skin.

The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers.[6,9,10]

- **The epidermis** – thin protective outer layer.
- **The dermis** – the tough elastic second layer.
- **The hypodermis** – layer of fatty and connective tissue.

Basic Components Of Transdermal Drug Delivery Systems

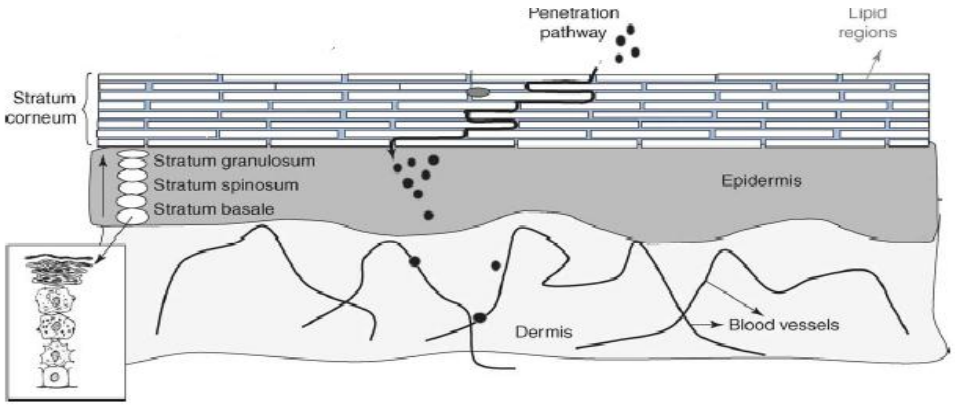


Figure No 2. Penetration pathway of drug molecules through the skin.

The components of transdermal devices include

a) Polymer matrix or matrices
b) The drug
c) Permeation enhancers
d) Other excipients

1.3 Techniques used in TDDS

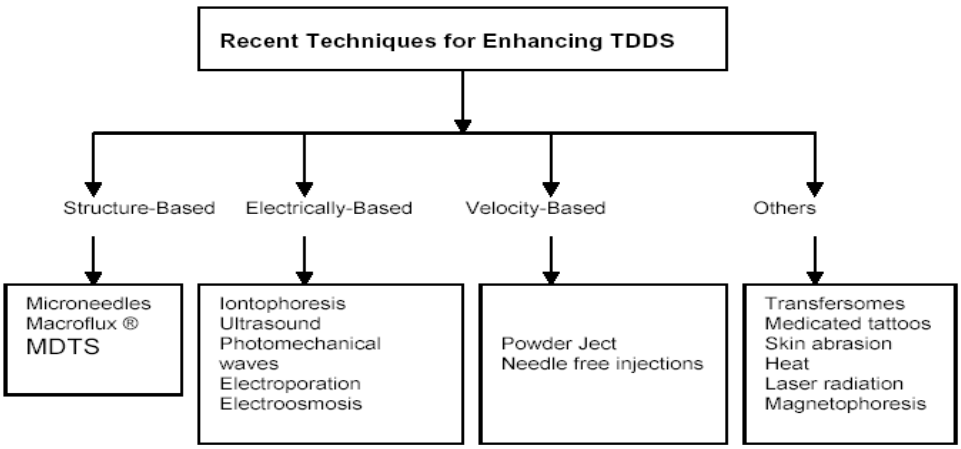


Figure No. 3 Techniques based on active transport for enhancing TDDS.

2. LITERATURE REVIEW

Madhulatha A (2013) investigated that to develop sustained release transdermal therapeutic system containing Ibuprofen with different ratios of chitosan, HPMC and combination of chitosan-HPMC by solvent-evaporation technique. The physicochemical compatibility of the drug and the polymers was by Fourier Transform Infra Red (FTIR). The results suggested no physicochemical incompatibility between the drug and the polymers. Drug loaded films were prepared and evaluated for thickness, percentage flatness, tensile strength, weight uniformity, drug content, moisture content, moisture uptake, swelling index, water vapor transmission, skin irritation and invitro-drug permeation study. The results followed Higuchi kinetics (r = 0.9382) and the mechanism of release was diffusion controlled release and further it was found to be linear with korsemeyer-peppas equation (r = 0.9698 and slope n = 0.5075) and confirmed that diffusion follows Non-Fickian law. Based on the invitro dug permeation studies using rat skin, D4 formulation (0.2% plain chitosan+HPMC) produce 86% drug release in 24 hours.

Lincy john (2013) studied to design and evaluates Amlodipine transdermal patches using polymers such as ethyl cellulose. Matrix type transdermal patches containing Amlodipine were prepared by solvent casting method by using polymers like ethylcellulose 1%, 1.5%, 2% and 2.5% and a total of eight formulations were prepared. Plasticizers used were propylene glycol and dibutylpthalate. The transdermal patches were evaluated for their physicochemical properties like folding endurance, thickness, percentage moisture loss, percentage moisture absorption, drug content and water vapour transmission rate. Formulation E6 (1.5% Ethylcellulose with dibutylphthlate) as plasticizers showed a maximum release of 99 % in 24 hours. Out of these eight formulations of EC, 1.5% Ethylcellulose (E6) was optimized since they produced a sustained and a complete release over a period of 24 hours. Thus the knowledge on the use of ethyl cellulose to control drug release in transdermal delivery systems might be applicable to other transdermal drug delivery system as well.

G.V.Radha (2013) reported that the transdermal drug delivery systems are becoming more popular in the field of modern pharmaceutics. The present study has been carried out to develop matrix type transdermal films containing Enalapril maleate with different ratios of HPMC (hydroxyl propyl methyl cellulose) alone, EC (ethyl cellulose) alone and combination of both HPMC & EC. Formulated transdermal films were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and analysed by using various

kinetic models. Kinetic data revealed that the drug release followed first order kinetics and the mechanism of release was found to be non fickian diffusion.

Gudapa Reddy Rajareddy (2013) investigated that to develop a suitable matrix type transdermal patch of Candesartan Cilexetil, using blends of two different types of polymeric combinations viz. HPMC K100 and Eudragit RL100 prepared formulations were subjected to various physiochemical evaluation tests like moisture content loss, moisture absorption, flatness to study the stability of the formulations, in vitro dissolution was performed to determine the amount of Candesartan present in the patches. Drug excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopy technique.

Priyanka Rathore (2012) The aim of this research was to formulate a matrix-type transdermal therapeutic system containing drug ciprofloxacin with different ratios of hydrophobic (ethyl cellulose) polymer by solvent evaporation technique, using 15% w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of isopropyl myristate were used to enhance the transdermal permeation of Ciprofloxacin. Formulated transdermal films were physically evaluated with regard to thickness, weight variation and drug content. All prepared formulations showed good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. Formulation T3 showed best in-vitro skin permeation through goat skin as compared to all other formulations.

Gottipati Dinesh Babu (2012) Main objective of the present work is to develop transdermal patches of Valsartan with hydrophilic and hydrophobic polymers containing the drug reservoir by solvent evaporation method. Valsartan is a poorly soluble drug with poor bio availability. In this experiment, the membranes of ethylcellose and Eudragit RS 100 and Eudragit RL 100 along with HPMC combination were used to achieve controlled release of the drug. The prepared patches showed satisfactory physiochemical characteristics of weight variation, thickness, folding endurances, moisture absorption and drug content. Results for in-vitro permeation studies were done by using Franz diffusion cell with cellophane membrane. The effect of non- ionic surfactant like tween 80 and span 80 on drug permeation were studied. Based on the kinetic studies, the patch containing both HPMC and Eudragit RS100 showed satisfactory drug release pattern.

Neha Pachisia (2012) researched that matrix controlled transdermal systems of anti-diabetic drug glimepiride were prepared using natural polymer chitosan for the extended and controlled delivery of the drug. Characterization was done by physicochemical studies. Optimization of the system was done using in vitro drug permeation studies through rat skin. Skin irritation tests and pharmacokinetic evaluations were carried out in healthy rats. Blood glucose reducing hypoglycemic activity of the systems was studied in diabetic rats. The *in vitro* permeation rate across the rat skin varied with the varying drug: polymer ratio in the patch. The patch with the maximum flux rate of 10.465 ± 0.261mcg/cm2 was chosen for the further studies. The patch exhibited negligible skin irritation. The hypoglycemic response was gradual but sustained for prolonged period of time with the transdermal system.

3. DRUG PROFILE

Ondansetron Hydrochloride Dihydrate

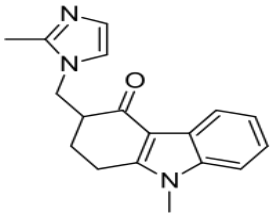
Proprietary name: Zofran; Zophren.

IUPAC Name: 1, 2, 3, 9-Tetrahydro–9–methyl–3-[(2–methyl–1H-imidazol–1–yl)methyl] 4Hcarbazol– 4–one hydrochloride dehydrate

Molecular formula: C18H19N3O, HCL, $2H_2O$.

Molecular weight: 365.9.

Structure



HCL

Description: A white crystalline solid from water/isopropanol with m.p. 178.5° to 179.5°. It is Soluble in aqueous solutions but solubility decreases with pH >5.7.

Dissociation Constant: Hydrochloride dihydrate; pKa7.4.

Pharmacokinetics Parameters

Bioavailability: 60% (young healthy subjects), 65% (elderly); 85% (patients with cancer) and 100% (severe hepatic impairment).

Half–life: 3 h (young healthy subjects), 5 h (elderly) and 15 to 32 h (severe hepatic impairment).

Volume of distribution: Approx. 140 to 160 L; also reported as 1.3 to 2.9 L/kg. 3.05 L/kg (mild liver disease); 3.36 L/kg (moderate); 3.86 L/kg (severe); 2.5 L/kg (healthy individuals).

Clearance: 16.6 L/h (patients with mild liver disease); 15.9 L/h (moderate liver disease); 11.6 L/h (severe); 28.3 L/h (healthy volunteers).

Distribution in blood: Blood: plasma ratio is 0.83. It distributes into erythrocytes and circulates bound within.

Protein binding: 70 to 75%.

Dose: Adult: 8 mg (orally) before treatment followed by 8 mg every 12 h. 16 mg daily (by rectum administration) or 32 mg (intravenously). Children: 5 mg/m2 (intravenously) immediately before treatment and then 4 mg orally every 12 h. alternatively, 100 g/kg (maximum 4 mg) (over 2 years old).

4. MATERIALS AND METHODS

Table 1: List of Material Used In the Formulation Development.

Material	Source
Ondasartan HCL	Sura Labs
Eudragit S 100	Merck Specialities Pvt Ltd
Ethylcellulose	Merck Specialities Pvt Ltd
Chloroform	Merck Specialities Pvt Ltd
Oleic Acid	Merck Specialities Pvt Ltd
Methanol	Merck Specialities Pvt Ltd
Propylene glycol	Merck Specialities Pvt Ltd

Table 2: List of equipments used in the study.

Name of equipment	Manufacturer
Double beam UV Visible Spectrophotometer	Lab India UV 3000
Digital weigh balance	Sartourious
FTIR Spectrophotometer	Bruker
Magnetic Stirrer 2MLH	Remi Equipments, Mumbai, India.
Franz diffusion cell	Remi Equipments, Mumbai, India.

4.1 METHODOLOGY

Analytical method development

A.UV scan

- A 100mg of Ondansetron Hydrochloride was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-600nm.

B. Construction of calibration curve

- A 100mg of Ondansetron Hydrochloride was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 4 to 16 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 305 nm.

4.2 Compatibility study

FTIR study

- The infrared spectrum of the pure Ondesartan Hydrochloride sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

4.3 Preformulation study

A. Colour, Odour, Taste and Appearance

The drug sample was evaluated for its Colour, Odour and Appearance.

B. Melting point determination

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility

- The solubility of Ondesartan hydrochloride was determined by adding excess amount of drug in the solvent.
- The ondansetron hydrochloride has very low aqueous solubility. Its solubility is not reported in any official book, so determination of solubility is important. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.
- Saturated solution of Ondansetron hydrochloride prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 305 nm and 303 nm for phosphate buffer and distilled water respectively.

4.4 Formulation of transdermal patches[47]

a. Preparation of blank patches

- Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

b. Formulation of Drug Incorporated Transdermal Patches

- The matrix-type transdermal patches containing Ondansetron Hcl were prepared using different concentrations of ethyl cellulose and Eudragit S 100. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Propylene glycol was used as plasticizers. Oleic acid was used as the penetration enhancer. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 8 mg.

Table 3: Formulation of ondesarton hydrochloride Patches.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eudragit S 100	1%	2%	3%	-	-	-	0.5%	1%	0.5%
Ethylcellulose N50	-	-	-	1%	2%	3%	0.5%	0.5%	1%
PG	5%	5%	5%	5%	5%	5%	5%	5%	5%
Oleic acid	10%	10%	10%	10%	10%	10%	10%	10%	10%
Chloroform : methanol (1:1)	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml

4.5 Evaluation Parameters of patches

Physical evaluations

a. Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

c. Weight variation

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

Where,

I2 = Final length of each strip

I1 = Initial length of each strip

***4.6 In-vitro* Drug Diffussion Study**

The in vitro study of drug permeation through the semi permeable membrane was performed using a franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled

with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5^{0}C. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 305 nm.

4.7 Drug release kinetics

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

4.8 Zero-Order Kinetics

- Zero order as cumulative amount of Percentage drug released vs time
- C=K0t
- Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics

- First order as log cumulative percentage of log (%) cumulative drug remaining vs time,
- $Log C = Log C o - k t / 2.303$
- Where C0 is the initial concentration of drug, k is the first order constant and t is the time.

Higuchi Model

- Higuchi's model as cumulative percentage of drug released vs square root of time
- Q = K t 1/2
- Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations

- Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.
- $Mt/M\infty=Ktn$

- Where Mt/M∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

5. RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

5.1 Analysis of drug

A. UV scan

The lambda max of ondesartan hydrochloride was found to be 305 nm.

B. construction of calibration curve

Table 4: Standard graph of ondesartan HCL.

Concentration(µg/ml)	Absorbance(at 305 nm)
0	0
2	0.01
4	0.165
6	0.262
8	0.357
10	0.447
12	0.555
14	0.663
16	0.756

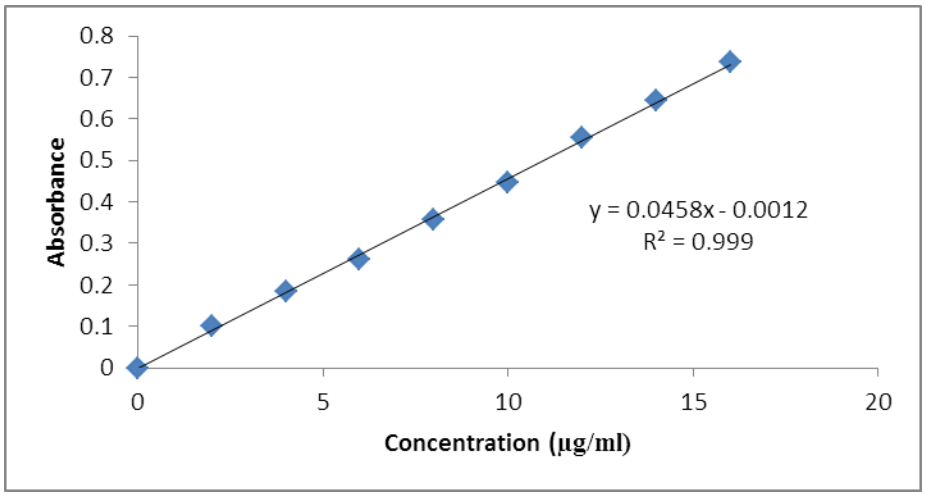


Figure 4: Standard calibration curve of ondesartan hydrochloride.

5.2 Compatibility studies

IR Spectroscopy

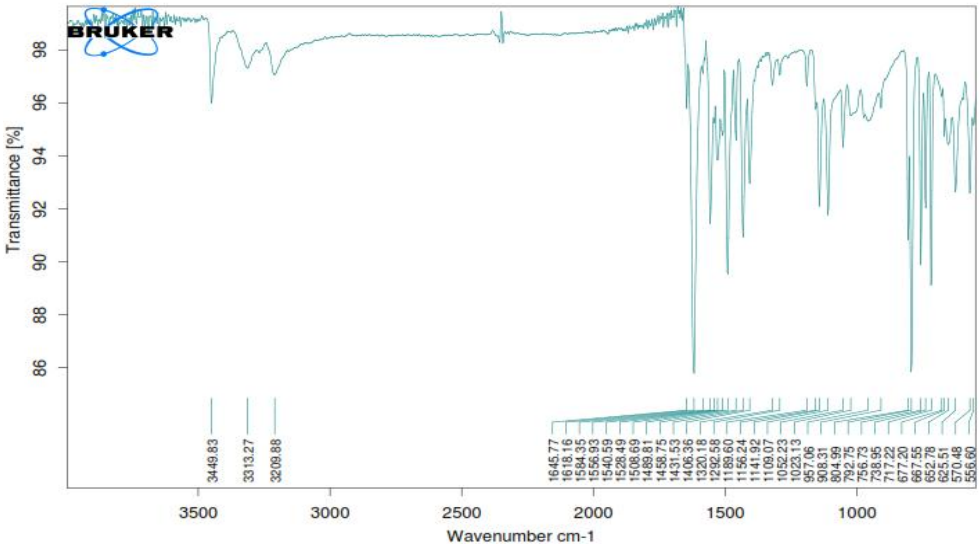


Figure 5: FTIR Spectrum of pure Ondesartan hydrochloride drug.

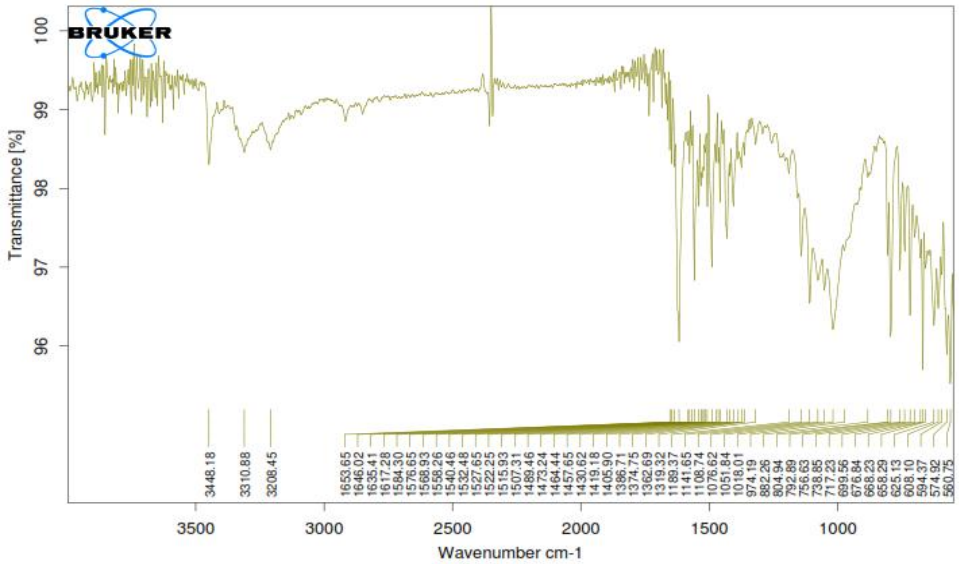


Figure 6: FTIR of Optimized formulation.

The compatability studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

5.3 Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was

found to be in between 0.032 ± 0.002 to 0.036 ± 0.003 mm. All formulations from F1 to F9 shows weight variation in between 63.33 ± 0.22 to 67.83 ± 0.18 mg.

Folding endurance from formulations F1 to F9 was found to be in between 72 ± 1.05 to 77 ± 1.13 which can withstand the foldings of the skin.

All formulations showed % drug content from 97.3 ± 1.57 to 99.98 ± 0.98.

Table 5: Evaluation of patches.

Formulation Code	Weight variation (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F1	64.23 ± 0.13	0.036 ± 0.003	75 ± 0.86	100	Transparent	98.4 ± 1.26
F2	63.33 ± 0.22	0.032 ± 0.002	76 ± 1.05	100	Transparent	99.98 ± 0.98
F3	65.37 ± 0.31	0.034 ± 0.001	77 ± 1.13	100	Transparent	99.45 ± 1.14
F4	66.74 ± 0.14	0.032 ± 0.001	75 ± 0.96	99	Transparent	97.3 ± 1.57
F5	67.83 ± 0.18	0.035 ± 0.002	72 ± 1.05	100	Transparent	98.05 ± 1.12
F6	65.24 ± 0.21	0.034 ± 0.001	74 ± 1.25	100	Transparent	99.52 ± 0.95
F7	63.47 ± 0.26	0.033 ± 0.003	75 ± 1.10	100	Transparent	99.22 ± 1.04
F8	66.59 ± 0.31	0.032 ± 0.001	73 ± 1.08	100	Transparent	98.68 ± 1.14
F9	64.51 ± 0.24	0.034 ± 0.002	76 ± 1.34	99	Transparent	99.64 ± 0.41

5.4 In vitro diffusion study

All the formulation in vitro diffusion study was carried out by using franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5^{o}C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 6: *In vitro* drug permeation of Ondansetron hydrochloride containing different concentrations of eudragit S-100.

Time (hr)	F1	F2	F3
0	0	0	0
1	19.46 ± 0.95	14.79 ± 1.13	10.38 ± 1.64
2	28.74 ± 1.13	22.32 ± 1.34	18.48 ± 1.23
3	39.38 ± 1.06	35.38 ± 0.98	25.34 ± 2.03
4	51.29 ± 1.42	46.52 ± 1.06	37.48 ± 0.95
5	64.38 ± 0.86	55.27 ± 1.11	45.14 ± 1.24
6	76.39 ± 1.56	62.38 ± 0.96	54.3 ± 1.53
7	84.29 ± 1.34	71.38 ± 1.65	63.19 ± 1.63
8	99.48 ± 2.04	82.28 ± 2.03	70.23 ± 1.47
9		91.28 ± 1.43	77.37 ± 1.38
10		99.29 ± 2.11	86.23 ± 2.06
11			92.41 ± 1.11
12			99.63 ± 1.51

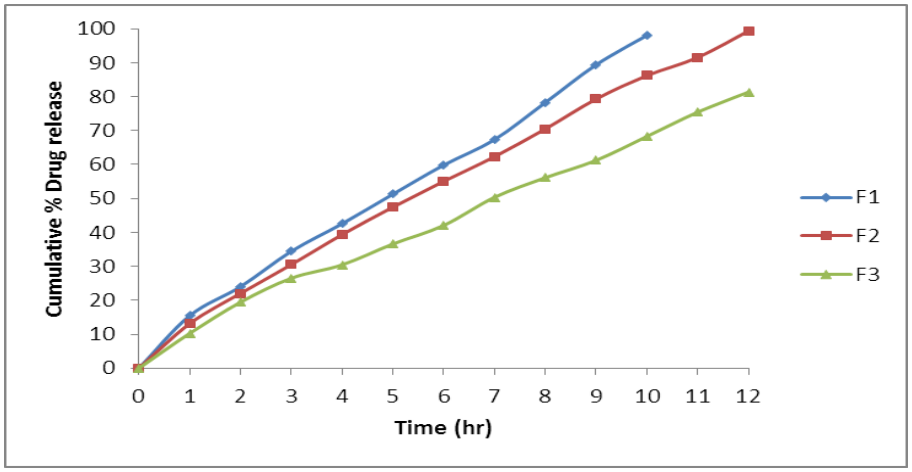


Figure: 7 Cumulative % drug permeation of ondansetron hcl patch (F1, F2 and F3).

The formulations F1 to F3 were prepared by different concentrations of eudragit S100 (0.5%, 1% and 2%), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 8 hours it was total amount of drug was permeated. The 1% concentration of polymer was showed maximum drug released at 10 hors 95.48 ± 1.85%. The 2% concentration of polymer was showed maximum drug release 99.63 ± 1.51 at desired time period. Hence in that 3 formulation F3 formulations showed total drug release at desired time period.

Table 7: *In vitro* drug permeation of Ondansetron hydrochloride containing different concentrations of ethyl cellulose.

Time	F4	F5	F6
1	28.34 ± 1.62	16.34 ± 1.02	11.27 ± 1.14
2	39.74 ± 1.22	23.36 ± 0.98	19.34 ± 1.62
3	50.48 ± 1.38	34.27 ± 1.23	26.23 ± 2.04
4	68.74 ± 0.95	42.45 ± 1.43	34.47 ± 1.82
5	77.19 ± 1.08	57.46 ± 1.51	39.19 ± 1.31
6	85.48 ± 1.46	64.63 ± 1.13	46.28 ± 1.28
7	97.18 ± 2.13	73.28 ± 0.86	52.37 ± 1.74
8	97.29 ± 1.15	80.29 ± 1.05	60.46 ± 2.13
9		89.32 ± 2.11	69.28 ± 2.21
10		95.48 ± 1.85	77.37 ± 1.48
11		95.24 ± 1.43	85.21 ± 1.36
12			94.36 ± 2.04

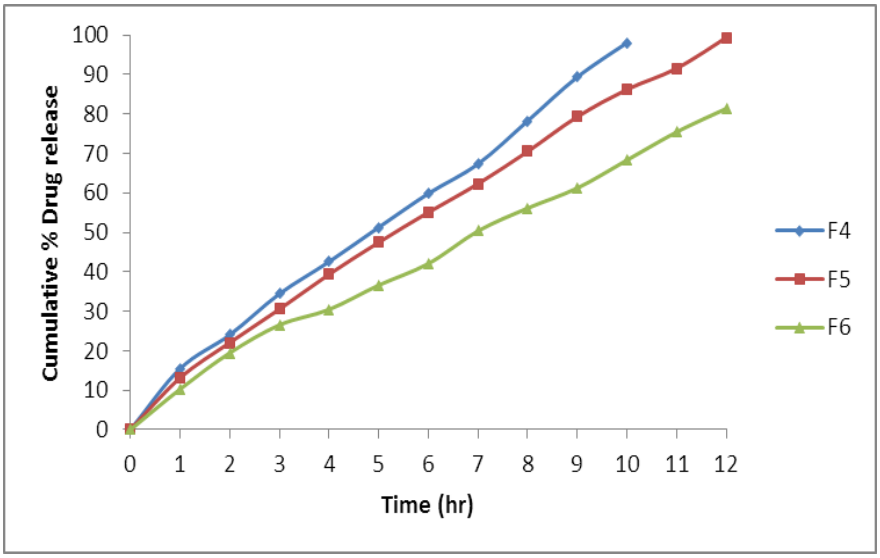


Figure 8: Cumulative % drug permeation of ondansetron HCL patch (F4, F5 and F6).

The formulations F4 to F6 were prepared by different concentrations of ethylcellulose (0.5%, 1% and 2%), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 0.5% (F4) concentration of polymer was showed maximum drug release 97.18 ± 2.13 within 7 hours. The 1% (F5) concentration of polymer was showed maximum drug released at 10 hors 95.48 ± 1.85%. The 2% (F6) concentration of polymer was showed maximum drug release 94.36 ± 2.04 at desired time period. Hence in that 3 formulation F6 formulations showed total drug release at desired time period.

Table 8: *In vitro* drug permeation of Ondansetron hydrochloride containing different concentrations of combination of eudragit S100 and ethyl cellulose.

Time	F7	F8	F9
0	0	0	0
1	15.47 ± 1.34	13.15 ± 1.66	10.28 ± 1.06
2	24.03 ± 1.63	22.06 ± 2.13	19.46 ± 1.58
3	34.43 ± 2.05	30.52 ± 1.81	26.52 ± 2.11
4	42.56 ± 1.14	39.37 ± 2.03	30.47 ± 1.69
5	51.27 ± 2.16	47.46 ± 1.43	36.61 ± 1.54
6	59.84 ± 1.59	55.08 ± 1.13	42.07 ± 2.03
7	67.34 ± 0.98	62.31 ± 2.11	50.36 ± 2.14
8	78.25 ± 1.37	70.49 ± 1.52	56.13 ± 1.81
9	89.38 ± 1.51	79.30 ± 1.37	61.23 ± 1.34
10	98.04 ± 2.03	86.21 ± 2.06	68.31 ± 1.66
11		91.55 ± 1.48	75.43 ± 1.71
12		99.37 ± 1.21	81.37 ± 1.38

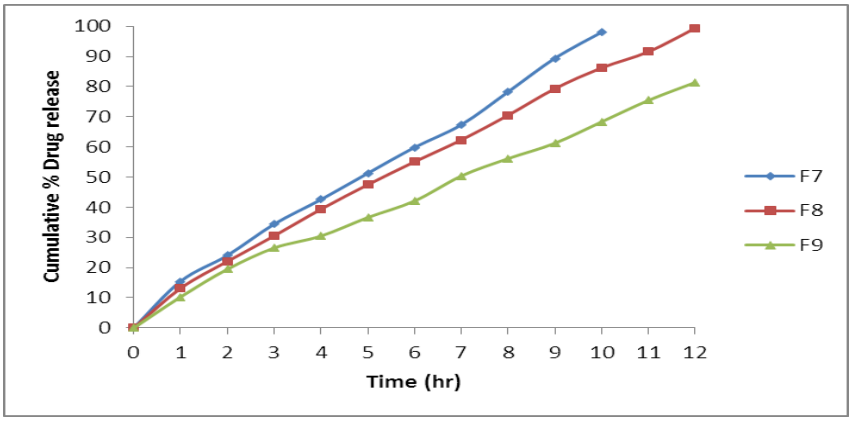


Figure 9: Cumulative % drug permeation of ondansetron hcl patch (F7, F8 and F9).

The formulations F7 to F9 were prepared by different concentrations of eudragit and ethylcellulose (0.5%, 1% and 2%), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 0.5% (F7) concentration of polymer was showed maximum drug release 98.04 ± 2.03 within 10 hours. The 1% (F8) concentration of polymer was showed maximum drug released at 12 hors 99.37 ± 1.21%. The 2% (F9) concentration of polymer was showed maximum drug release after 12 hours. Hence this was not considered.

Among all 9 formulations F8 formulation showed good drug permeation from the patch.

Among all in vitro evaluation parameters F8 formulation passed all evaluation parameters.

5.5 Kinetic models for Ondansetron hydrochloride

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model.

Table 9: Kinetics data of F8 Ondesartan hydrochloride patch.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
13.15	1	1.000	1.119	0.000	1.939
22.06	2	1.414	1.344	0.301	1.892
30.52	3	1.732	1.485	0.477	1.842
39.37	4	2.000	1.595	0.602	1.783
47.46	5	2.236	1.676	0.699	1.720
55.08	6	2.449	1.741	0.778	1.652
62.31	7	2.646	1.795	0.845	1.576
70.49	8	2.828	1.848	0.903	1.470
79.3	9	3.000	1.899	0.954	1.316
86.21	10	3.162	1.936	1.000	1.140
91.55	11	3.317	1.962	1.041	0.927
99.37	12	3.464	1.997	1.079	-0.201

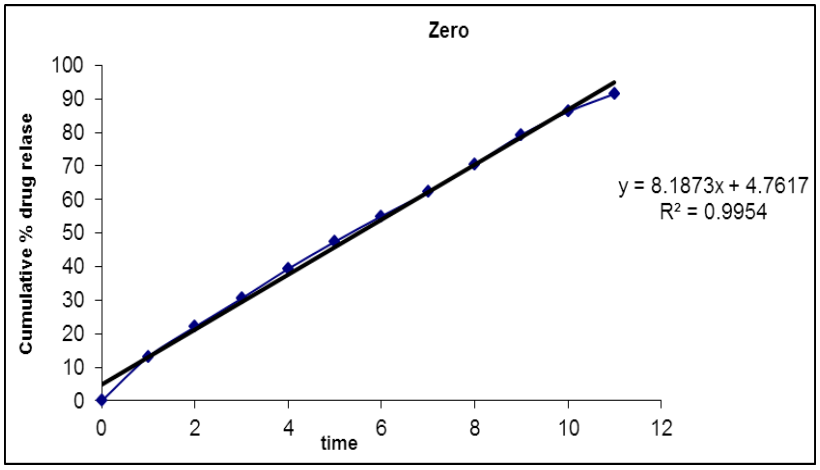


Figure 10: Graph of Zero order kinetics.

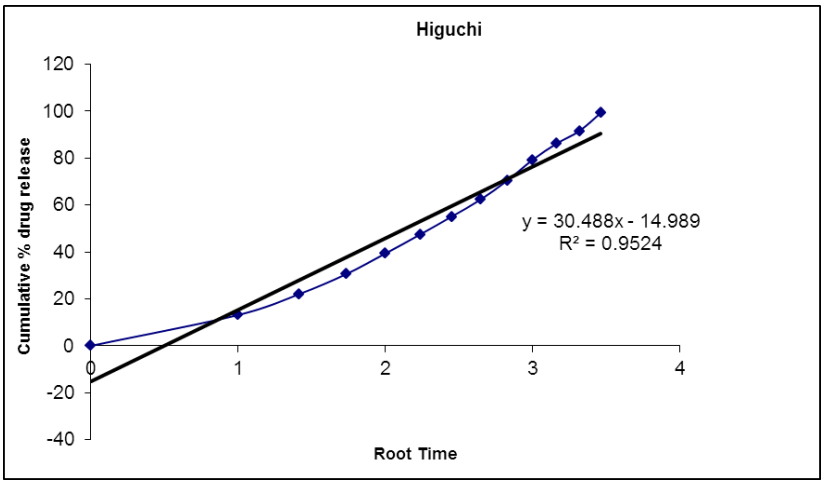


Figure 11: Graph of Higuchi release kinetics.

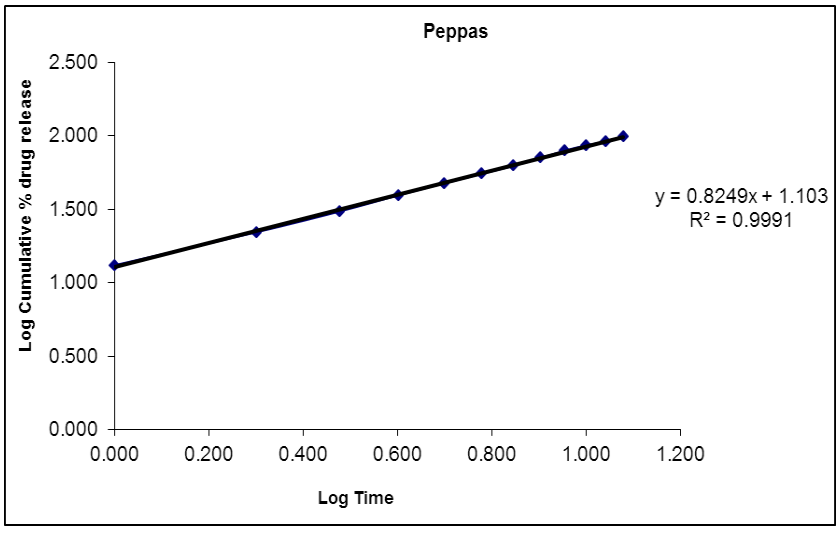


Figure 12: Graph of peppas release kinetics.

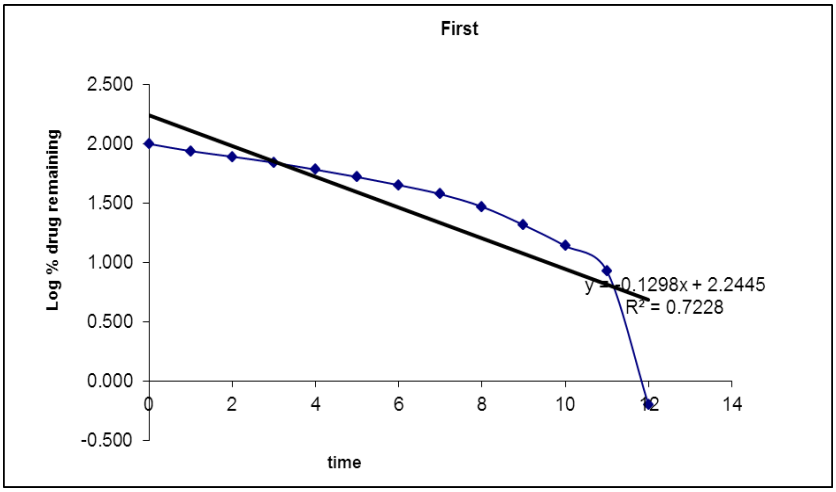


Figure 13: Graph of First order release kinetics.

From the above data the optimized formulation followed peppas release kinetics (n=0.8) non fickian rule.

6. CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Ondansetron hydrochloride patches using different types of polymers by solvent evaporation technique and mercury substrate method. The drug used is the best studied for therapy in treating hypertension.

Ondansetron hydrochloride was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.

From the experimental results obtained, F8 formulation has been selected as the best formulation among all the other formulations. The *in-vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.

The data obtained from the *in-vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model.

From the kinetic data it was found that drug release follows peppas order release by diffusion technique from the polymer.

Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Ondansetron hydrochloride patches was found to be successful in the release of the drug for an extended period of 12 hrs.

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